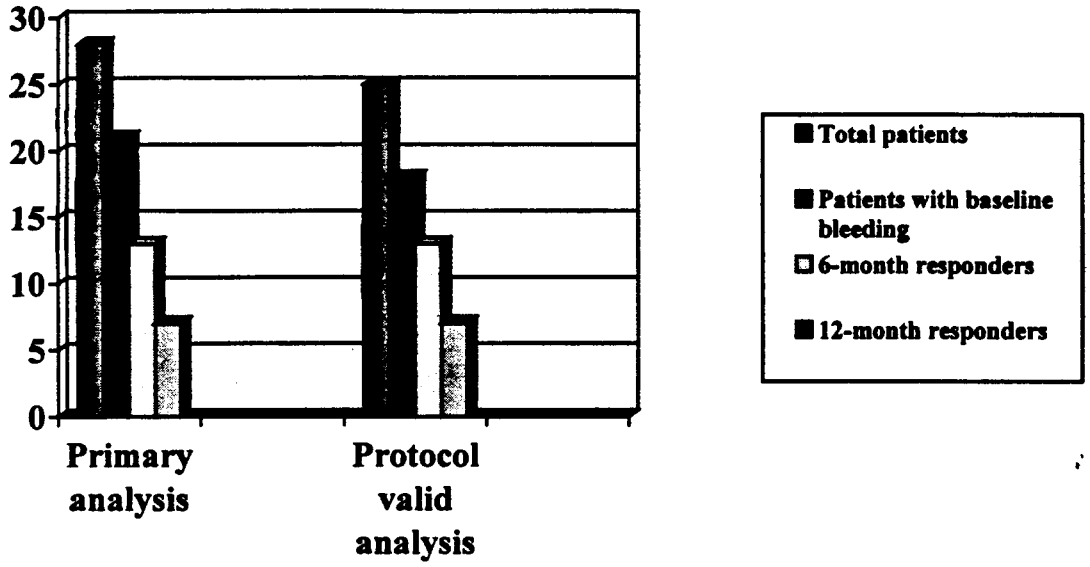
Of the 25 protocol-valid patients who were treated with tamoxifen citrate, only 18 (72%) exhibited evidence of vaginal bleeding at baseline. Of these, the same 13 (72%) experienced cessation of vaginal bleeding for an interval of at least 180 days while on study treatment. Seven patients (54%) showed cessation of vaginal bleeding for the 12-month treatment period (Figure 3).

Figure 3: Responder analysis: number and percent of patients who had no vaginal bleeding episodes for a 6-month period and for a 12-month period on treatment



Coonclusions:

- There was an approximately two-fold reduction in the frequency of bleeding episodes on tamoxifen therapy when compared to the pre-study period.
- Between 66.7% (primary analysis) and 72 % (protocol-valid analysis) of patients with pre-baseline vaginal bleeding experienced a ≥ 50% reduction in frequency of bleeding episodes.
- Between 33% (primary analysis) and 54% (protocol-valid analysis) of patients with pre-baseline vaginal bleeding experienced a complete cessation of bleeding for the one-year duration of the study.
- The reduction in frequency of vaginal bleeding was associated with a mean reduction in duration from 2.96 days to 2.41 days.
- While the trend is toward improvement in a majority of patients, some patients had a higher frequency of bleeding episodes during the treatment and some patients without vaginal bleeding during the pre-study period developed menses during the study.

- The conclusions are limited by the small number of patients enrolled, the short duration of the study, the variability in the frequency of vaginal bleeding during pre-study period, some missing data, and the retrospective nature of the data collection.

F.3.III.4. Reduction in bone age advancement

Bone age advancement was defined as the ratio between the bone age change (ΔBA) for the time interval of interest and the chronological age change (ΔCA) for the same time interval. The sponsor named the ΔBA/ΔCA ratio "rate of increase in bone age". This term is used in the review for consistency with the sponsor's data although it can be confusing at times (especially when one discusses increases and/ or decreases in the "rate of increase in bone age"). Reduction of bone age advancement to ≤ 6 months in a 6-month period means, in the sponsor's interpretation, that the rate of increase in bone age is less than or equal to the increase in chronological age in either 6-month period of the 12-month study.

Bone age trial data were collected at screening (a six week interval prior to the first dose of medication), Month 6 and Month 12 (end of trial). The pre-screening (i.e. baseline) bone age data were retrospective (i.e. collected from medical records).

Table 15 presents the descriptive statistics for **bone age** data at various timepoints during the trial (pre-baseline, screening=baseline, Month 6, and Month 12). Three datasets are analyzed (primary analysis, protocol-valid analysis, and "complete data" analysis. The three datasets showed similar trends despite some variations in mean values.

Table 15: Bone age characteristics for patients included in the primary, protocol-valid, and complete dataset analysis

Type of analysis	Time of bone age data collection	Descriptive statistics					
		N	Mean	Median	SD	Min.	Max.
Primary	Pre-baseline	25	8.80	9.22	2.33		
	Screening	24	9.13	9.73	2.45		
	Month 6	24	9.70	10.42	2.37		
	Month 12	26	10.10	10.63	2.37		
Protocol-valid	Pre-baseline	23	8.79	9.22	2.32		
	Screening	22	9.04	9.73	2.52		
	Month 6	23	9.61	9.99	2.38		
	Month 12	25	10.01	10.32	2.37		
Complete data	Pre-baseline	18	8.54	9.00	2.58		
	Screening	18	9.37	9.73	2.24		
	Month 6	18	9.78	9.97	2.19		
	Month 12	18	10.12	10.26	2.29		

Source: Tables 17, 18 and T 9.3
N=Number of patients.

Table 16 presents the descriptive statistics for **bone age rate of increase** (ΔBA/ΔCA) for all three types of analyses: primary, protocol-valid, and "complete data". In all three datasets, the mean bone age rate of increase decreased on treatment when compared with pre-study values. The reduction was noted during the first 6 months of the trial and continued for the next six months of the study. In addition, the mean rate of increase in bone age changed from a ratio>1 (bone age growth faster than chronological age growth for the interval) to a <1 ratio (i.e. bone age advancement slower than chronological age advancement for the interval measured). The change in mean bone age rate of increase during the trial reached statistical significance for the primary and protocol-valid analyses when compared to baseline values.

It is noteworthy that not all patients had bone age measurements at pre-baseline, screening and end of the trial. Only 21 out of 28 patients could be evaluated for changes in bone rate increases from the pre-study period to the on-study period through the final visit due to missing data. Therefore, in addition to the primary analysis and to the protocol-valid analysis, an analysis of patients who had a complete dataset was added.

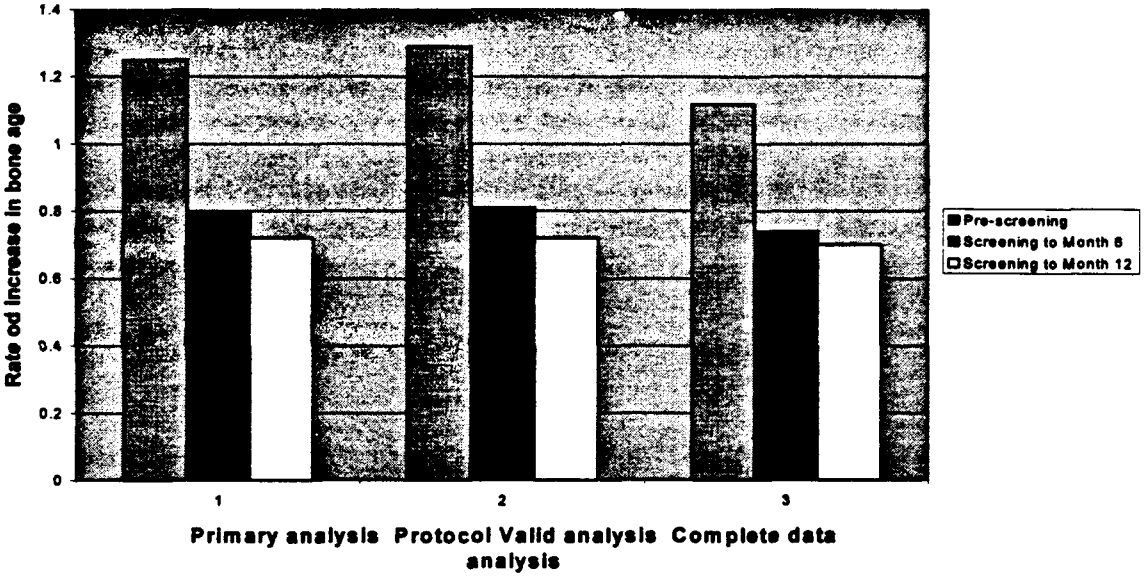
Table 16: Rate of increase in bone age: for patients included in the primary, protocol-valid, and complete data analysis

Type of analysis	Interval analyzed	Descriptive statistics						p-value
		N	Mean	Median	SD	Min.	Max.	
Primary	Pre-baseline to screening	22	1.25	1.44	0.79			
	Screening to Month 6	21	0.80	0.65	0.66			
	Month 6 to Month 12	24	0.67	0.59	0.48			
	Screening to Month 12	23	0.72	0.66	0.36			
Change from screening to Month 12		21	-0.54	-0.34	0.97			0.0203
Protocol-valid	Pre-baseline to screening	20	1.29	1.44	0.72			
	Screening to Month 6	20	0.81	0.76	0.68			
	Month 6 to Month 12	23	0.65	0.58	0.48			
	Screening to Month 12	22	0.72	0.62	0.37			
Change from screening to Month 12		20	-0.62	-0.63	0.91			0.0066
Complete data	Pre-baseline to screening	18	1.12	1.26	0.77			
	Screening to Month 6	18	0.74	0.64	0.54			
	Month 6 to Month 12	18	0.66	0.54	0.50			
	Screening to Month 12	18	0.70	0.66	0.29			
Change from screening to Month 12		18	-0.42	-0.22	0.97			0.0816

Source: Tables 17, 18 and T 9.3
N=Number of patients.

