CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-109 (17-970/S-050)

Clinical Pharmacology and Biopharmaceutics Review

WORD VERSION

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-109	Submission Date(s): 03-01-02
Brand Name	Nolvadex™
Generic Name	Tamoxifen Citrate
Reviewer	Xiaoxiong "Jim" Wei, M.D., Ph.D.
Co-Reviewer	Sang Chung, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPE II
Clinical division	HFD-510
Sponsor	AstraZeneca
Submission Type	Priority
Formulation; Strength(s)	Tablets, 20 mg
Indication	McCune Albright Syndrome
Purpose of supplement	Pediatric exclusivity

7.2.02 JW

EXECUTIVE SUMMARY

Submission

AstraZeneca has submitted a pediatric study report (6157US/0013) for the use of tamoxifen for the treatment of pediatric female patients with McCune Albright Syndrome (MAS) in order to obtain a Pediatric Exclusivity. The primary objective of study was to evaluate the safety, efficacy and pharmacokinetics of tamoxifen 20 mg daily in 28 female children (less than 10 years of age). These patients were diagnosed with classic or atypical McCune-Albright Syndrome. MAS is a rare disorder manifested by progressive precocious puberty, episodes of vaginal bleeding, and/or significantly advanced bone age (at least 12 months beyond chronological age). The study was an open label, uncontrolled multi-center trial.

Tamoxifen is a nonsteroidal and potent antiestrogenic agent. N-desmethyl tamoxifen is the major metabolite of tamoxifen. The biological activity of N-desmethyl tamoxifen appears to be similar to that of tamoxifen. Tamoxifen has been marketed for the treatment and prevention of breast cancers.

The Agency issued a Pediatric Written Request on April 5, 2000 to request a population pharmacokinetic study conducted during the clinical trial. There were 28 patients enrolled in the study. Each patient received tamoxifen 20 mg once daily for up to 12 months. Based on the Agency's Written Request, the sponsor collected four sparse samples from each patient. The sponsor collected the first sample between 0 to 3 hours and the second sample between 3 to 24 hours after the first tamoxifen dose and two additional blood samples randomly at anytime after 3 months. The purpose of the population pharmacokinetic analysis was to characterize the pharmacokinetics of tamoxifen and an active metabolite, N-desmethyltamoxifen in these pediatric patients and compare the pharmacokinetics to adult female subjects. To build the structural pharmacokinetic model, pharmacokinetic data was used from previous studies of tamoxifen in female patients with breast cancer.

The final one-compartment population pharmacokinetic model with the first order absorption and elimination described the tamoxifen citrate plasma concentration data in pediatric female patients. Population pharmacokinetic analysis has found that body weight may influence clearance. Clearance (L/hr/kg) in female children was approximately 2.3 fold higher than that in adult female patients with breast cancer. The youngest cohort of pediatric patients (ages 2 to 6 years) had the highest values for clearance, 2.6 fold of that in adult patients. However, because of the small body weight, the exposure to

tamoxifen citrate in the pediatric patients was actually approximately 30% higher for the pediatric patients. Exposure to the active metabolite, N-desmethyltamoxifen, was comparable between the pediatric and adult patients.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed the pharmacokinetics component in this pediatric exclusivity submission and found it acceptable. This recommendation and labeling comments should be sent to the sponsor as appropriate.

However, if the new indication, McCune Albright Syndrome, is not approved by the Agency due to safety concerns, the pharmacokinetic information on pediatric patients should be completely deleted in the label. In addition, the sponsor studied only one dose (20 mg) for the new indication. Therefore, it is recommended that exposure-response relationships be explored for the new indication.

The optional Inter-OCPB Divisions level briefing was held on June 26, 2002 and attendees were Henry Malinowski, John Lazor, John Hunt, Hae-Young Ahn, He Sun, Sam Haidar, Jim Wei, Steven B. Johnson, Sang M. Chung, and Dragos Roman.

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QUESTION BASED REVIEW

Was the population pharmacokinetic model appropriate for pediatric patients?

The data from previous studies, Trials 6157IL/0002 and 6157US/0005 were used to develop the base model. Patients in Trial 6157IL/0002 were randomized to be given two formulations of tamoxifen citrate in a two-way crossover design for a bioequivalence study. Patients in Trial 6157US/0005 were randomized to one of two treatment sequence groups. One group first received a 10-mg tamoxifen citrate tablet twice daily for three months and then for the next three months received a 20-mg tamoxifen citrate tablet once daily. The other group first received a 20-mg tamoxifen citrate tablet once daily and then a 10-mg tamoxifen citrate tablet twice daily. The demographic characteristics in study population was summarized in Table 1.

