CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

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

Statistical Review(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-109
Name of drug:	**Nolvadex (tamoxifen) 20 mg tablets**
Applicant:	AstraZeneca
Indication:	McCune-Albright Syndrome
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Documents reviewed	\\CDSESUB1\N21109\N_000\2002-02-28\clinstat\uncontrolled\us0013.pdf
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Dates:	Received 2/28/02; user fee (6 months) 8/1/02
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Keywords: NDA review, clinical study, one-study application, pediatric exclusivity

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1 Introduction

The sponsor submitted a single uncontrolled, open-label study to support the safety and efficacy of Nolvadex (tamoxifen) 20mg daily in pediatric female patients with McCune-Albright Syndrome (MAS). The study was conducted in response to an April 5, 2000, FDA Written Request (WR) MAS is a rare disorder characterized by precocious puberty, polyostotic fibrous dysplasia, and cafe au lait spots.

2 Design

The study duration was 1 year and was to include a six-month observational period prior to initiation of treatment. All patients were to receive Nolvadex treatment. Table 1 shows the major design characteristics.

Table 1. Study characteristics.

Trial #/ Centers/ Dates	Patients	# treated	Design Primary endpoint	Duration
6157US/0013 20 centers 3/30/00 – 10/30/01	Females age 10 or younger with McCune-Albright Syndrome (MAS)	N=28	Open-label Partial or complete response based on 4 criteria related to vaginal bleeding episodes, bone age and growth rate.	1 year treatment 6-month observational period prior to treatment

Females age 10 years or younger were screened for eligibility based on the following criteria: (1) demonstrated classic or atypical MAS and (2) signs or symptoms of precocious puberty manifested by signs of pubertal development, episodes of vaginal bleeding [1], or significantly increased bone age (>2 SD above the mean, later amended to 12 months beyond chronological age). Vaginal bleeding and bone age criteria were therefore each sufficient but not necessary conditions for study enrollment.

The primary objective of the study was to evaluate the safety and efficacy of Nolvadex 20mg in patients with MAS. The primary efficacy endpoint per the WR was clinical response to treatment, classified as partial or complete response, based on the following criteria:

1. Reduction of at least 50% in the number of vaginal bleeding episodes during the study period

[1] The sponsor used the term vaginal bleeding in the Final Report which replaced he terms menses and menstrual bleeding used in the protocol

2. Cessation of vaginal bleeding (no episodes in a six-month period)

3. Reduction in bone age increase to ≤6 months in a six-month period

4. Reduction of growth velocity to ≤0.8 standard deviations above normal for chronological age.

A complete responder was a patient who met criteria 2, 3 and 4. A partial responder was a patient who met any of the criteria (criteria 1, 2, 3 or 4).

The sponsor interpreted the FDA request for a 6-month observational period prior to treatment by obtaining past medical histories. Actual durations of pre-study periods were delineated by the dates corresponding to the records the sponsor obtained for each patient As a result, pre-study durations varied considerably from patient to patient, from 2½ months to 2½ years. Patients could also have different pre-study periods for each efficacy variable (vaginal bleeding, bone age, growth).

In a May 10, 2002 teleconference, the sponsor confirmed that multiple pre-study records for a patient on the same measurement were sometimes available to the study. In this case, the sponsor selected the measurement closest to six months prior to treatment. The sponsor decided in some cases to obtain prospective pre-study x-rays when the retrospective data were of poor quality. The sponsor did not elaborate on the specific criteria used to judge data quality.

Patients were screened for MAS at Visit 1. Following Screening (up to 6 weeks later), eligible patients were treated with Nolvadex at Month 0 (Visit 2) and observed for 12 months. Clinic visits were scheduled at Months 0, 3 (Visit 3), 6 (Visit 4) and 12 (Visit 5).

The WR specified that a number of statistical tests be performed. One-sample t tests were to be used to compare pre-study growth rate and bone age increase to rates during treatment. Exact 95% confidence intervals were to be calculated for: (1) the proportion of patients with a ≥50% reduction in the number of vaginal bleeding episodes during the study period; (2) the proportion of patients with complete cessation of vaginal bleeding episodes; and (3) the proportion of patients who were complete responders.