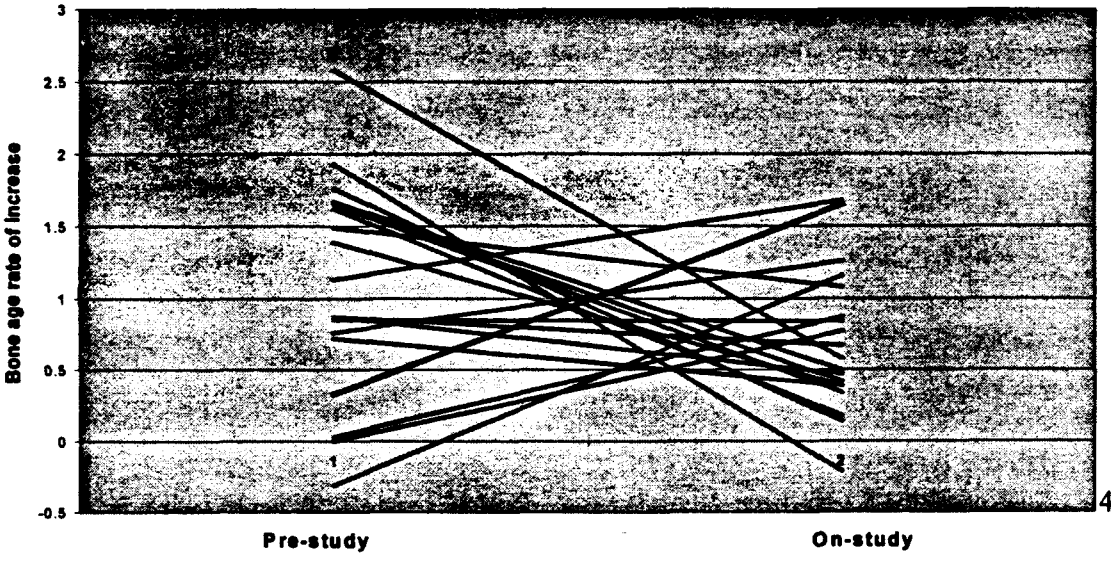
The mean bone age rate of increase changes are summarized in Figure 4:

Figure 4: Mean Rate of Increase in Bone Age: Pretrial to On-trial Comparison



Despite the consistent trend noted for the mean reduction of bone age rate of increase, examination of individual values identifies considerable heterogeneity. Figure 5 displays the bone age rate of increase during the pre-study and during the on-study periods for each of the 19 patients who had all measurements.

Figure 5: Bone Age Rate of Increase Changes in 19 Patients with Complete Data



In addition to providing descriptive statistics data related to the **bone age** and **bone age rate of increase**, the sponsor conducted a **responder analysis** for the rate of increase in bone age endpoint (primary endpoint). The WR defined this endpoint as a "reduction of bone age advancement to ≤ 6 months in a 6-month period" (i.e. the increase in bone age is less than or equal to the increase in chronological age in a six-month period).

This analysis is limited to a subgroup of patients who have a bone age rate of increase that was > 1 during the pre-study period (i.e. bone age grew faster than chronological age for this specific time interval). A responder is a patient that has a bone age rate of increase ≤ 1 while on study treatment (i.e. bone age growth becomes lower or equal to chronological growth).

The sponsor interpreted the six-month period as either of the six-month periods of the one-year study (Month 0 to Month 6, and Month 6 to Month 12). According to this interpretation of the requested analysis a patient was considered a responder if she had a slow down in bone age rate of increase during one of the two six-month periods despite advancing during other 6-month period.

Of the 28 patients enrolled in the study, 9 patients were unevaluable since they lacked one ore more bone age measurements (pre-study or during the clinical trial). Thus, only 19 patients could be considered for this responder analysis (i.e. had pre-baseline,screening, Month 6, and Month 12 measurements). Out of these 19 patients only 10 had a pre-study period bone age acceleration (rate of increase in bone age>1). Of these, all showed a reduction in the rate of increase in bone age in at least one of the two six months intervals of the study and were thus considered responders (all ten patients were also protocol-valid). Only six, however, showed a reduction in bone age rate of increase for **both** six-month intervals of the study. One patient (007/001) showed steady reduction in bone age increase over time. Two patients had higher bone age rate of increase over baseline for one of the two 6-month intervals (Table 17).

Table 17. Rate of increase in bone age during study in 10 patients with accelerated bone age rate of increase during the pre-study period and complete data

Center/Pt. No.	Rate of increase in bone age				Responder (criterion C)
	Pre-study	Screening to Month 6	Month 6 to Month 12	Screening to Month 12	
0004/0001	2.58	0.40	0.58	0.49	yes
0007/0001	1.93	1.12	-0.21	0.56	yes
0009/0001	1.65	0.41	0.42	0.41	yes
0015/0002	1.49	0.12	1.08	0.57	yes
0018/0001	1.13	0.49	1.68	1.02	yes
0018/0002	1.76	0.63	0.14	0.44	yes
0028/0001	1.67	0.42	0.50	0.46	yes
0030/0001	1.65	0.40	0.34	0.38	yes
0030/0002	1.39	1.55	0.39	1.05	yes
0033/0001	1.62	0.27	0.18	0.23	yes

Source: Table 20. Highlighted are 6-month bone age rate of increase>1.

Two patients (0023/0001 and 0052/0001) did not qualify for this responder analysis because they did not have a bone age radiograph at Month 6. Both had pre-study bone age rate of increase >1 which decreased to <1 for the entire 12-month period of the study.

The responder analysis needs to be interpreted cautiously. The periods of time analyzed are relatively short (six months) and bone age changes over such relatively short periods of time may not disclose significant changes. In addition, bone age measurements are notoriously difficult to assess accurately over short period of times.

In addition to the rate of increase in bone age data the sponsor also provides individual patient information on bone age to chronological age (BA/CA) ratio on all the enrolled patients. Invariably, the 28 patients enrolled in the study had BA/CA ratios >1, consistent with an advancement of bone maturity with respect to chronological age. The smallest ratios noted were 1.04 and 1.06. The highest was 2.4. For the majority of patients, the overall trends observed in this dataset were a reduction in the ratio of bone age to chronological age over the duration of the treatment period (out of 28 patients, 23 had BA/CA information at screening and at the end of the trial; 22 out of 23 showed a higher BA/CA ratio at the beginning of the treatment compared to the end of the trial). Only small changes are to be expected for such a short period of time for BA/CA ratio evaluations.

Interestingly, many patients displayed some improvement in BA/CA ratio even during the pre-baseline period (11 patients out of 25 patients who had a bone age evaluation at this time). Although the sponsor does not comment on this finding it is possibly related to the fact that the patients may have been receiving other medications before starting the tamoxifen citrate treatment (the exclusion criterion "previous drug therapy" was to be applied only for the two months preceding the trial enrollment, thus leaving open the

possibility of other therapies for the remainder of the baseline period. Indeed, according to table G3.2 in the submission many patients received anastrazole, testolactone, medroxyprogesterone, letrozole, some within the year 2000 (the enrolment for study 6157US/0013 started in March 2000). This raises the possibility that the benefits of tamoxifen citrate on bone age changes may have been more significant if the pre-baseline period of observation would have included a longer period off antiestrogens.

Conclusions:

- Tamoxifen use was associated with a reduction in mean bone age rate of increase during the 12-month trial.
- The change in bone age rate of increase from baseline was statistically significant. This finding needs to be interpreted in the context of a trial with largely retrospective baseline data, uneven pre-study period among patients, and missing datapoints.
- Despite the mean decrease in bone age rate of increase on-trial, individual changes were remarkably heterogeneous.
- A responder analysis of 10 patients with advanced pre-study bone age rate of increase and complete data was overall favorable. The small number of patients and the fact that many of these patients had pre-study periods <6 months in duration limit the ability to draw firm conclusions.

F.III.5. Reduction in the growth rate

Growth rate (=height velocity) is defined as the increase in height divided by the duration of the time interval of interest and is expressed as cm/year or as a Z-score. The height data was collected retrospectively from medical charts. Pre-study height data was collected in all patients. Consequently, all 28 enrolled patients had growth rates calculated for the pre-study period. In contrast, only 26 patients have growth rate data beyond the baseline period. This was due to the fact that two patients dropped out in the first half of the trial. An additional patient (patient 0051/0001) completed only approximately 8 months of trial. Her 8 month height measurement was included as a 12 month measurement.

One patient (patient 0030/0004) contributed to the growth analysis only the baseline measurements and should have been excluded from the analysis.

Growth rate data for the **primary analysis population** are summarized in Table 18 in cm/year and as Z-score. The mean and median growth rate decreased by 1.68 cm and 2.29 cm, respectively, on-treatment and reached statistical significance when compared to pre-study period ($p<0.05$). Similarly, the growth rate Z-score decreased from a positive value during pre-study (i.e. faster than age and sex-matched normal children) to negative values on-treatment (i.e. slower than age and sex-matched normal children). The on-treatment Z-score change was statistically significant when compared to pre-baseline Z-score.

Table 18: Growth rate pre-study and during study for the primary analysis population

Parameter / Interval	Tamoxifen citrate 20 mg qd N = 28				
	n	Mean (SD)	Median	Range	p-value[a]
Growth rate (cm/yr)					
Pre-baseline to Month 0	28	7.58 (2.61)	7.08		
Month 0 to Month 12/final visit	26	5.79 (3.01)	5.68		
Change from baseline	26	-1.68 (2.75)	-2.29		0.0046
Growth rate (Z-score[b])					
Pre-baseline to Month 0	28	1.26 (2.72)	0.99		
Month 0 to Month 12/final visit	26	-0.61 (3.00)	-0.57		
Change from baseline	26	-1.84 (2.90)	-2.41		0.0034

[a] p-value is from a two-sided t-test at the 0.05 significance level.
[b] Z-score is defined as the growth rate from the previous visit to the current visit, minus the mean growth rate, divided by the standard deviation, where the mean and standard deviation are the age- and gender-specific statistics from the NCHS - Fels Research Institute data study, and age is the age at the current visit. See Table G10.2 for the reference table of age-dependent means and standard deviations of growth rate.
qd once daily.
SD Standard deviation.
Data were derived from Table T10.1.

