CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-246

JOINT MEDICAL AND STATISTICAL REVIEWS

Statistical Review
NDA 21-246, SN 000

Date of submission: June 15, 2000
Date received: June 16, 2000

Applicant: Hoffman-LaRoche Inc.
340 Kingsland Street
Nutley, NJ 07110-1199

Drug name: Oseltamavir phosphate

Trade name: Tamiflu

Formulation: Oral suspension, 12 mg/ml after reconstitution

Proposed indication: Treatment of influenza in children ages 1-12 years

A joint clinical and statistical review has been completed and filed by Medical Officer: Linda Lewis, MD and Mathematical Statistician: Andrei Breazna, Ph.D.

/s/

Andrei Breazna
12/20/00 02:14:52 PM
BIOMETRICS

Joint Clinical/Statistical Review
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Date of submission: June 15, 2000
Date received: June 16, 2000
Draft Review: December 11, 2000
Final Review: December 14, 2000

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Chemical structure:

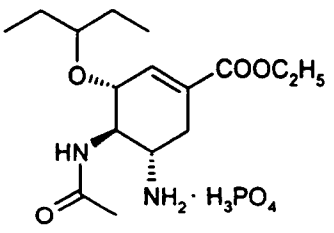


Table of Contents

1. Introduction and Background

Tamiflu (oseltamivir phosphate, Ro 64-0796) oral suspension is an ethyl ester pro-drug of the selective influenza virus neuraminidase inhibitor Ro 64-0802 (oseltamivir carboxylate). The compound is active against the neuraminidase of both influenza A and B. After ingestion the pro-drug is rapidly absorbed and converted almost completely to the active metabolite. The capsule formulation of Tamiflu was approved for the treatment of uncomplicated influenza infection in adults in October, 1999 (NDA 21-087). A supplement to that NDA for the prevention of influenza in adults was approved in November, 2000. This submission requests an extension of the indication for Tamiflu to treat acute influenza in children older than 1 year of age.

Influenza A and B, viruses of the orthomyxovirus family, are responsible for substantial morbidity and for seasonal (winter) epidemics of influenza infection affecting millions of individuals across the country. Acute influenza is characterized by sudden onset of fever, chills, respiratory symptoms (cough, coryza, sneezing), myalgias, headache, and in children, a significant degree of gastrointestinal complaints. Yearly surveillance tracks significant increases in mortality, primarily in the very young and the very old, associated with influenza outbreaks. Young children, because of their lower rates of seropositivity and subsequent high attack rate, are thought to be the critical players in the spread of influenza in the community. Recently published studies document that healthy young children are infrequently immunized against influenza and are hospitalized at rates that are similar to those of high risk adults (Neuzil, NEJM 2000;342:225-31 and Izurieta, NEJM 2000;342:232-9). Like high risk adults and the elderly, young children with influenza infection are at increased risk of secondary bacterial infections that contribute to the need for antibiotics and hospitalization. The authors of these studies suggested that expanded use of influenza vaccine in young children might prevent significant excess morbidity.

In the absence of universal influenza vaccination for children, treatment of acute influenza may provide both symptomatic relief and, theoretically, a reduction in transmission of virus within the community. Currently available antiviral agents for the treatment of influenza include amantidine (Symmetrel) and rimantidine (Flumadine), inhibitors of the influenza A M2 ion channel, and zanamivir (Relenza), another neuraminidase inhibitor. Amantidine, which is approved for use in children, is active only against influenza A. It has no activity against influenza B, which lacks the M2 protein, and it has a significant adverse effect profile. Zanamivir, which is delivered via a disk inhaler device, is approved for use in children 7 years or older but not in younger children. With these circumstances in mind, the sponsor began a pediatric development program in children between the ages of 1 and 12 years for Tamiflu using a suspension formulation.

2. Relevant Reviews from Other Disciplines

2.1. Chemistry

For a detailed review of the chemistry and manufacturing issues relating to the suspension formulation of Tamiflu please see the review by Dr. Dan Boring. Of importance in the clinical review is the fact that the clinical trials of Tamiflu suspension in children were conducted with formulation type I (/V06 and /V20), , while the product to be marketed is formulation type II (/V36 and /V37). The formulation was changed in order to allow better filling of the mix into bottles, to reduce the amount of inactive ingredients and to improve the taste. A number of minor changes in the manufacturing process were made relatively late in product development as problems were identified with in some of the early batches and analysis of some batches showed homogeneity problems in the filled bottles from the beginning to end of the manufacturing run. These problems were resolved to the satisfaction of the Chemistry review team as described by Dr. Boring.

It should be noted that while this product is described as a suspension, the active drug is completely in solution in the liquid phase of the suspension. The component in suspension is the titanium dioxide used as a

2.2. Pharmacology/Toxicology

Please see the review by Drs. Ita Yuen and James Farrelly who have reviewed the pharmacologic/toxicologic pre-clinical data provided in this submission.

2.3. Microbiology

Please see the review by Dr. Narayana Battula who has evaluated all virologic studies submitted with this report. He has paid particular attention during his review to the potential development of influenza isolates resistant to Tamiflu and the other neuraminidase inhibitors. In prior studies of other anti-influenza drugs, it appeared that resistant influenza virus isolates occurred more frequently in children than in adults infected with the same strain of influenza. It has been speculated that this phenomenon may be due to a higher viral burden in children and longer periods of virus shedding seen in children compared to the adult population.

The sponsor has identified several children shedding virus with mutations in the neuraminidase enzyme that resulted in high level resistance. In this instance, "resistance" refers to a decrease in susceptibility of the mutant virus' neuraminidase to the inhibitor. In looking at only patients with paired pre- and post-treatment isolates of influenza from the clinical trials, 9 of 105 or 8.6% of children receiving Tamiflu developed resistant influenza compared to none of 140 children receiving placebo. This is significantly higher than the previously reported rate of resistance in adult patients (1.3%) using the same method of calculation.

Review of the electronic Case Reports and sponsor provided case summaries for the 9 children with pre- and post-treatment isolates documenting emergence of mutant virus reveals no specific pattern of influenza-associated symptoms or secondary illness. However, the median time to freedom from illness, the primary endpoint, was somewhat longer in the children with resistant virus (median 175 hours) than in the other children with documented influenza who received Tamiflu (median 99 hours). Because the number of resistant isolates is so small, these calculations may not have much significance. Eight of the children had mutant virus isolated on Day 6 and in 7 children follow-up cultures on Day 10 were negative for influenza. The remaining child had resistant virus isolated on Day 4 and had negative cultures on Days 6 and 10. At least one other child enrolled in the pivotal study had resistant influenza identified on Day 6 but had no baseline isolate with which to compare. Given that the use of Tamiflu at the time was limited to research studies, it is unlikely that this child was primarily infected with resistant influenza.

Reviewer's comments:
The issue of emerging resistance to the new neuraminidase agents is an important one. Initial studies in adults, using a similar method of identifying resistant isolates, revealed a rate of approximately 1.3% of resistant influenza. During the pre-NDA meeting, the sponsor proposed to document resistant isolates by determining the proportion of resistance in only those patients with paired pre- and post-treatment isolates. In the NDA submission and the proposed label, however, the sponsor has reported the proportion of resistant isolates in patients with a post-treatment culture taken, whether positive or negative (10 of 247 or 4%). Unfortunately, a negative culture result may represent poor culturing technique or variable shedding rather than elimination of sensitive virus. Given the variable culture patterns documented in the study population, this may significantly underestimate the prevalence of resistant virus. The review team believes the most prudent way to represent this data is the originally agreed upon method of calculating proportion of resistant isolates in paired samples.

The sponsor suggests that the resistant virus is less fit (and therefore less transmissable) than wild-type influenza based on in vitro data. This is not tremendously reassuring since there has been no study of these isolates in humans. To date, no transmission of resistant influenza virus has been documented but in the pediatric study contacts of subjects found to be shedding resistant virus were not cultured. In addition, it is not clear exactly what role mutations in the hemagglutinin protein play in resistance to the neuraminidase inhibitors. It is not known whether influenza virus with mutations in neuraminidase or hemagglutinin will be antigenically different from wild-type influenza in humans. The very limited clinical data available in the 9 subjects identified with mutant virus suggests that these patients may have had a longer course of illness than the larger population. It is premature to suggest that these resistant viruses are harmless. The sponsor should continue efforts to characterize these isolates and their pathogenic potential in future studies.

2.4. Review of Otitis Media in WV15758 – HFD-520

This submission included data intended to [redacted]

The pivotal study was designed to stratify children at the time of enrollment according to the presence or absence of OM and then follow all children for subsequent development of OM. The Division of Anti-Infective Drug Products (DAIDP) was consulted because of their extensive experience reviewing trials of OM treatment in children. Please see the consulting review by Dr. Thomas Smith, medical reviewer in DAIDP, for his assessment of the study design, identification of endpoints and analysis of this aspect of the pivotal Tamiflu pediatric trial.

3. Pharmacokinetics and Pharmacodynamics

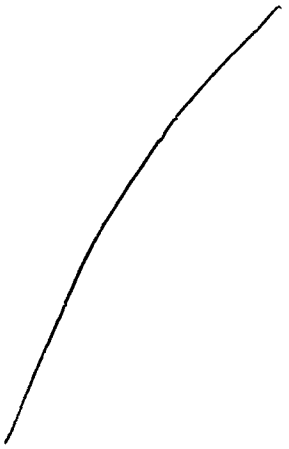
For a complete discussion of the pharmacokinetic properties of Tamiflu suspension, see the review of Dr. Jenny Zheng, the reviewer from the division of Pharmacology and Biopharmaceutics. Pharmacokinetic data were available from a single dose PK study in children ages 5-18 years (NP15826) and the pivotal trial (WV15758). Some of the issues that surfaced in the evaluation of the sponsor's proposed dosing recommendations for pediatrics will be briefly summarized in this review but are described in more detail in Dr. Zheng's review.

As noted in Dr. Zheng's review, there were multiple comparisons of the clinical trial suspension and the proposed market suspension. The initial bioequivalence study of Tamiflu suspension (type I) and Tamiflu capsules suggested that the oral suspension produced lower drug exposure than the capsules. After the manufacturing process was optimized, a final bioequivalence study was performed comparing the clinical trial suspension, the final market suspension and the approved capsules. This study demonstrated bioequivalence of the 2 suspensions and similar AUCs of the market suspension and the capsules.

Tamiflu oral suspension is easily absorbed, rapidly and extensively converted to the active metabolite Ro 64-0802 and finally excreted in the urine. The active metabolite follows linear pharmacokinetics in all ages, however, the sponsor did identify an age-related difference in clearance. Young children clear Ro 64-0802 more quickly than older children, exhibiting a lower drug exposure for a given mg/kg dose. Children older than 13 years of age have roughly the same exposure to active metabolite as adults when given an equivalent dose.