3 Reviewer's methods

The sponsor submitted the Final Study Report and raw data to the Electronic Document Room (EDR).

All Tables and Figures were created by this reviewer.

If the reviewer's data summaries or statistical results differed from the sponsor's, the differences were noted.

Results for the response variables (Criteria1-4, partial and complete response) are found in the Appendix. Responder status was evaluated only for patients in whom the symptom existed prior to treatment. This reviewer chose not to include 95% confidence intervals for response rates due to the lack of reliable clinical benchmarks for comparison. Vaginal bleeding, bone age and growth rate were examined as continuous measures rather than as categorical measures in the main body of the review.

4 Baseline / demographics

The trial enrolled 28 female patients from 20 US centers. The mean age of patients at screening was 6.5 years (range: 2.9-10.9 years). Table 2 shows key demographic/ baseline characteristics for all enrolled patients.

Table 2. Key demographic / baseline variables

Variable	Nolvadex 20mg (n=28)
Age (yrs) [1]	
Mean (SD)	6.5 (2.4)
Min	
Max	
Race (n,%) [1]	
Caucasian	15 (54%)
African American	5 (18%)
Asian	2 (7%)
Hispanic	5 (18%)
Other	1 (4%)
Height (cm) [2]	
Mean	123.9 (15.3)
Min	
Max	
Weight (kg) [2]	
Mean	27.5 (9.8)
Min	
Max	

[1] At Screening (Visit 1)
[2] Measured at Month 0 (Visit 2)

5 Disposition

All patients received some exposure to Nolvadex. Twenty-five (25) of 28 patients completed one year of Nolvadex treatment. The 3 patients who discontinued early received at least 5 months of treatment (Table 3).

Table 3. Patients discontinued early from treatment

Patient ID	Reason for discontinuation	Duration of treatment (days)
0025/0001	Informed consent withdrawn	167
0030/0004	Lost to follow-up	148
0051/0001	Progression of disease	265

Patient 0051/0001 withdrew early due to disease progression, specifically an increase in vaginal bleeding from 1 episode pre-study to 3 episodes during the first 6 months of treatment and a total of 5 episodes during 8 months of treatment.

6 Efficacy

6.1 Bone age

Bone age (BA) x-ray data were collected prospectively at screening, Month 6 and Month 12.. Retrospective x-rays were obtained from the sites and used for the purpose of computing pre-study rates of increase to serve as historical controls. All x-rays were evaluated by the ——— if available. If no actual film was available as pre-screening data, then the radiology report became the source record. It is not known how many pre-screening x-rays were available to the study.

Pre-Screening assessments of bone age were made an average of 283 days (~9 months) prior to screening. The median duration was 220 days. Assessments were highly variable with respect to the time they were conducted prior to screening (range: 90 to 918 days).

The standard unit of measure for bone age is years. The sponsor defined the ***rate of increase*** in bone age over a specified time period as the change in bone age in years (ΔBA) divided by the change in chronological age (ΔCA) in years:

$$\text{Rate of increase in bone age per time interval} = \Delta BA \; / \; \Delta CA$$

The therapeutic goal was to reduce the rate of increase from >1 pre-study to <1 during Nolvadex treatment.

Table 4 shows raw bone age measurements and bone age rates of increase for all treated patients with data. Due to missing data before or at screening, pre-study rates of increase could not be calculated for 6 patients. Twenty-one (21) of the 28 treated patients (75%) furnished endpoint data, i.e., had both pre-study and on-study rates of increase. The last line of the Table shows summary data for the change from pre- to on-study (12 month) bone age rates of increase. A negative change for a patient indicated the rate of increase slowed during treatment, a beneficial clinical outcome. A positive change for a patient indicated the rate of increase accelerated during treatment, a negative clinical outcome.