Similar observations can be made with respect to the growth rate data for the protocol-valid population. They are presented in Table 19. The mean and median growth rate expressed in cm/year decreased on-treatment by 1.56 and 2.17 cm, respectively, and reached statistical significance when compared to pre-study period ($p<0.05$). Similarly, the growth rate Z-score decreased from positive value (pre-study) to negative values (on-treatment). This observation was also statistically significant.

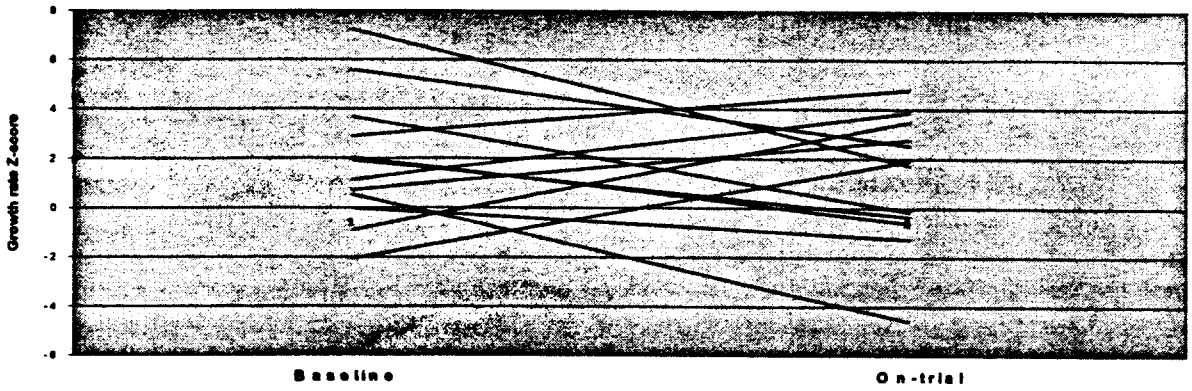
Table 19: Growth rate pre-study and during study for the protocol-valid population

Parameter / Interval	Tamoxifen citrate 20 mg qd N = 28				
	n	Mean (SD)	Median	Range	p-value[a]
Growth rate (cm/yr)					
Pre-baseline to Month 0	25	7.51 (2.47)	7.11		
Month 0 to Month 12/final visit	25	5.95 (2.96)	5.70		
Change from baseline	25	-1.56 (2.74)	-2.17		0.0087
Growth rate (Z-score[b])					
Pre-baseline to Month 0	25	1.25 (2.65)	1.15		
Month 0 to Month 12/final visit	25	-0.45 (2.94)	-0.56		
Change from baseline	25	-1.70 (2.87)	-2.39		0.0068

[a] p-value is from a two-sided t-test at the 0.05 significance level.
[b] Z-score is defined as the growth rate from the previous visit to the current visit, minus the mean growth rate, divided by the standard deviation, where the mean and standard deviation are the age- and gender-specific statistics from the NCHS - Fels Research Institute data study, and age is the age at the current visit. See Table G10.2 for the reference table of age-dependent means and standard deviations of growth rate.
qd once daily.
Data were derived from Table T10.2.

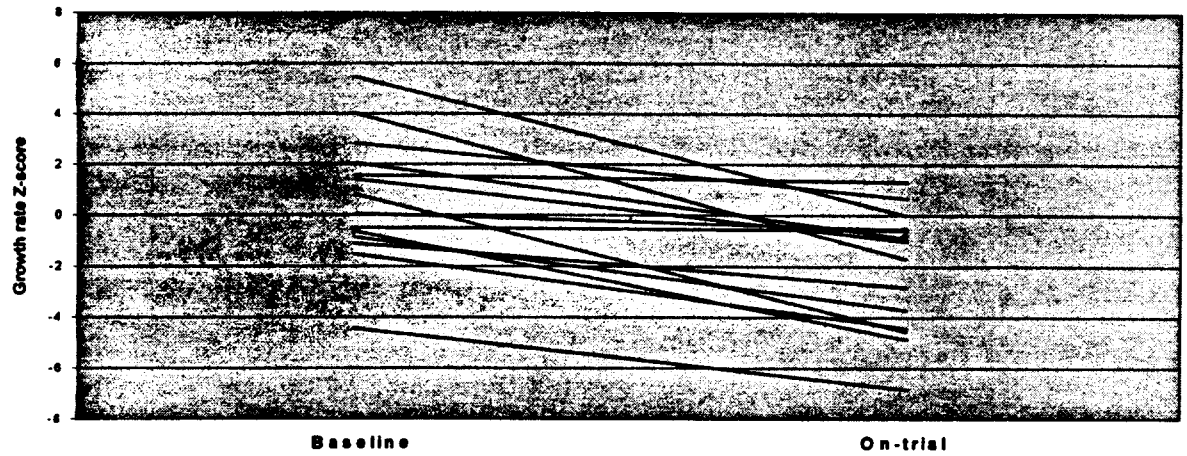
Out of the 26 evaluable patients, 21 (80.7 %) showed a reduction in growth rate Z-score during the trial when compared to pre-study values. However, this change was not uniformly seen across all stages of bone maturity. In a group of patients with chronological age < 7 years (mean bone age of 7.6 years) the growth rate change was highly heterogeneous (Figure 6). Five out of 12 patients did not show a reduction in growth rate. They were patients 0004/0001, 0005/0001, 0012/0001, 0015/0001, and 0028/0001.

Figure 6: Growth Rate Changes During Trial for Patients < 7 Years of Age



In a group of patients with chronological ages > 7 years and mean bone age of approximately 11 years, the growth rate response was uniformly favorable (Figure 7). It should be noted that in this group the treatment response is confounded by the natural reduction in linear growth rate which accompanies mid to late puberty.

Figure 7: Growth Rate Changes During Trial for Patients > 7 Years of Age



As stipulated in the Written Request, the sponsor conducted a responder analysis for the reduction of growth velocity criterion (primary efficacy endpoint). This analysis is limited to a subgroup of patients whose pre-study growth rate is > 0.8 SD for chronological age. A responder was defined as a patient whose growth velocity during the trial was reduced to ≤ 0.8 standard deviation above normal for chronological age.

Of the 28 patients enrolled in the trial, two patients were unevaluable for this analysis because they did not have the 12-month height measurement (patients 0025/0001 and 0030/0004). Of the remainder 26 patients, only 14 had pre-study growth rates > 0.8 SD for age. Nine (64.2%) of these 14 patients in the primary analysis population, and 8 (61.5%) of the 13 patients in the protocol-valid population, experienced a reduction in growth rate to a value that was ≤ 0.8 SD above the mean for a normal female of that patient's age during the on-study period and were therefore considered responders by this criterion. (Table 20).

Table 20: Responder analysis in 14 patients with accelerated* pre-study growth rate

Center/Pt. No.	Pre-study		On-study		Responder [Criterion (d)]
	Mean + 0.8 SD growth rate for baseline age (cm)	Actual pre-study growth rate (>0.8 SD) (cm)	Mean + 0.8 SD growth rate expected at end of study (cm)	Actual on-study growth (cm)	
0007/0001	6.64	10.87	6.48	7.65	no
0007/0002	6.35	8.03	6.96	6.83	yes
0009/0001	6.79	12.77	6.58	7.36	no
0012/0001	8.60	11.23	7.69	12.18	no
0013/0001	6.48	7.54	6.35	4.97	yes
0015/0002	6.37	7.02	6.47	6.91	no
0016/0001**	6.35	6.37	6.66	1.90	yes
0028/0001	8.60	9.04	7.69	11.13	no
0030/0001	6.20	8.04	6.65	5.64	yes
0030/0002	7.44	10/50	6.96	6.07	yes
0030/0003	6.40	10.44	6.35	5.70	yes
0031/0001	7.69	9.07	7.20	5.78	yes
0051/0001	6.50	7.11	6.40	4.94	yes
0052/0001	6.40	9.21	6.35	4.31	yes

*(mean + 0.8 SD growth rate in cm for patient's chronological age). ** Not protocol valid. Source: Table 23.

Of the 12 patients who did not have a growth rate > 0.8 SD for age during pre-study, 9 of had growth rates that remained below 0.8 SD for the duration of the trial, while three had growth rates > 0.8 during the trial (patients 0004/0001, 0005/0001, and 0015/0001).

Conclusions:

- The mean growth rate change on-trial reached statistical significance when compared to the mean growth rate of the pre-study period.
- The mean growth rate reduction was 1.68 cm for the duration of the trial.
- 80.7% of patients showed a reduction in growth rate Z-score during the trial when compared to pre-trial growth rate Z-score. This apparent favorable response was not seen uniformly across all stages of bone maturity. Among patients with less advanced bone maturation the response to tamoxifen was mixed.
- In a responder analysis of patients with growth rate > 0.8 SD for chronological age, 64.2 % of patients (in the primary analysis) and 61.5 of patients (in the protocol-valid analysis) showed a decrease in growth rate ≤ 0.8 SD for chronological age.

F.3.III.6. Responder analysis and the Written Request

The Written Request required an analysis of the following endpoints:

a) A 50 % reduction of the number of menstrual bleeding episodes during the study.
b) Cessation of menses (no episodes in a six-month period).
c) Reduction of bone age advancement to ≤ 6 months in 6-month period.
d) Reduction of growth velocity to ≤0.8 standard deviation above normal for chronological age.

A **complete responder** was defined as a patient who met criteria (b), (c), and (d). A **partial responder** was defined as a patient who met any one of the primary endpoints (a), (b), (c), or (d).

Due to the wide variability in patients' clinical symptoms at baseline not all the WR pre-defined signs and symptoms of precocious puberty were manifested in every patient with MAS. Under these circumstances the sponsor re-defined the **complete responder** as any patient in whom all signs/symptoms of precocious puberty that existed prior to receiving trial therapy resolved and no new signs and symptoms were observed on-trial. Under this definition, if a patient exhibited only one or two signs/symptoms described in the criteria above pre-study, and both signs/symptoms resolved, that patient was classified a **complete responder.**

The number of patients who satisfied the **complete** and **partial responder** criteria are presented in table 21 for both the primary analysis population and the protocol-valid population.

