CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-246

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-246
TYPE:	P
DRUG:	Oseltamivir (Tamiflu) 12mg/ml (— dry powder for oral suspension
APPLICANT:	Hoffmann-La Roche
PRIMARY REVIEWER:	Jenny H. Zheng, Ph.D.
TEAM LEADER:	Kellie Reynolds, Pharm.D.
CLINICAL DIVISION:	530
SUBMISSION DATE:	June 15, 2000
PDUFA GOAL DATE:	December 15, 2000

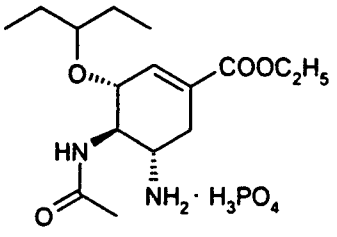
Executive Summary

Tamiflu (oseltamivir phosphate) has been previously approved as a capsule formulation for treatment and prophylaxis of influenza in adults. This NDA seeks approval of Tamiflu oral suspension for use in the treatment of influenza in children at least 12 months of age. The major PK issue is the dosing regimens for pediatric patients. The applicant proposed

weight. The dose used in the Phase III trials in children is 2 mg/kg, which is the only dose level with available efficacy and safety data. There is a concern that safety and tolerability data are not available for pediatric patients at doses higher than 2 mg/kg. Another concern is the fact that there are little PK data available for children under 5 years old.

Two alternative dosing regimens have been discussed: and a weight-based fixed mg dose. The dilemma is convenience versus uncertainty regarding tolerability. The final decision from the clinical division is a weight-based fixed mg dose.

Background



Oseltamivir phosphate

Oseltamivir (also referred to Ro 64-0796) is an ethyl ester prodrug of oseltamivir carboxylate (Ro 64-0802), an inhibitor of the neuraminidase enzyme of influenza virus. This enzyme catalyzes the cleavage of terminal sialic acid residues resulting in the release of the virus from infected cells. Inhibition of the neuraminidase enzyme has been suggested to cause a decrease in the duration of illness. Oseltamivir is readily absorbed from the gastrointestinal tract after oral administration and is extensively converted (>75%), predominantly by hepatic esterases, to oseltamivir carboxylate. Oseltamivir has been previously approved as a capsule formulation for treatment and prophylaxis of influenza in adults. The studies in adults showed that treatments for 5 days at doses of 75 mg BID or 150 mg BID are both efficacious and safe. Therefore, the approved dosing regimen for treatment of influenza in adults is 75 mg BID of oseltamivir, with or without food, for 5 days. The approved dosing regimen for prophylaxis of influenza in adults is 75 mg QD, for up to 42 days.

This NDA seeks approval of Tamiflu oral suspension for the treatment of influenza in children at least 12 months old. A total of 1029 patients aged 1-12 years participated in Phase III trials (WV 15758 and WV15759/WV15871), of whom 504 were randomized to receive 2mg/kg oseltamivir BID for five days. The available PK data are from 5 children (aged 3-11 years) in one of the Phase III trials and 18 healthy children (aged 5-12 years) in a single dose study. For labeling, the applicant proposed [redacted]

Synopsis

This review focuses on the clinical pharmacology and biopharmaceutics of oseltamivir (Ro 64-0796) and its active metabolite (Ro 64-0802, refer to active species in the original NDA 21-087 review). The following questions have been addressed:

Throughout the review, the clearance for the active metabolite was normalized by using the greatest potential amount of metabolite: (MWm/MWp) x (Amount of parent given), where MWp is the molecular weight of the parent and MWm is the molecular weight of the metabolite. Molecular weight of Ro 64-0796 is [redacted] The molecular weight of Ro 64-0802 is [redacted]

Appendices contain composition of clinical trial oral suspensions and proposed commercial oral suspension (Appendix A, Page 14) and individual study reviews (Appendix B, Page 15).

1. What are the proposed dosing regimens for the oseltamivir capsule and the oral suspension in children at least 12 months old?

The applicant suggested that for the treatment of influenza in adolescents 13 years and older, the dose of oseltamivir capsule is 75 mg twice daily for 5 days.

The proposed dose of oral suspension for pediatric patients 1 year and older or adult patients who cannot swallow a capsule is:

30 mg twice daily
45 mg twice daily
60 mg twice daily
75 mg twice daily

2. What PK studies were submitted to support the dosing regimens and approval of the oral suspension formulation?

a. BA/BE studies (150 mg oral dose)
   - Protocol WP15979. An open-label, relative bioavailability study of the phase III pediatric clinical trial and market formulations of Ro 64-0796 in healthy volunteers. (Volumes 17-18)
   - Protocol WP16137. An open-label, bioequivalence study of the phase III pediatric clinical trial and market oral suspension formulations of Ro 64-0796 in healthy volunteers. (Volumes 19-20)
   - Protocol NP15810. An open-label, relative bioavailability study of the clinical trial and market capsule formulations of Ro 64-0796 in healthy subjects. (Volumes 21-22)
   - Protocol WP 16225 (Pivotal BE study). An open label, relative bioavailability study of the market oral suspension, the clinical trial oral suspension and the market capsule formulations in healthy subjects. (Separate submission, 9/29/00)

b. PK studies
   - Protocol NP 15826. An open label study of the pharmacokinetics of Ro 64-0796/GS4104 in children. (Volumes 14-16)
   - Protocol WV15758. A double blind, randomized, stratified, placebo-controlled study of Ro 64-0796 in the treatment of children with influenza. (Volumes 36-37)

c. Drug interaction
   - Protocol NP15901. An open-label, two-way crossover randomized pharmacokinetic drug interaction study of neuraminidase inhibitor Ro

64-0796/GS4104 and amoxicillin in healthy volunteers. (Volumes 25-26)

d. Special population
   - Protocol PP15974. A single oral dose, multi-center study of the PK, safety and tolerability of Ro 64-0796/GS4104 in ESRD subjects on hemodialysis & peritoneal dialysis. (Volumes 27-29)

WV15758 is a pivotal Phase III clinical trial. This was a multiple center, double blind, randomized, placebo-controlled study in children aged 1-12 years with influenza-like illness. Patients were assigned to one of two groups:

- Treatment A: 2 mg/kg of Ro 64-0796 BID for 5 days (n = 344)
- Treatment B: Matching placebo BID for 5 days (n = 351)

3. What PK studies were reviewed for this NDA application?

Of the BA/BE studies, only Protocol WP 16225 was reviewed. Protocol NP15810 was reviewed in NDA 21-087. Protocols WP 15979 and WP 16137 were not reviewed in this NDA because the proposed market oral suspensions in these studies were different from the current proposed market oral suspension (see Question 5 below). In Study WP 16225, the relative bioavailability of the proposed market oral suspension (with improved process), the clinical trial oral suspension and the current market capsule formulation of Ro 64-0796 in healthy subjects were compared.

The dosing regimens that the applicant proposed were based on two PK studies: NP 15826 and WV15758. Study NP 15826 is a single dose (2 mg/kg Ro 64-0796) study in healthy children aged 5- 18 years (n=18), while Study WV15758 is a Phase III trial with Ro 64-0796 2mg/kg BID for 5 days in children aged 1-12 years infected with influenza (5 out of 344 patients in the active treatment group are used for PK).

The drug interaction study and the PK study in ESRD subjects are reviewed in NDA 21-087 supplement, which is for prophylaxis of influenza in adults.

4. Has an exposure-response relationship been established?

The exposure-response relationship was not studied in children. The PK/PD studies in adult subjects experimentally inoculated with human influenza virus (Type A or B) showed that average viral AUC is similar across the dose groups (20 mg BID, 100 mg BID, 200 mg QD or 200 mg BID in Study GS 97-801, 75 mg or 150 mg QD in Study NP 15717, see Dr. Rajagopalan's review for NDA 21-087). A relationship between exposure and response was not identified. However, subjects administrated the various doses of oseltamivir did demonstrate lowered viral AUC and higher efficacy compared to the placebo. The previous Phase III studies in adults demonstrated that 75 mg BID and 150 mg BID of oseltamivir have similar safety and efficacy. The 75 mg BID dosing regimen was approved for the treatment of influenza in adults.

5. Are there any chemistry issues related to the oral suspension formulations?

The applicant conducted two bioequivalence studies between an earlier proposed market oral suspension formulation (/V36) and clinical trial formulation (/V06). However, the first study (WP 15979) failed to demonstrate bioequivalence. The applicant claimed that the failure of the study was caused by the methods of suspension preparation and administration. By standardizing the methods of suspension preparation and administering oseltamivir directly into the volunteers' mouth from the oral syringe, bioequivalence was demonstrated in the second study (WP 16137). However, this earlier proposed market oral suspension has a homogeneity problem. The applicant then improved the manufacturing process to solve the problem, and claims that the new market oral suspension formulation (/V37) does not have the homogeneity problem.

Because of the homogeneity problem associated with the earlier proposed market oral suspension, the reviewer asked the applicant to provide data to show that the clinical trial oral suspensions (V06 and V20) did not have this problem. The applicant then provided us data from one batch of each of these formulations. The chemistry reviewer has reviewed the data, and indicated that the data did show there was no indication that the manufacturing problems existed in formulations V06 and V20.

The two clinical trial oral suspensions V06 and V20 are otherwise identical except for the proportion of [redacted] in the [redacted] The chemistry reviewer comments that the difference between these two formulations is very subtle. Studies NP 15979 and NP 15180 have shown that the 90% confidence intervals of V06/current market capsule and V20/current market capsule were both within 80-125% for AUC, but both V06 and V48 have decreased C_{max} (17% and 48%, respectively) compared to the current market capsule. The difference may be due to inter-study variability.

In both the clinical trial oral suspensions and the proposed market oral suspensions, the active ingredient oseltamivir is [redacted], even though inactive ingredients are [redacted] No dissolution study needs to be conducted.