Table 1. Summary of demographic characteristics by study population

Covariant	6157US/00013 N = 27	6157IL/0002 N = 29	6157US/0005 N = 30
Age(yr)			
Mean (SD)	6.0 (2.5)	59.7 (7.2)	61.5 (8.6)
Median	6.0	59.0	63.0
Range	2 – 10.9	50 – 73	43 – 75
Body weight (kg)			
Mean (SD)	27.2 (9.9)	70.4 (12.0)	71.7 (20.8)
Median	25.7	73.0	65.1
Range	14.1 – 57.8	46 – 96.2	45.3 – 150.5
Sex			
Female	27 (100%)	29 (100%)	30 (100%)
Male	0	0	0
Race			
Caucasian	14 (52%)	29 (100%)	25 (83%)
African American	5 (19%)	0	2 (7%)
Asian	2 (7%)	0	0
Hispanic	5 (19%)	0	3 (10%)
Other	1 (4%)	0	0

Tamoxifen concentration-time profiles in pediatric subjects (6157US/0013) were shown in Figure 1.

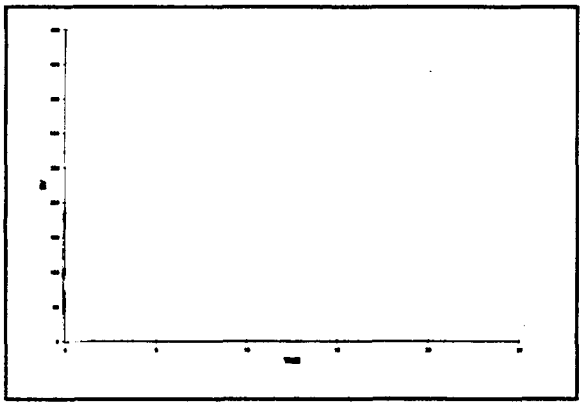


Figure 1. Plasma concentration time profiles after the first dose (red) and after the multiple doses (blue) in pediatric patients

Once an appropriate base pharmacokinetic model had been developed, individual model parameters were generated in NONMEM and relationships between covariates and individual pharmacokinetic parameter were graphically explored. The statistical significance of each covariant-parameter relationship was tested individually in a step-wise parameter addition method in NONMEM. The least significant parameter was then removed from the model. The resulting model is known as the final NONMEM model. The Figure 2 showed the individual population predicted versus observed tamoxifen concentrations from the final model. The final model was evaluated graphically by comparing the individual and population predictions with the observed concentrations. . Typical predicted tamoxifen steady state concentration time profile with 95% confidence bands for an adult subject and observed pediatric steady state concentrations were shown in Figure 3.

Figure 2.

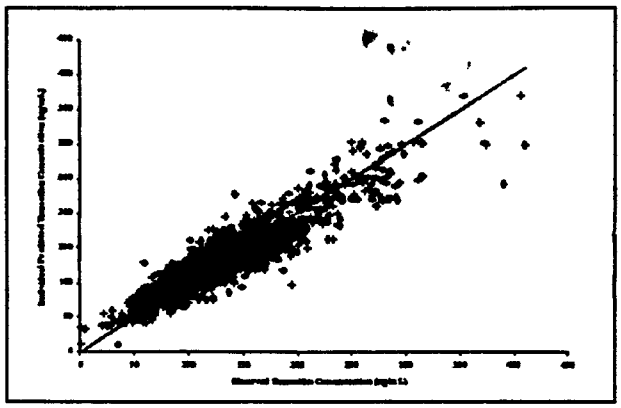


Figure 3.