Table 4
Bone age and rate of increase in bone age for all treated patients

	N	Mean (SD)	Median	Range
Bone age (yrs)				
Pre-Screening	25	8.80 (2.33)	9.22	
Screening	24	9.13 (2.45)	9.73	
Month 6	24	9.70 (2.37)	10.42	
Month 12/ final visit	26	10.10 (2.37)	10.63	
Rate of increase in bone age (unit-less)[1]				
Pre-screening to screening ("pre-study")[2]	22	1.25 (0.79)	1.44	
Screening to Month 6	21	0.80 (0.66)	0.65	
Month 6 to Month 12 /final visit	24	0.67 (0.48)	0.59	
Screening to Month 12 /final visit	23	0.72 (0.36)	0.66	
Change from pre-study to M12/final visit[3]	21	-0.54 (0.97)	-0.34	

[1] Defined as the change in bone age (yrs) divided by the change in chronological age (yrs) over a given time period
[2] The pre-study period serves as a historical baseline for each patient.
[3] Stated more precisely, this endpoint is the absolute difference between pre-study and on-study bone age rates of increase

Figure 1 shows the raw bone age measurements for each patient at each measured time point. The vertical line (Month 0) indicates the initiation of Nolvadex treatment. Since no radiograph was taken at Month 0 (Visit 2), the radiographs on the graph closest to Month 0 are the Screening visit radiographs (Visit 1) which could occur anytime up to six weeks before Month 0. The graph clearly shows the marked variability in pre-study assessment times relative to screening. .

Figure 1

Individual patient data for raw bone age (years)

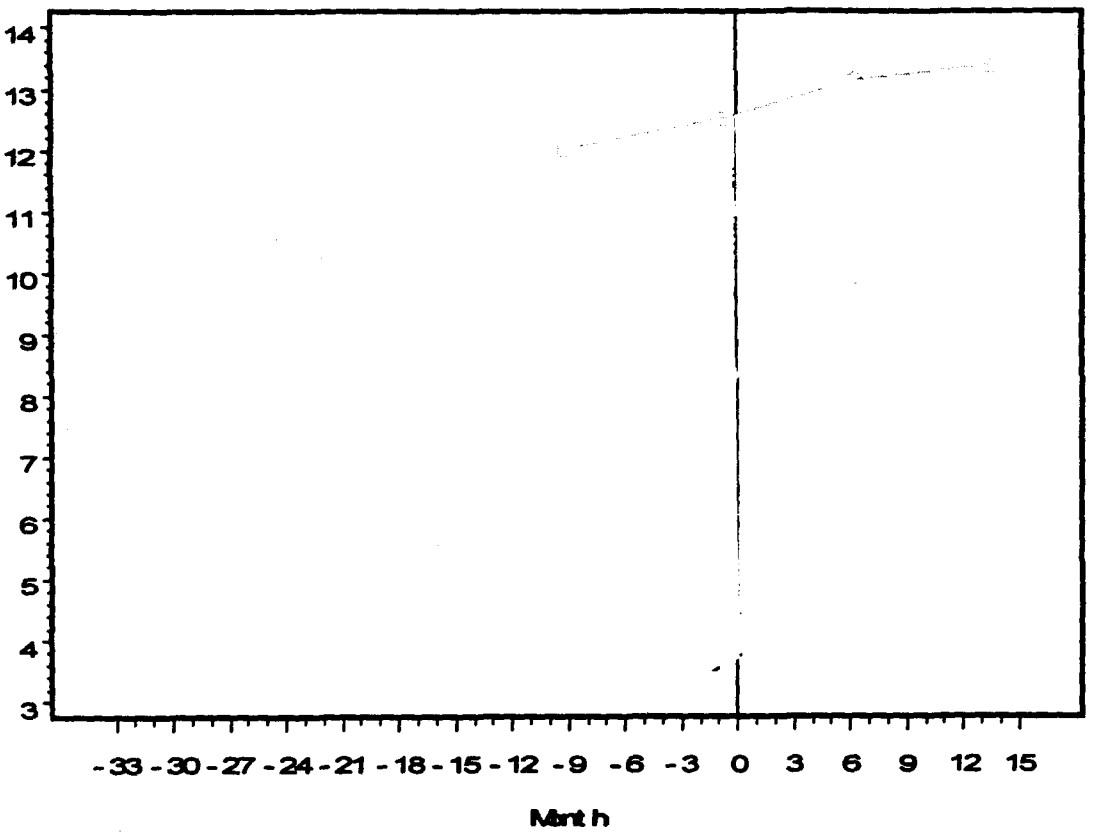
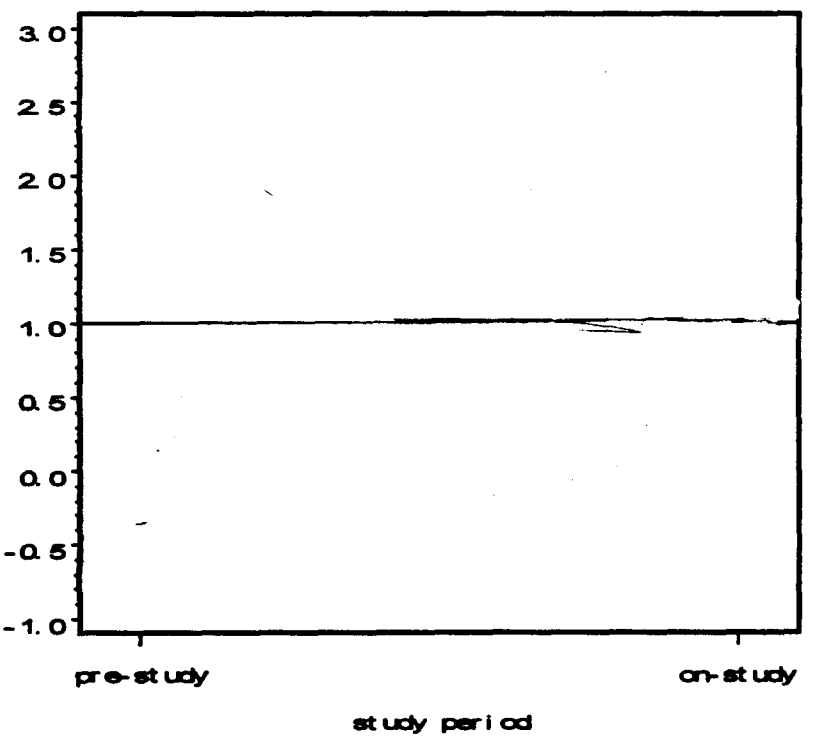