Table 21: Number of complete responders and partial responders in the primary analysis population and protocol-valid population

Category	Tamoxifen citrate 20 mg qd		
	N	% of patients in category	95% Confidence Interval for the % of patients in category
Primary analysis population			
Complete responders	6	21.4	8.3 to 41.0
Partial responders	18	64.3	44.1 to 81.4
Non-responders	4	14.3	4.0 to 32.7
Protocol-valid population			
Complete responders	6	24.0	9.4 to 45.1
Partial responders	17	68.0	46.5 to 85.1
Non-responders	2	8.0	1.0 to 26.0

qd once daily.
Data were derived from Tables T6.1.1 and T6.1.2.

Both the primary analysis and the protocol-valid analysis displayed similar trends. Six patients were classified as **complete responders** (21.4% in the primary analysis patients and 24% of the protocol-valid patients). They were patients: 0010/0001, 0018/0001, 0018/0002, 0030/0001, 0030/0002, and 0033/0001. Of the 28 patients in the primary analysis population, 18 (64.3%) patients satisfied at least one of the MAS criteria and thus were classified as **partial responders** for the trial period. One of these 18 patients (patient 0016/0001) was not included in the protocol-valid population; thus, 68% of patients were classified as **partial responders** for the protocol-valid population. Fewer patients in the protocol-valid population (8%) were identified as non-responders when compared to the 14.3% in the primary analysis population.

It should be noted that among the 6 "**complete responders**" only one patient (0030/0001) showed a reduction in all three endpoints analyzed. Three patients showed improvement in two endpoints and did not meet baseline criteria for analysis in one endpoint. Two patients are labeled as "**complete responders**" on the basis of improvement in signs/symptoms related to one endpoint (and on the absence of analyzable symptoms for two other endpoints). Thus, the term of "**complete responder**", although concordant with the sponsor's applied definitions, is not consistent with the intent of the Written Request, leads to overinterpretation of the responder data, and should be used with caution. Table 22 lists the six "**complete responders**" and their clinical response on-therapy in the three endpoints analyzed.

Table 22: List of complete responders and clinical response

Center/Patient No.	Cessation of vaginal bleeding	Reduction in rate of increase in bone age	Reduction in growth rate
0010/ 0001	yes	N/A	N/A
0018/ 0001	yes	yes	N/A
0018/ 0002	N/A	yes	N/A
0030/ 0001	yes	yes	yes
0030/ 0002	N/A	yes	yes
0033/ 0001	yes	yes	N/A

Source: Table 27.

N/ A= the MAS sign/ symptom related to the response criterion was not present at baseline nor during the study.

The number and percentage of patients who showed clinical response in the **individual criteria** (i.e. endpoints) are shown in Table 23 for both the primary analysis and the protocol-valid analysis. The percent of patients who showed improvement in individual criteria were similar across endpoints (between 60% and 70 %). It should be noted again that not all 28 patients were evaluable for each criterion due to absence of symptoms at baseline or due to missing data at various times during the trial (especially bone age). The table also includes the number of patients who developed new MAS signs/symptoms while on study medication for each endpoint. The numbers are very small to permit generalizations.

Table 23: Number of patients meeting individual response criteria for the primary analisys population and the protocol-valid.

Criteria[a]	Tamoxifen citrate 20 mg qd					
	MAS sign/symptom present pre-study[b]	Met the response criterion		MAS sign/symptom pre-study N		New MAS sign/symptom appeared while on- study
	N	N (%)	95% CI[c]	Not present	Unknown	N
Primary analysis population						
Criterion A	21	14 (66.7)	43.0 to 85.4	7	0	2
Criterion B	21	13 (61.9)	38.4 to 81.9	7	0	2
Criterion C	13	10 (76.9)	46.2 to 95.0	9	6	7
Criterion D	15	9 (60.0)	32.3 to 83.7	13	0	3
Protocol-valid population						
Criterion A	18	13 (72.2)	46.5 to 90.3	7	0	2
Criterion B	18	13 (72.2)	46.5 to 90.3	7	0	2
Criterion C	12	10 (83.3)	51.6 to 97.9	8	5	6
Criterion D	13	8 (61.5)	31.6 to 86.1	12	0	3

[a] Criterion A - A ≥ 50% reduction frequency of vaginal bleeding episodes over the 12-month trial period; Criterion B - cessation of vaginal bleeding (0 episodes during any consecutive 180 day period); Criterion C - reduction in the rate of increase in bone age to ≤ 6 months during any 6 month period; Criterion D - reduction in growth rate during the trial to ≤ 0.8 SD above mean normal for chronological age.

[b] If the MAS sign/symptom was unknown pre-study (or during study), the response was 'unevaluable'; if the MAS sign/symptom was not present pre-study and appeared during the study, the response was 'new MAS sign/symptom'; if the MAS sign/symptom was not present pre-study and did not appear during the study, the response was 'not applicable'.

[c] CI 95% Confidence interval for the % of patients that met the response criteria.

MAS McCune-Albright syndrome.

N Number of patients.

qd once daily.

Data were derived from Tables T6.2.1 and T.6.2.2.

[redacted]

It should be noted that, according to the ap
who showed worsening in signs/symptoms
be classified as a **partial responder** if she
Table 24 lists all **partial responders** and h
and symptoms where applicable. Ten out c
signs/symptoms that worsened during treatr

Table 24: List of partial responders

Eenter/Patient No.	≥50% reduction in vaginal bleeding	Cessat vagina bleedin
0004/ 0001	yes	yes
0005/ 0001	yes	yes
0005/ 0002	yes	no
0005/ 0003	yes	yes
0007/ 0001	N/A	N/A
0007/ 0002	NS/S	NS/S
0009/ 0001	yes	yes
0012/ 0001	yes	yes
0013/ 0001	N/A	N/A
0015/ 0001	yes	yes
0015/ 0002	no	yes
0016/ 0001*	yes	no
0026/ 0001	yes	no
0028/ 0001	N/A	N/A
0030/ 0003	yes	yes
0031/ 0001	NS/S	NS/S
0051/ 0001	no	no
0052/ 0001	yes	yes

Source: Table 27.
NS/ S =the MAS sign/ symptom related to the response c
during the study.
Unevaluable=the MAS sign/ symptom was unknown pre
N/ A=the MAS sign/ symptom related to the response cri
study.
*Not protocol-valid.

[redacted]

The **non-responders,** on the other hand, did not
any of the endpoints analyzed. Some of them cc
endpoints due to missing data. Others did not h
the endpoints. They are listed in Table 25:

Table 25: List of non-responders

Center/Patient No.	≥50% reduction in vaginal bleeding	Cessation of vaginal bleeding	Reduction in rate of increase in bone age	Reduction in growth rate
0023/ 0001	no	no	unevaluable	N/A
0025/ 0001	no	no	unevaluable	unevaluable
0030/ 0004*	no	no	unevaluable	unevaluable
0045/ 0001	no	no	NS/S	N/A

Source: Table 27.
NS/ S =the MAS sign/ symptom related to the response criterion was not present at baseline, but appeared during the study.
Unevaluable=the MAS sign/ symptom was unknown pre- study or during the study.
N/ A=the MAS sign/ symptom related to the response criterion was not present at baseline nor during the study.
*Not protocol-valid

Conclusion:

- 21.4 % of patients (primary analysis) and 24 % of patients (protocol-valid) were "complete responders". However, the **complete responder** analysis should be interpreted with caution since not all signs/symptoms of precocious puberty were present at baseline in each patient. The definition of **complete responder** applied by the sponsor leads to overinterpretation of the data.
- **Partial responder** analysis showed on the average a 60-70 % response in individual signs/symptoms. In this context, 56% of the **partial responders** had signs/symptoms of precocious puberty that worsened during treatment.
- Among the 21 patients with pre-study vaginal bleeding episodes, 14 (66.7%) showed ≥50% reduction in frequency and 13 (61.9%) showed cessation over a six-month period of the trial irrespective of the reduction or increase during the other 6-month period.
- Among 13 patients with bone age rate of increase >1 at baseline, 10 (76.9%) showed reduction < 1 during a six-month interval irrespective of the reduction or increase during the other 6-month interval.
- Among 15 patients with growth rate >0.8 for chronological age, 9 (60%) showed a reduction to ≤0.8 SD for chronological age for the duration of the trial.
- Any numerical discrepancies between the sponsor's responder analysis and the responder analysis presented earlier in this review is due to the choice of the denominator (the sponsor selects all patients with baseline data, while this reviewer selects all patients with baseline data and complete on-trial data).

F.3.III.7. Predicted adult height

The predicted adult height was calculated as the observed height divided by a published factor (Bayley and Pinneau, 1952). Since the predicted adult height is very difficult to estimate for children under 6 years of age, only patients over the age of 6 had estimates performed and reported. Change in the predicted adult height was assessed between the baseline and the end of the 12-month study period.

Table 26 presents the mean predicted adult height (PAH) at screening and at the end of the trial. A small increase in the PAH was observed in both the primary analysis and protocol valid populations. No statistical inferences are presented. The short duration of the study was not expected to show significant PAH changes. An increase of 1.4 cm in mean predicted adult height was observed in the primary analysis population following 12 months of tamoxifen therapy. A similar increase of 1.5 cm in mean PAH was observed in the protocol-valid population. This observation appears to be consistent with the mean reduction in the rate of increase in bone age. Due to missing data, the PAH predictions are based on variable number of measurements at different timepoints.