After conducting a single dose PK study in children 5 to 18 years old, the sponsor chose to study a dose of 2 mg/kg in their pediatric clinical trials. This dose was chosen to target drug exposure similar to that seen in the adult clinical trials which had previously shown safety and efficacy of doses of 75 and 150 mg BID. This dosing did not, however, take into consideration the more rapid clearance of the younger children. After analyzing their

pediatric PK data, the sponsor proposed dosing (for marketing) the suspension [redacted]



4. Description of Data Sources

4.1. Primary data

This submission consists of 137 volumes of study documents and electronic datasets containing Sections 11 and 12, the Case Report Forms and Case Report Tabulations. The sponsor submitted complete study reports for their pivotal pediatric clinical efficacy trial, WV15758. This study included safety and efficacy data derived from 698 children enrolled in the trial, 342 of whom received at least one dose of Tamiflu suspension. Supportive safety and efficacy data was included from 2 pediatric treatment studies: WV15731, a small pilot study enrolling 10 children, and WV15759/WV15871, a larger combined study enrolling 335 children with known asthma. Pharmacokinetic and safety data were submitted from 3 single dose studies, NP15826, NP15881, and NP15912. Additionally, since adolescents 13-17 years of age were enrolled in some of the adult trials, study reports were submitted for the adult efficacy trial M76001 and the adult prophylaxis study WV15799. These adolescents were included in the sponsor's safety database.

Safety and efficacy data from the CRTs was submitted in electronic format (as SAS transport files) to the CDER Electronic Document Room. Because the electronic files were very large and cumbersome to manipulate, the sponsor was asked to

provide some of the primary endpoint data in a more easily manipulated format as a reviewer's aid. This supplemental submission contained no new data or analysis. The review team also requested copies of the CRFs for all children who were diagnosed with OM during the trial and this information was submitted separately.

Table 1: Studies included in the pediatric submission

Study	Description	Dose Groups	Strata	Ages (years)	Number Enrolled (received Tamiflu)
Pediatric Studies: Suspension formulation					
WV15758	Pediatric treatment	Placebo 2 mg/kg BID	Otitis media	1-12	695 (342)
WV15759/ WV15871	Pediatric treatment (with asthma)	Placebo 2 mg/kg BID	Asthma severity	6-12	335 (170)
WV15731	Pediatric dose ranging, PK	1 mg/kg BID 2 mg/kg BID 3 mg/kg BID	Age	1-12	10 (10)
NP15826	Pediatric single dose PK	Placebo 2 mg/kg	None	6-18	18 (18)
NP15881	Pediatric taste test	2 mg/kg	None	6-12	28 (28)
NP15912	Pediatric taste test	2 mg/kg	None	6-12	12 (12)
Adult Studies in which Adolescents were Recruited: Capsule formulation					
M76001	Time to treatment start	Placebo 75 mg BID	None	13-80	140 (94)*
WV15812/ WV15872	Treatment of chronically ill adults	Placebo 75 mg BID	COAD	> 13	8 (4)*
WV15799	Post-exposure prophylaxis	Placebo 75 mg QD	None	> 13	206 (111)*

*Refers to number of adolescents 13-17 years enrolled.

4.2. Postmarketing experience

There is no expanded access program for children and no postmarketing surveillance experience with adolescents receiving the previously approved capsule formulation. Two children have received Tamiflu on a compassionate use basis, one for rhabdomyolysis and one for encephalitis associated with influenza. Both of these patients are included in the Integrated Summary of Safety reported by the sponsor.

5. Review Methods

The sponsor's study reports were reviewed and conclusions regarding safety and efficacy were confirmed by independent FDA analysis of the data. Dr. Andrei Breazna performed the statistical analysis confirming the primary endpoint, length of time to freedom from illness, in the pediatric pivotal study and the supportive asthma study and evaluating some of the secondary endpoints. This MO reviewer evaluated study demographics, adverse events, and laboratory monitoring data using the JMP Statistical Discovery Software. Additional analysis was performed in conjunction with HFD-520 reviewers who were consulted regarding the sponsor's [redacted]

6. Review of Efficacy

6.1. Pivotal Pediatric Trial – WV15758

6.1.1. Study Design

Study WV15758 was designed as a randomized, placebo-controlled study to evaluate the safety, tolerability and efficacy of Tamiflu oral suspension in the treatment of influenza in children from 1 to 12 years of age. Children 1 to 12 years of age were eligible to enroll in the study if they presented with symptoms of influenza, defined as fever (otic temperature $\geq 100^{\circ}$ F or $\geq 37.8^{\circ}$ C) plus one respiratory symptom (cough and/or coryza), for < 48 hours during a time when influenza was known to be circulating in the community. Children were excluded if they were determined to have RSV at the time of presentation as determined by rapid diagnostic testing. They were also excluded if they were known to be HIV seropositive, transplant recipients, or to have uncontrolled underlying disease (examples listed in protocol), to be allergic to test medication or acetaminophen, had recent treatment with antiviral therapy for influenza, were females of child-bearing potential or had recent participation in another clinical trial. Subjects were to be stratified at the time of study entry according to the presence or absence of OM determined by tympanometry at baseline. The treatment regimens included:

Group A – 2 mg/kg Tamiflu oral suspension BID for 5 days (10 doses)
Group B – Matching placebo suspension BID for 5 days (10 doses)

The stated objectives of the study were to:

- Investigate the effect of treatment with Tamiflu on children with influenza
- Investigate the safety and tolerability of Tamiflu in children with influenza
- Investigate the effect of treatment with Tamiflu on medical and other health care resources associated with influenza and its complications
- Investigate the effect of treatment with Tamiflu on viral activity in children with influenza

- Obtain information on plasma concentration of Tamiflu and its active metabolite during treatment of pediatric patients with influenza and thereby characterize any PK differences within this population and adults

At Baseline, patients were questioned regarding medical history and examined including tympanometric examination, laboratory monitoring for safety assessments and serum influenza antibody titers, nasal/throat swabs for influenza virus culture and RSV determination. Parents were instructed on how to complete the Canadian Acute Respiratory Illness and Flu Scale (CARIFS) questionnaire diary card and record temperature. The CARIFS questionnaire used in this study asked parents to assess 18 symptoms of influenza illness (poor appetite, irritability, needing extra care, tired, sore throat, muscle aches, nasal congestion, etc.). Each symptom was rated on a 4-point scale with 0 = no problem, 1 = minor problem, 2 = moderate problem and 3 = major problem. The questionnaire had been validated in another population of children with influenza during the previous flu season. "Relief medication" (acetaminophen) and thermometers were provided. Parents were asked not to give study participants any other medication for relief of symptoms. Follow-up visits or home visits were scheduled as follows:

- Day 2: Vital signs recorded.
- Day 6: Vital signs recorded, examination for acute OM, nasal/throat swabs collected for virology, blood and urine samples collected for safety monitoring
- Day 10: Vital signs recorded, examination for acute OM, nasal/throat swabs collected for virology, CARIFS questionnaires collected and second set issued.
- Day 28: Physical examination (including OM assessment), blood samples for influenza antibody titer and follow-up for monitoring labs if needed. Medical history to assess any secondary illnesses occurring since the previous visit.
- In a subset of patients additional nasal/throat swabs were collected for virology on Days 2 and 4.

On all days the parent/guardian was instructed to complete the CARIFS card and record use of any additional medications twice daily. Temperature was to be recorded 3 times daily through Day 3, then twice daily through Day 10. Unused study medication and empty containers were returned to the investigator. After Day 10 the CARIFS cards were filled out once daily through Day 27. Parents were asked to make note of any secondary illnesses occurring throughout the study. Additional visits for adverse events, possible complications of influenza or study treatment, were performed as needed. Adverse events were recorded on the CRFs; their severity was graded according to the WHO four-point scale (mild, moderate, severe, life-threatening) and causality in relation to study drug was assessed.

Drug monitoring was preformed at "all sites where possible". Subjects had a series of 3 samples for drug concentration drawn (sparse sampling). These samples were obtained after at least 24 hours of dosing and were obtained immediately before scheduled dosing (sampled during 2 scheduled visits) and at 2-4 hours after dosing. At selected sites full PK profiles were obtained with drug concentration sampling over 12 hours.

6.1.2. Analysis Plan

Efficacy Analysis

The primary efficacy endpoint was identified in the study protocol to reflect the duration of illness and was defined as the length of time until all of the following conditions were met: 1) first alleviation of cough (a score of 0 = no problem, or 1 = minor problem), 2) first alleviation of nasal congestion (coryza), 3) first return to normal health and activity, and 4) first return to afebrile state (temperature $\leq$ 98.9° F or $\leq$ 37.2° C). This composite endpoint was to be calculated from the initiation of study drug (time 0) until all of the above conditions were met and remained so for at least 24 hours (21.5 hours allowed for the completion of diary cards on consecutive days with a 10% window).

Several secondary efficacy parameters were also defined in the protocol. "Return to normal health and activity", defined as return to the pre-influenza health and activity level as assessed by the parent/guardian, was identified as a secondary endpoint. Length of time to this endpoint was to be calculated as described above for the composite primary endpoint. The length of time until alleviation of all 18 of the CARIFS symptoms (as described above) was identified as a secondary efficacy parameter. Because the CARIFS included many non-specific symptoms such as irritability and clinginess, it was felt that it might not be sensitive enough to identify the true end of influenza symptoms and therefore was not assessed as a primary endpoint. To assess extent and severity of symptoms, a calculated AUC for the total CARIFS score was identified as a secondary efficacy parameter. CARIFS scores for all symptoms recorded on the diary cards twice daily for the first 10 days and then once daily up to day 28 were totaled and the AUC of these scores calculated for each patient using the trapezoidal rule. The occurrence of specified secondary illnesses diagnosed after at least 48 hours of study drug and the use of associated antibiotics were also designated as a secondary efficacy parameter.

Reviewer's comments:
The secondary endpoint called "return to normal health and activity" is included in the composite primary endpoint. It is very likely that this component may require the longest time to alleviation in the composite and may "drive" the primary endpoint. It is probably the most subjective of the 4 components. It seems inappropriate to include it as a secondary endpoint, especially since none of the other components will be analyzed individually.

Several tertiary efficacy parameters were described in the study protocol. These included an assessment of secondary illness defined as the proportion of children without OM at Baseline who developed OM during study and the proportion of children with OM at Baseline who resolved their OM during the study period. The proportion of subjects requiring antibiotics from the time of study drug initiation through the study period was identified as a tertiary efficacy parameter. Resolution of symptoms was to be assessed using the time to a ratio of the total CARIFS score (total score at follow-up visit divided by total score at Baseline) reaching a level of ≤ 0.25 and a similar ratio for AUC of total CARIFS score. Resolution of temperature was assessed by calculating a temperature AUC for each patient, by evaluating the proportion of subjects with fever on a daily basis, by calculating the time to last fever after initiating study drug and the time to afebrile state. Use of symptom relief medication was evaluated in terms of total relief medication consumption as well as an AUC of medication cumulative dose and as the total number of days of use of relief medication. The proportion of patients requiring a physician visit other than those scheduled for study follow-up and the proportion of subjects requiring hospitalization were also calculated.