Figure 2 shows individual patient data for bone age rates of increase during pre- and on-study (12 month) periods. The horizontal line at 1 indicates the therapeutic goal. Data for the same patient are connected by a solid line to illustrate the change in rates after exposure to Nolvadex.

Thirteen (13) of the 21 patients with data had negative changes in bone age increase from pre-study to on-study. The mean change for the 21 patients with data was –0.54 (95%CI -0.98, -0.09). The sponsor conducted a paired t test of the difference in rates of increase in bone age between pre-study and on-study periods. The difference was statistically significant (p=.020). Although the data were roughly normally distributed (Wilk-Shapiro test for normality was not significant), due to the small sample size this reviewer performed a (nonparametric) signed rank test. The result was also statistically significant (p=.017).

Figure 2

Individual patient data for bone age rates of increase
(Rate of increase = (change in bone age) / (change in chronological age))



The Figure shows clearly that pre-study rates of increase were more variable than on-study rates. The variance of pre-study rates was 0.62 compared to 0.13 for 12-month on-study rates, a nearly 5-fold difference (see Table 3 which shows the standard deviations). Pre-study rates of increase ranged from –0.31 to +2.54 whereas on-study rates ranged from +0.23 to +1.22, a nearly 3-fold difference in ranges. The larger variability of the pre-study rates may be due in part to some patients (n=8) who had assessments close to screening (<180 days) since there was a general trend for the variability of on-study rates to diminish when the bone age rate of increase was observed over longer time periods.