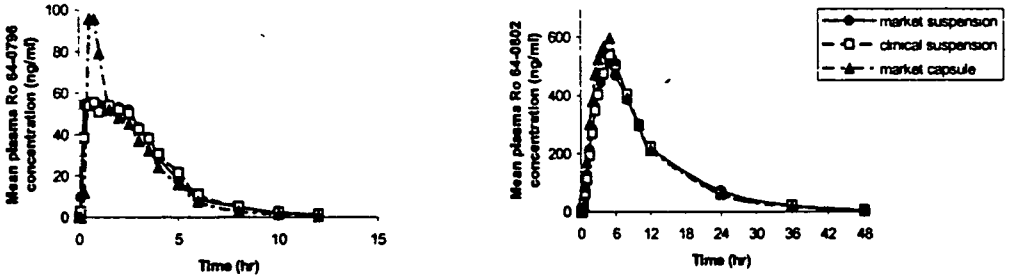
6. Is the proposed market oral suspension bioequivalent to the clinical trial oral suspension and the current market capsule formulation?

The proposed market oral suspension is bioequivalent to the clinical trial oral suspension. However, neither of the suspensions is bioequivalent to the current market capsule formulation based on the C_{max} of the prodrug. In Study WP 16225, a single dose of 150 mg of Ro 64-0796 was administered to healthy subjects under fasted conditions. The results below show that the proposed market oral suspension is bioequivalent to the clinical trial oral suspension, based on the point estimate and 90% CI of Ro 64-0796 and Ro 64-0802. However, C_{max} of Ro 64-0796 is reduced by about 40% in the proposed market oral suspension and the clinical trial oral suspension, compared to that in the current market capsule. Since the active metabolite (Ro 64-0806) is bioequivalent among the suspensions and the current market capsule formulation, and AUCs of Ro 64-0796 are comparable, comparable therapeutic effects are expected.

Ro 64-0796 parameter	A (Market suspension) Mean (SD)	B (Clinical suspension) Mean (SD)	C (Capsule) Mean (SD)	Ratio A/B (90% CI)	Ratio C/B (90% CI)	Ratio A/C (90% CI)
C_{max} (ng/ml)	83 (25)	79 (32)	133 (54)	106 (91.1, 124)	**167 (143, 195)**	**63.8 (54.5, 74.5)**
AUC_{last} (ng.hr/ml)	258 (69)	241 (64)	241 (64)	106 (99.9, 113)	101 (94.4, 107)	106 (99.2, 113)
AUC_{inf} (ng.hr/ml)	263 (70)	246 (59)	247 (63)	106 (99.6, 113)	101 (94.6, 107)	106 (98.8, 112)
CL/F (ml/min)	10100 (2650)	10700 (2440)	10800 (2680)	N/A	N/A	N/A
T_{max} (hr)	1.0 (1.0)	1 8 (1.2)	0.9 (0 6)	N/A	N/A	N/A
Half-life (hr)	2.3 (1.0)	2.5 (2.1)	2.0 (2.0)	N/A	N/A	N/A

Ro 64-0802 parameter	A (Market suspension) Mean (SD)	B (Clinical suspension) Mean (SD)	C (Capsule) Mean (SD)	Ratio A/B (90% CI)	Ratio C/B (90% CI)	Ratio A/C (90% CI)
C_{max} (ng/ml)	546 (101)	538 (140)	615 (147)	103 (97.0, 109)	115 (108, 122)	89 6 (84.4, 95.2)
AUC_{last} (ng.hr/ml)	6680 (1330)	6200 (1270)	6780 (1580)	108 (104, 112)	110 (106, 114)	98 7 (95 1, 102)
AUC_{inf} (ng hr/ml)	6870 (1360)	6400 (1290)	7010 (1610)	108 (104, 111)	109 (106, 113)	98.4 (95 0, 102)
CL/F (ml/min)	343 (61)	371 (76)	340 (70)	N/A	N/A	N/A
T_{max} (hr)	5.1 (1.5)	5.1 (0.9)	4.5 (1.0)	N/A	N/A	N/A
Half-life (hr)	7.2 (1.7)	7 1 (1.7)	6 6 (1 6)	N/A	N/A	N/A

The mean plasma Ro 64-0796 and Ro 64-0802 concentration-time profiles following administration of the proposed market oral suspension, the clinical trial formulation and the current market capsule formulation under fasting conditions are shown below.



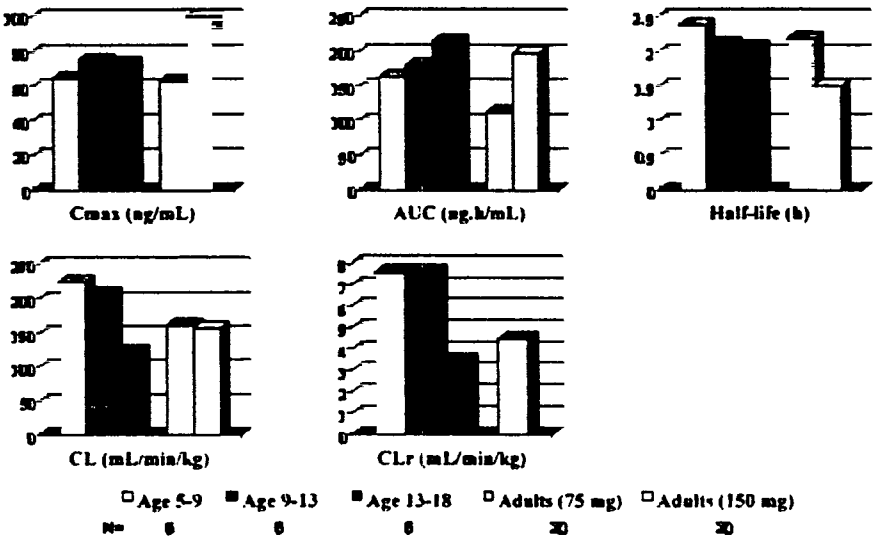
7. Are oseltamivir basic PK characteristics in children comparable to those in adults?

The data show that exposure after a single oral 2 mg/kg dose of Ro 64-0796 in children is less than in adults given comparable doses, due to more rapid drug clearance of both prodrug and active metabolite in children. With advancing age, the difference in exposure between children and adults became less, such that the pharmacokinetic profile in children over 13 years of age was similar to that in adults.

The following figures compare pharmacokinetic parameters of prodrug Ro 64-0796 in children and adults after single dose administration. In children 5 to 13 years of age, C_{max} of Ro 64-0796 following a 2 mg/kg dose was similar to that of a 75 mg (1 mg/kg) dose in adults, and AUC was between that of a 75 and 150 mg (2 mg/kg) dose in adults. In children 13 to 18 years of age, C_{max} was similar to that of a 75 mg dose in adults, and AUC was comparable to that of a 150 mg dose in adults. In all three groups

of children, half-life was similar to that of a 75 mg dose in adults. Higher clearance was observed in children aged 5 to 13 years compared to that in adults.

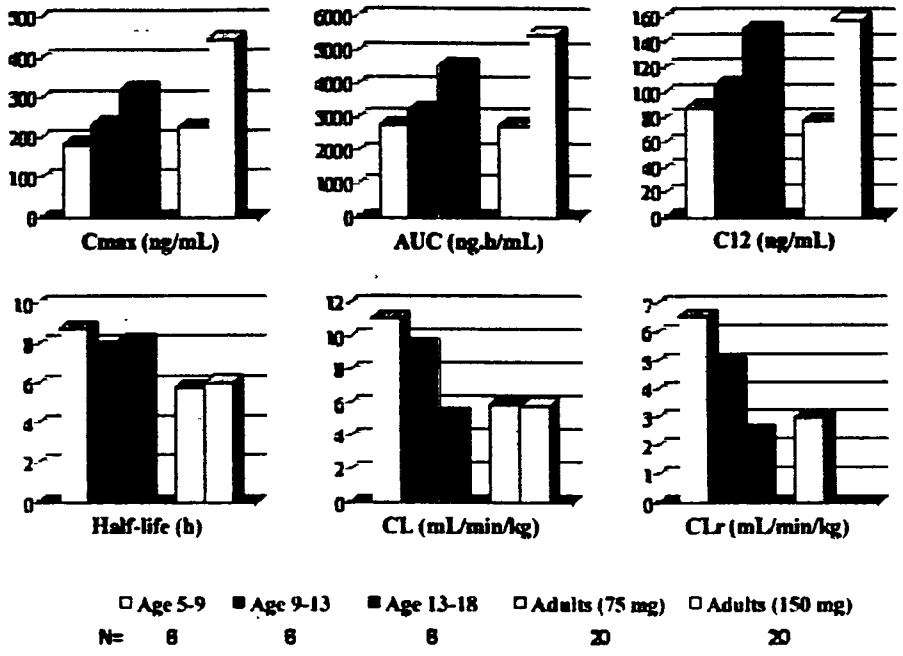
Comparison of Pharmacokinetics of Ro 64-0796 in different age groups:



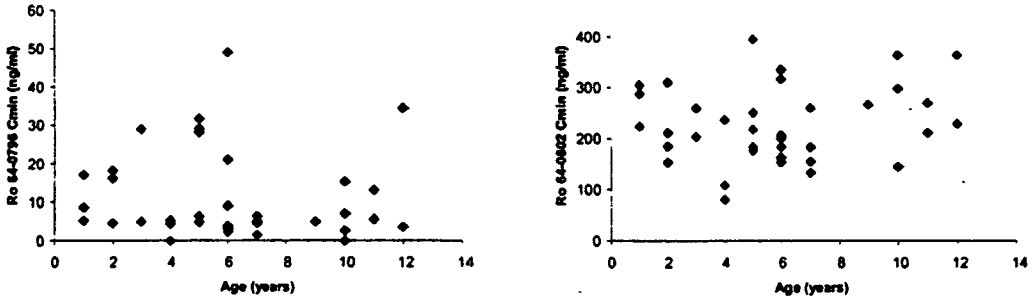
The following figures compare pharmacokinetic parameters of Ro 64-0802 in children (NP 15826) and adults (NP 15717) after single dose administration. The table below lists pharmacokinetic parameters of Ro 64-0802 in different studies from children and adults. Compared to adults in challenge study (NP 15717) and Phase III studies after 75 mg BID of Ro 64-0796, total clearance of Ro 64-0802 is comparable in children aged 13-18 years (Study NP 15826), and higher in children less than 13 years old (Studies WV 15758 and NP 15826). Compared to older children, the 3 year-old child has slower absorption with a prolonged elimination half-life. Prolonged elimination half-life was also seen for Ro 64-0796 for this patient. Since PK data available for children aged less than 5 years are from only one child, no conclusion can be drawn for this age group. However, sparse data from children down to age 1 show that C_{min} in this group of children is similar to that in older children, which indicated that PK of Ro 64-0796 and Ro 64-0802 in children younger than 5 years should follow the trend observed in older children.