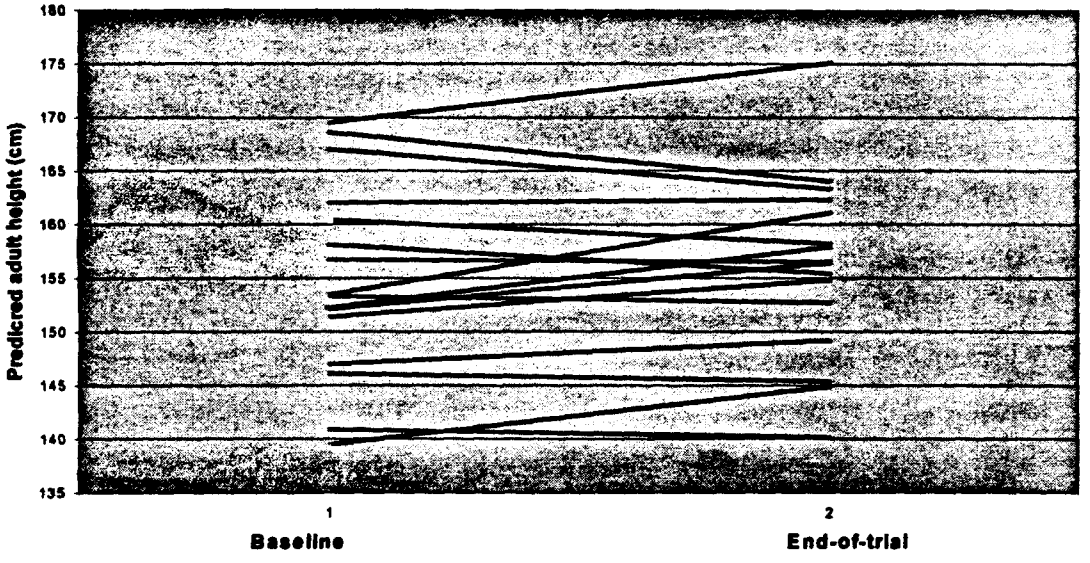
Table 26: Predicted adult height for the primary analysis and protocol-valid populations

Population	Tamoxifen citrate 20 mg qd			
Visit	n	Mean (SD)	Median	Range
Primary analysis population				
Predicted adult height (cm) at screening visit[a]	17	155.1 (8.83)	153.5	
Predicted adult height (cm) at month12/final visit	22	156.5 (7.60)	157.1	
Percent change in predicted adult height, screening to month 12/final visit	16	0.8 (2.41)	0.1	
Protocol-valid population				
Predicted adult height (cm) at screening visit	15	155.8 (8.58)	153.5	
Predicted adult height (cm) at month12/final visit	21	157.3 (6.84)	157.4	
Percent change in predicted adult height, screening to month 12/final visit	15	0.9 (2.47)	0.2	

[a] Predicted adult height equals the current height divided by a factor (the fraction of final adult height) based on current bone age and current bone age relative to chronological age, classified as retarded, average, or advanced: retarded is defined as current bone age (yr) < (chronological age [yr] - 1); advanced is defined as current bone age (yr) > (chronological age [yr] + 1); otherwise, bone age is classified as average. See Table G11.2 for the reference table of values for the calculation of predicted adult (mature) height attained at each bone age - method of Bayley and Pinneau.
qd once daily.
Data were derived from Tables 11.1 and T11.2.

Analysis of individual patient data displays marked heterogeneity in adult height predictions. Only 16 of the 28 patients had all the necessary datapoints to calculate PAH at baseline and at end-of-trial (15 were also protocol-valid). Of these 16 patients, eight (50 %) had an increase in PAH and 50% had a decrease in PAH. Individual trends are displayed in Figure 8.

Figure 8: Predicted Adult Height at Baseline and End-of-trial



F.3.III.8. Mean ovarian and uterine volumes

Pelvic ultrasounds were performed at screening, Month 6 and Month 12. Table 27 records the mean ovarian volume data for the primary and for the protocol-valid analysis. Consistent with the diagnosis of MAS, the average ovarian volume at baseline was greater than normal. Overall, there was a small increase in the mean ovarian volume at the end of treatment in both primary analysis population (1.14 cc) and in the protocol-valid population (0.94 cc). A wide range of measurement results, as well as asymmetric fluctuations in ovarian size/presence of asymmetric ovarian cysts were described. No count of the number of cysts is provided.

Tamoxifen citrate has been associated with ovarian cyst formation in adult and pediatric patients. However, it is difficult to interpret the significance of the increase in mean ovarian size in MAS, a condition in which ovarian cyst formation is a background phenomenon. In addition, there is no clear standard to which one can compare the 1 cc (or approximately 15%) mean increase in ovarian volume.

Table 27: Average ovarian volume for the primary analysis and protocol-valid populations

Population		Tamoxifen citrate 20 mg qd		
Visit	n	Mean (SD)	Median	Range
Primary analysis population				
Average ovarian volume (cc) at screening visit[a]	28	6.10 (8.51)	2.61	——
Average ovarian volume (cc) at month 12/final visit	26	7.61 (8.57)	4.52	——
Change in average ovarian volume (cc), screening to month12/final visit[b]	26	1.14 (11.28)	1.80	——
Protocol-valid population				——
Average ovarian volume (cc) at screening visit	25	6.35 (8.89)	2.67	
Average ovarian volume (cc) at month 12/final visit	25	7.29 (8.59)	4.41	——
Change in average ovarian volume (cc), screening to month12/final visit	25	0.94 (11.46)	1.22	——

[a] Calculated volume is 0.5*(longitudinal *anteroposterior*transverse), if all three linear dimensions were recorded on the CRF. Average ovarian volume is calculated as 0.5*(volume of left ovary + volume of right ovary).
[b] Change was calculated only for those patients with data at the screening visit and month 12/final visit.
cc cubic centimeters.
qd once daily.
SD Standard deviation.
Data were derived from Tables T12.1 and T12.2.

Pelvic ultrasounds were performed at screening, Month 6 and Month 12. Table 28 records the mean uterine volume data for the primary and for the protocol-valid analysis. By 12 months of tamoxifen therapy, mean uterine volume had more than doubled (it increased from 9.1 ± 6.7 cc to 21.5 ± 11.8 cc for the primary analysis population and from 8.5 ± 6.3 cc to 21.1 ± 11.9 cc for the protocol-valid population, respectively). The sponsor points out that the mean uterine volume following 12 months of tamoxifen citrate therapy, although increased, remained within one SD of the mean uterine volume for pubertal girls, that the mean uterine volume at baseline were comparable to published data for normal pubertal girls (Orsini, 1984). There are no published data in the medical literature which describe the changes in uterine volume in patients with MAS.

The sponsor states that myometrial enlargement, rather than an increase in the endometrial thickness, would likely account for any increase in uterine volume. However, no data are provided that evaluates endometrial thickness at the beginning and at the end of the trial.

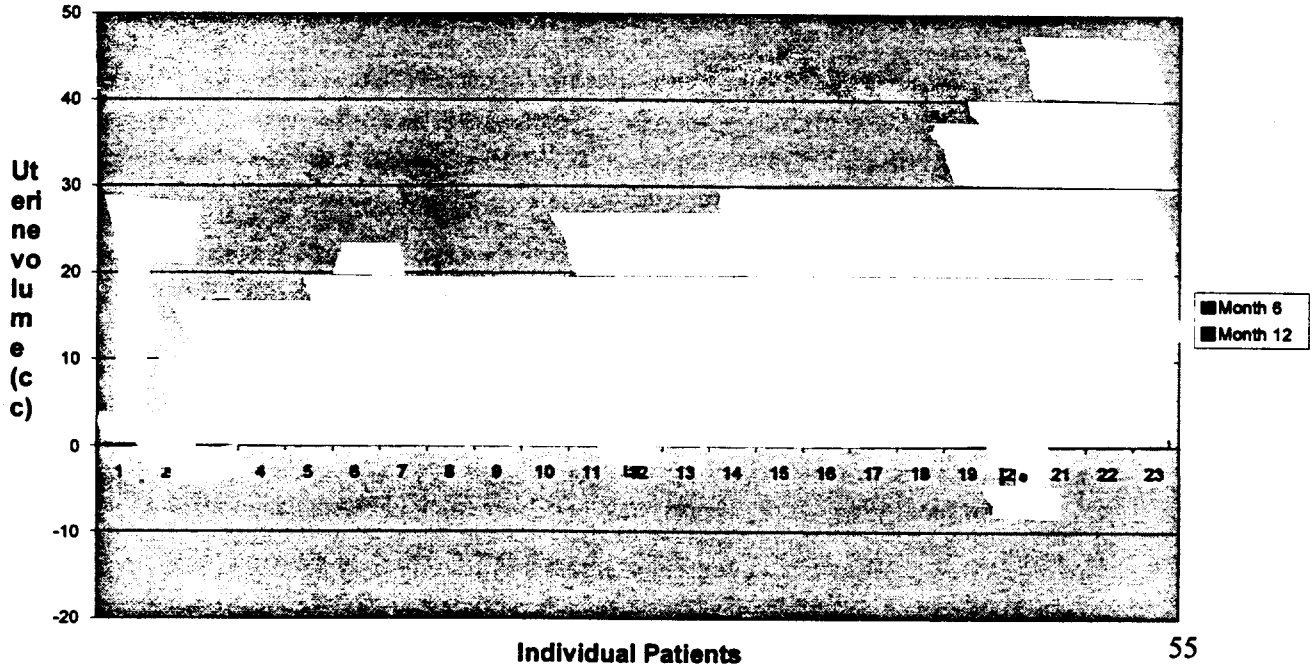
Table 28: Uterine volume for primary analysis and protocol-valid populations

Population		Tamoxifen citrate 20 mg qd		
Visit	n	Mean (SD)	Median	Range
Primary analysis population				
Uterine volume (cc) at screening visit[a]	28	9.12 (6.69)	6.82	
Uterine volume (cc) at month 12/ final visit	24	21.54 (11.81)	22.29	
Change in uterine volume (cc), screening to month12/ final visit[b]	24	12.02 (9.20)	13.36	
Protocol-valid population				
Uterine volume (cc) at screening visit	25	8.46 (6.33)	5.11	
Uterine volume (cc) at month 12/ final visit	23	21.10 (11.88)	22.11	
Change in uterine volume (cc), screening to month12/ final visit	23	12.23 (9.35)	13.82	

[a] Calculated volume is 0.5*(longitudinal *anteroposterior*transverse), if all three linear dimensions were recorded on the CRF.
[b] Change was calculated only for those patients with data at the screening visit and month 12/final visit.
cc cubic centimeter.
qd once daily.
SD standard deviation.
Data were derived from Tables T13.1 and T13.2.

Individual uterine volume changes during the trial show considerable interpatient variability (Figure 9). Uterine volume enlargement is clearly noted by Month 6 and that it increases further by Month 12 (end of trial) in most patients.