Overall, there were several negative characteristics of the pre-study bone age data: (1) substantially higher variability in rates of increase during pre-study relative to the 12-month on-study period; (2) a nontrivial percentage of missing pre-study x-rays (>20%); and (3) the differing quality in the pre-study data collection process for some patients (retrospective for some and prospective for others). Due to these shortcomings, this reviewer conducted analyses of the on-study (12-month) rates of increase without pre-study data. The objective of these analyses was to test the null hypothesis that the mean 12-month rate of increase was ≥1 vs the alternative that the mean rate was <1. A one-sided 2.5% level one-sample t test of the 12-month rates was used to test the null hypothesis.

Results of the analysis showed the mean rate of increase (+0.72, Table 1) was statistically significant (p<.001) thus providing strong statistical evidence in support of the alternative hypothesis that the mean rate was smaller than 1. This calculation used data for 23 patients and did not include the 5 patients with missing 12-month rates. This reviewer conducted a sensitivity analysis which showed the result was not materially influenced by the missing data [2].

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[2] While many such sensitivity analyses are possible, this reviewer selected an analysis that calculated the worst (highest) rate the 5 patients could have had and still have retained nominal statistical significance (p=.025) over the entire sample of 28 patients.

The sensitivity analysis showed that all 5 patients could have been assigned a 12-month rate of increase equal to +1.48 to obtain p=.025 for the entire sample. (Less extreme results for the 5 patients (imputed rates of increase smaller than 1.48) will always produce smaller, more significant p-values.) The imputed rate is high relative to the observed data for the rest of the sample and relative to other data for some of the same 5 patients. Specifically, only 2 of 23 patients had observed 12-month rates higher than the imputed rate. Three of the 5 patients with missing 12-month data had 6-month data for the period from Month 6 to Month 12. The observed 6-month rates for these patients were 0.59. 0.92, and 0.20 which are smaller than the imputed rate. Based on this exercise, the statistical result appeared to be robust to the missing 12-month data.

6.2 Growth rate

Height was measured prospectively at all visits. Retrospective height data was collected to allow calculation of pre-study growth rates. Pre-study measurements were made an average of 9½ months prior to Month 0 and, like bone age, were highly variable with respect to the time they were conducted prior to treatment (range: 2.6 months to 2.7 years before Month 0). Pre-study height assessments used in the study were often not performed on the same day x-rays used for pre-study were performed.

Table 5 shows growth rates for all treated patients with data. The Z-score is the growth rate from the previous to the current visit minus the mean divided by the SD where the mean and SD are the age- and gender-specific data from the study. Age is the age of the current visit.