Also listed as tertiary efficacy parameters were a number of virologic assessments. The distribution of post-baseline influenza antibody titers will be evaluated. In the study population the proportion of patients with viral shedding at each visit was calculated. In a subset of subjects the time to cessation of viral shedding was calculated from the time of study drug initiation to the time of first negative culture with no subsequent positive cultures. Quantitative virus titer over time was calculated as an AUC from baseline. Finally, viral isolates collected during the study were investigated to determine the potential development of resistance. The proportion of study subjects with laboratory proven influenza was determined by either a positive nasal/throat swab culture or by documenting a four-fold increase in influenza antibody titer from baseline.

Safety Analysis

Safety parameters in the study included both clinical adverse events and laboratory abnormalities. All clinical adverse events were recorded and graded according to the WHO grading scale. Symptoms and common sequelae of influenza were collected as efficacy endpoint data and therefore were not considered adverse events unless they met the criteria as a Serious Adverse Event (SAE). Symptoms that were specifically excluded as adverse events included: cough, dyspnea or difficulty breathing, tachycardia, sore throat, nasal congestion, earache, coryza, conjunctivitis, headache, fatigue, myalgia, fever, rigors, malaise or asthenia and chills. Severity and causality were assigned by the investigators for all clinical events. All adverse events were followed until resolution or until a reasonable explanation for persistence could be made.

Laboratory abnormalities were also rated according to the WHO grading scale. Abnormal values were repeated and followed until resolution or until an adequate

explanation for a persistent abnormality was identified. Laboratory monitoring included: complete blood count with differential and platelet count, serum electrolytes, BUN, creatinine, glucose (random), liver function tests, uric acid, albumin, and total protein and quantitative urinalysis.

Study Populations

The sponsor identified 4 study populations for analysis purposes.

- Safety population: All subjects who were randomized, who received at least one dose of study medication and for whom at least one follow-up was available. This population was used in the sponsor's safety analysis.
- Intent-to-treat (ITT) population: All subjects who were randomized and received at least one dose of study medication, analyzed according to their original randomization. This population was used for descriptive summaries of efficacy endpoints but was not used for the sponsor's primary efficacy analysis.
- Intent-to-treat-infected (ITTI) population: All subjects who were randomized, received at least one dose of study medication and were proven to have influenza by either culture or a four-fold or greater increase in influenza serum antibody. This population was used in the sponsor's primary efficacy analysis.
- Standard (per protocol) population: All subjects who had no major protocol violations, had proven influenza and who received six doses of study medication in the first 72 hours or at least 9 doses of medication including 5 within the first 72 hours of treatment. The sponsor used this population for some summaries of efficacy endpoints.

Analysis of the primary efficacy parameter was performed on the ITTI population and also on the ITT and Standard populations. Analysis of the secondary efficacy parameters was performed on the ITTI and Standard populations. Analysis of tertiary efficacy endpoints was performed using only the ITTI population. For the safety analysis all subjects included in the Safety Population will be analyzed and those who received drug other than the randomized assignment were analyzed according to the therapy received. Rules for handling missing primary efficacy data were determined prior to unblinding.

6.1.3. Efficacy in Treatment of Influenza

Study Subject Demographics and Baseline Characteristics

Study WV15758 enrolled 698 children between 1 and 12 years of age, 695 of whom received study medication. Three study subjects never received study drug and 2 who were randomized to receive Tamiflu actually received placebo, resulting in 342 children who received Tamiflu and 353 who received placebo. Study subjects were enrolled at 70 U.S. sites (631 subjects) and 10 Canadian sites (67 subjects). All ages and ethnic/racial backgrounds were represented, although Asians and African Americans were enrolled in smaller numbers than Caucasians.

Very few of the children enrolled had been vaccinated against influenza either the flu season during which the study was conducted or during the flu season prior to the study. Children were stratified at the time of enrollment according to the presence or absence of OM. According to the study report, 123 children were identified as having OM at the time of presentation (61 received Tamiflu and 62 received placebo). The baseline characteristics of the study population are summarized in Table 2.

Since the sponsor proposed [redacted], the study analyses were reported according to 3 age groups: 1-2 years (inclusive), 3-5 years (inclusive), and 6-12 years. Baseline characteristics were well matched across all of the age groups.

Table 2: Baseline Characteristics of the Enrolled Subjects Receiving Study Medication (Safety Population)

Characteristic	Entire Population (N = 695)	Tamiflu (N = 342)	Placebo (N = 353)
Age			
1-2 years	171 (24.6%)	78 (22.8%)	93 (26.3%)
3-5 years	219 (31.5%)	113 (33.0%)	106 (30.0%)
6-12 years	305 (43.9%)	151 (44.2%)	154 (43.6%)
Sex			
Male	350 (50.4%)	169 (49.4%)	181 (51.3%)
Female	345 (49.6%)	173 (50.6%)	172 (48.7%)
Race/Ethnicity*			
Asian	16 (2.3%)	8 (2.3%)	8 (2.3%)
Black	76 (10.9%)	37 (10.8%)	39 (11.0%)
Caucasian	451 (64.9%)	220 (64.3%)	231 (65.4%)
Hispanic	127 (18.3%)	64 (18.7%)	63 (17.8%)
Other/Mixed	25 (3.6%)	13 (3.8%)	12 (3.4%)
Otitis Media at Presentation			
Present	123 (17.7%)	61 (17.8%)	62 (17.6%)
Absent	572 (82.3%)	281 (82.2%)	291 (82.4%)
Influenza Vaccination			
Year of study	21 (3.0%)	11 (3.2%)	10 (2.8%)
Previous year	34 (4.9%)	21 (6.1%)	13 (3.7%)

*The listing of Race/Ethnicity differs slightly from the summary statistics reported in the sponsor's ISS since the database recorded 27 separate listings that this reviewer re-classified. The "Other/Mixed" category includes Indian, East Indian, Middle Eastern, Arabic, any dual listings (ie., black/white, Caucasian/Hispanic, etc.). Subjects listed as Filipino were reclassified as Asian by this reviewer.

The proportion of subjects who had laboratory confirmed influenza was similar in the pediatric and adult studies. The diagnosis of influenza was confirmed by either a positive culture or a four-fold or greater rise in influenza specific antibody from baseline to Day 28. Cultures were obtained by swabbing both the nose and

throat of subjects and inoculating both swabs into a single viral transport media. In this study 423 subjects had influenza infection confirmed by culture on at least one visit. An additional 29 subjects had serologic confirmation of infection. Overall, 65% of those who participated in the study had laboratory confirmed influenza infection. Unlike the pattern of infection documented in the adult clinical trials, a significant proportion of children enrolled in WV15758 had laboratory confirmed influenza B (33% of confirmed influenza cases). One subject, receiving Tamiflu, was documented to have both influenza A, cultured at baseline and Day 2, and influenza B, cultured on Days 2 and 6. Table 3 summarizes the infection status of children participating in the pivotal study.

Table 3: Influenza Status of WV15758 Subjects Receiving Study Drug (Safety Population)

Influenza Status	Tamiflu (N = 342)	Placebo (N = 353)
No influenza identified	125 (37%)*	118 (33%)*
All confirmed cases	217 (63%)*	235 (67%)*
Influenza A	150 (69%)**	153 (65%)**
Influenza B	66 (30%)**	82 (35%)**
Influenza A/B#	1 (<1%)**	0

Source: Integrated Summary of Efficacy, Table 4, Vol. 33, page 28.
*Proportion of cases in population.
**Proportion of cases of subtype in total confirmed cases.
#One subject had both Influenza A and Influenza B isolated.

Adherence to study treatment was determined by evaluating the dosing information recorded on the diary cards. Adherence was very good with a reported 90% of children receiving $\geq$ 9 doses of study medication. There was no apparent difference in adherence between the Tamiflu and placebo groups.

Forty children were withdrawn from the study prematurely. The reasons for these withdrawals are listed in Table 4. Because the number of premature withdrawals from the study was small, it is unlikely that these withdrawals had any impact on the results of the study. Ten of the subjects withdrew secondary to adverse events or illness. The withdrawals related to adverse events will be discussed in more detail in the Integrated Summary of Safety.

Table 4: Premature Withdrawals from WV15758 (Safety Population)

Reason for Withdrawal	Tamiflu (N = 342)	Placebo (N = 353)
Total number of premature withdrawals	20 (5.8%)	20 (5.7%)
Withdrew consent	8	9
Adverse event/intercurrent illness	6	4

Failure to return	4	5
Admin/Other	1	2
Did not cooperate	1	0

Source: Study Report for WV15758, Table 5, Vol. 36, page 53.

Treatment of Influenza – Primary and Secondary Efficacy Parameters

The primary efficacy parameter, time to freedom from illness, was a composite endpoint that measured the time to alleviation of cough, coryza and fever and a return to the pre-influenza level of activity. The sponsor submitted results of analysis in the ITTI population as the primary efficacy analysis but included the ITT and Standard population analyses in the study report. The FDA confirmatory analysis included the ITTI (as primary) and ITT populations but did not use the Standard population for any analyses. This method of analysis is consistent with that performed for the adult treatment trials submitted with the Tamiflu capsule NDA.

In the sponsor's analysis of the ITTI population, median time to freedom from illness was 1.5 days (35.8 hours) less in the Tamiflu group than in the placebo group. This represents a 26% decrease in the median time to freedom from illness with the active treatment. Three of the 4 components of the endpoint (cough, fever, and return to normal activity) were significantly shortened in the Tamiflu group while the component coryza was not (it also was numerically decreased but failed to reach statistical significance). Table 5 summarizes the sponsor's analysis of the primary efficacy parameter and its 4 components.

Table 5: Time to Freedom from Illness Analysis and Endpoint Components – WV15758 (ITTI Population)

Efficacy Endpoint or Component	Tamiflu (N = 217)	Placebo (N = 235)
Time to Freedom from Illness		
N	209	225
Median (hours)	101.3	137.0
Range	13.5 – 651.1	9.3 – 660.0
95% CI for within group median	88.8 – 118.3	124.5 – 149.6
Difference in medians	35.8	NA
P value	<0.0001	NA
Time to Return to Normal Activity		
N	217	235
Median (hours)	67.1	111.7
Range	0.0 – 645.0	0.0 – 638.3
95% CI for within group median	60.5 – 80.6	99.2 – 118.5
Difference in medians	44.6	NA
P value	<0.0001	NA

Time to Alleviation of Cough		
N	183	197
Median (hours)	38.7	70.8
Range	0.0 – 651.1	0.0 – 421.0
95% CI for within group median	32.0 – 51.3	63.1 – 80.8
Difference in medians	32.1	NA
P value	0.0008	NA
Time to Alleviation of Coryza		
N	179	196
Median (hours)	43.4	65.9
Range	0.0 – 306.7	0.0 – 639.8
95% CI for within group median	31.3 – 53.4	42.5 – 77.0
Difference in medians	22.5	NA
P value	0.09	NA
Time to Return to Afebrile State		
N	207	225
Median (hours)	43.5	68.0
Range	4.3 – 260.3	6.2 – 660.0
95% CI for within group median	40.2 – 47.6	55.3 – 77.6
Difference in medians	24.5	NA
P value	<0.0001	NA

NA = not applicable
Source: Integrated Summary of Efficacy, Tables 5 and 6, Vol. 33, page 30.