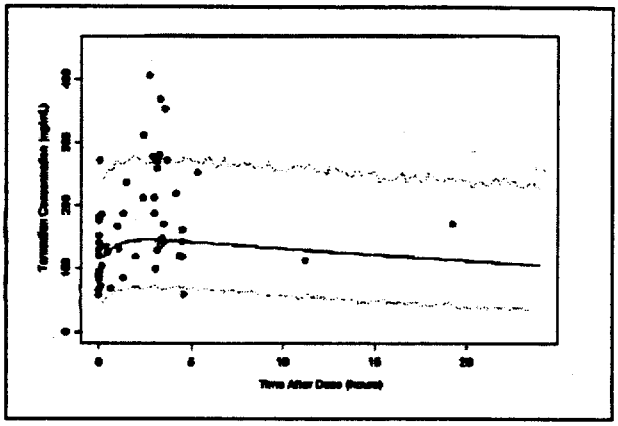
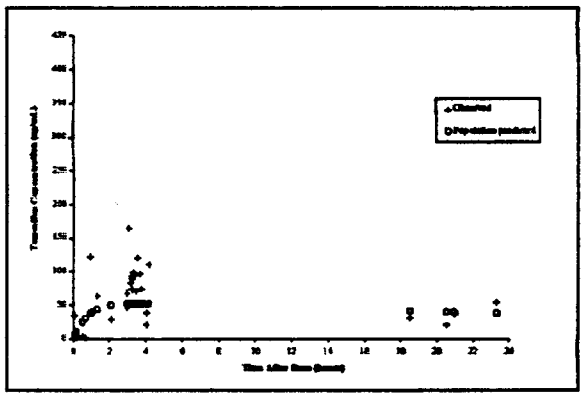
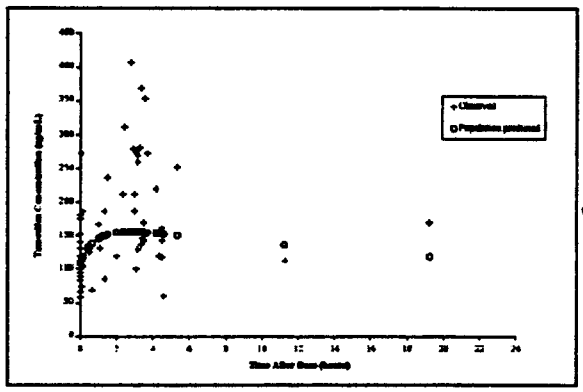


Figure 4 showed that population predicted and observed tamoxifen concentrations versus time after dose for the pediatric subjects (left panel :single dose data and right panel: steady state data).

Figure 4a.



4b.



Reviewer's comment:
The reviewers agree with the sponsor that population pharmacokinetic model adequately described pharmacokinetic profiles in pediatric patients.

What are the main pharmacokinetic parameters in pediatric patients? Is Clearance of tamoxifen in pediatric patients lower than that in adult female patients?

In the original submission, the sponsor described the tamoxifen clearance in female patients was approximately 22% lower than that in adult female breast cancer patients (Group 1). The youngest cohort of pediatric patients (ages 2 to 6 years, Group 0)) had the lowest values for clearance, with a mean value of 4.84 L/hr (range: [redacted] L/hr) (31% lower than adults) (Figure 5).

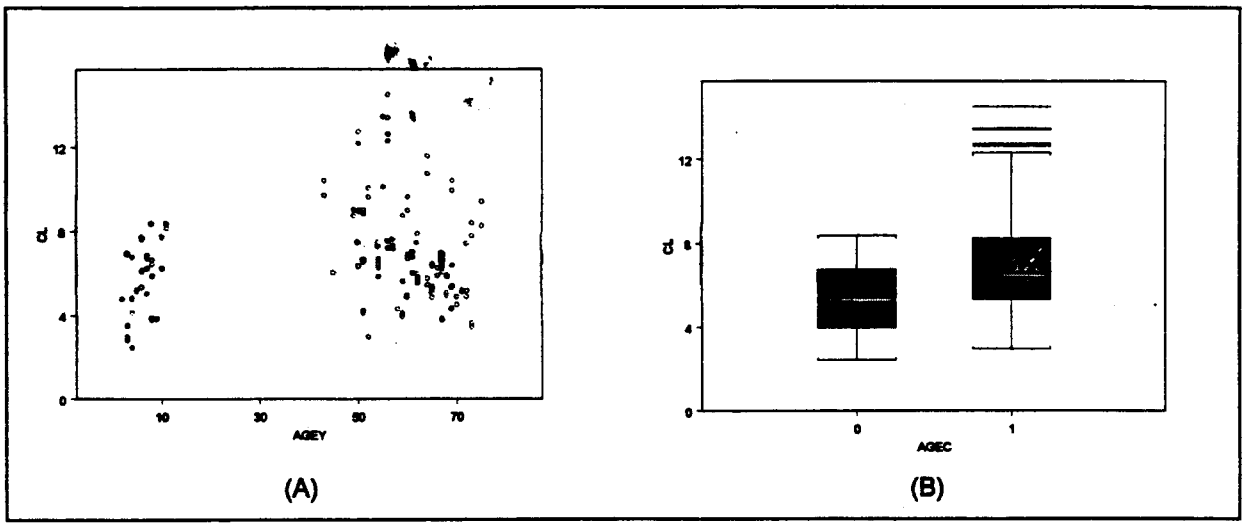


Figure 5. Relationship between age (year) and clearance (L/hr) (A) and age (0;pediatric, 1;adult) and clearance (L/hr) (B). Panel (B) is a Box-and-Whisker plot. In the plot, the interior horizontal line, box, and Whiskers represented the sample median, the interquartile distance (IQD), and a distance of 1.5*IQD, respectively. Data points falling outside the Whiskers may be outliners.