Table 5. Growth rates for all treated patients

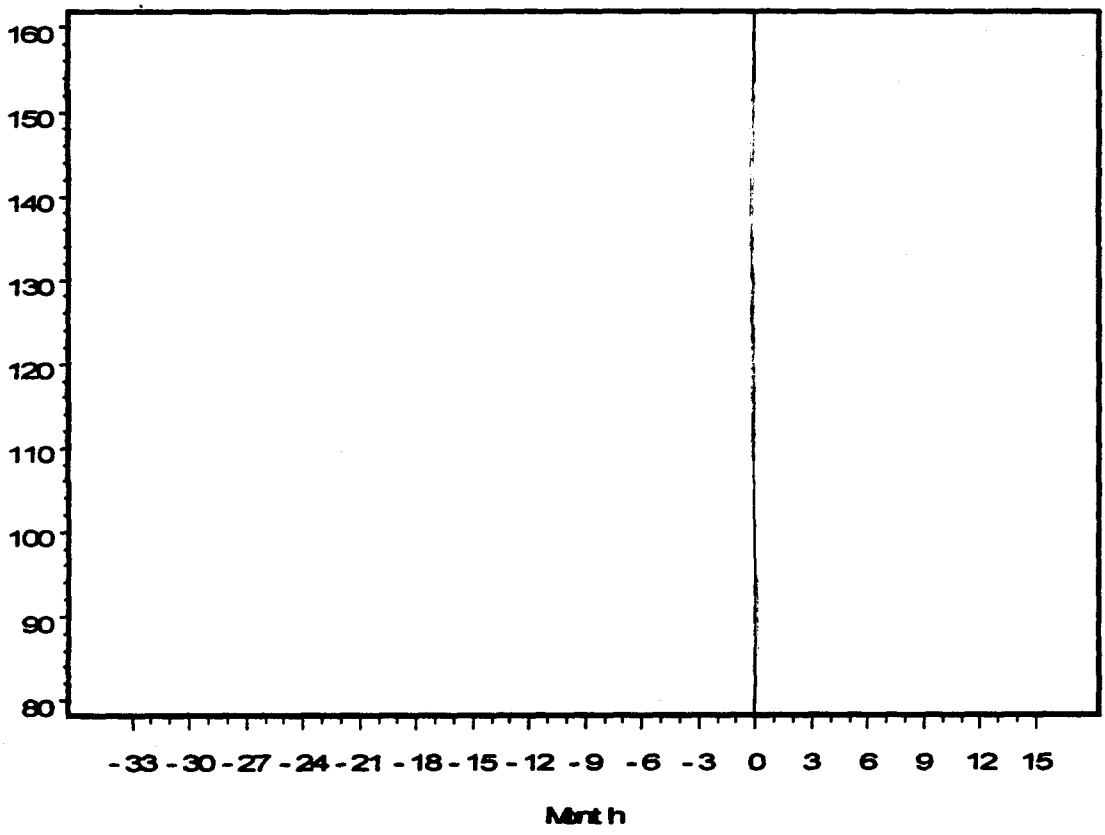
	N	Mean (SD)	Median	Range
Growth rate (cm/yr)				
Pre-screening to Month 0 [1]	28	7.58 (2.61)	7.08	
Month 0 to Month 12 / final visit	26	5.79 (3.01)	5.68	
Change from pre-screening	26	-1.68 (2.75)	-2.29	
Growth rate (Z-score [2])				
Pre-screening to Month 0 [1]	28	1.26 (2.72)	0.99	
Month 0 to Month 12 / final visit	26	-0.61 (3.00)	-0.57	
Change from pre-screening	26	-1.84 (2.90)	-2.41	

[1] Includes 2 patients with pre-screening and Month 0 data only

[2] Z-score is the growth rate from the previous to the current visit minus the mean divided by the SD where the mean and SD are the age- and gender-specific data from the study. Age is the age of the current visit.

Figure 3 shows the raw height measurements (cm) for each patient at each time point. The vertical line (Month 0) indicates the initiation of Nolvadex treatment. The Figure clearly shows that pre-study assessment times varied considerably from patient to patient.

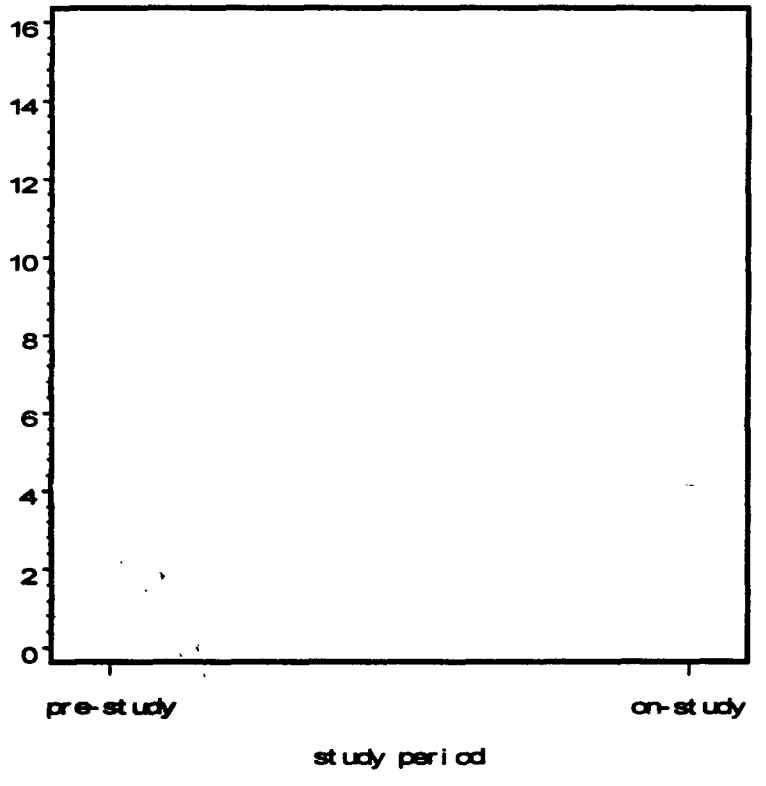
Figure 3
Individual patient raw data for height (cm)