Kaplan-Meier curves comparing the proportion of children reaching the primary endpoint, time to freedom from illness, for subjects in the Tamiflu and placebo groups show a separation in the curves beginning at about 24 hours. The higher proportion of children reaching the endpoint is maintained in the active treatment arm from 24 hours to > 10 days.

Reviewer's comments:
The FDA review team's analysis confirmed the sponsor's conclusions that treatment with Tamiflu resulted in a shorter time to freedom from illness by approximately 1.5 days. Similarly, when the analysis was performed on the entire ITT population (N = 695), treatment with Tamiflu decreased the time to reach the primary endpoint by approximately 1 day. For this population, the effect of treatment was diluted by the significant number of children in the trial who did not have influenza, in whom we would expect no benefit. See the Section headed "FDA Statistical Analysis" contributed by Dr. Andrei Breazna, statistical reviewer.

Some of the secondary analyses performed by the sponsor warrant mention in this review, the time to "return to normal health and activity", the time to alleviation of all CARIFS symptoms and the total CARIFS symptom score AUC. These secondary efficacy parameters attempt to measure duration, extent and severity of symptoms. The sponsor reports that subjects receiving Tamiflu returned to normal health and activity a median of 44 hours sooner than those receiving

placebo. This is approximately ½ day greater reduction in this symptom than is seen in the composite primary endpoint of which it is part. The median time to alleviation of all CARIFS symptoms was significantly shorter in patients receiving Tamiflu than in those receiving placebo (63.4 hours compared to 99.6 hours). In evaluating the sponsor's graphical depiction of the median total CARIFS score, it is apparent that the median total score at baseline is similar for the 2 treatment arms and by Day 6 they are again similar. The greatest difference in the curves representing the Tamiflu and placebo groups occurs between Days 2 and 4. Similarly, the median total CARIFS symptoms score AUC measured from the initiation of study drug to the time at which all symptoms were alleviated was significantly less in the active treatment arm compared to the placebo arm (960.4 score.hours versus 1358.3 score.hours). Thus, it appears that treatment with Tamiflu suspension does decrease the extent and severity of symptoms of acute influenza in children.

Another of the secondary efficacy parameters analyzed in this study was the proportion of study subjects developing specified secondary illnesses requiring antibiotics. The specified secondary illnesses that were tracked in the study included bronchitis, OM, pneumonia and sinusitis that were identified by the investigator after the first 48 hours of study treatment. The sponsor states that these specified secondary illnesses required antibiotics in 28% (65/235) of the placebo subjects and 17% (36/217) of the Tamiflu subjects. This calculation is driven by the numbers of children diagnosed with OM on or after Day 3 of study. The numbers of children diagnosed with bronchitis, pneumonia and sinusitis were similar in the 2 treatment groups. The diagnosis of OM in the study and analysis of prevention of OM will be addressed separately in this review.

Reviewer's comment:
In evaluating the secondary endpoints, FDA analysis could not confirm the 44 hour reduction in "time to return to normal health and activity". Our analysis gave a median difference of approximately 1.5 days, similar to the difference in the primary endpoint. This discrepancy appears to be due to differences in the numbers of subjects included in the analyses and perhaps differences in the method of imputing missing data. However, similar discrepancies were not identified in the results of the primary endpoint analysis. It is counterintuitive that a child would return to normal health and activity sooner than he was free of illness.

Criteria for the diagnosis of secondary infections other than OM in this study were not described in the protocol. Individual investigators identified bronchitis, pneumonia and sinusitis based on their own criteria and judgement, often with no supporting objective data. While this does, unfortunately, reflect the methods by which children are diagnosed with these infections in general pediatric practice,

As an additional comment, it appears that the sponsor included in this analysis of

secondary infections children who had received antibiotics at the time of presentation and this may have had some impact on subsequent development of secondary infections.

FDA Statistical Analyses

Incomplete Data

We do not have complete records for all patients. STAT Table 1 details the frequencies of incomplete data for the two populations. Patients with partial records have information relevant for the evaluation of health status collected for a number of days, but the information about the occurrence of the primary endpoint time to freedom of illness (TTFOI) is missing (we can safely assume that the endpoint was achieved after the last available record).

STAT Table 1: Patients with Missing or Partial Records

Population	No Record No. (%)		Partial Record No. (%)	
	Tamiflu	*Placebo*	*Tamiflu*	*Placebo*
ITT	13/342 (3.8%)	13/353 (3.7%)	20/342 (5.8%)	20/353 (5.6%)
ITTI	8/216 (3.7%)	10/236 (4.2%)	13/216 (6.0%)	15/236 (6.9%)

Approximately 10% of patients had no or incomplete records for which to assess the primary endpoint. To assess the impact of incomplete data on the primary analysis, we used three different ways of imputing missing data. Method A excluded patients with no records and used the last available record date as the endpoint for patients with partial records. Method B replaced any missing data (no or partial records) with the maximum observed time to freedom of illness (612 hours). Method C excluded all patients with no or partial records. Median and mean time to freedom of illness were calculated for the ITTI and ITT populations using these methods. The primary analysis results were robust for different methods of handling missing and incomplete data as shown in STAT Tables 2 and 3.

Primary Endpoint Analysis

The efficacy analyses can be done on two populations: Intent To Treat (ITT), containing all randomized patients, and Intent To Treat – Infected (ITTI), which is the sub-population of ITT subjects who were confirmed as having influenza. The ITTI is the primary population, but the results obtained in the ITT population are more likely to be duplicated in clinical practice.

The primary endpoint is "time to freedom of illness" (TTFOI), a composite time-to-event endpoint. Its components are time to alleviation of cough, time to alleviation of nasal symptoms (coryza), time to alleviation of fever, and time to "return to normal health and activities". Secondary analyses on the components of TTFOI and all recorded CARIFS symptoms are also shown.

STAT Table 2 summarizes the primary efficacy analyses for the ITTI population. An important secondary analysis of the primary endpoint is the replication of the primary analysis in the ITT population. STAT Table 3 summarizes those results. The results in the ITT population confirm those obtained in the ITTI one, although the magnitude of the improvement seen with Tamiflu use in the ITT population is reduced to approximately 1 day.

STAT Table 2: ITTI Population, Time To Freedom of Illness (hours)

Method	No.[◆]	Tamiflu[•]	Placebo[•]	Difference[•] (95%CI)[••]	P-value[••]	P-value[#]
A	208/226	130(100)	165(133)	35(33) (13.22, 58.28)	0.0019	0.0021
B	216/236	165(109)	207(140)	42(31) (10.86,73.86)	0.0085	0.0004
C	195/211	117(94)	159(133)	42(39) (23.61, 61.50)	<0.0001	0.0003

◆ Subjects taking Tamiflu/Placebo
• Mean (Median)
•• Difference of the Means (Placebo-Tamiflu)
Median Test (Number of Points Above Median)

STAT Table 3: ITT Population, Time To Freedom of Illness (hours)

Method	No.[◆]	Tamiflu[•]	Placebo[•]	Difference[•] (95%CI)[••]	P-value[••]	P-value[***]
A	329/340	125(100)	156(122)	31(22) (1.08,49.07)	0.0004	0.0006
B	342/353	165(111)	191(134)	26(23) (0.92,50.63)	0.0421	0.0045
C	309/320	118(100)	148(122)	30(22) (15.32,44.84)	<0.0001	0.0004

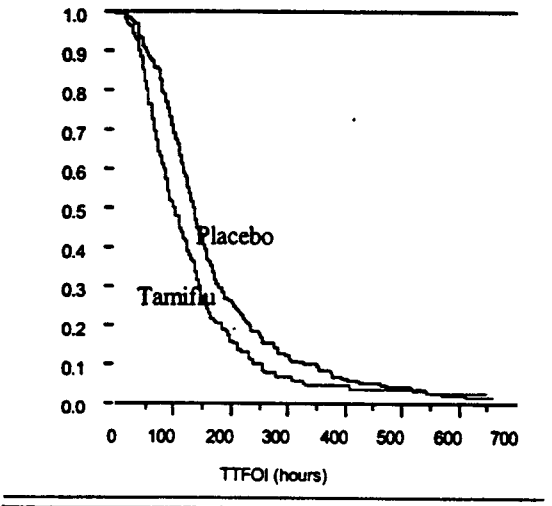
◆ Subjects taking Tamiflu/Placebo
• Mean (Median)
•• Difference of the Means (Placebo-Tamiflu)
Median Test (Number of Points Above Median)

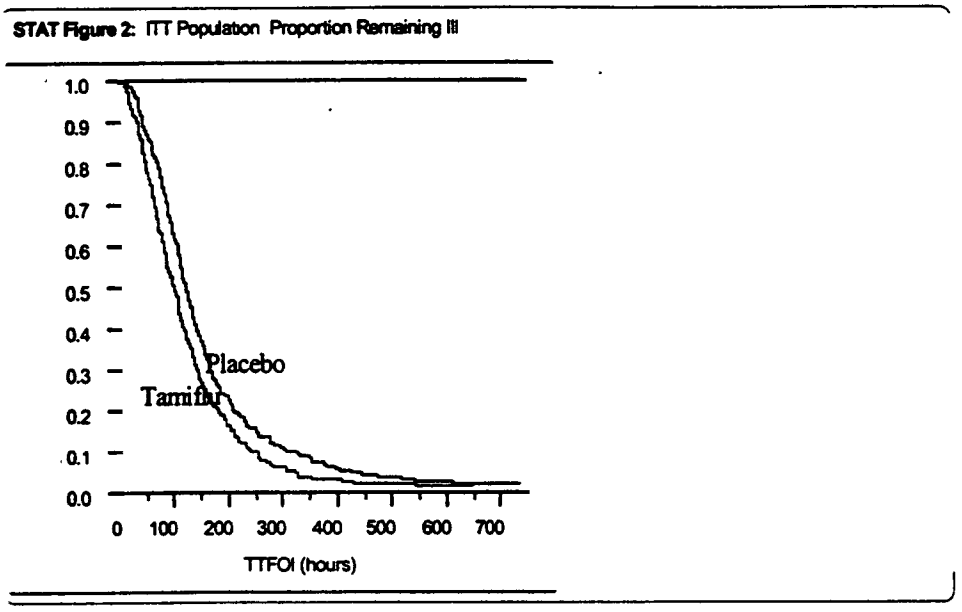
Secondary Endpoint Analysis

In this section we will briefly examine the primary endpoint, its individual components and the time to alleviation of all CARIFS symptoms using the Kaplan-Meier method. In this method the missing data was censored at the moment of the last available record. This postulates that the patients with missing data had similar outcomes to those that did not experience the endpoint until that time. Kaplan-Meier "survival" will be displayed. We have to caution that the term "survival" is a little misleading in this study. That term was devised for analyses in which the primary event of interest was death or significant injury, while here we have as endpoints time to cessation of one or more symptoms. In this case "survival" means the proportion of subjects who have not reached the endpoint "time to freedom from illness" or the proportion of subjects remaining ill at any

given time. The "survival" curve is one minus the cumulative distribution function of the endpoint. The Kaplan-Meier method is statistically sound and reliable, but censoring may be an issue, and the clinical effect size is not obvious in this context. STAT Figure 1 displays the Kaplan-Meier curve for the ITTI population in the primary endpoint analysis with non-completers censored while STAT Figure 2 represents the same analysis for the ITT population.