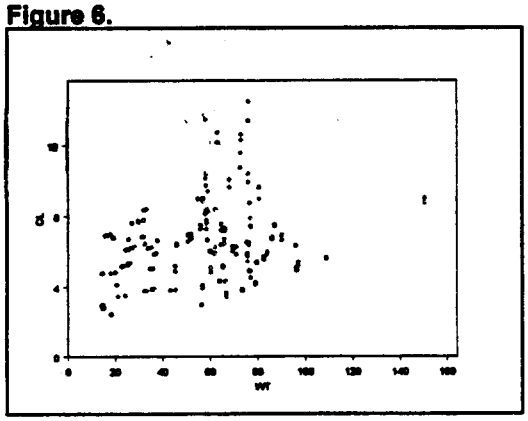
The volume of distribution in female children was approximately 40% lower than that in the breast cancer patients. Model predicted mean values for volume were 261 L (range: — L) for the pediatric patients and 438 L (range: — L) for the adult patients. Exposure to tamoxifen was approximately 30% higher for the pediatric patients compared to the female breast cancer patients. Model predicted values for steady state Cmax and AUC (0-tau) were 187 ng/mL (range: — ng/mL) and 4109 ng.hr/mL.

Exposure to the major active metabolite, N-desmethyltamoxifen, was calculated from the individual mean metabolite to parent concentration ratio and tamoxifen pharmacokinetic parameters. For the pediatric subjects, mean estimates for Cmax and AUC (0-tau) for N-desmethyltamoxifen were 320 ng/mL (range: — ng/mL) and 7420 ng.hr/mL (. — ng.hr/mL), respectively. Exposure to the active metabolite, N-desmethyltamoxifen, was comparable between the pediatric and adult patients.

Reviewer's comments:

The pharmacokinetic parameters in the submission were not body weight adjusted. The reviewers analyzed the relationship between body weight and clearance (Figure 6).

Figure 6.



The relationship between body weight and tamoxifen apparent clearance (L/hr/kg) with subcategory in pediatric subjects is presented in Figure 7 [AGEC –1 (2-6 years), 0 (7-11 years) and 1 (adult)].

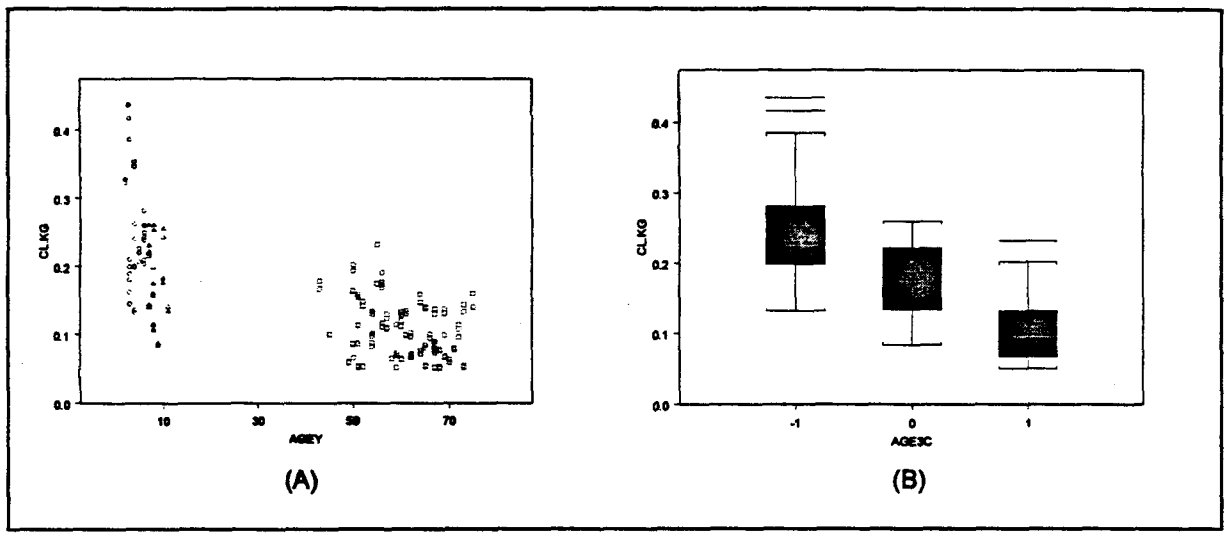


Figure 7 Relationship between age (year) and clearance (L/hr/kg) in panel (A) and age (-1; 2-6 years, 0; 7-11 years, and 1; adult) and clearance (L/hr/kg) in the panel (B)