Figure 9:Uterine Volume Change at Month 6 and Month 12 Compared Screening



F.3.III.9. Tanner staging

Tanner staging was a secondary endpoint in the Written Request. These Tanner staging data were to be collected at baseline, during the trial and at the end of the trial. However, the sponsor noted late in the study that the CRFs combined the breast staging and the pubic staging data making the interpretation of this endpoint impossible.

F.3.III.10. Hormonal assessment

Hormonal assessments were done at screening, Month 6, and Month 12 (end of trial). The following hormonal data were collected (all serum levels):estradiol, estrone, dehydroepiandrosterone-sulfate (DHEA-S), insulin-like growth factor-1 (IGF-1), follicle-stimulating hormone (FSH; ultrasensitive) and luteinizing hormone (LH; ultrasensitive).

The serum estradiol and estrone mean levels at screening, Month 6, and month 12 are presented in table 29. The mean estradiol serum levels at screening were pubertal (143.44 pmol/L), as they were at Month 6 (410.96) and Month 12 (275.25 pmol/L). The mean was higher at Month 6 due to markedly increase in estradiol levels in several patients (serum levels as high as 3278, 1344 and 1105, respectively, were observed in three patients).

Table 29: Summary of estradiol and estrone levels for the primary analysis population

		Tamoxifen citrate 20 mg qd (N = 28)			
Hormone	Visit	N	Mean (SD)	Median	Range
Serum estradiol (pmol/L)	Screening	27	143.44 (242.26)	37.00	
	Month 6 visit	23	410.96 (727.88)	81.00	
	Month 12/final visit	24	275.25 (335.69)	81.00	
Serum estrone (pmol/L)	Screening	27	70.04 (59.19)	37.00	
	Month 6 visit	24	181.58 (293.72)	57.50	
	Month 12/final visit	23	141.87 (143.14)	74.00	

Source:Table 14.

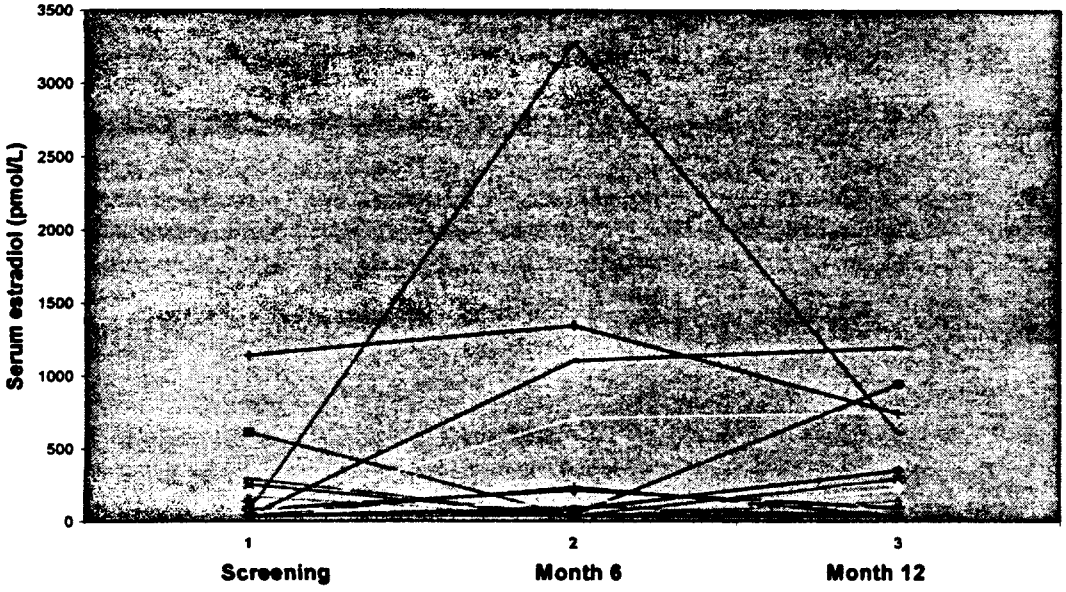
Examination of the individual data reveals marked variability in serum estrogen levels among patients at any particular timepoint, and for the same patients at different timepoints.

Many patients had prepubertal estrogen levels at different times of assessment. For instance, 19 patients (70.3%) had prepubertal estradiol levels at baseline; 11 (47.8%) patients had prepubertal serum estrogen levels at Month 6; 10 (41.6%) patients were prepubertal at the end of the one-year trial. The majority of patients experienced periodic

elevations above the upper limit of normal for prepubertal girls in serum estradiol (73.4 pmol/L). Three patients had all serum estradiol measurements in prepubertal range (0005/0003, 0015/0001, and 0018/0002). Two additional patients missed data for one timepoint but were prepubertal for the remaining two measurements (0031/0001 and 0007/0001; both had normal estrone levels at the time of the missing estradiol levels). **Only two patients had pubertal serum estradiol levels at all three timepoints (0004/0001 and 0033/0001).**

Figure 10 illustrated the variability and the general trends based on the three serum estrogen measurements available.

Figure 10: Summary of Estradiol Levels-Primary Population Analysis



Evaluation of serum levels for other hormones assessed during the study did not reveal any unexpected information. In general, the serum estrone levels followed similar trends as the serum estradiol levels for both means and individual values.

The mean DHEA-Sulfate serum levels increased over time (consistent with advancing age and/or the onset of adrenarche.

The mean FSH and LH serum levels increased over the first 6-month interval and then appeared to plateau over the subsequent 6 months, but remained in the prepubertal range. No changes were observed in the mean IGF-1 levels over the course of the 12-month study.

F.3.III.11. Correlations between serum estrogen levels and efficacy variables

The majority of clinical symptoms in MAS are due to periodic elevations of serum and tissue estrogens which are the results of autonomous estrogen secretion by ovarian cysts. Correlations between serum estrogen levels and the efficacy variables (vaginal bleeding, bone age advancement, and growth rate), although desirable, are difficult to make due to several factors. Estrogen levels were followed only intermittently, at six months intervals (Month 0, Month 6, and Month 12 of the trial) and therefore represent only occasional snapshots of a complex and unpredictable process. Elevated or normal levels between these measurements are entirely possible. In addition, bone age and growth rate are complex processes which have a complex temporal relationship to serum estrogen level changes. Therefore, no clear correlations could be made between measured serum estrogen levels and any of the endpoints.

With limitations in mind, I made an attempt to correlate mean serum estrogen levels with the three efficacy endpoints. Mean serum estrogen levels were arbitrarily divided in three categories (700 to 1300 pmol/L, 103 to 499 pmol/L, and 37 to 98 pmol/L) based on the serum estrogen levels reached during the trial. All three categories are above the pubertal serum estradiol level of 73 pmol/L. Only 23 patients had estradiol levels for all three timepoints and could, thus, be included in this analysis.

Table 30 evaluates response in vaginal bleeding episodes in all three categories. With exception of one patient (0018/0001) all patients showed a reduction in frequency of vaginal bleeding. This reduction was substantial in most patients (50-100% reduction). This benefit was visible in al three categories. Highlighted is a patient who had an increase in number of vaginal bleeding episodes.

Table 30: Serum Estrogen Levels and Reduction in Vaginal Bleeding

Estrogen level category	Center/Pt. No.	Vaginal Bleeding Episodes				
		Pre-study		During study		% change pre-study to during study
		Actual number	Annualized	Actual number	Annualized	
Mean estrogen levels 700-1300 pmol/L	0045/ 0001	CIB*	CIB*	CIB*	CIB*	NA
	0033/ 0001	4	8	1	1	-87.5%
	0010/ 0001	4	8	1	1	-87.5 %
Mean estrogen levels 103-499 pmol/L	0005/ 0002	3	6	3	3	-50%
	0016/ 0001	3	6	1	3**	-50%
	0018/ 0001	1	2	3	3	50%
	0007/ 0002	0	0	3	3	NA
	0030/ 0001	1	2	0	0	-100%
	0005/ 0001	1	2	0	0	-100%
	0030/ 0003	1	2	0	0	-100%
	0052/ 0001	4	8	1	2**	-74.8%
	0015/ 0002	2	4	3	3	-25%
	0004/ 0001	1	2	0	0	-100%

	0012/ 0001	1	2	1	1	-50%
	0009/ 0001	2	4	0	0	-100%
Mean estrogen levels 37-98 pmol/L	0013/ 0001	0	0	0	0	NA
	0030/ 0002	0	0	0	0	NA
	0028/ 0001	0	0	0	0	NA
	0026/ 0001	6	12	4	4	-66.7%
	0018/ 0002	0	0	0	0	NA
	0007/ 0001#	0	0	0	0	NA
	0005/ 0003	3	6	0	0	-100%
	0015/ 0001	3	6	0	0	-100%

Source: tables 9 and 13.

*CIB=Continuous intermittent bleeding (inappropriate to apply definition of episode to the data). NA=Not applicable.

**Calculated under a worse case scenario due to missing data.

There was no 6 month estrogen measurement.

Table 31 fails to show a correlation between serum estrogen level category and the change in bone age rate of increase (both increases and decreases in bone age advancement occurred for each serum estradiol category). Highlighted are patients who did not show reductions in the bone age rate of increase on study drug.