STAT Figure 1: ITTI Population, Proportion Remaining Ill





STAT Table 4 shows the results produced by the Kaplan-Meier method on different endpoints or components of the primary endpoint.

Table STAT 4: Endpoints and Components, Significance by Kaplan-Meier

Population	Endpoint	Log-Rank p-value	Wilcoxon p-value
ITTI	TTFOI	0.0013	<0.0001
	Return To Normal Activities	0.0001	<0.0001
	Cough Alleviated Before TTFOI	0.0001	<0.0001
	Nasal Alleviated Before TTFOI	<0.0001	<0.0001
	Fever Alleviated Before TTFOI	<0.0001	<0.0001
	TTALL	0.0003	0.0003
ITT	TTFOI	0.0009	<0.0001
	Cough Alleviated Before TTFOI	0.0273	0.0118
	Nasal Alleviated Before TTFOI	0.0081	0.0106
	Fever Alleviated Before TTFOI	<0.0001	<0.0001
	Return To Normal Activities	0.0005	0.0001
	TTALL	0.0138	0.0169

Finally, similar analyses were performed assessing the differences between effects in influenza A and influenza B infection. In this study, influenza A accounted for approximately 67% of the 452 subjects with proven influenza while influenza B accounted for 33%. STAT Table 5 and STAT Table 6 show the effects of Tamiflu therapy on treatment of the 2 different types of influenza.

STAT Table 5: Influenza A, Time to Freedom of Illness (hours)

Method	No.[♦]	Tamiflu[•]	Placebo[•]	Difference[•] (95%CI)[••]	P-value[••]	P-value[#]
A	142/147	129(89)	164(134)	35(45) (6.77,64.12)	0.0156	<0.0001
B	149/154	168(99)	202(141)	34(42) (-5.37,73.57)	0.0902	0.0005
C	132/132	111(87)	155(132)	44(45) (21.12,66.39)	0.0002	<0.0001

♦ Subjects taking Tamiflu/Placebo
• Mean (Median)
•• Difference of the Means (Placebo-Tamiflu)
Median Test (Number of Points Above Median)

STAT Table 6: Influenza B, Time to Freedom of Illness (hours

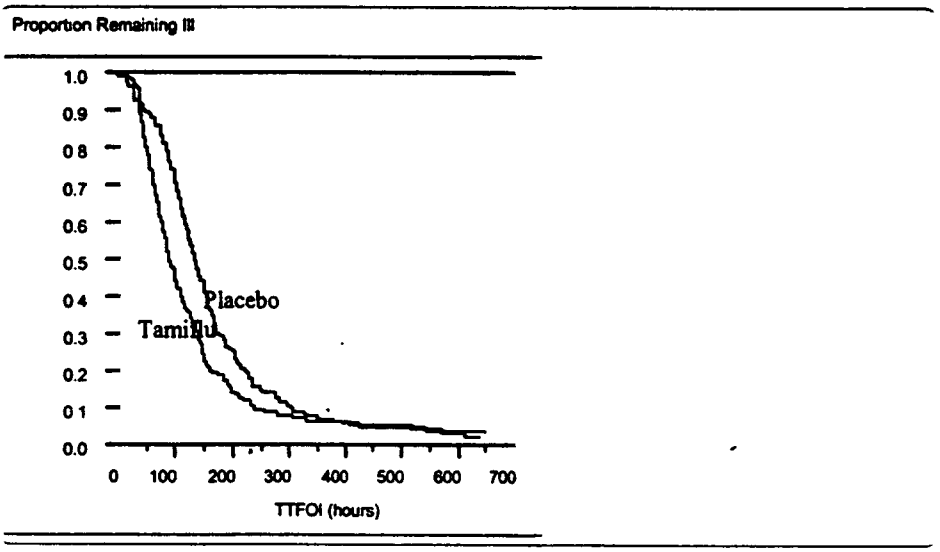
Method	No.[♦]	Tamiflu[•]	Placebo[•]	Difference[•] 95%CI[••]	P-value[••]	P-value[#]
A	65/79	131(124)	167(132)	36(8) (-0.81,72.64)	0.0553	0.4941
B	66/82	158(125)	216(139)	58(14) (5.35,111.45)	0.0312	0.3227
C	62/73	129(124)	168(134)	39(10) (4.00,73.88)	0.0292	0.3404

♦ Subjects taking Tamiflu/Placebo
• Mean (Median)
•• Difference of the Means (Placebo-Tamiflu)
Median Test (Number of Points Above Median)

STAT Figure 3 shows the "survival" curves for the primary endpoint TTFOI in subjects infected with influenza A, with non-completers censored. The Figure lists the p-values for the Kaplan-Meier analysis. The activity of Tamiflu in this subgroup of patients is evident. STAT Figure 4 shows the same analysis for subjects with documented influenza B infection. In the case of influenza B there appears to be a skewed distribution of TTFOI. This may explain the discrepancies between the smaller p-values obtained in the test for equality of means compared to the larger p-values obtained in the tests for equality of medians (see STAT Table 6). The discrepancy between the p-values for the Log-Rank test and the Wilcoxon test (STAT Figure4) is explained by the fact that the Log-Rank statistics puts more emphasis on the right–hand tails of the distributions, while the

Wilcoxon test statistics puts more emphasis on the left-hand side of the distributions tails. In this trial, the ratio of influenza A to influenza B subjects is about 2 to 1, so the separate statistical computations made on the subjects infected with influenza B have less power.

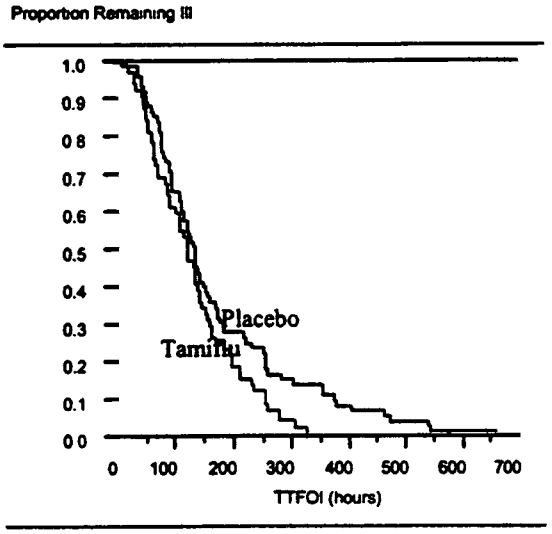
STAT Figure 3, Influenza A



Tests Between Groups

Test	p-value
Log-Rank	0.0044
Wilcoxon	<.0001

STAT Figure 4, Influenza B



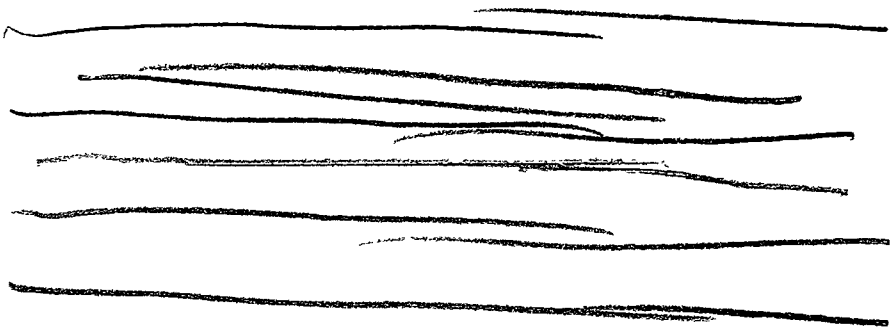
Tests Between Groups

Test	p-value
Log-Rank	0.0432
Wilcoxon	0.1516

Comparing the "survival" curves for the two types of influenza, it is apparent that the general shapes of the curves are different. One explanation would be that many subjects infected with influenza B would achieve the endpoint within the first few days, even if they were not treated with Tamiflu. However, patients who had symptoms for a longer time benefited from the treatment with Tamiflu.

A proportional hazards model that had as endpoint TTFOI and as independent variables the treatment and the influenza type revealed that the treatment is a significant factor (p-value = 0.0015), while the influenza type was not statistically significant (p-value = 0.5452). This reassures us that, even if the mechanism differs slightly with the type of influenza, Tamiflu has activity against both types of virus but to different degrees.

[redacted]



6.2. Supportive Studies - WV15731 and WV15759/WV15871

6.2.1. WV15731

Study WV15731 was the initial pilot trial of Tamiflu suspension in children and was designed as a placebo-controlled, dose ranging study of 1 mg/kg, 2 mg/kg and 3 mg/kg. The study was conducted at sites in Australia, New Zealand and Hong Kong. Children were enrolled in the study if they had symptoms suggestive of influenza, defined as cough and coryza and temperature of $\geq 38.5^{\circ}$ C and were within 48 hours of the onset of symptoms. This study opened for enrollment after the peak of influenza season and only recruited 10 children. Some subjects from this study were included in the sponsor's Integrated Summary of Safety but were not analyzed for efficacy parameters.

6.2.2. WV15759/WV15871

Study WV15759 was an efficacy study of Tamiflu in children with known asthma to be conducted at multiple sites in Europe. This study planned to enroll 500 subjects but enrollment was slower than expected and WV15871 was opened as a Southern hemisphere continuation of WV15759 during the same flu season. The studies were identical in design and differed only in the hemisphere being studied. Total enrollment for the 2 studies was 335 children, not enough to be powered for efficacy results, and the sponsor chose not to open the studies for a second flu season. Results of these studies were analyzed as a single multicenter study by the sponsor and presented as data supporting the NDA. They were also analyzed as a single study by the FDA review team.

Study Design

This study's design and endpoint analysis were very similar to that conducted in the pivotal trial. Key differences were the ages of children enrolled, 6 to 12 years of age in WV15759/WV15871, and that all children had documented chronic asthma. Enrollment was stratified based on determination of the severity of asthma, either mild or moderate/severe (severity categories were defined in the protocol), and children were required to perform pulmonary function tests to be

eligible. Children in this study were allowed to receive inhaled or oral steroids as part of their chronic asthma therapy. Other inclusion and exclusion criteria were similar to those in WV15758. All children enrolled were randomized to receive either placebo or 2 mg/kg of Tamiflu suspension given orally twice daily. All children had spirometry performed at the study center to determine forced expiratory volume (FEV1) at baseline and on Day 6 and were given a peak flow meter to determine peak expiratory flow rate (PEFR) at home each morning before taking bronchodilators. Parents/guardians recorded medication dosing, temperature, PEFR and all flu-related symptoms (CARIFS questionnaire) on diary cards and returned to clinic or were visited on Days 2, 6, 10 and 28. In this study, not all children had nasal/throat swabs for influenza virus cultures performed as some sites utilized in WV15871 did not have adequate facilities for processing virology specimens. All children had blood sampling for laboratory safety monitoring (baseline and Day 6) and influenza antibody titers (baseline and Day 28).