Even though there are only a small amount of steady state PK data from children, single dose total clearance is generally predictive of steady state total clearance.

Comparison of Pharmacokinetics of Ro 64-0802 in different age groups:



C_{min} from Sparse data:



Pharmacokinetic parameters of Ro 64-0802:

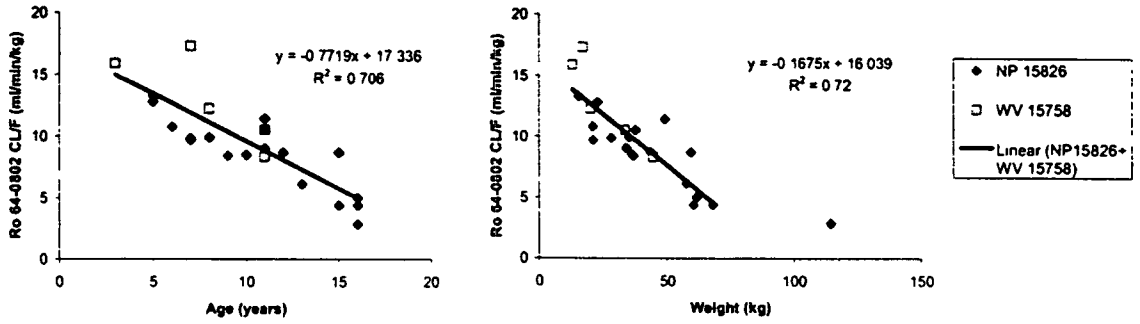
Ro 64-0802 Parameter	Study NP 15758 [c]			Study NP 15826 [d]			Study NP 15717 [b]		Phase III studies [a,b]
Age (yr)	3	7-8	11	5-9	9-13	13-18	Adults Day 1	Day 5/7 (s.s)	Adults Day 5/7 (s.s)
N	1	2	2	6	6	6	20	20	
C_{max} (ng/ml)									
Mean	178	248	374	183	231	319	225	348	398
SD	-	56	26	36	46	76	49	64	103
95% CI	-	-	-	154-212	194-268	258-380	204-246	320-76	357-439
t_{max} (hr)									
Mean	6.0	3.6	3.0	3.7	3.7	4.3	3.76	3.03	3.05
SD	-	0.6	0	0.5	0.5	0.8	1.0	0.7	1.0
95% CI	-	-	-	3.3-4.1	3.3-4.1	3.7-4.9	3.3-4.2	2.7-3.3	2.6-3.5
$AUC_{0-\infty}$ (ng.hr/ml)									
Mean	1907 [e]	2113 [e]	3266 [e]	2746	3208	4534	2227	2719 [e]	3450 [e]
SD	-	514	542	368	394	929	410	538	1018
95% CI	-	-	-	2452-3040	2893-3523	3791-5277	2047-2406	2483-2955	3043-3857
$t_{½}$ (hr)									
Mean	16.7	5.8	7.5	8.8	7.8	8.1	5.49	5.79	7.94
SD	-	0.5	2.5	2.0	1.8	2.2	1.4	1.3	2.9
95% CI	-	-.	-	7.2-10.4	6.4-9.2	6.3-9.9	4.9-6.1	5.2-6.3	6.8-9.1
CL/F (ml/min/kg)									
Mean	15.9	14.8	9.4	11.1	9.4	5.3	6.0 [f]	6.6 [g]	5.2 [g]
SD	-	3.6	1.6	1.6	1.3	2.0	-	-	-
95% CI	-	-	-	9.8-12.4	8.4-10.4	3.7-6.9	-	-	-
CL_r (ml/min/kg)									
Mean	-	-	-	6.5	4.9	2.5	3 [f]	-	3.1 [g]
SD	-	-	-	1.4	2.1	0.9	-	-	-
95% CI	-	-	-	5.9-7.1	4.0-5.8	2.1-2.9	-	-	-
C_{12} (ng/ml)									
Mean	160	84.7	202.6	87	106	150	75 [f]	138	175
SD	-	74.1	135.8	9	17	30		30	57.75
95% CI	-	-	-	80-94	92-120	126-174		125-151	152-198

[a] Protocols WV 15670, WV15671, WV15730
[b] 75 mg BID
[c] 2 mg/kg BID
[d] 2 mg/kg single dose
[e] AUC_{0-12}
[f] Estimated from the graph sent by the applicant
[g] Estimated based on the reported clearance normalized to standard adult's body weight 70 kg

8. How did the applicant select the pediatric dosing regimens?

For the active metabolite Ro 64-0802, a linear decrease in apparent total clearance with increasing age or body weight (up to 70 kg) was demonstrated. The relationship between weight and clearance is probably due to the correlation between age and weight. The clearance vs. weight profiles show that clearance was not significantly changed in a child with weight 115 kg (age 16) compared to 70 kg children and adults. This also indicates that clearance in adolescents is similar to that in adults.

A B



The applicant proposed [redacted], based on the linear relationship between apparent total clearance and age. The target AUC_{12} is 2700 ng·h/ml (range: 2160-3239 ng·h/ml), which was average AUC_{12} in adults after 75 mg BID of Ro 64-0796 oral dose in a challenge study (NP 15717). The dosing regimen also allows AUC to be extended to as high as comparable to AUC in adults after 150 mg BID of Ro 64-0796 oral dose (mean: 5500 ng·h/ml, range: 4402-6598). Although the approved dose in adults is 75 mg BID, safety was similar at 150 mg BID. In the calculation, the applicant used CL values from the regression line of clearance vs. age profiles and ideal body weight (IBW) for age. The predicted AUCs following 30 mg, 45 mg and 60 mg of 12 mg/ml oral suspension and a 75 mg dose were calculated. The mg/kg dose of a 12 mg/ml oral suspension formulation required to deliver mean exposures equivalent to the adult recommended therapeutic 75 mg dose (2700 ng·h/ml) and the mg/kg dose given based on the proposed dose were also determined.

Age (yr)	IBW (kg)	CL/F Pred (mL/min/kg)	CL/F Pred (L/h/kg)	2 mg/kg bid	30 mg (2.5mL) bid	45 mg (3.75mL) bid	60 mg (5.0mL) bid	75 mg capsule bid	mg/kg to give 2700 ng.h/ml	mg/kg given based on the proposed dose
1	10	16.6	1.0	2012	**3019**	4528	6037	7546	2.7	3.0
2	12	15.8	0.9	2111	**2638**	3958	5277	6596	2.6	2.5
3	15	15 0	0 9	2219	2219	**3329**	4438	5548	2.4	3.0
4	17	14.2	0.9	2339	2064	**3096**	4128	5161	2.3	2.6
5	18	13.5	0.8	2473	2061	**3092**	4122	5153	2.2	2.5
6	20	12.7	0.8	2624	1968	2952	**3936**	4919	2.1	3.0
7	23	11.9	0.7	2793	1822	2733	**3644**	4555	1.9	2.6
8	25	11.2	0.7	2987	1792	2688	**3584**	4480	1.8	2.4
9	28	10.4	0.6	3209	1719	2578	**3438**	4297	1.7	2.1
10	32	9.6	0.6	3466	1625	2437	**3249**	4062	1.6	1.9
11	36	8.8	0.5	3769	1570	2355	**3140**	3926	1.4	1.7
12	40	8.1	0 5	4129	1548	2322	**3097**	3871	1.3	1.5
13	47	7.3	0.4	4565	1457	2186	2914	**3643**	1.2	1.6
14	55	6.5	0.4	5105	1392	2088	2785	**3481**	1.1	1.4
15	60	5.8	0.3	5790	1447	2171	2895	**3618**	0.9	1.3
16	65	5.0	0.3	6686	1543	2314	3086	**3857**	0.8	1.2
17	70	4.2	0.3	7911	1695	2543	3390	**4238**	0.7	1.1
18	70	3.4	0.2	9685	2075	3113	4151	**5188**	0.6	1.1

Note: The predicted clearance values and resulting AUC values are based on the assumption that the linear relationship between age and clearance holds across the entire age range. However, the data indicate there is little change in clearance after age 13.

The applicant suggested that, for the treatment of influenza in adolescents 13 years and older, the dose of oseltamivir capsule is 75 mg twice daily for 5 days.

The proposed dose of oral suspension for pediatric patients 1 year and older or adult patients who cannot swallow a capsule is:

30 mg twice daily
45 mg twice daily
60 mg twice daily
70 mg twice daily

9. Do the data support the applicant's proposed dosing regimens?

The dosing regimens were based on data collected from pediatric subjects following a 2 mg/kg single dose (aged 5-18 years, n=18) and 2 mg/kg BID (aged 1-12 years, n = 5). We do see that clearance is age or body weight dependant. Based on PK data, the applicant's proposal is generally acceptable, except for However, we have some concerns regarding safety.

. Even though the PK data suggest the proposed dosing regimens are logical, we do not have enough PK data for children under 5 years old nor safety data to support over 2 mg/kg dose in children. The proposed dosing regimens totally rely on the assumption that the same exposure-response relationships hold in adults and children. The previous PK/PD studies of oseltamivir in the treatment of volunteers experimentally infected with human influenza viruses (Studies GS 97-801 and NP15717) have failed to demonstrate a relationship between exposure and response (viral AUC). The current Phase III study would have been more helpful if the applicant used the same dosing regimens they now propose for labeling. There are no significantly changes in clearance between adolescents (>= 13 years old) and adults, and efficacy and safety has been studied in adolescents combined with adults. Therefore, the proposed dosing regimens for adolescents are acceptable.