The reviewers communicated with the sponsor about this issue and the sponsor made a change for clearance calculation by body weight adjustment, which has incorporated into the Table 2.

Table 2.

Population pharmacokinetic Parameters Mean (SD)	Pediatric Subjects (2 – 6 yr) N = 14	Pediatric Subjects (7 – 10.9 yr) N = 13	All Pediatric Subjects (2 – 10.9 yr) N = 27	Adult Subjects (43 – 75 yr) N = 59
Parent drug				
CL/F/kg (L/hr/kg)	0.262 (0.098)	0.192 (0.068)	0.227(0.090)	0.102(0.040)
V/F (L)	247(55.4)	277 (65.4)	261 (61.2)	438 (119)
C_{ssmax} (ng/ml	209 (73.0)	163 (73.0)	187 (64.4)	141 (44.7)
AUC_{tss} (ng/mL)	4630 (1710)	3550 (1050)	4110 (1510)	3180 (1070)
t_{max} (hr)	8.40 (1.32)	7.71 (0.744)	8.07 (1.12)	8.26 (1.41)
ka (hr^{-1})	1.18 (0.28)	1.24 (0.12)	1.21 (0.21)	1.27 (0.24)
$t_{1/2}$ (hr)	38.7 (14.7)	33.1 (9.07)	36.0 (12.4)	47.4 (17.3)
N-desmethyltamoxifen				
C_{ssmax} (ng/mL)	359 (125)	319 (108)	340 (117)	339 (112)
AUC ($_{t-tau}$) (ng.hr/mL)	7910 (2681)	6893 (2336)	7420 (2526)	7606 (2590)

Is there any correlation between low efficacy and high clearance for pediatric female patients with McCune-Albright Syndrome?

Dr. Drago Roman, the reviewing medical officer, raised an issue to clinical pharmacology reviewers that 5 younger patients did not respond at all to tamoxifen therapy in terms of the reduction of growth rate, one of clinical endpoints. Those patients were 3.14, 4.8, 3.1, 3.4, and 3.4 years old, respectively. Is there any correlation between low clinical efficacy and pharmacokinetic features?

Although on average the younger patients tended to have higher clearance, only one of these 5 younger patients actually fell into the higher clearance range. Four other patients had CL/F=0.193, which was close to the medium clearance value for older children (CL/F=0.192). Figure 8 shows relationship between body weight (BW) and apparent clearance (CL/KG) of tamoxifen in pediatric subjects. Red circles represent plasma concentration from subjects showed low efficacy (growth rate). Figure 9 shows plasma concentration (DV, dependent variable)) and time profile of tamoxifen.

Figure 8.

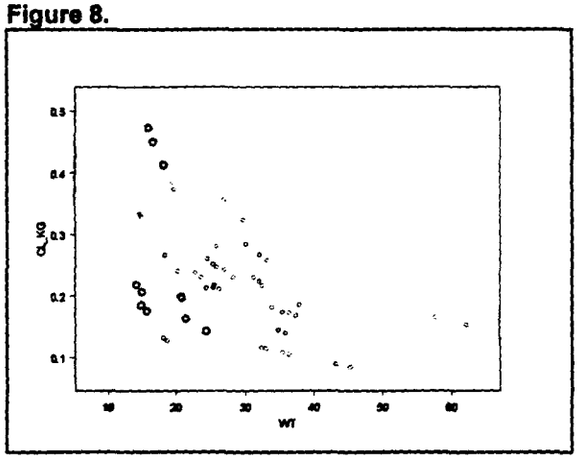
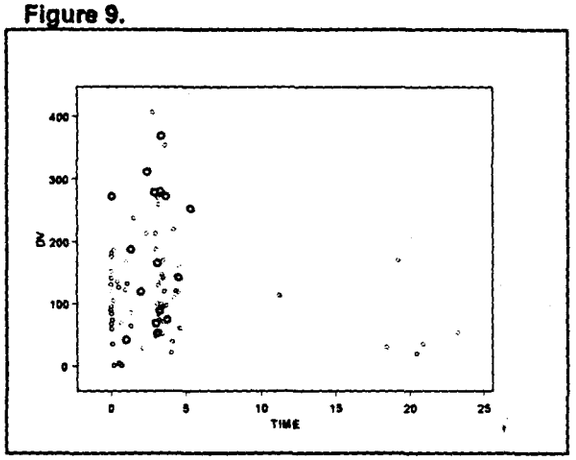