Efficacy Endpoints

The primary efficacy parameter was the same composite endpoint used in WV15758, time to freedom from illness (defined as time to alleviation of fever, cough, nasal congestion and return to normal health and activity level). Secondary and tertiary efficacy parameters were also similar to those in the pivotal trial and evaluated duration and severity of symptoms, specified secondary illnesses and antibiotic use, individual symptoms, use of symptom relief medication, and additional physician/hospital visits. This study also attempted to analyze exacerbation of asthma symptoms and changes in pulmonary function tests between the placebo and active treatment groups. Viral shedding and development of resistance could only be assessed at selected sites. No pharmacokinetic determinations were performed during this study. The analysis plan for WV15759/WV15871 was similar to that described for WV15758 and similar analysis populations were defined (Safety, ITT, ITTI and Standard).

Study Results

As previously stated the study did not fully enroll even after extending it into the southern hemisphere influenza season. No subjects were incorrectly randomized although 5 subjects were incorrectly stratified according to asthma severity. As in the pivotal study, the vast majority of study subjects (320/335 enrolled or 96%) received at least 9 of their 10 scheduled doses of study medication. Subject disposition and the entry characteristics of the study population are summarized in Tables 6 and 7.

Table 6: Subject Disposition – WV15759/WV15871

Disposition	Total	Tamiflu	Placebo
Patients randomized	335	170	165
Patients receiving drug	334	170	164
Number of withdrawals	12	5	7
Withdrawals due to AEs	6	2	4
Patients completing study	322	165	157
Number Infected	179	84	95
Influenza A	104	52	52
Influenza B	75	32	43

Source: Study Report WV15759/15871, Table 5, Vol. 71, page 53.

Table 7: Baseline Characteristics of WV15759/WV15871 Study Population

Characteristic	Total (N = 334)	Tamiflu (N = 170)	Placebo (N = 164)
Age			
Mean/Median	8.7/9	8.7/9	8.6/9
Range	5-12	5-12	5-12
Sex			
Male	213	111	101
Female	122	59	63
Race/Ethnicity*			
Asian	6	4	2
Black	16	8	8
Caucasian	293	149	143
Hispanic	5	1	4
Mixed/Other	15	8	7
Asthma Severity			
Mild	151	74	76
Moderate/severe	163/21	83/13	80/8
Influenza Vaccination			
Year of study	66	31	34
Previous year	76	39	37

*Designations are this reviewer's not the sponsor's. It must be noted that racial/ethnic designations may not have the same connotations when applied to populations outside the United States.

The ITTI population for this study was also fairly evenly balanced for the characteristics described above. The sponsor notes that there were slightly more subjects with moderate asthma and slightly more males enrolled in the active treatment group compared to the placebo group but it is unlikely that these minor imbalances had any impact on study outcome. The vast majority of participants (90-92%) continued to take their previously prescribed asthma medications during

not include the patients who received 1 mg/kg (n = 4) and 3 mg/kg (n = 3). This yields a total of 515 children who received treatment with Tamiflu and are included in the sponsor's safety summary. There were 517 study subjects receiving placebo in these pediatric treatment trials. The sponsor also provided a re-analysis of the safety data collected from the adolescent patients enrolled in the adult clinical treatment and prophylaxis trials of Tamiflu. Since these data were analyzed at the time of the original Tamiflu capsule NDA, they were not re-analyzed during this review. The populations presented in the sponsor's ISS are described in Table 8 below.

Table 8: Safety populations evaluated in ISS

Study	Description	Dose	Ages (years)	Number Receiving Tamiflu
Studies of Pediatric Oral Suspension				
WV15758	Pediatric treatment	2 mg/kg BID	1-12	342
WV15759/ WV15871	Pediatric treatment (with asthma)	2 mg/kg BID	6-12	170
WV15731	Pediatric dose ranging, PK	2 mg/kg BID	1-12	3
Studies in which Adolescents Recruited into Adult Trials				
M76001	Time to treatment start	Placebo 75 mg BID	13-80	94*
WV15812/ WV15872	Treatment of chronically ill adults	Placebo 75 mg BID	> 13	4*
WV15799	Post-exposure prophylaxis	Placebo 75 mg QD	> 13	111*

*Refers to number of adolescents 13-17 years enrolled.

In all of the studies conducted the sponsor collected data on symptoms that were consistent with influenza infection in the efficacy endpoints and these symptoms were specifically not included in adverse event reporting unless the investigator considered them unrelated to influenza. Similarly, acute bronchitis, OM, pneumonia and sinusitis were considered secondary illnesses and were tracked in the efficacy endpoints. Some of these episodes, however, were reported as adverse events. The sponsor also divided the adverse events into those occurring "on-treatment", defined as events beginning during study drug administration and the following 2 days (ie., the first 7 days of study) and those occurring "off-treatment", defined as events beginning more than 2 days after completing study medication. Both the sponsor and this reviewer concentrated on the "on-treatment" period in evaluating adverse events.

During the 28 day study period a majority of children enrolled in the pediatric trials experienced at least 1 adverse event. In WV15758 470 children reported 983 adverse

events while in WV15759/WV15871 222 children reported 473 adverse events. Many of these listings include more than one sign or symptom related to the same illness, eg., listing both vomiting and diarrhea as separate events in a child who has them simultaneously. In the combined pediatric treatment studies, 85 patients experienced 109 adverse events that were classified as probably/possibly/remotely or unknown causally related to study drug and of moderate to severe intensity. Thirty-seven of these patients received Tamiflu while 48 received placebo. There was no identifiable pattern to these more severe events.

Approximately 75% of the children who reported adverse events and 60% of those events occurred during the "on-treatment" period. The pattern of adverse events occurring during the first 7 days of study ("on-treatment" period) was no different than that occurring during the last 21 days ("off-treatment" period). The profile of adverse events associated with Tamiflu use in children is very similar to that observed in adults, with gastointestinal complaints leading the list. Table 9 presents the most frequently reported "on-treatment" adverse events in the pooled pediatric studies.

Table 9: Most Commonly Reported "On-treatment" Adverse Events in Pediatric Treatment Trials with Tamiflu

Reported Adverse Event (Preferred Term)	Tamiflu (N = 515)	Placebo (N = 517)
Vomiting NOS	**77 (15%)**	48 (9.3%)
Diarrhea	49 (9.5%)	**55 (10.6%)**
Otitis media	45 (8.7%)	**58 (11.2%)**
Abdominal pain	**24 (4.7%)**	20 (3.9%)
Asthma (including aggravated)	18 (3.5%)	**19 (3.7%)**
Nausea	17 (3.3%)	**22 (4.3%)**
Epistaxis	**16 (3.1%)**	13 (2.5%)
Pneumonia NOS	10 (1.9%)	**17 (3.3%)**
Ear disorder	**9 (1.7%)**	6 (1.2%)
Sinusitis NOS	9 (1.7%)	**13 (2.5%)**
Bronchitis NOS	8 (1.6%)	**11 (2.1%)**
Conjunctivitis	**5 (1.0%)**	2 (0.4%)
Dermatitis NOS	5 (1.0%)	**10 (1.9%)**
Lymphadenopathy	5 (1.0%)	**8 (1.5%)**
Tympanic membrane disorder NOS	5 (1.0%)	**6 (1.2%)**

Source: Integrated Summary of Safety, Table 6, Vol. 34, page 42.

Vomiting is the adverse event most significantly associated with use of Tamiflu in children, particularly in subjects without documented influenza. As in the adult clinical trials, vomiting occurred in most children within the first 2 to 3 days of study, although in adults it occurred more frequently in those with proven influenza. Unlike in the adult study in which vomiting occurred twice as often in female subjects, there was no gender difference for this adverse effect in the pediatric studies. In the large

adult clinical trial, there was no appreciable difference in the incidence of vomiting between the 2 doses studied. While there was only a single dose studied in the pediatric trial (2 mg/kg), the difference in clearance of Tamiflu with age probably led to the older children receiving a higher exposure of Tamiflu than the younger children. In the pivotal trial, the proportion of children receiving Tamiflu and reporting vomiting increased with age while in the placebo group the proportion of children with vomiting decreased with age, as shown in Table 10. This increase in vomiting in the older children may correlate with increased drug levels compared to the younger children. While this is a crude and indirect method to assess whether vomiting as an adverse event may be dose-related in children, there is too little PK data to make a more direct assessment.

Table 10: Proportion of Children in WV15758 Reporting Vomiting as an Adverse Event According to Age Groups

Age Groups (N on Tamiflu/N on Placebo)	Total	Tamiflu	Placebo
1-2 years (78/93)	20 (11.7%)	7 (9.0%)	13 (14.0%)
3-5 years (113/106)	23 (10.5%)	15 (13.3%)	8 (7.5%)
6-12 years (151/154)	36 (11.8%)	27 (17.9%)	9 (5.8%)
All ages (342/353)	79 (11.4%)	49 (14.3%)	30 (8.5%)

In addition to vomiting, there were 4 other adverse events that were reported in numerically more children receiving Tamiflu than placebo. These included abdominal pain, epistaxis, ear disorder and conjunctivitis. The differences in frequency of these 4 adverse events between subjects receiving Tamiflu and placebo were very small. Similarly, diarrhea, OM, asthma, nausea, pneumonia, sinusitis, bronchitis, dermatitis, lymphadenopathy, and tympanic membrane disorders were reported in numerically more subjects receiving placebo but none of these differences reached statistical significance.

The sponsor also evaluated the incidence of adverse events in the population according to whether influenza infection was documented. These data are summarized in Table 11. As stated above, the incidence of vomiting was greater in those children without proven influenza infection receiving Tamiflu but in children with documented influenza the incidence of vomiting was similar regardless of study medication. Likewise, abdominal pain was reported in similar numbers in the treatment arms in those with proven influenza but was reported more often in those receiving Tamiflu in uninfected children. The incidence of diarrhea was similar in both infected and uninfected children receiving Tamiflu but was more frequent in influenza-infected children receiving placebo. It is interesting to speculate that these differences in adverse event reporting are indicative of drug activity in the influenza-infected children or adverse drug reactions in the non-infected children but the numbers are too small to draw any firm conclusions.