10. What dosing regimens do we recommend?

Since 2 mg/kg BID in children aged 1-12 years was studied in the Phase III trials, ideally, 2 mg/kg BID should be in the labeling. However, there were some discussions within the clinical division regarding convenience of dosing vs. the potential for decreased tolerability at doses >2 mg/kg BID. It is noted that the predicted AUC for children who receive the applicant's proposed regimen would be similar to AUC in adults who received 75 mg BID. Also, using a [redacted] may decrease medication errors because there is no calculation.

The final decision from the clinical division is to use a fixed dose by weight [redacted] which insures that underweight children will not get a higher mg/kg dose than the proposed dose based on the IBW. The reviewer has recalculated the predicted AUCs following 30 mg, 45 mg, and 60 mg of 12 mg/ml oral suspension and a 75 mg capsule dose. The mg/kg dose of a 12 mg/ml oral suspension formulation required to deliver mean exposures equivalent to the adult recommended therapeutic 75 mg dose (2700 ng·h/ml) and the mg/kg dose given based on the proposed dose were also calculated. Target AUC (in bold) includes 95% CI of AUC after 75 mg BID from the challenge study and Phase III studies in the adults, which is 2483-3857 ng·h/ml.

BW (kg)	BW (lb)	CL/F pred (ml/min/kg)	CL/F pred (l/h/kg)	2 mg/kg bid	30mg bid	45 mg bid	60 mg bid	75 mg capsule bid	mg/kg to give 2700 ng.h/ml	mg/kg given based on the proposed dose
10.0	22.1	14.4	0.86	2321	**3481**	5221	6962	8702	2.3	3.0
12.0	26.5	14.0	0.84	2376	**2970**	4455	5940	7425	2.3	2.5
13.6	30.0	13.8	0.83	2422	**2671**	4006	5342	6677	2.2	2.2
15.0	33.1	13.5	0.81	2464	**2464**	**3696**	4929	6161	2.2	2 0
17.0	37.5	13.2	0.79	2527	2230	**3344**	4459	5574	2.1	2.6
18.0	39.7	13.0	0.78	2559	2133	**3199**	4266	5332	2.1	2.5
20.0	44.1	12.7	0.76	2627	1970	**2955**	3940	4926	2.1	2.3
23.0	50.7	12.2	0.73	2735	1784	**2676**	**3568**	4460	2.0	2.0
25.0	55.1	11.9	0.71	2813	1688	**2531**	**3375**	4219	1.9	2.4
28.0	61.7	11.3	0.68	2937	1573	2360	**3147**	3934	1.8	2.1
30.0	66.2	11.0	0.66	3026	1513	2270	**3026**	**3783**	1.8	2.0
32.0	70 6	10.7	0.64	3121	1463	2195	**2926**	**3658**	1.7	1.9
35.0	77.2	10.2	0 61	3276	1404	2106	**2808**	**3509**	1 6	1.7
36.0	79.4	10.0	0.60	3330	1388	2081	**2775**	**3469**	1.6	1.7
40 0	88.2	9.3	0.56	3569	1338	2008	**2677**	**3346**	1 5	1 5
47 0	103.6	8.2	0.49	4082	1303	1954	2605	**3257**	1 3	1.6
55.0	121.3	6.8	0.41	4883	1332	1998	2663	**3329**	1.1	1.4
60.0	132.3	6.0	0.36	5566	1391	2087	2783	**3479**	1.0	1.3
65.0	143.3	5.2	0.31	6471	1493	2240	2986	**3733**	0.8	1.2
70.0	154 4	4 3	0.26	7727	1656	2484	3311	**4139**	0.7	1.1

The recommended dosing regimens for children 12 months and older are:

<= 15 kg	or	<= 33 lb	30 mg twice daily
> 15 kg to 23 kg	or	> 33 lb to 50 lb	45 mg twice daily
> 23 kg to 40 kg	or	> [redacted]	60 mg twice daily
> 40 kg	or	> [redacted]	75 mg twice daily

The 75 mg capsule is an alternative dosing regimen only for children over 40 kg or 80 lb. No specific studies have been conducted for efficacy and safety in the adolescent population. However, children aged 13 years or older (IBW = 47-70 kg) were included in trials using the 75 mg capsule in the winter season of 1998-1999. Even though the new dosing regimens allow more than 2 mg/kg dose for younger children, the recommended doses are mostly within 2.0 to 2.5 mg/kg in these groups, compared to 2.5 to 3.0 mg/kg in the dosing regimen proposed by the applicant. The recommended dosing regimens also reduce possibility of overdose in underweight children.

We still have concern regarding the small amount of PK data available for children younger than 5 years old. However, sparse data from children down to age 1 show that C_{min} in this group of children is similar to that in older children, which suggested that PK of Ro 64-0796 and Ro 64-0802 in children younger than 5 years might be similar to older children. We have requested the applicant to collect more PK data in prophylaxis study in children, especially in children younger than 5 years old.

Recommendation:

The data submitted by the applicant are acceptable to describe the pharmacokinetics of oseltamivir and its active metabolite in children 5-12 years of age. The data also indicate that the proposed market oral suspension is interchangeable with the clinical trial oral suspension.

Jenny H. Zheng, Ph.D.
Reviewer, Pharmacokinetics
Division of Pharmaceutical Evaluation III, OCPB

Concurrence:

Kellie S. Reynolds, Pharm. D
Team Leader, Antiviral Drug Products Section
Division of Pharmaceutical Evaluation III, OCPB

cc: HFD-530 /NDA 21214
/MO/LLewis
CSO/GCarmouze
HFD-880 /JHZheng
/TL/KReynolds

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APPENDIX A

Comparison of the clinical trial oral suspensions and the proposed market formulation

Two types of powder formulations were developed, referred to as types I and II. Formulation type I is a [redacted], and was used in clinical trials. Formulation type II, which is proposed for commercial production, is manufactured by a conventional [redacted] process. The compositions of these two types of formulation are presented in the table below.

Components *(figures in mg)*	Formulation of Ro 64-0796/ Type I /V06	Type I /V20	Type II /V37 (/V36)*
Oseltamivir phosphate			
Sorbitol			
[redacted]			
[redacted]			
Titanium dioxide			
[redacted]			
Sodium benzoate			
[redacted]			
[redacted]			
Xanthan gum			
[redacted]			
Monosodium citrate			
Saccharin sodium			
[redacted] Tutti Frutti			
Total:			
[redacted][4]			
[redacted]			

[1] The compositions of formulations /V37 and /V36 are identical; the only difference is the bottle fill weight; the supportive stability batches used formulation /V36

[2] Proportion of [redacted]

[3] Proportion of [redacted]

[4] A mixture of [redacted] is used during [redacted] the [redacted]

[5] Approximate figures

Formulation Type I was replaced by Type II for the following reasons:

[redacted]

The two clinical trial oral suspensions V06 and V20 are otherwise identical except for the proportion of [redacted] in the [redacted] The chemistry reviewer comments that the difference between these two formulations is very subtle. Studies NP 15979 and NP 15180 have shown that the 90% confidence intervals of V06/current market capsule and V20/current market capsule were within 80-125% for AUC, but both V06 and V20 have decreased C_{max} (17% and 48%, respectively) compared to the current market capsule. The difference may be due to variability.

The proposed market oral suspension is V37.

APPENDIX B

Individual Study Reviews

Table of contents

An Open Label, Relative Bioavailability Study of the Market Oral Suspension, the Clinical Trial Oral Suspension and the Market Capsule Formulations in Healthy Subjects
(Protocol WP 16225, Submission 9/29/00)

Background: The Applicant conducted two bioequivalence studies between the original proposed market oral suspension formulation and clinical trial formulation. However, the first study (WP 15979) failed to demonstrate bioequivalence. By standardizing the methods of suspension preparation and administering oseltamivir directly into the volunteers' mouth from the oral syringe, bioequivalence was demonstrated in the second study (WP 16137). However, the original proposed market oral suspension has a homogeneity problem. The applicant has improved the manufacturing process to solve the problem, and claims that the new formulation does not have the homogeneity problem. In this study, the relative bioavailability of the proposed market oral suspension (with improved process), the clinical trial oral suspension, and the current market capsule formulations of Ro 64-0796 in healthy subjects was evaluated.

Objective: To assess the relative bioavailability of the proposed market oral suspension (with improved process), the clinical trial oral suspension, and current market capsule formulations of Ro 64-0796 in healthy subjects.

Subjects: A total of 24 male or female subjects aged from 18 to 45 years were enrolled in this study.

Study design: This is a single center, open-labeled, randomized, and single dose study in healthy subjects. Subjects were randomly assigned to receive the following treatments under fasted conditions in a three-way crossover fashion.
Treatment A: Single 150-mg dose of oseltamivir (/V37, market oral suspension)
Treatment B: Single 150-mg dose of oseltamivir (/V20, clinical trial oral suspension)
Treatment C: Single 150-mg dose of oseltamivir (/V22, current market capsule formulation)
The treatments will be separated by a washout period of at least 7 days.

Blood sample collections: Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 36 and 48 hours post-dose, to measure blood concentrations of oseltamivir and Ro 64-0802.

Formulation: Ro 64-0796 current market capsules (/V22, 75 mg), Ro 64-0796 clinical trial oral suspension (/V20-01, 6 mg/ml) and Ro 64-0796 market oral suspension (/V37, 12 mg/ml) were used in this study. The oral suspensions were prepared by reconstitution of dry powder.

Analytical methodology: Plasma samples were assayed for concentrations of Ro 64-0796 and its active metabolite Ro 64-0802 by an HPLC/MS/MS analytical method. The limit of quantitation was [redacted] for Ro 64-0796, and [redacted] for Ro 64-0802. Values below the limit of quantitation were treated as zero in statistical summaries.

Pharmacokinetic data analysis: Pharmacokinetic parameters were estimated by noncompartmental methods. ANOVA with terms for sequence, subject within sequence, period and treatment was applied to log transformed C_{max} and AUC. The point estimates and 90% confidence intervals were obtained following analysis of variance.