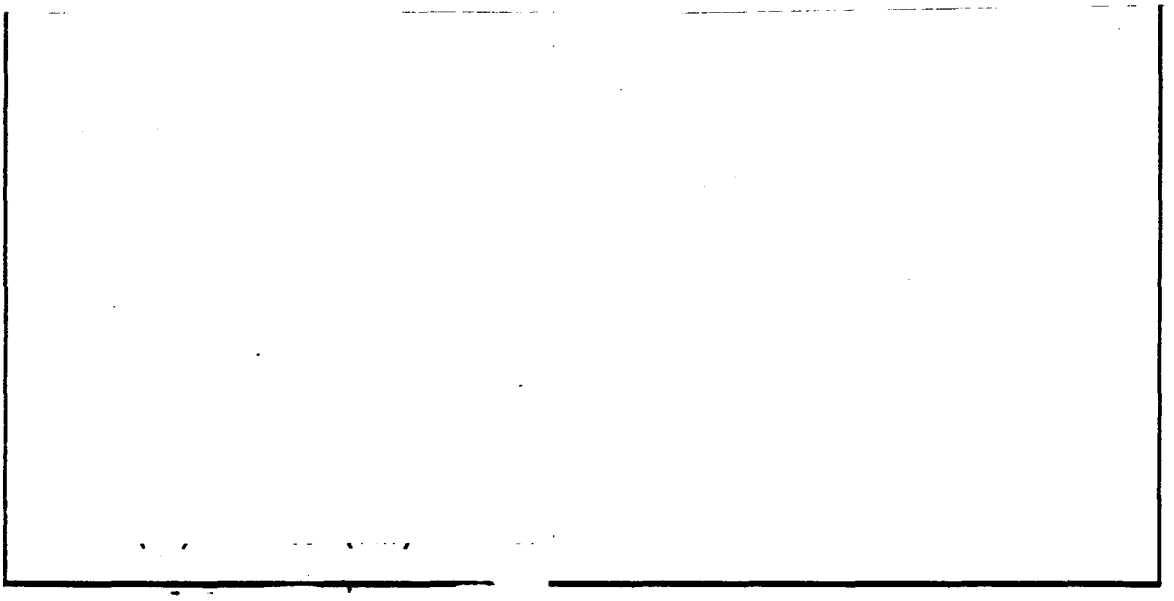
Figure 9.



From the above analysis, we may not be able conclude that there is any correlation between the failed response in the reduction of growth rate and clearance of tamoxifen. Some other factors may contribute to the failure. This analysis has been conveyed to the medical reviewer.

LABELING COMMENTS:

(~~Strikeout text~~ should be removed from labeling; Underlined text should be added to labeling; = indicates an explanation only and is not intended to be included in the labeling)



1 pages redacted from this section of the approval package consisted of draft labeling

SUMMARY

The primary objective of study 6157US/0013 was to evaluate the safety and efficacy of tamoxifen 20 mg daily in female children (less than 10 years of age) with McCune-Albright Syndrome (MAS). The purpose of the current population pharmacokinetic analysis was to characterize the pharmacokinetics of tamoxifen and an active metabolite, N-desmethyltamoxifen, in these pediatric subjects and compare the pharmacokinetics to adult female subjects.

Study 6157US/0013 was an open-label, multi-center trial in 28 female patients (age 10 years or less) who have classic or atypical McCune-Albright Syndrome with progressive precocious puberty. There were 28 patients who enrolled in the study. Each patient received tamoxifen 20 mg once daily for up to 12 months. Two blood samples were collected during Month 1; the first sample was collected between 0 to 3 hours after the first tamoxifen dose, the second sample was collected between 3 to 24 hours after the first tamoxifen dose. Two additional blood samples were collected randomly at anytime after 3 months on tamoxifen therapy.