Table 31: Serum Estrogen Levels and Reduction in the Rate of Increase in Bone Age

Estrogen level category	Center/Pt. No.	Rate of increase in bone age				Change in rate from screening to month 12
		Pre-study	During study			
			Screening to month 6	Month 6 to month 12	Screening to month 12	
Mean estrogen levels 700-1300 pmol/L	0045/ 0001	0.76	0.05	1.26	0.46	-0.30
	0033/ 0001	1.62	0.27	0.18	0.23	-1.39
	0010/ 0001	0	1	0.77	0.88	0.88
Mean estrogen levels 103-499 pmol/L Mean estrogen levels 700-1300 pmol/L	0005/ 0002	1.49	0.12	1.08	0.57	-0.92
	0016/ 0001	-0.31	0.65	1.16	0.88	1.19
	0018/ 0001	1.13	0.49	1.68	1.02	-0.11
	0007/ 0002	NAV	NAV	NAV	NAV	NA
	0030/ 0001	1.65	0.40	0.34	0.38	-1.27
	0005/ 0001	NAV	2.53	1.09	1.85	NA
	0030/ 0003	0.03	1.59	0.87	1.22	1.19
	0052/ 0001	2.19	NAV	NAV	0.77	-1.42
	0015/ 0002	1.49	0.12	1.08	0.57	-0.92
	0004/ 0001	2.58	0.40	0.58	0.49	-2.09
	0012/ 0001	0.87	1.25	0.47	0.88	0.01
	0009/ 0001	1.65	0.41	0.42	0.41	-1.24
Mean estrogen	0013/ 0001	0.87	1.42	0.67	1.05	0.18
	0030/ 0002	1.39	1.55	0.39	1.05	-0.34
	0028/ 0001	1.67	0.42	0.50	0.46	-1.21

levels 37-98 pmol/L	0026/ 0001	0.33	-0.46	1.65	0.50	0.17
	0018/ 0002	1.76	0.63	0.14	0.44	-1.32
	0007/ 0001	1.93	1.12	-0.21	0.56	-1.37
	0005/ 0003	NAV	NAV	0.59	NAV	NA
	0015/ 0001	NAV	1.02	0.19	0.66	NA

Source: Tables 9 and 20. NAV=not available (measurement missing). NA=Not applicable (variable could not be calculated).

Similar to prior observations made for bone age advancement, the growth rate failed to correlate with on specific mean serum estrogen level (Table 32). Highlighted are patients who did not show reductions in growth rate Z-score.

Table 32: Serum Estrogen Levels and Reduction in Growth Rate Z-score

Estrogen level category	Center/Pt. No	Growth rate Z-score		
		Baseline to Month 0	Month 0 to Month 12	Change from baseline to end of study
Mean estrogen levels 700-1300 pmol/L	0045/ 0001	-4.44	-6.83	-2.39
	0033/ 0001	-0.02	-1.26	-1.24
	0010/ 0001	-0.86	-3.71	-2.85
Mean estrogen levels 700-1300 pmol/L	0005/ 0002	-0.63	-4.86	-4.23
	0016/ 0001	0.82	-4.55	-5.37
	0018/ 0001	-1.10	-2.81	-1.71
	0007/ 0002	2.84	0.66	-2.18
	0030/ 0001	1.92	-0.35	-2.27
	0005/ 0001	0.72	2.76	2.04
	0030/ 0003	5.46	0	-5.46
	0052/ 0001	4.01	-1.70	-5.71
	0015/ 0002	1.57	1.32	-0.25
	0004/ 0001	-2.05	1.90	3.95
	0012/ 0001	2.90	4.80	1.90
	0009/ 0001	7.23	1.72	-5.51
Mean estrogen levels 37-98 pmol/L	0013/ 0001	2.05	-0.89	-2.94
	0030/ 0002	3.68	-0.14	-3.82
	0028/ 0001	1.15	3.87	2.72
	0026/ 0001	-1.52	-4.43	-2.91
	0018/ 0002	-0.49	-0.58	-0.09
	0007/ 0001	5.59	2.53	-3.06
	0005/ 0003	0.54	-4.61	-5.15
	0015/ 0001	-0.90	3.49	4.39

Source: Tables 9 and 23. NAV=not available (measurement missing). NA=Not applicable (variable could not be calculated).

F.4. Efficacy Conclusions

Tamoxifen citrate showed efficacy in improving signs/ symptoms of precocious puberty in a very heterogeneous group of patients with MAS treated with 20 mg daily dose for one year.

Tamoxifen therapy resulted in a two-fold reduction in the frequency of vaginal bleeding and reduced the mean duration of vaginal bleeding from 3 days to 2.41 days. Among the patients who exhibited vaginal bleeding during the pre-study period, 66.7 % showed ≥ 50% reduction in vaginal bleeding episodes during the trial. 62% of all patients showed cessation of bleeding over a six-month period and 33% showed complete cessation of bleeding for the duration of the trial.

Not all patients improved on treatment (two patients showed an increase in the frequency of vaginal bleeding on-trial and two patients without evidence of vaginal bleeding during the pre-study period developed menses while on tamoxifen therapy.

Tamoxifen therapy was associated with a reduction in the mean bone age rate of increase. This change reached statistical significance when compared with pre-study bone age rate of increase. Individual responses, however, were very heterogeneous and not all patients improved on therapy.

Tamoxifen citrate therapy was associated with a reduction in the mean growth rate. The mean growth rate Z-score decreased from a mean positive value (advanced) to a negative mean value (slower than normal children). This change reached statistical significance when on-trial growth rates were compared to pre-study growth rates. The growth rate Z-score improved in 21 (80.7%) patients and worsened in five patients (19.2%). This apparent favorable response was not seen uniformly across all stages of bone maturity. Among patients with less advanced bone maturation the response to tamoxifen was mixed. A responder analysis in a subgroup of patients with advances in growth rates in excess of 0.8 SD for normal chronological age and complete data on trial identified 64.2% responders in the primary analysis and 61.5 % in the protocol valid analysis.

Several factors limit the ability to draw firm conclusions about the efficacy of tamoxifen. Among them, a particular concern is the fact that the pre-study data was obtained retrospectively, was not uniformly collected, and had missing datapoints.

G. Integrated Review of Safety

G.1. Brief Statement of Conclusions

Tamoxifen treatment for one year is associated with a doubling in the mean uterine volume. This finding can be significant in the light of the known risk of endometrial cancer and myometrial neoplasms associated with tamoxifen use in adult females and it should be clearly stated in the drug labeling. No other distinct safety signals are detected. The safety of tamoxifen citrate beyond one year of treatment in girls with MAS and precocious puberty has not been established.

G.2. Description of Patient Exposure

Twenty patients were enrolled in trial 615US/0013 and 25 of them completed 12 months of therapy. The mean duration of study treatment was 351 days (ranging between 148 days to 398 days). Three patients withdrew prematurely and received trial medication for 148, 167 and 265 days, respectively. Mean compliance was 93%. The duration of exposure to study medication during trial 615US/0013 is presented for the primary analysis patient population in Table 33. Compliance with the study drug is included.

Table 33: Duration of tamoxifen citrate treatment and compliance with study treatment at last visit and at month 12 visit (primary analysis population)

Tamoxifen citrate 20 mg qd	Duration of study treatment (days)		% Compliance	
(N = 28)	At last visit	At Month 12	At last visit	At month 12
n	28	22	28	22
Mean (SD)	351.3 (59.17)	372.3 (9.78)	93.8 (6.04)	93.9 (4.75)
Median	367.5	369	96.0	96.0
Range				

qd once daily.
SD Standard deviation.
Data were derived from Tables T4.1 and T4.2.

One patient (0007/0001) had a drug holiday of 47 days due to presumed poor drug tolerability which subsequently resolved. The patient has completed 364 days of trial but the actual time she has been in the trial is 317. All efficacy and safety assessments for this patient have been based on the 364 day duration of trial treatment.

G.3. Methods and Specific Findings of Safety Review

G.3.1. Deaths

There were no deaths reported during the trial.

G.3.2. Serious adverse events other than deaths

Two patients (7.1%) out of the 28 patients who received trial therapy experienced serious adverse events (SAE). Patient 0015/0001 (3 1/2 year old) had a 24-hour hospitalization for an asthma attack on day 145 of trial treatment which resolved following asthma therapy. Patient 0030/0002 (5 year old) underwent a right femoral proximal osteotomy followed by two other procedures (repositioning of the hip and placement of a femoral rod); the surgical interventions were in response to progression of the underlying fibrous dysplasia. None of the SAEs listed above were judged as treatment-related by the respective investigators.

G.3.3. Withdrawals

Reportedly, none of the 28 patients receiving tamoxifen citrate withdrew due to adverse events. Three patients withdrew prematurely: one patient withdrew consent (parent refused to continue in the study), one patient was lost for follow-up, and one patient withdrew due to lack of drug efficacy. Table 34 lists and the reasons for withdrawals and the duration on trial for each patient dropout.

CENTER/ PATIENT	PROTOCOL VALID POPULATION	DATE OF FIRST DOSE	DATE OF LAST DOSE	DATE OF WITHDRAWAL	DURATION OF STUDY TREATMENT AT WITHDRAWAL	REASON FOR WITHDRAWAL
0025/0001	NO	29SEP2000	14MAR2001	02MAY2001	167	INFORMED CONSENT WITHDRAWN
0030/0004	NO	13OCT2000	08MAR2001	09MAR2001	148	LOST TO FOLLOW UP (DROPOUT)
0061/0001	YES	06APR2000	26DEC2000	26DEC2000	264	PROGRESSION OF DISEASE

Table 34: List of patients who withdrew prematurely and reasons for withdrawal

G.3.4. Frequent adverse events

Twenty-three patients (82%) in the primary analysis population experienced at least one adverse event during the treatment period (including up to 30 days after the patient's last dose). Adverse events summarized by body system are presented in Table 35. The most commonly reported (>10%) adverse events in order of decreasing frequency, were pharyngitis (39.3%), rhinitis (17.9%), headache (17.9%), fever (14.3%), abdominal pain (10.7%), infection bacterial (10.7%), pain (10.7%), pathological fracture (10.7%), cough increased (10.7%), and otitis media (10.7%). With the exemption of a single episode of asthma (patient 0015/0001) which was labeled as severe in intensity, al other adverse events were in the mild and moderate category. The vast majority of the adverse events were consistent with signs and symptoms associated with childhood illnesses. Further inferences are limited due to the small number of patients and the absence of a control group.

Table 35: Adverse events occurring in two or more patients during treatment (primary population analysis)

Adverse Event	Number (%) of patients with adverse event (N=28)
Abdominal pain	3 (10.7)
Accidental injury	2 (7.1)
Back pain	2 (7.1)
Fever	4 (14.3)
Flu syndrome	2 (7.1)
Headache	5 (17.9)
Infection bacterial	3 (10.7)
Neck pain	2 (7.1)
Pain	3 (10.7)
Diarrhea	2 (7.1)
Bone disorder	2 (7.1)
Pathological fracture	3 (10.7)
Cough increased	3 (10.7)
Pharyngitis	11 (39.3)
Rhinitis	5 (17.9)
Sinusitis	2 (7.1)
Rash	2 (7.1)
Otitis media	3 (10.7)

N=total number of patients exposed to the drug.
Adverse events are included in this table if they started during study treatment or within 30 days of the last day of study treatment. A patient may have had more than 1 adverse event.