Pharmacokinetic results:

(1) Bioequivalency assessment

The mean plasma Ro 64-0796 and Ro 64-0802 concentration-time profiles following administration of the proposed market oral suspension, the clinical trial formulation and the current market capsule formulation under fasting conditions are shown in Figure 1. Individual values of C_{max} and $AUC_{0-\infty}$ are shown in Figure 2 and the results of the statistical analyses are summarized in Tables 1 and 2.

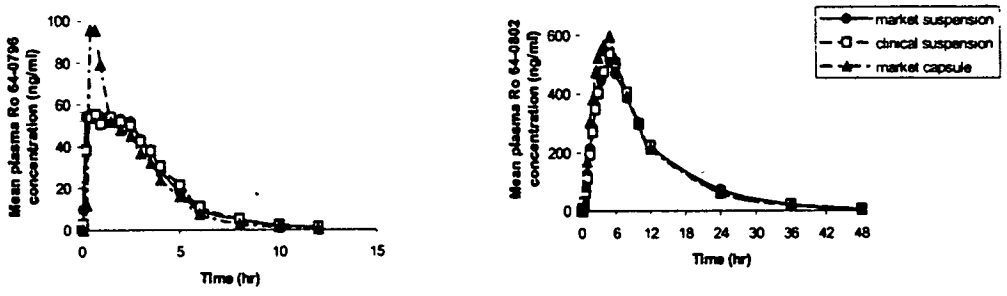


Figure 1

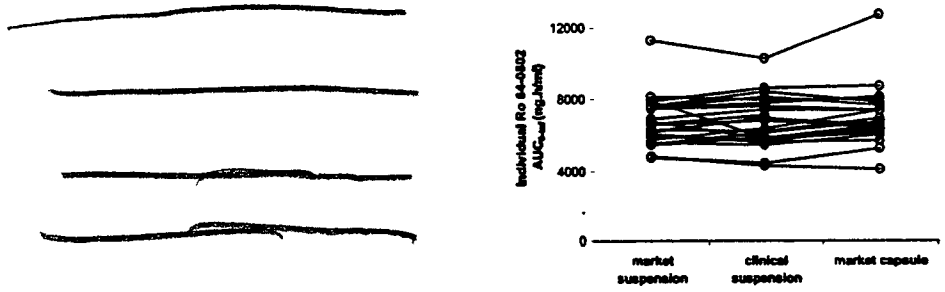


Figure 2

Ro 64-0796 parameter	A (market suspension) Mean (SD)	B (clinical suspension) Mean (SD)	C (capsule) Mean (SD)	Ratio A/B (90% CI)	Ratio C/B (90% CI)	Ratio A/C (90% CI)
C_{max} (ng/ml)	83 (25)	79 (32)	133 (54)	106 (91.1, 124)	**167 (143, 195)**	**63.8 (54.5, 74.5)**
AUC_{last} (ng.hr/ml)	258 (69)	241 (64)	241 (64)	106 (99.9, 113)	101 (94.4, 107)	106 (99.2, 113)
AUC_{inf} (ng.hr/ml)	263 (70)	246 (59)	247 (63)	106 (99.6, 113)	101 (94.6, 107)	106 (98.8, 112)
CL/F (ml/min)	10100 (2650)	10700 (2440)	10800 (2680)	N/A	N/A	N/A
T_{max} (hr)	1.0 (1.0)	1.8 (1.2)	0.9 (0.6)	N/A	N/A	N/A
Half-life (hr)	2.3 (1.0)	2.5 (2.1)	2.0 (2.0)	N/A	N/A	N/A

Table 1

Ro 64-0802 parameter	A (market suspension) Mean (SD)	B (clinical suspension) Mean (SD)	C (capsule) Mean (SD)	Ratio A/B (90% CI)	Ratio C/B (90% CI)	Ratio A/C (90% CI)
C_{max} (ng/ml)	546 (101)	538 (140)	615 (147)	103 (97 0, 109)	115 (108, 122)	89 6 (84 4, 95 2)
AUC_{last} (ng.hr/ml)	6680 (1330)	6200 (1270)	6780 (1580)	108 (104, 112)	110 (106, 114)	98 7 (95 1, 102)
AUC_{inf} (ng hr/ml)	6870 (1360)	6400 (1290)	7010 (1610)	108 (104, 111)	109 (106, 113)	98 4 (95 0, 102)
CL/F (ml/min)	343 (61)	371 (76)	340 (70)	N/A	N/A	N/A
T_{max} (hr)	5.1 (1.5)	5.1 (0 9)	4.5 (1 0)	N/A	N/A	N/A
Half-life (hr)	7.2 (1.7)	7.1 (1 7)	6.6 (1.6)	N/A	N/A	N/A

Table 2

Statistical analyses indicate that the proposed market oral suspension and the clinical trial oral suspension are bioequivalent based on AUC and C_{max} of Ro 64-0806 and Ro 64-0796. The proposed market oral suspension and the clinical trial oral suspension are bioequivalent to the current market capsule based on active metabolite Ro 64-0806. However, C_{max} of Ro 64-0796 is reduced by about 40% in the proposed market oral suspension and the clinical trial oral suspension, compared to that in the current market capsule. Since AUCs of Ro 64-0796 are comparable between formulations and the active metabolite (Ro 64-0806) is bioequivalent among the three formulations, the lower C_{max} of the prodrug Ro 64-0796 in the proposed market oral suspension and the clinical trial oral suspension is not expected to be clinically significant.

Because of a homogeneity problem associated with the previous proposed to market liquid formulation, we have asked the applicant to provide data to show that the clinical trial oral suspensions (V06 and V20) did not have this problem. The applicant then provided us data from one batch of each of these formulations. The chemistry reviewer has reviewed the data, and indicated that the data did show there was no indication that the manufacturing problems existed in formulations V06 and V20.

Conclusions: The proposed market oral suspension and the clinical trial oral suspension were found to be bioequivalent, and the current market capsule formulation is expected to have comparable therapeutic effects compared to the oral suspensions.

An open label study of the pharmacokinetics of RO 64-0796/GS4104 in children
(Protocol NP15826, Volumes 14-16)

Background: The Applicant has developed a liquid formulation of Ro 64-0796 for the treatment of influenza in children. *In vivo*, Ro 64-0796 is converted to the active drug, Ro 64-0802, by esterases. Ro 64-0796 has been evaluated at doses of 75 mg and 150 mg BID (1- to 2- mg/kg BID) for the treatment of influenza in the adult population, and is being evaluated at dose of 75 mg QD for prophylaxis of influenza in Adults. In this study, the Applicant evaluated the pharmacokinetics of Ro 64-0796 after single oral doses of 2mg/kg in children.

Objective: To assess the single dose pharmacokinetics of Ro 64-0796 and its active metabolite Ro 64-0802 in children.

Subjects: 18 children (6 in each of the following age ranges 5 - 9, 9 - 13 and 13 – 17) completed the study.

Study design: This was an open label, single-dose study at a single center in healthy children. The children received a single oral dose of approximately 2 mg/kg Ro 64-0796 as a suspension with water, followed immediately by a standard breakfast.

Formulations: Each bottle contained Ro 64-0796/V06 as a dry powder such that, when reconstituted with water to 100 ml, test medication was present at a concentration of 6 mg/ml.

Sample collection: Blood samples (2 ml) were collected at predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours after drug administration. Urine samples were collected during the following time periods: 0-4, 4-6, 6-8, 8-12 and 12-24 hours after dosing.

Analytical methodology: Plasma and urine samples were assayed for concentrations of Ro 64-0796 and its active metabolite Ro 64-0802 by an HPLC/MS/MS analytical method.

Pharmacokinetic data analysis: Pharmacokinetic parameters were estimated by noncompartmental methods.

Pharmacokinetic results and discussions:

(1) Data handling

In the pharmacokinetic analysis of data from this study, plasma concentrations below quantifiable limits (BQL) were not included. In addition, plasma concentrations of Ro 64-0796 below [redacted] measurable values occurring after BQL values, and other values near the quantifiable limits but suggestive of enterohepatic recycling or a prolonged elimination phase not evaluable in all subjects were not included.

Reviewer's remark: Some criteria for data exclusions are not acceptable: excluding measurable values after BQL and values suggestive of enterohepatic recycling or a prolonged elimination phase not evaluable. The exclusion criteria are subjective and misleading. The exclusions started as early as 8 hr in some subjects. Table 1 lists the percentage of exclusion, BQL, and no sample (NS) at different time points. However, since the exclusions are mostly for the parent drug, and we are mostly interested in active metabolite, it will not affect the overall evaluation.

Time		8 hr	10 hr	12 hr	24 hr
Parent	Exclusion (%)	11.1	22.2	33.3	5.5
	BQL (%)	0	27.8	33.3	83.3
	NS (%)	0	0	5.5	5.5
	Total (%)	11.1	50	72.1	94.3
Metabolite	Exclusion (%)	0	5.5	0	0
	BQL (%)	0	0	0	0
	NS (%)	0	0	5.5	11.1
	Total (%)	0	5.5	5.5	11.1

Table 1

(2) Pharmacokinetics.

Children were dosed based on bodyweight, 2mg/kg up to 100mg. In the age group of 13-18, all six children weighed more than 50 kg and were dosed with 100 mg of Ro 64-0796. Ro 64-0796 and active metabolite Ro 64-0802 plasma concentrations were normalized to a 2 mg/kg dose. Figure 1 shows the mean (+SD) plasma concentration-time profiles for Ro 64-0796 and Ro 64-0802 after a single oral dose of 2 mg/kg.