To compare the pharmacokinetics of tamoxifen for pediatric subjects with that for the adult female subjects and to determine the structural pharmacokinetic model, the rich data from Studies 6157IL/0002 and 6157US/0005;0001 which included subjects with breast cancer were included in the analysis. Subjects in Study 6157IL/0002 were randomized to be given 2 formulations of tamoxifen in a two-way crossover design: the ROW (rest of world) sales formulation or the US sales formulation, both taken orally once daily for three months. The treatment order was determined by a randomization code. Blood samples were collected at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 13, 16, 20 and 24 hours after dosing. Subjects in study 6157US/0005;0001 were randomized to one of two treatment sequence groups. One group first received a 10 mg ZD6157 (tamoxifen citrate, NOLVADEX™) tablet twice daily for three months and then for the next three months received a 20 mg NOLVADEX-D tablet once daily. The other group first received 20 mg NOLVADEX-D tablet once daily and then 10 mg ZD6157 (tamoxifen citrate, NOLVADEX™) tablet twice daily. Blood samples were collected within 1 hour before dosing and at 1, 2, 3, 5, 7, 12, 13, 14, 15, 17, 19, and 24 hours after the initial dose. For those patients who received 10 mg ZD6157 (tamoxifen citrate, NOLVADEX™), the second 10 mg dose was given 12 hours after the initial dose.

The pharmacokinetics of tamoxifen were analyzed using population pharmacokinetics analysis techniques. The analysis evaluated demographic (age, weight, and race) variables, as well as the metabolite to parent ratio, that may contribute to differences in the pharmacokinetic profiles between female children with MAS and adult female breast cancer patients.

Two models were fit to the tamoxifen concentration-time data: one- and two-compartment models with first order absorption and first order elimination. Review of the minimum objective function (OF), diagnostic plots, and parameter estimates showed that the one-compartment model provided the best fit to the data. The one-compartment model was parameterized in terms of CL/F, V/F, and ka. Random residual error was expressed using the combined additive and proportional model. The effect of the demographic variables and the metabolite to parent concentration ratio on the pharmacokinetic parameters was evaluated.

The final one-compartment population pharmacokinetic model with first order absorption and elimination adequately described the tamoxifen plasma concentration data. Body weight and the

individual mean metabolite to parent concentration ratio were found to influence clearance. For the pediatric subjects with a median individual mean ratio of 1.88, values for clearance increased by 23% over the range of observed body weights (14.1 to 57.8 kg). Similarly, for a median body weight of 26 kg, values for clearance increased by 36% over the range of observed pediatric individual mean ratios (0.78 to 2.86). Body weight was found to influence volume of distribution. For the pediatric subjects with body weights of 14 to 58 kg, values for volume of distribution increased by 40%.

According to the final model, the disposition of tamoxifen in pediatric girls between 2 to 10.9 years with MAS was described by a mean clearance of 5.43 L/hr (range: — L/hr) and a mean volume of distribution of 261 L (range: — L). Model predicted mean individual peak tamoxifen concentrations were 187 ng/mL (range: — ng/mL) and occurred approximately 8 hours after dosing (range: —). The mean area under the tamoxifen concentration time curve over the 24-hour dosing interval was 4109 ng.hr/mL (range: — ng.hr/mL). The mean steady state elimination half-life was approximately 36 hours (range: —).

Exposure to the major active metabolite, N-desmethyltamoxifen, was calculated from the individual mean metabolite to parent concentration ratio and tamoxifen pharmacokinetic parameters. For the pediatric subjects, mean estimates for C_{max} and $AUC_{(0\text{-}tau)}$ for N-desmethyltamoxifen were 340 ng/mL (range: — ng/mL) and 7420 ng.hr/mL (— ng.hr/mL), respectively.

For the comparison of pediatric and adult tamoxifen pharmacokinetics, the pediatric patients were split into two age cohorts to determine if the youngest subjects had a higher exposure to tamoxifen. Clearance in female children was approximately 22% lower than in adult female breast cancer patients. The youngest cohort of pediatric patients (ages 2 to 6 years) had the lowest values for clearance, with a mean value of 4.84 L/hr (range: — L/hr) (31% lower than adults).

The volume of distribution in female children was approximately 40% lower than in the breast cancer patients. Model predicted mean values for volume were 261 L (range: — L) for the pediatric patients and 438 L (range: — L) for the adult patients.