Two patients receiving trial medication experienced an adverse event that was regarded by the physician to be possibly related to trial treatment. Patient 0005/0002 had elevated ALT (SGPT) and AST (SGOT) levels at her 6-month visit (ALT 75 U/L; AST 54 U/L) and 12-month visit (ALT 76 U/L; AST 52 U/L) visits. At baseline, the enzyme levels for this patient were at the upper end of the normal ranges: ALT of 42 (normal: 0 - 45 U/L) and AST of 44 (normal: 0 - 42 U/L). Subsequent follow-up laboratory tests were not performed by the investigator since these elevations were less than 1x greater than normal and not considered to be clinically significant. Patient 0026/0001 reported alopecia following 312 days of trial therapy, which resolved.

G.3.5. Abnormal clinical laboratory findings

Two patients (0026/0001 and 0045/0001) had ALT (SGPT) levels above the upper limit of normal at their screening visit (51 U/L and 48 U/L, respectively); subsequent levels were normal. One patient (0005/0002) had ALT levels elevated at Month 6, and Month12 (75, and 76 U/L, respectively). The elevations were not ≥3x the upper limit of the normal range.

Five patients had AST (SGOT) levels above the upper limit of normal at some point during the trial (4 at their screening visit, patients 0005/0002; 0026/0001; 0033/0001; and 0045/0001, and 1 at the month 3 visit, patient 0015/0001). In all cases, the elevated enzyme levels were not considered to be clinically significant. With the exemption of patient 0005/0002, all recorded AST elevations resolved on subsequent measurements. The elevated AST levels for patient 0005/0002 were 54 and 52/L respectively at Month 6 and Month 12, respectively.

One patient (0031/0001) did not have ALT and AST measurements performed at screening. However, at all subsequent visits through the 12-month visit patient 0031/0001 had ALT and AST levels within normal limits.

No patient reported an elevation in either ALT (SGPT) or AST (SGOT) levels that was ≥3x the upper limit of the normal range.

G.3.5. Concomitant medications

A variety of concomitant treatments were taken throughout the trial by patients. These concomitant treatments included medications routinely taken by children, as well as medications taken by patients who suffer from MAS. The most commonly used medicines were cold remedies, analgesics, antibacterials, antifungals, and vitamins. Five patients (Patients 0005/0002; 0005/0003; 0026/0001; 0030/0001; and 0052/0001) were treated with leuprolide acetate for central precocious puberty prior to starting tamoxifen citrate therapy. Two patients (0026/0001 and 0030/0001) continued leuprolide acetate treatment while on-study, and 2 additional patients (Patients 0018/0001 and 0051/0001) developed central precocious puberty while on-study and were subsequently treated with leuprolide acetate. Four patients (Patients 0012/0001; 0016/0001; 0031/0001; and 0051/0001) were being treated for either hyperthyroidism (Patients 0012/0001 and 0051/0001), hypothyroidism following thyroid ablation (Patient 0016/0001), or thyrotoxicosis (Patient 0031/0001) during the study.

G.4. Adequacy of Safety Testing

Study 615US/0013 includes only 28 patients treated for one year. Despite this small patient exposure, since MAS is a very rare disease, this study represents the largest therapeutic clinical trial in this patient population.

The duration of the clinical trial (one year) is shorter than the anticipated use of tamoxifen citrate in this patient population. If one assumes an age of onset of therapy of 3 years and a lower limit of acceptable onset of puberty of 8 years, it is to be expected that tamoxifen therapy will be used for at least 5 years.

Patients enrolled in the study had clinical evaluations, clinical chemistries, pelvic ultrasounds, hormone assessments, and slit-lamp exams. The clinical chemistries seem to be limited to ALT/AST measurements. The study evaluated the drug-specific concerns

listed in the Written Request (nausea, vomiting, liver abnormalities, and cataracts). It is not clear, however, how many patients had eye exams performed (data not presented).

Important safety information associated with tamoxifen use comes also from the oncologic literature. In clinical trials of high dose tamoxifen, reversible liver failure and asymptomatic QT prolongation were noted. There was no liver toxicity noted during this trial (only one patient had mild and persistent liver enzyme elevation < 3XULN). ECGs were not done during the trial; there were no adverse events recorded which may suggest arrhythmias. It is desirable that ECGs should evaluated with future use of tamoxifen.

G.5. Summary of Critical Safety Findings and Limitations of Data

The results of this trial provide an evaluation of the safety and tolerability of tamoxifen citrate in girls with MAS and precocious puberty treated for one year.

The most important safety signal identified is a doubling in the mean uterine volume. This finding is not completely understood; it shows variability among patients, can be seen by 6 month of treatment and continues to progress over the next 12 months. Uterine enlargement is an important safety signal, especially in the light of the known risk of endometrial cancer and myometrial hypertrophy/neoplasms associated with tamoxifen use in adult females.

The majority of the adverse events reported were mild or moderate in intensity. No patient had an adverse event that led to withdrawal from this study, and no patient died during this study. Two serious adverse events were reported in this study. Neither event was considered to be treatment-related.

There were two patients who reported adverse events that were possibly treatment-related. Patient 0005/0002 had a mild elevation in AST and ALT enzyme levels at her 12 month visit and patient 0026/0001 reported alopecia at her 6 month visit. Neither of these events was considered serious.

The small increase in mean ovarian volume (approximately 15% over baseline volume) may be significant since high-dose tamoxifen use has been associated with ovarian cyst formation. A different dosage used in this trial and lack of ovarian size standards in patients with MAS limit the ability to characterize this finding.

With the exemption of the uterine volume enlargement there were no outstanding safety issues associated with the use of tamoxifen for one year in this patient population. The results describing the uterine volume changes should be added to the proposed drug labeling.

H. Dosing, Regimen, and Administration Issues

The clinical trial did not attempt to establish a minimally effective dose or a dose-range of efficacy. This undertaking would be very difficult due the rarity of the disease and the limited number of patients enrolled. In accordance to the Written Request specifications trial 6157US/0013 included a single dose regimen (20 mg). It should be noted that the same dose has been given to patients whose ages range between 2.9 years and 10.9 years at enrollment and whose weights range between 13.8 kg and 57.8 kg (mean of 27.5 kg). The 20 mg dose shows efficacy despite a wide dosage spectrum (between 1.45 mg/kg and 0.35 mg/kg). It is not known if a different dose regimen may show better efficacy or a better safety profile. Individualization of the dose regimen based on the PK study does not appear to be feasible. It should be noted that there is no pediatric formulation and no data has been provided about how the medication has been administered during the study (14 patients were less than 7 years of age and unlikely to be able to swallow whole tablets).

I. Use in Special Populations

Trial 6157US/0013 enrolled only pediatric female patients. This was consistent with the predefined entry criteria formulated by the Agency in the Written Request. The ethnic origin for the 28 patients enrolled in the study are presented in Table 36:

Table 36: Ethnic Origin (Trial 6157US/0013)

	Number and %
White	15 (53.6)
African-American	5 (17.9)
Asian	2 (7.1)
Hispanic	5 (17.9)
Other	1 (3.6)

Source: Table T2.1

The small number of patients in the trial does not allow to evaluate for effects of ethnicity on either safety or efficacy.

J. Conclusions and Recommendations

Tamoxifen citrate showed efficacy in suppressing signs and symptoms of precocious puberty in patients with McCune-Albright syndrome in a non-comparative open-label one-year trial at a daily dose of 20 mg orally. Understanding of the true size of this favorable effect may be hampered by limitations in the trial design (the pre-study baseline data were collected retrospectively).

Treatment with tamoxifen citrate for one year has been associated with a doubling of the mean uterine volume. The nature of this safety signal has not been elucidated and needs to be fully characterized due to the known carcinogenic risk associated with tamoxifen use in adults (Mourits et al, 2001). The safety of tamoxifen citrate beyond one year of therapy has not been fully established in girls with MAS and precocious puberty.

The efficacy and safety information collected by this clinical trial is larger than any clinical experience recorded in the medical literature in girls with MAS and precocious puberty. This clinical information, if incorporated in the drug labeling, can be of great help in assisting the practicing physician in the daily care of MAS patients. Therefore, the proposed labeling changes should be approved with additional corrections (see proposed labeling section, below).

In order to further enhance the safe use of tamoxifen in girls with MAS and precocious puberty this reviewer is recommending the following Phase 4 studies and risk management steps:

- A sizable group of girls with MAS who receive tamoxifen treatment should be followed for the whole duration of intended therapy. Such a group can be similar in size to the cohort evaluated in the clinical study (a minimum of 20 evaluable patients). All patients should have pelvic ultrasounds performed every 6 months which should evaluate uterine size, endometrial/myometrial changes, and ovarian size/structure. Strong consideration should be given to a centralized registry that should capture all significant reproductive organ changes in all girls with MAS who receive tamoxifen.
- All patients enrolled in the Phase 4 study should be followed with annual eye exams which should evaluate the presence of ocular adverse events noted in adult patients taking tamoxifen (such as corneal changes, cataracts, etc). This evaluation should continue for the whole duration of intended therapy.
- Most patients enrolled in the Phase 4 study should have EKG exams to rule out QT_c prolongation. This evaluation should be done at steady-state tamoxifen serum levels.
- Strong consideration should be given to the development of a pediatric formulation.

The following changes and additions to the proposed labeling should be made:

- The responder analysis should be de-emphasized and replaced with data describing mean changes and individual trends noticed on-therapy for the major endpoints (vaginal bleeding, bone age rate of increase, and growth rate). Methodological limitations on the efficacy data should be included in the clinical section of the drug labeling (retrospective data collection).
- The safety information concerning the doubling in mean uterine volume size should be included along with a description of the time frame of occurrence. The lack of definition of this safety signal should be emphasized.

This reviewer recommends the following changes to the sponsor's proposed labeling:

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

Pages
70-71

K. Appendix: Bibliography

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