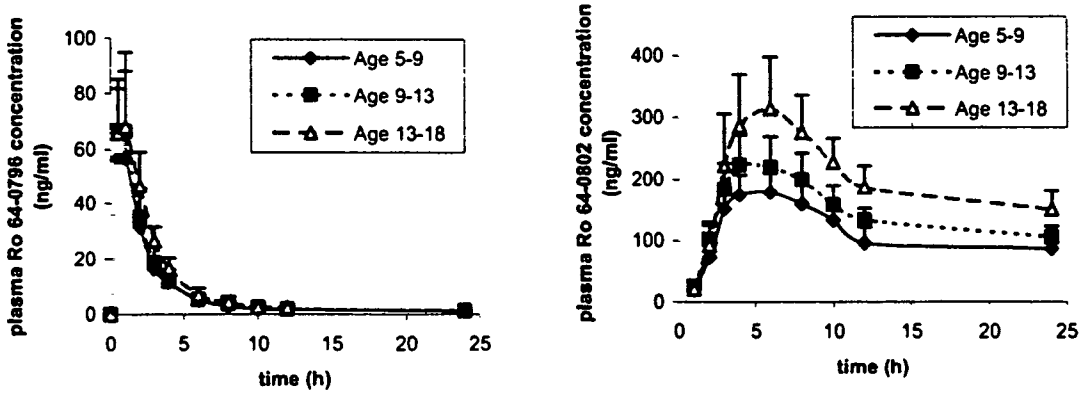


Figure 1

Table 2 summarized the mean (SD) pharmacokinetic parameters of Ro 64-0796 and Ro 64-0802 after a single oral dose of 2 mg/kg.

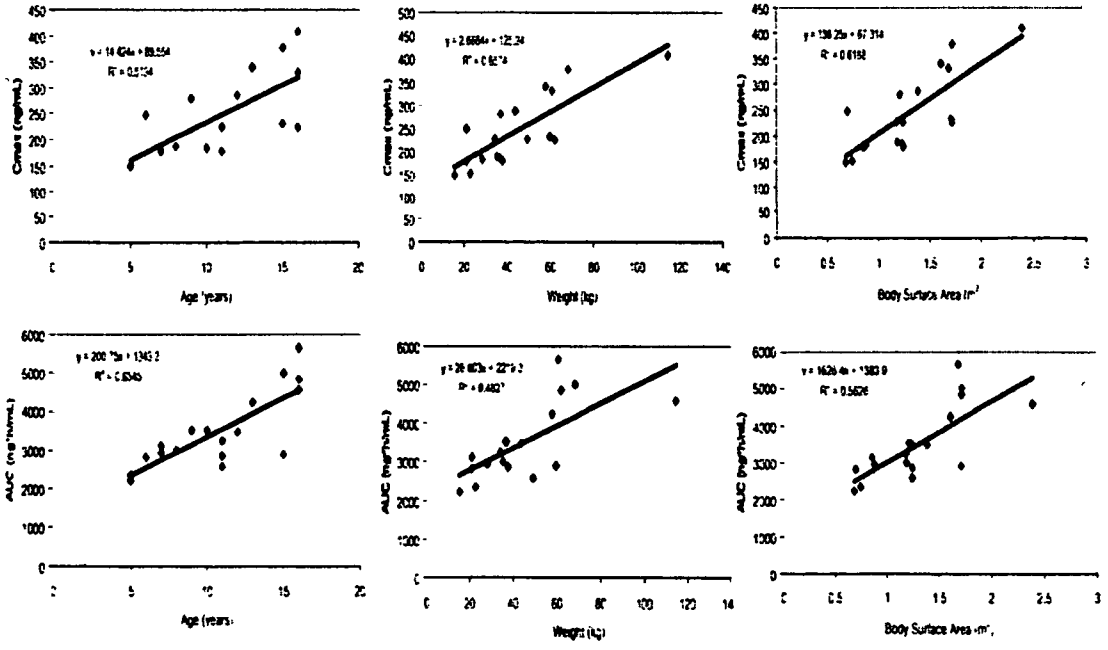
Parameter	Ro 64-0796 (pro-drug), Age (n=6 per group)			Ro 64-0802 (active metabolite), Age (n=6 per group)		
	5-9	9-13	13-18	5-9	9-13	13-18
C_{max} (ng/ml)	64 (14)	75 (25)	73 (19)	183 (36)	231 (46)	319 (76)
t_{max} (hr)	0.8 (0.3)	0.7 (0.3)	0.8 (0.3)	3.7 (0.5)	3.7 (0.5)	4.3 (0.8)
$AUC_{0-\infty}$ (ng.hr/ml)	163 (41)	180 (60)	215 (31)	2746 (368)	3208 (394)	4534 (929)
$t_{½}$ (hr)	2.4 (0.8)	2.1 (0.6)	2.1 (0.5)	8.8 (2.0)	7.8 (1.8)	8.1 (2.2)
CL_t/F (ml/min/kg)	225 (69)	208 (59)	123 (31)	11.1 (1.6)	9.4 (1.3)	5.3 (2.0)
CL_r (ml/min/kg)	7.6 (2.9)	7.6 (2.5)	3.4 (1.8)	6.5(1.4)	4.9 (2.1)	2.5 (0.9)
C_{12} (ng/ml)	< 5.0	< 5.0	< 5.0	87 (9)	106 (17)	150 (30)

Table 2

The figure and table shows that maximal plasma concentrations of pro-drug occurred less than 1 hour post-dose, and maximal plasma concentrations of active metabolite occurred 3 to 5 hours post-dose. Ro 64-0802 has at least 3-fold higher C_{max}, and more than 10-fold higher AUC compared to its pro-drug Ro 64-0796. These data indicate that the drug is rapidly absorbed and substantially converted to the active metabolite. The data also show that the younger children cleared both pro-drug and active metabolite faster than older children, resulting in lower exposure to the drug for a given mg/kg dose.

(3) The effect of age, body weight or body surface area on PK parameters

For Ro 64-0802, pharmacokinetic parameters change with age, body weight, and body surface area. Regression analyses (Figure 3) show that similar results were obtained for the analysis of pharmacokinetic parameter of Ro 64-0802 against age, weight, and body surface area.



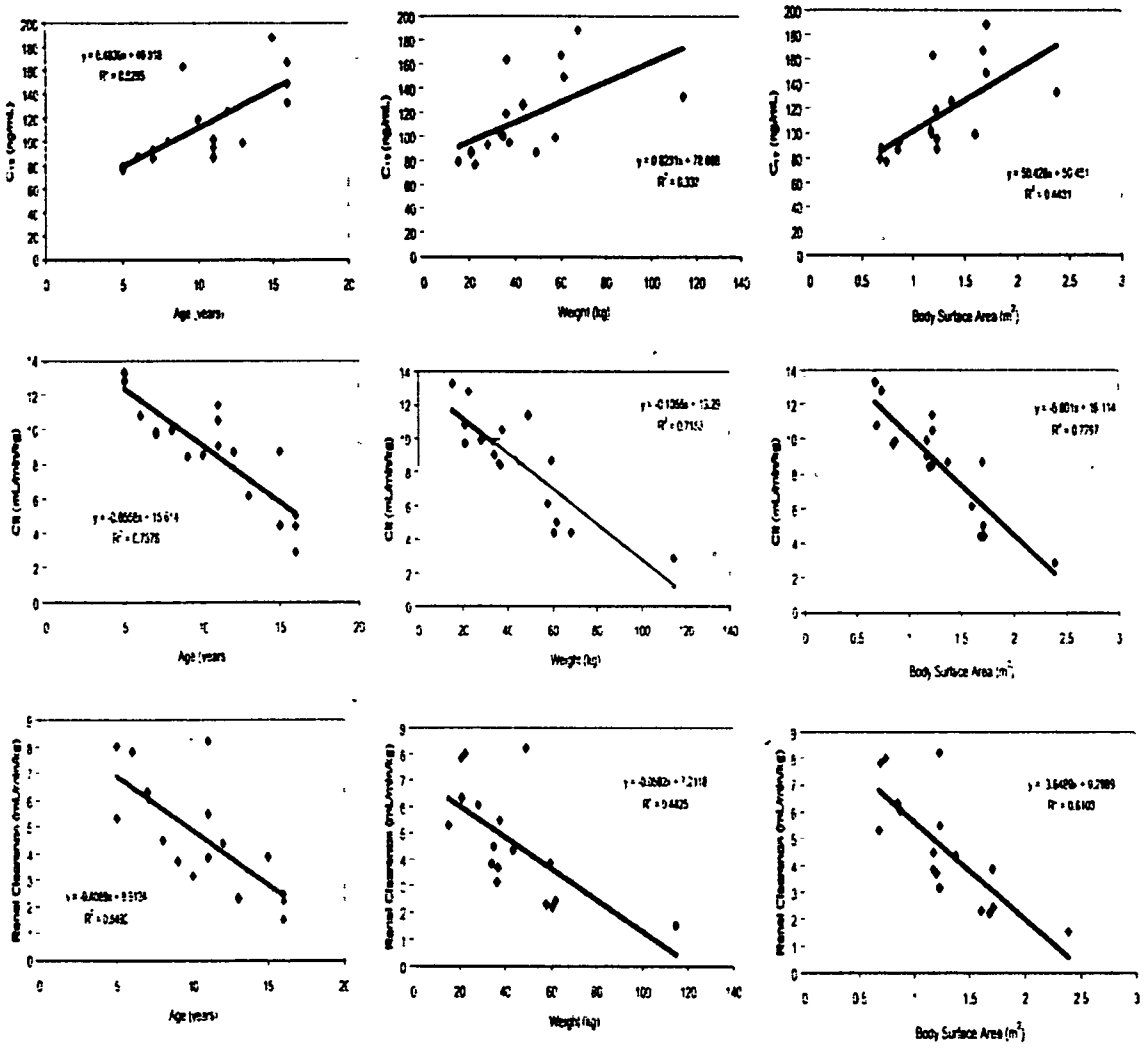


Figure 3

However, it needs to be noted that children included in the study are healthy children within normal range of body weight (±20%) for their age, except for one 16-year old child that weighed 115 kg. For children that are underweight or overweight, no information was provided in this study to indicate that the same drug exposure-age relationships would still hold. The applicant proposed an age-based dosing regimen based on the linear relationship between apparent total clearance and age. For a detailed discussion of dosing regimen, please see the synopsis (Pages 10-13).