Table 11: Selected "On-treatment" Adverse Events in Pediatric Treatment Trials Reported According to Influenza Status

Adverse Events	Influenza Infected		Non-Influenza Infected	
	Placebo (N = 331)	Tamiflu (N = 302)	Placebo (N = 186)	Tamiflu (N = 213)
Vomiting NOS	33 (10.0%)	36 (11.9%)	15 (8.1%)	41 (19.2%)
Diarrhea	43 (13.0%)	30 (9.9%)	12 (6.5%)	19 (8.9%)
Otitis media NOS	40 (12.1%)	20 (6.6%)	18 (9.7%)	25 (11.7%)
Abdominal pain	18 (5.4%)	10 (3.3%)	2 (1.1%)	14 (6.6%)
Asthma	12 (3.6%)	8 (2.6%)	7 (3.8%)	10 (4.7%)
Nausea	17 (5.1%)	9 (3.0%)	5 (2.7%)	8 (3.8%)
Epistaxis	11 (3.3%)	13 (4.3%)	2 (1.1%)	3 (1.4%)
Pneumonia NOS	7 (2.1%)	1 (0.3%)	10 (5.4)	9 (4.2%)
Ear disorder	5 (1.5%)	4 (1.3%)	1 (0.5%)	5 (2.3%)
Conjunctivitis	2 (0.6%)	2 (0.7%)	0 (0.0%)	3 (1.4%)

Source: Integrated Summary of Safety, Table 8, Vol. 34, page 44.

7.2. Drug Interruptions due to Adverse Events

A relatively small number of subjects required study drug discontinuation; a total of 17 of 1039 subjects had study drug discontinued during the pediatric treatment trials. An additional 3 subjects (2 placebo and 1 Tamiflu) in WV15758 had their study drug dose "adjusted", although this practice was not suggested in the protocol. Most of the events leading to study drug discontinuation were thought to be possibly or probably related to study drug (7 children with possibly related and 5 with probably related AEs). Of the children who had presumed drug related adverse events, 8 of 12 discontinued because of vomiting (5 Tamiflu, 3 placebo). One of these children discontinuing study because of vomiting was enrolled at 1mg/kg Tamiflu in study WV15731. Three children developed urticaria while another developed "hypersensitivity" that was not further described. All 4 of these children had documented influenza, 2 received Tamiflu and 2 received placebo. Five of the children experienced adverse events designated as unrelated to study drug but resulted in discontinuation. These included 2 cases of pneumonia, 1 of OM, 1 child with unspecified chest pain and 1 child with viral encephalitis. Regardless of presumed causality, the discontinuations were evenly distributed between children receiving Tamiflu and placebo.

7.3. Serious Adverse Events

Serious adverse events (SAEs) were reported infrequently in the pediatric treatment trials occurring as only 17 SAEs in 16 patients. None of the SAEs were thought to be study drug related by either the investigator or the sponsor. These SAEs are summarized in Table 12. Several of the events for which these children were

hospitalized may have represented bacterial infections, particularly pneumonias, misdiagnosed as influenza. Only 5 of the 17 subjects requiring hospitalization were proven to have influenza. On the other hand, regardless of influenza status, of the subjects who received Tamiflu only those who experienced vomiting and abdominal pain had serious adverse events which in retrospect might have been related to study drug.

Table 12: Serious Adverse Events Reported in the Pediatric Treatment Trials

Patient (Protocol)	Study Day	Serious Adverse Event	Influenza Infected	Treatment
1587 (15758)	26	Caustic ingestion	Yes (A)	Placebo
3292 (15758)	1	Pneumonia	No	Placebo
3730 (15758)	4	Dehydration – secondary to flu symptoms	Yes (B)	Placebo
3278 (15758)	4	Pneumonia	No	Tamiflu
3311 (15758)	1	Pneumonia	No	Tamiflu
4900 (15758)	3	Pneumonia	No	Tamiflu
6009 (15758)	1	Dehydration, + rotavirus	No	Tamiflu
4021 (15759)	3	Pneumonia	No	Placebo
4032 (15759)	1	Vomiting	Yes (B)	Tamiflu
4082 (15759)	11	Abdominal pain	Yes (A)	Tamiflu
1040 (15871)	1	Asthma aggravated	No	Tamiflu
1070 (15871)	2	Pneumonia	No	Tamiflu
1500 (15871)	4	Pneumonia	No	Tamiflu
1500 (15871)	24	Asthma	No	Tamiflu
4265 (15871)	4	Sinusitis	No	Tamiflu
4275 (15871)	2	Viral encephalitis	Yes (B)	Placebo
1501 (15731)	7	Diarrhea and vomiting	No	Tamiflu

7.4. Deaths

There were no deaths reported during either the pivotal pediatric trial or any of the supporting studies. No deaths occurred among adolescents enrolled in the adult treatment and prophylaxis studies.

7.5. Laboratory Abnormalities

Laboratory safety analyses were reported by the sponsor on each of the pediatric studies individually and on the pooled data from the treatment trials. In all instances the sponsor performed their analyses on "transformed" laboratory data. This was done in an attempt to compare laboratory data for which there were multiple laboratory reference ranges. For example, using this calculation the sponsor "transformed" all hemoglobin values on female subjects and younger subjects to fit

the male standard reference range. It is unlikely that this method of analysis resulted in any significant differences in mean changes from Baseline in the pediatric data but it may have produced differences in the numbers of patients with extreme values or shifts from Baseline in WHO toxicity grade. This reviewer assessed both the "transformed" data using the sponsor's "standard" reference ranges and cross-checked the results using data from the central laboratory using the laboratory's stated reference ranges.

The sponsor notes no significant changes in mean change from baseline for routine hematological or biochemical laboratory parameters associated with the use of Tamiflu in the pediatric trials. Very minor changes were noted in some parameters (platelets, alkaline phosphatase) but these are of no clinical significance. There also appear to be very infrequent shifts from Baseline in WHO toxicity grade and these are balanced between the Tamiflu and placebo groups. There were a few subjects whose WBC and platelets shifted from Grade 0 (normal) or 1 to Grade 3 or 4 toxicity. In reviewing these subjects, the original data does not show these shifts although the "transformed" data does.

The sponsor lists a number of extreme laboratory values from the pediatric treatment studies, as shown in Table 13. These extreme values are defined in the study report and use the "transformed" laboratory data. They represent lab values that are not only outside the Roche reference range but also are thought to show clinically significant changes from baseline. There were no significant differences in the occurrence of these extreme values between subjects receiving Tamiflu compared to placebo.

Table 13: Marked Hematological and Biochemical Abnormalities in the Pooled Pediatric Treatment Studies

Laboratory Value	Placebo (N = 485)	Tamiflu (N = 478)
Hematological		
Hemoglobin (high)	1	1
White blood cells (high)	0	1
White blood cells (low)	12	3
Platelets (high)	2	3
Platelets (low)	15	3
Neutrophils (low)	82	67
Lymphocytes (high)	13	11
Lymphocytes (low)	0	3
Monocytes (low)	2	1
Eosinophils (high)	0	1
Basophils (high)	0	1

Biochemical		
Chloride (high)	3	2
Chloride (low)	1	0
Sodium (high)	0	1
Uric acid (high)	2	0
SGOT (high)	3	5
SGPT (high)	2	3
GGT (high)	2	0
Alkaline phosphatase (high)	1	0
Total protein (high)	0	2

Source: Integrated Summary of Safety, Table 37, Vol. 34, page 102.

There were significant differences in the sponsor's "transformed" data and the original data for some laboratory tests. For example, The "transformed" dataset for platelet counts indicated that 9 subjects had platelet counts < 50 x 10^9/L while the original dataset contained no values < 50 x 10^9/L and only 3 values < 100 x 10^9/L. For other laboratory tests (eg., WBC), the numbers of patients with abnormally low values were similar between the 2 datasets but the patients identified were different. For still other hematological parameters (eg., total neutrophils) no transformation of the data was performed. For some of the serum biochemical tests resulting data were transformed (eg., albumin, serum protein) but not for others (eg., BUN, creatinine, SGOT and SGPT).

In spite of the difficulty presented by cross-checking 2 laboratory datasets, no specific hematological or biochemical abnormalities could be attributed to use of Tamiflu. One hundred and eighty-seven subjects had WBC < 4.0 x 10^9/L (WHO Grade 1 toxicity) during the study period. These values were balanced between the Tamiflu and placebo groups and between Day 1 values and Day 6 or follow-up values. Only 3 Tamiflu and 4 placebo subjects had WBC < 2.0 x 10^9/L (Grade 3 or 4 toxicity). While a number of subjects had SGOT and SGPT values that were slightly above the normal range, only a few study subjects in the pediatric treatment trials had significant elevations of liver transaminases (> 2.5 x upper limit of normal). No subjects had significant renal dysfunction (BUN or creatinine > 2.5 x upper limit of normal) at any time during the study.

Reviewer's comments:
It is not clear why the laboratory data "transformation" is necessary or even desirable. In children some laboratory values are age-dependent and such a "transformation" to a universal (age-independent) reference range might make final analyses easier. However, this assumes that all age's and all children's laboratory parameters vary in the same way and at the same rate. This process "corrects" or "normalizes" the original data. It is also not clear why hematologic parameters for which toxicity is generally measured at an absolute value (eg., WBC < 2.0 x 10^9/L) rather than a proportional increase over normal (eg., ALT > 2.5 x upper limit of

normal) should be transformed. This practice led to some "transformed" laboratory values that were very different from the original values, including in one case a platelet count of –20 x 10^9/L.

In the case of Tamiflu, there were very few associated laboratory abnormalities and it is unlikely that the sponsor's method of analysis masked any toxicity. In another submission, this method may introduce additional difficulties in interpreting data. In future submissions the sponsor will be encouraged to conduct the primary safety analyses using raw data using the laboratory's published reference ranges.

The majority of laboratory abnormalities identified during the review were hematological. These are difficult to attribute to study drugs or procedures since children often develop relatively low WBC during viral illnesses. It is very likely that many of the children who did not have documented influenza may have had some other viral infection circulating in the community during the same period. There were so few laboratory abnormalities noted during the study that an assessment by age or other criteria was not useful.

8. Use in Special Populations

This NDA supports the use of Tamiflu in children from 1 year to 12 years of age. The sponsor found no evidence of differences in either efficacy or adverse effect profile according to gender or racial/ethnic background. It is somewhat difficult to assess differences according to racial/ethnic background because of the way subjects are classified in these studies. Investigators and subjects in worldwide studies may not identify with these categories in the same way this reviewer or the sponsor does. Also, there were relatively few black study subjects enrolled in these trials.

There are other populations that might benefit from use of Tamiflu oral suspension in which it has not been specifically tested. Certainly some adults, particularly elderly adults, who have difficulty swallowing capsules may prefer to take the suspension. The oral suspension may provide a more accurate formulation for dosing patients with moderate or severe renal failure in whom the capsule formulation could yield supra-therapeutic exposures.

9. Review of Package Insert

The Tamiflu package insert initially written for the capsule formulation will be used for the suspension also and has been revised to include pediatric pharmacokinetic data, dosing recommendations for children, efficacy data from the pediatric pivotal trial and pediatric safety data from both WV15758 and WV15759/WV15871. The division suggested some changes in the sponsor's proposed label. The major label revisions are described below.