Exposure to tamoxifen was approximately 30% higher for the pediatric patients compared to the female breast cancer patients. Model predicted values for steady state C_{max} and $AUC_{(0\text{-}tau)}$ were 187 ng/mL (range: — ng/mL) and 4109 ng.hr/mL (range: — ng.hr/mL) for the pediatric patients and 141 ng/mL (range: — ng/mL) and 3181 ng.hr/mL (range: — ng.hr/mL) for the breast cancer patients, respectively. The youngest cohort of pediatric patients (2-6 years old), had the highest exposure to tamoxifen, with mean C_{max} and $AUC_{(0\text{-}tau)}$ values of 209 ng/mL (range: — ng/mL) and 4629 ng.hr/mL (range: — ng.hr/mL), respectively. Compared to adult breast cancer patients, this cohort of pediatric patients had approximately 50% increase in the exposure to tamoxifen.

The mean steady state metabolite to parent ratio was lower in the pediatric patients compared to the adult breast cancer patients with mean values of 1.85 (range: —) and 2.47 (range: —), respectively. As a result of the lower mean ratio, exposure to the active metabolite, N-desmethyltamoxifen, was comparable between the pediatric and adult patients. The range of adult C_{max} and $AUC_{(0\text{-}tau)}$ values estimated in this analysis was similar to the values previously reported (Report No. 6157US/0005;0001 1992, Report No. 6157IL/0002 1999).

Overall, there was approximately 30% increase in the exposure to tamoxifen for the pediatric girls compared to female adult breast cancer patients. This increase in exposure is, however, not considered to be clinically important since tamoxifen has been used in children in doses as high as 200 mg/m^2/day without significant side effects (Metzger and Kerrigan 1994; Maddalozzo et al 1993; Tolis et al 1994; Pollack et al 1997; Kucukaydin et al 1994). Furthermore, doses of up to 160 mg per day have been given for many months to women with malignant gliomas, without safety problems (Couldwell 1996).

Summary Table 1 Summary statistics of the individual model predicted pharmacokinetic parameters from the final model

Population Pharmacokinetic Parameters	Pediatric Subjects (2 – 6 yr) N = 14	Pediatric Subjects (7 – 10.9 yr) N = 13	All Pediatric Subjects (2 – 10.9 yr) N = 27	Adult Subjects (43 – 75 yr) N = 59
CL/F (L/hr)				
Mean (SD)	4.84 (1.60)	6.05 (1.57)	5.43 (1.67)	7.02 (2.47)
Median	4.77	6.20	5.31	6.53
Range		—		
V/F (L)				
Mean (SD)	247 (55.4)	277 (65.4)	261 (61.2)	438 (119)
Median	251	266	257	422
Range		—		
C^{ss}_{max} (ng/mL)				
Mean (SD)	209 (73.0)	163 (45.3)	187 (64.4)	141 (44.7)
Median	190	156	171	136
Range		—		
$AUC_{(0-tau)}$ (ng.hr/mL)				
Mean (SD)	4629 (1711)	3548 (1054)	4109 (1510)	3181 (1067)
Median	4195	3225	3765	3063
Range		—		
t_{max} (hr)				
Mean (SD)	8.40 (1.32)	7.71 (0.744)	8.07 (1.12)	8.26 (1.41)
Median	8.79	7.79	8.10	8.06
Range		—		
ka (hr^{-1})				
Mean (SD)	1.18 (0.28)	1.24 (0.12)	1.21 (0.21)	1.27 (0.24)
Median	1.15	1.26	1.22	1.28
Range		—		
$t_{1/2}$ (hr)				
Mean (SD)	38.7 (14.7)	33.1 (9.07)	36.0 (12.4)	47.4 (17.3)
Median	33.7	32.9	33.0	44.8
Range		—		

Summary Table 2 Summary statistics of the individual model predicted N-desmethyltamoxifen pharmacokinetic parameters

Population Pharmacokinetic Parameters	Pediatric Subjects (2 – 6 yr) N = 14	Pediatric Subjects (7 – 10.9 yr) N = 13	All Pediatric Subjects (2 – 10.9 yr) N = 27	Adult Subjects (43 – 75 yr) N = 59
C^{ss}_{max} (ng/mL)				
Mean (SD)	359 (125)	319 (108)	340 (117)	339 (112)
Median	343	296	320	333
Range		—		
$AUC_{(0-tau)}$ (ng.hr/mL)				
Mean (SD)	7910 (2681)	6893 (2336)	7420 (2526)	7606 (2590)
Median	7771	6613	7069	7361
Range		—		

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/s/

Sang Chung
7/2/02 04:01:09 PM
PHARMACOLOGIST

Hae-Young Ahn
7/2/02 05:55:33 PM
BIOPHARMACEUTICS