(4) Adverse events

Ro 64-0796 was well tolerated by all subjects in this study, with minimal reports of adverse events. The most frequently reported adverse events following test drug were bruising and headache. All adverse events were mild in intensity and were considered to

be unrelated to treatment. There were no serious adverse events and no clinically relevant changes in vital signs or clinical laboratory tests results.

(5) Comparison of exposure in children to adults

The data from the children in this study were compared to data obtained from adults after 75 and 150 mg single doses of Ro 64-0796 in previous studies (Figure 4 and Figure 5).

Ro 64-0796:

The data show that, in children 5 to 13 years of age, C_{max} of Ro 64-0796 following a 2 mg/kg dose was similar to that of a 75 mg (1 mg/kg) dose in adults, and AUC was intermediate between that of a 75 and 150 mg (2 mg/kg) dose in adults. In children 13 to 18 years of age, C_{max} was similar to that of a 75 mg dose in adults, and AUC was comparable to that of a 150 mg dose in adults. In all three groups of children, half-life was similar to that of a 75 mg dose in adults. Higher clearance was observed in children aged 5 to 13 years compared to that in adults.

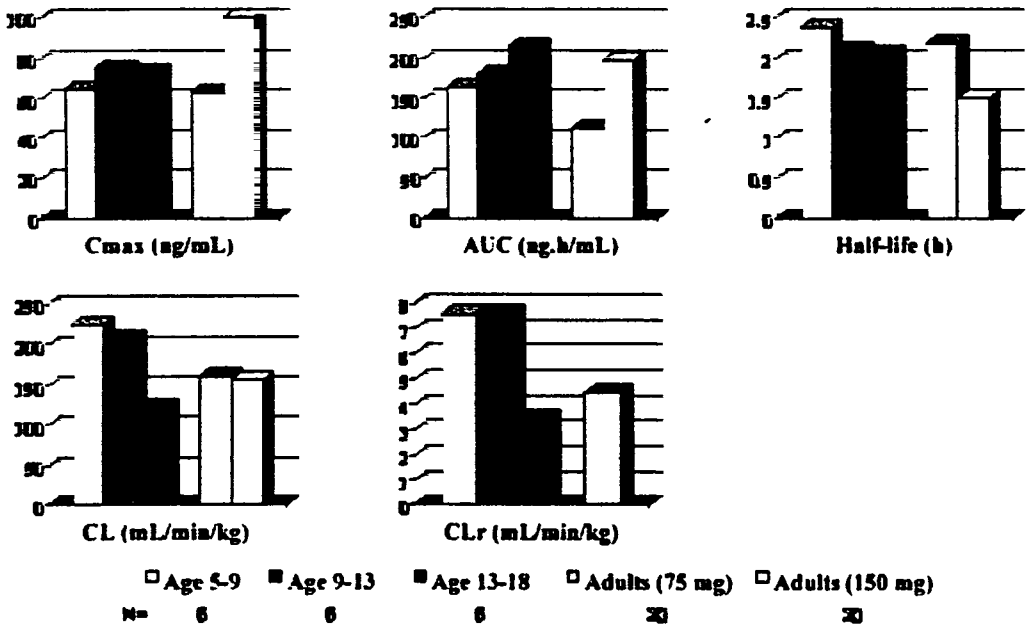


Figure 4. Comparison of Pharmacokinetic parameters of Ro 64-0796 in children and adults

Ro 64-0802:

The data show that, in children 5 to 9 years of age, exposure to Ro 64-0802 following a 2 mg/kg dose was similar to that of a 75 mg (1 mg/kg) dose in adults. In children 9 to 13 years of age, exposure was intermediate between that of a 75 and 150 mg dose in adults. In children 13 to 18 years of age, exposure was similar to a 150 mg (2

mg/kg) dose in adults. In all three groups of children, plasma levels 12 hours after dosing were within the range of values observed 12 hours after a single 75 or 150 mg dose in adults. There is clear trend that clearance decreased with increasing age in children, and approached the level in adults after 13 years old (adolescents).

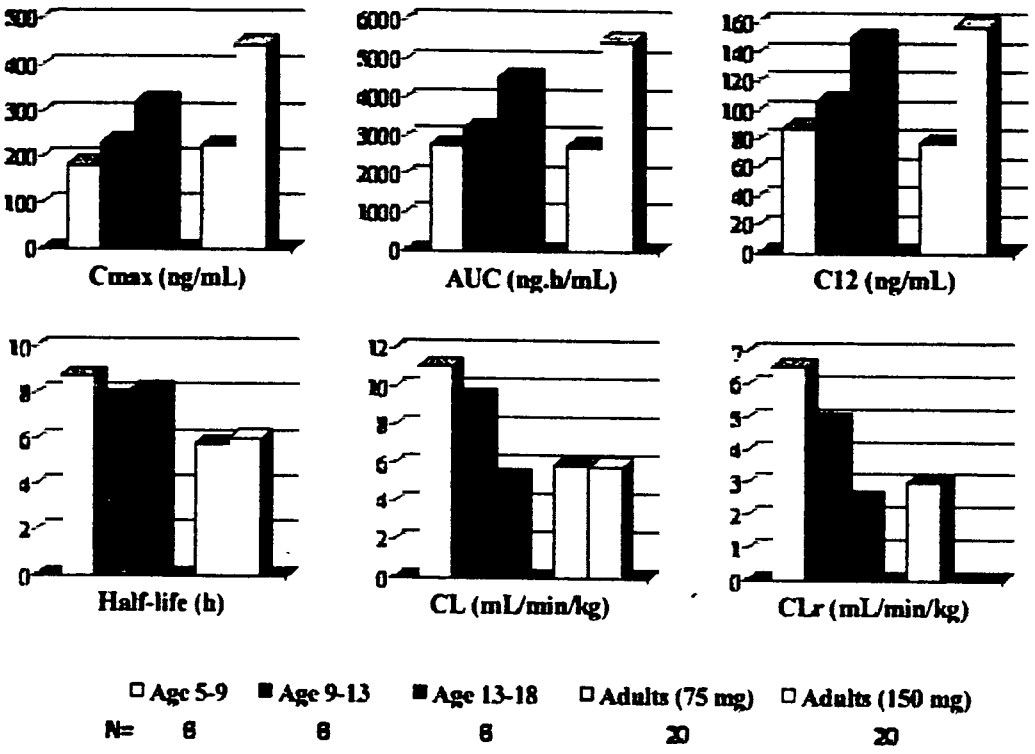


Figure 5. Comparison of Pharmacokinetic parameters of Ro 64-0802 in children and adults

(6) Food effect

The study was conducted under fed conditions, and the food effect was not studied for oral suspensions. However, we do not expect the food effect will be clinically significant. The previous study for the current market capsule formulation (NP 15729) showed that food reduced the rate of absorption but not the extent of absorption of oseltamivir based on Ro 64-0802 concentrations. However, based on Ro 64-0796 concentrations, food decreased the rate of absorption but increased the extent of absorption. However, the effect is not expected to be clinically significant. The approved dosing regimen for capsules is with or without food.

Conclusions: Exposure after a single oral 2 mg/kg dose of Ro 64-0796 in children is less than in adults given comparable doses, due to more rapid drug clearance of both prodrug and active metabolite in children. With advancing age, the difference in clearance between children and adults became less, such that the clearance in children over 13 years of age was similar to that in adults.

A Double-blind, Randomized, Stratified, Placebo-controlled Study of Ro 64-0796 (also known as GS 4104) in the Treatment of Children with Influenza
(Protocol WV15758, Volumes 36-37)

Background: This is a pivotal phase III clinical study in children with influenza.

Objective:

1. To investigate the effect of treatment with Ro 64-0796 in children with influenza
2. To investigate the safety and tolerability of Ro 64-0796 in children with influenza
3. To investigate the effect of treatment with Ro 64-0796 on medical and other health care resources associated with influenza and its complications.
4. To investigate the effect of treatment with Ro 64-0796 on viral activity in children with influenza.
5. To obtain information on plasma concentrations of Ro 64-0796 and Ro 64-0802 during treatment of pediatric subjects with influenza and thereby characterize any pharmacokinetic differences between this population and adults.

Subjects: 698 male and female subjects aged between 1 and 12 with influenza-like-illness.

Study design: This was a multiple center (70 centers in the United States and 10 centers in Canada), double-blind, randomized, placebo-controlled study stratified for the presence or absence of acute otitis media at baseline. Patients were assigned to one of two groups:

Treatment A: 2 mg/kg of Ro 64-0796 BID for 5 days
Treatment B: Matching placebo BID for 5 days

Plasma concentrations of Ro 64-0796 and Ro 64-0802 were collected from 5 patients for evaluation of concentration vs. time profile. These patients had 8 blood samples at pre-dose, and at 1, 2, 3, 4, 6, 8, and 12 hr post-dose (profile day). If the profile day was on treatment day 1 or 2, the patient was to provide an additional pre-dose sample during a later clinic or home visit. Standard pharmacokinetic parameters were computed for this group. Sparse sampling was done for a larger number of subjects. Sparse samples were collected as Samples 1, 2, and 3. Samples 1 and 2 (trough concentrations) were collected after at least 24 hours of dosing and immediately prior to a scheduled dose of study medication. Sample 3 (maximal plasma concentration) was to be collected 2 to 4 hours after Sample 1 or Sample 2.

Formulations: Dry powder was reconstituted with water. Two batches were used:
Ro 64-0796/V20-01 ([redacted]); batch no. G HK 0180/05
Ro 64-0796/V20-01 ([redacted]); batch no. G HK 0180/06

Analytical methodology: Plasma and urine samples were assayed for concentrations of Ro 64-0796 and its active metabolite Ro 64-0802 by an HPLC/MS/MS analytical method.

Pharmacokinetic data analysis: Pharmacokinetic parameters were estimated by noncompartmental methods.