9.1 Several revisions to the proposed label's Microbiology Section incorporating data from the pediatric clinical trials have been suggested to the sponsor.

- Restore the previous resistance rate of 1.3% (4/301) in adults as was agreed upon in the adult treatment indication.
- In the description of the pediatric patients, substitute a resistance rate of 8.6% (9/105). This represents the resistance rate calculation using the method that was agreed upon at the pre-NDA meeting, using only paired pre- and post-therapy isolates.
- Delete the sentences that claim [redacted] We believe that currently available data fail to support this claim.
- Delete the line stating [redacted] Given the relatively small number of isolates of influenza B studied we believe there are insufficient data to say there is [redacted]
- Since the pediatric studies contain sufficient numbers of subjects infected with influenza B to provide assurance that Tamiflu is effective in these patients, we propose that the sponsor delete [redacted] These references are no longer necessary.

9.2 The following suggestions related to the description of the pediatric clinical trial were discussed with and agreed to by the sponsor:

- In *Description of Clinical Studies – Treatment of Influenza: Pediatric Patients*, it was suggested that the sponsor follow the format used in the description of the adult treatment trials. This section should include the total number of patients enrolled, the number of subjects with proven influenza, the dose administered in the trial and the primary endpoint expressed in days [redacted]
- The sponsor was asked to delete the reference to [redacted] in subjects receiving Tamiflu. After careful consideration and consultation with colleagues in DAIDP, we feel that this endpoint was inconsistently diagnosed and confirmatory testing was not done as per protocol. The data generated does not support this conclusion. We are willing to continue to discuss with the sponsor the best use of their database for assessing ear symptoms.
- The sponsor was also asked to remove the sentence regarding the endpoint [redacted], ' since this secondary endpoint is a component of the primary endpoint. It is potentially misleading to suggest that a child may [redacted] sooner than he is free of illness.

9.3 Several suggestions regarding the pediatric pharmacokinetic data and dosing recommendations for children and adults using the suspension formulation were discussed with the sponsor.

- In the Clinical Pharmacology: Pharmacokinetics section, it was suggested that a sentence regarding the changes in clearance with age be added.
- The review team proposed a weight-based fixed dosing schedule for children over 1 year of age and agreed on the dosing shown in the table below.

Dosing Recommendations for Children

By kg weight		By lb weight		Dose in mg
<= 15 kg		<= 33 lb		30 mg
> 15 kg -	23 kg	> 33 lb -	51 lb	45 mg
> 23 kg-	40 kg	> 51 lb -	88 lb	60 mg
> 40 kg		> 88 lb		75 mg

- It was recommended that the sponsor provide some guidance regarding appropriate dosing of Tamiflu (ie., volumes required) in the event a family accidentally loses or damages the dosing dispenser.

10. Phase 4 Commitments

The following list of Phase 4 commitments has been proposed and agreed upon by the sponsor. Some of these requests may overlap some of the Phase 4 commitments agreed to during previous Tamiflu NDA reviews.

- Using all available resistant clinical isolates from both adult and pediatric trials, evaluate these isolates for cross-resistance to other neuraminidase inhibitors. Isolates should also be characterized for the emergence of drug-dependent variants (to be completed by Jan., 2002).

- In future clinical studies (treatment or prophylaxis) further characterize the clinical aspects of infection with influenza resistant to neuraminadase inhibitors in children including: manifestations and duration of clinical disease, transmission within households or to other contacts, and virological characteristics of the isolates including detailed assessments of the kinetics of growth and clearance of resistant isolates (to be completed by Jan., 2003).

- Complete additional studies to evaluate the antibody responses to both wild-type and resistant influenza with respect to their cross-protective potential (to be completed by Jan., 2003).

- In additional studies, further evaluate the oseltamivir carboxylate pharmacokinetic profile (not sparse sampling) of the to-be-marketed dose of Tamiflu suspension in children younger than 5 years of age (to be completed by Jan., 2003).

11. Reviewer's Conclusions

There are currently few treatment options for children who develop influenza. Amantidine was approved for treatment and prophylaxis of acute influenza in all ages in the late 1970's while rimantidine was approved for treatment of adults with influenza and prophylaxis of influenza in children in 1994. Neither of these agents has achieved widespread use in children because of concerns for safety and the rapid emergence of resistant virus. Influenza continues to infect millions of infants and children worldwide in its seasonal epidemics. Children are thought to play a critical role in the spread of influenza in communities and, along with the elderly, sustain a disproportionate amount of the serious morbidity associated with influenza. Recent publications documented that younger children are hospitalized much more frequently for influenza-associated events with children under 1-2 years having the highest rates of hospitalization.

This NDA submission contains data from one large, well-controlled study of Tamiflu suspension for treatment of acute influenza-like illness in otherwise healthy children from 1 to 12 years of age and supportive data from a second study in children with known asthma ages 6 to 12 years. Safety data on the use of Tamiflu in adolescents drawn from previously reviewed adult treatment and prophylaxis studies was included for completeness. The submission was generally well organized and clearly presented, although the electronic datasets were somewhat cumbersome to analyze using FDA software.

Review of the pivotal pediatric trial, WV15758, reveals that children with influenza receiving Tamiflu suspension within 48 hours of the onset of flu-like illness experienced a 1.5 day median reduction in the calculated time to freedom from illness compared to children receiving placebo. This modest improvement in the length of illness was similar to that seen in the adult treatment trials. Children enrolled in the trial who did not have influenza derived no discernable benefit from Tamiflu. Therefore, the median benefit was somewhat less (approximately 1 day) when the analysis included all children in the study population and not only those with proven influenza. While 1.5 days may not seem much of an improvement in a generally self-limited viral infection, for parents of miserable children it may be well worth the extra expense and minimal risk of the medication. The sponsor provided additional analyses of secondary endpoints of duration and severity of symptoms that also suggested a significant drug effect. The review team concurs with these assessments and agrees that Tamiflu provides benefit in terms of the extent of symptoms of influenza.

The treatment benefit of Tamiflu was most notable for subjects with documented influenza A. Unlike the adult trials, in which very few subjects had influenza B, the pediatric trials provided a sufficient number of subjects with influenza B to assess antiviral efficacy in this subpopulation. While the treatment effect was not as marked in this group of childen, the improvement in the primary endpoint was still significant.

Among the secondary and tertiary efficacy endpoints for this study were assessments of specific secondary infections and use of antibiotics. The sponsor attempted to track bronchitis, OM, pneumonia and sinusitis during the trial and then determined if these events and the need for antibiotics were prevented by the use of Tamiflu. Unfortunately, the diagnostic criteria for these events were left entirely to the individual investigators and confirmatory testing was not done in all patients.

In study WV15759/15871, children with chronic asthma were enrolled in a study of similar design. This study failed to enroll adequate numbers of children to be powered to show a difference in Tamiflu compared to placebo. A small numerical improvement in time to freedom from illness did not reach statistical significance. It is interesting to note that there were accompanying small improvements in some measures of pulmonary function in the children receiving Tamiflu, although no difference in number of asthma exacerbations was identified between treatment groups. Tamiflu did not seem to have any adverse effect on the asthma status of children who received it. Because the study was not fully enrolled, it was not possible to interpret any differences in the secondary endpoints.

The overall safety profile of Tamiflu in children from 1 to 12 years of age was well characterized. Vomiting, the major toxicity identified in the adult trials, was also relatively common in children. In general, children with influenza infection have more vomiting as part of their illness than is observed in adults. Thus, the incidence of vomiting in both the placebo and Tamiflu groups was higher than observed in the adult trial. The difference in rates of vomiting between the 2 groups was similar to that seen in adults. Other adverse events occurred so infrequently that it was not possible to identify patterns specific to Tamiflu use. No significant laboratory abnormalities could be attributed to the use of Tamiflu in children. A small but significant proportion of children in both treatment arms experienced low WBC during the study but this may have been due to the underlying effects of viral illness.

A major safety concern is in the potential emergence of mutant viruses resistant to the neuraminidase inhibitors. As was seen in earlier anti-influenza drug studies, the rate of

resistance identified in the pediatric trials (8.6%) was much higher than that observed in the adult trials (1.3%). The mutant viruses were predominately identified in subjects who were infected with influenza A H1N1 and, to date, no mutant influenza B has been isolated. The sponsor asserts that mutant viruses are less pathogenic than wild type influenza, basing this belief primarily on in vitro data. While the number of children with resistant virus was small, the median time to freedom from illness in this subgroup was somewhat longer than that in the larger group of children with documented influenza receiving Tamiflu. It also appears that the mutant virus may be shed at high titers in some subjects before being cleared. Therefore, this reviewer has not been reassured that these viruses are harmless to the general population. The pediatric studies were not designed to determine if there was secondary spread of the mutant viruses to household or other contacts so there is no data regarding transmission of these viruses in vivo. Since these mutations involve the neuraminidase enzyme and to a lesser (but undefined) extent the hemagglutinin, there are also theoretical concerns that they could be antigenically distinct from wild type influenza. The review team believes that it will be of critical importance for the sponsor to further characterize these mutant viruses, the course of clinical disease associated with them, their potential for transmission in households and the nature of the antibody response to them compared to wild type influenza.

The sponsor proposed [redacted] Although early PK studies showed a linear decrease in clearance of Tamilfu with age, clinical trials were done with all children receiving a dose of 2 mg/kg. The sponsor's dosing recommendations would have [redacted] These are doses for which we have no safety data. Drug exposure was, however, probably in the same range as that measured in the adult trial in which a dose of 150 mg BID was evaluated. The adult study showed no difference in safety profile of 75 mg BID, the currently approved dose, and 150 mg BID. Given the drug's good safety profile, the review team suggested that a fixed dose based on weight would be acceptable as we projected that potentially fewer children might receive doses higher than the 2 mg/kg BID studied in clinical trials.

In summary, the sponsor has presented the results of a large, well-controlled pediatric study that confirms the benefit of Tamiflu oral suspension in the treatment of acute influenza in children older than 1 year of age. Supportive data from a study of children with chronic asthma reveals no evidence of worsening of asthma related to Tamiflu use. Previous adult trials enrolling adolescents revealed no differences in safety or efficacy in this age group. No significant safety concerns would preclude the use of Tamiflu in children, although there is heightened concern about the emergence of influenza virus resistant to the neuraminidase inhibitors.

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Concurrence:
HFD-530/ActDivDir/Birnkrant
HFD-530/MOTL/Murray
HFD-725/StatTL/Soon

Cc:
Orig. IND
HFD-530/Division File
HFD-530/CSO/Carmouze
HFD-530/MO/Lewis
HFD-530/MOTL/Murray
HFD-725/Stat/Breazna
HFD-725/StatTL/Soon
HFD-725/StatDivDir/Hugue
HFD-700/DepOfficeDir/Anello
HFD-520/MO/Smith
HFD-520/MOTL/Rakowsky