Pharmacokinetic results and discussion:

Sparse data:

(1) Data handling

Samples 1 and 2 (C_{min}) were collected over wide time intervals after dosing (2-36 hr), which deviated from the protocol where the scheduled trough sampling time was to be 12 hours after the last dose. For sample 3 (approximate peak), the concentration ranges of active metabolite were wide and included some low values (Table 1). Overall, the active metabolite concentration mean and range of Samples 1, 2 and 3 were not dissimilar, suggesting that these samples resemble random sampling rather than true peaks and troughs. Therefore, the applicant only provided samples 1 and 2 that were collected ≥ 10 and ≤ 14 hours after the last prior dosing and ≥ 48 hours after the first dosing to compute steady-state C_{min} values. If both samples 1 and 2 met the criteria, the two values were averaged to obtain the individual's steady-state C_{min} values. In addition, prodrug in Sample 2 for Patient 1195 was excluded due to extremely high value ([redacted], and active metabolite in Samples 1 and 2 for Patient 2172 were excluded since both values were below the quantitation limit. Samples from 36 subjects fulfilled above criteria, and were used for analysis.

Sample 1 (n=79)		Sample 2 (n=53)		Sample 3 (n=66)	
Mean (ng/ml)	Range (ng/ml)	Mean (ng/ml)	Range (ng/ml)	Mean (ng/ml)	Range (ng/ml)
157	[redacted]	207	[redacted]	202	[redacted]

Table 1: Ro 64-0802 plasma concentrations of sparse pharmacokinetic samples

(2) Pharmacokinetics

Steady state C_{min} values for Ro 64-0796 and Ro 64-0802 by three age groups 1-4, 5-8 and 9-12 years old are summarized in Table 2.

Age Group	1-4	5-8	9-12
Number of subjects	12	16	8
Mean Ro 64-0796 C_{min} (ng/ml)	10.4	13.1	9.7
SD	8.7	14.2	10.5
%CV	83.4	108.0	108.8
range	[redacted]	[redacted]	[redacted]
Mean Ro 64-0802 C_{min} (ng/ml)	214	220	268
SD	73.2	73.8	74.5
%CV	34.2	33.6	27.8
range	[redacted]	[redacted]	[redacted]

Table 2

Figure 1 shows the plots of individual C_{min} values for Ro 64-0796 and Ro 64-0802 versus age and body weight. Data show that there are no relationships between the mean steady state C_{min} values of Ro 64-0796 and Ro 64-0802 and age or body weight

(Table 2 and Figure 1). The previous single dose study in healthy children (Study NP 15826) shows that C_{min} values are increased with age or body weight. The discrepancy between this study and the single dose study is due to great inter-subject variability associated with this study.

Figure 1

Full pharmacokinetic analysis at selected sites:

(1) Data handling

Concentration versus time profiles were analyzed from only 5 out of 698 pediatric patients. Four of these five patients were sampled during Day 1 or Day 2 of treatment. A previous study (NP 15525) in healthy adults population indicated that steady-state conditions were reached after 3 to 5 days of repeat dosing, and AUC was increased by 60 to 80% following 7 days of repeat dosing for Ro 64-0802. The available information from the previous studies does not include trough concentration on Day 2 (Study NP1552). Therefore, it is not known whether steady state was achieved on Day 2. In the original submission, the applicant adjusted concentrations to steady state using a sample trough concentration (Sample 12) collected later in the study (presumably after steady state was attained). The adjustment was done by using the elimination rate constant (K_{el}, computed from the profile data) and the Sample 12 concentration. The difference

Comparison of pharmacokinetic parameters between studies and age groups:

(1) General

The PK parameters of Ro 64-0802 in Groups B and C (Table 3) are comparable to previous single oral dose of 2 mg/kg in healthy children within the same age range, with 30%-60% increase of Cmax (Ages 5-9 and 10-13, Study NP 15826, Table 4). Compared to adults in challenge study (NP 15717) and Phase III studies after 75 mg BID of Ro 64-0796, total clearance of Ro 64-0802 is comparable in children aged 13-18 years (Study NP 15826), and higher in children less than 13 years old (Studies WV 15758 and NP 15826). Compared to older children, the child of age 3 years has slower absorption with a prolonged elimination half-life. Prolonged elimination half-life was also seen for Ro 64-0796 for this patient. Since PK data available for children aged less than 5 years are from only one child, no conclusion can be drawn for this age group.

For Ro 64-0796, C_{max} is lower and t_{max} is longer in this study compared to Study NP 15826. However, since Ro 64-0796 is the prodrug, the slight difference in parameter estimation is acceptable.

(2) C_{min}

As we mentioned previously, sparse data in this study did not show the expected relationship between the mean steady state C_{min} values of Ro 64-0796 and Ro 64-0802 and age or body weight (Table 2 and Figure 1). However, the previous single dose study in healthy children (Study NP 15826) shows that C_{min} values are increased with age or body weight. The trough concentrations obtained after Day 3 from the five patients in the selected site also show a strong correlation with age or body weight, with a steeper increase with age or body weight compared to single dose data (Figure 3). Figure 3 also shows that trough concentration at steady state is normally higher than non-steady state trough concentration, ranging from 1- to 5-fold.

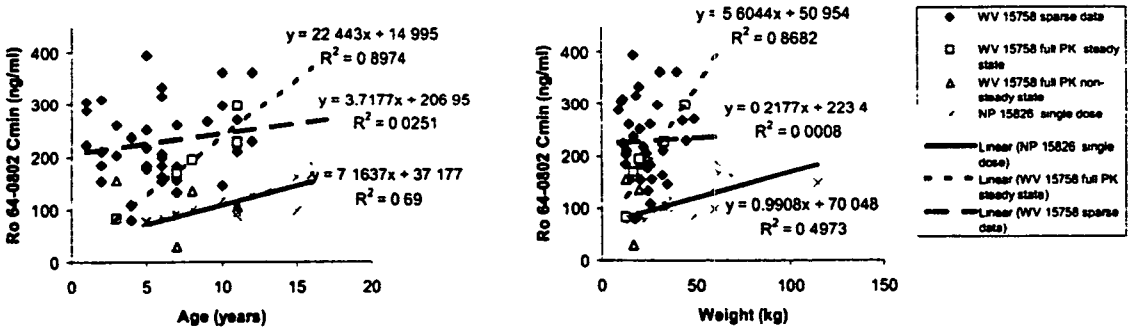


Figure 3

Parameter	Ro 64-0796 [c] (Study NP 15826)			Ro 64-0802 [c] (Study NP 15826)			Ro 64-0802 (Study NP 15717)		Ro 64-0802 [a,b] (Phase III studies)
Age	5-9	9-13	13-18	5-9	9-13	13-18	Adults Day 1	Day 5/7 (s.s)	Adults Day 5/7 (s.s)
N	6	6	6	6	6	6	20	20	
C_{max} (ng/ml)									
Mean	64	75	73	183	231	319	225	348	398
SD	14	25	19	36	46	76	49	64	103
95% CI	53-79	55-95	58-88	154-212	194-268	258-380	204-246	320-76	357-439
t_{max} (hr)									
Mean	0.8	0.7	0.8	3.7	3.7	4.3	3 76	3.03	3.05
SD	0.3	0.3	0.3	0.5	0.5	0.8	1.0	0.7	1.0
95% CI	0.6-1.0	0.5-0.9	0.6-1.0	3.3-4.1	3.3-4.1	3.7-4.9	3.3-4.2	2.7-3.3	2.6-3.5
$AUC_{0-\infty}$ (ng.hr/ml)									
Mean	163	180	215	2746	3208	4534	2227	2719 [d]	3450 [d]
SD	41	60	31	368	394	929	410	538	1018
95% CI	130-196	132-228	190-240	2452-3040	2893-3523	3791-5277	2047-2406	2483-2955	3043-3857
$t_{½}$ (hr)									
Mean	2.4	2.1	2.1	8.8	7.8	8.1	5.49	5.79	7.94
SD	0.8	0.6	0.5	2.0	1.8	2.2	1.4	1.3	2.9
95% CI	1.8-3.0	1.6-2.6	1.7-2.5	7.2-10.4	6.4-9.2	6.3-9.9	4.9-6.1	5.2-6.3	6.8-9.1
CL/F (ml/min/kg)									
Mean	225	208	123	11.1	9.4	5.3	6.0 [e]	6.6 [f]	5.2 [f]
SD	69	59	31	1.6	1.3	2.0	-	-	-
95% CI	170-280	161-255	98-148	9.8-12.4	8.4-10.4	3.7-6.9	-	-	-
CL_r (ml/min/kg)									
Mean	7.6	7.6	3.4	6.5	4.9	2.5	3 [e]	-	3.1 [f]
SD	2.9	2.5	1.8	1.4	2.1	0.9	-	-	-
95% CI	6.4-8.8	6.6-8.6	2.7-4.1	5.9-7.1	4.0-5.8	2.1-2.9	-	-	-
C_{12} (ng/ml)									
Mean	< 5.0	< 5.0	< 5.0	87	106	150	75 [e]	138	175
SD	-	-	-	9	17	30		30	57.75
95% CI	-	-	-	80-94	92-120	126-174		125-151	152-198

Table 4. Pharmacokinetic parameters of Ro 64-0796 and Ro 64-0802

[a] Protocols WV 15670, WV15671, WV15730
[b] 75 mg BID
[c] 2mg/kg single dose
[d] AUC_{0-12}
[e] Estimated from the graph sent by the applicant
[f] Estimated based on the reported clearance normalized to standard adult's body weight 70 kg.

Conclusion:

The [redacted] dosing regimens proposed by the applicant are not acceptable. We recommend alternative weight-based dosing regimens to insure that underweight children will not get overdosed. The recommended dosing regimens for children 12 months and older are:

<= 15 kg	or	<= 33 lb	30 mg twice daily
> 15 kg to 23 kg	or	> 33 lb to [redacted]	45 mg twice daily
> 23 kg to 40 kg	or	> [redacted]	60 mg twice daily
> 40 kg	or	> [redacted]	75 mg twice daily

For detailed dosing regimens discussion, please refer the synopsis (Pages 10-13). The applicant should collect more PK data, especially for children under 5 years of age, from prophylaxis study in children.

/s/

Jenny H. Zheng
12/14/00 05:36:25 PM
BIOPHARMACEUTICS

Kellie Reynolds
12/20/00 08:51:51 AM
BIOPHARMACEUTICS