Individual patient growth rates during pre-study and 12-month on-study periods are shown in Figure 4. Data for the same patient are connected by a solid line to illustrate the change in rates after exposure to Nolvadex. . Twenty (20) of the 26 patients with data had reductions in growth rates after Nolvadex treatment. Unlike bone age, the pre-study and on-study growth rates showed comparable variability.

Figure 4

Individual patient data for growth rates (cm/yr)



The mean pre-study growth rate was reduced from 7.5 cm/yr to 5.8 cm/yr on-study. The between-group difference was -1.7 cm/yr. Differences between pre-baseline and on-treatment growth rates, as measured by cm/yr and z-score, were statistically significant ($p \leq .0046$).

6.3 Vaginal bleeding episodes

Parents or patient guardians kept daily diaries during the study to record patient episodes of vaginal bleeding. An episode was defined as an interval of daily or intermittent vaginal bleeding which was followed by 14 days or longer with no vaginal bleeding. Thus to qualify as a distinct episode, the vaginal bleeding had to be separated by at least 14 days free of bleeding. Six patients had missing diary data at some time during the study: 0016/0001 (2 days) 0023/0001 (87 days), 0025/0001 (84 days), 0030/0004 (10 days), 0045/0001 (161 days) and 0052/0001 (1 day).

Parents or guardians were asked to remember all episodes occurring up to 6 months prior to the study (screening minus 180 days). These recollections served as pre-study data. All 28 sets of parents/guardians provided pre-study data.

Table 6 shows the frequency of pre- and on-study bleeding episodes. The Table also shows the sponsor's worst-case scenario. This scenario assumed bleeding occurred on days with missing diary entries.

Table 6. Frequency of bleeding episodes

Study period	N	Mean (SD)	Median	Range
Pre-study [1]	27 [4]	3.56 (3.30)	2	
On-study actual episodes [2]	27 [4]	1.04 (1.45)	0	
On-study worst-case [3]	27 [4]	1.73 (2.35)	1	

[1] Number of episodes per 6 months (Screening minus 180 days), annualized
[2] Actual (observed) number of episodes
[3] Number of episodes per 12 months, annualized, calculated on a worst-case basis in which bleeding was assumed to have occurred on days with missing diary entries
[4] Patient 0045/0001 omitted from calculations due to continuous intermittent bleeding so that the frequency of bleeding episodes could not be established

Nolvadex reduced the mean pre-study frequency by >50% from 3.56 to 1.73 (worst-case). The difference in frequency of episodes between study periods was statistically significant (reviewer's one sample t test, p=.007)

Table 7 shows the duration of pre-study and on-study (actual) episodes for patients experiencing at least one episode of vaginal bleeding [3]. Eleven patients had both pre- and on-study episodes and therefore contributed duration data to both pre- and on-study periods.

While patients experienced a decrease in the average number of episodes from pre- to on-study, on-study episodes lasted an average one day longer compared to pre-study episodes. This difference was not statistically significant.

Table 7. Average duration of vaginal bleeding episodes (includes only patients experiencing at least one episode)

Study period	N	Mean (SD)	Median	Range
Pre-study [1]	20 [3]	4.00 (3.13)	3	
On-study [2]	13 [4]	5.01 (2.89)	4.3	

[1] Covering the period from screening minus 180 days to screening
[2] Based on actual (observed) episodes
[3] Twenty (20) patients had ≥1 pre-study episode. Patients without a pre-study episode were not included in the Table
[4] Thirteen (13) patients had ≥1 on-study episode. .Patients without an on-study episode were not included in the Table

7 Summary and conclusions

The sponsor submitted data for a 1-year uncontrolled study of Nolvadex in 28 pediatric females with McCune Albright Syndrome. The sponsor interpreted the FDA request for a 6-month observational period prior to treatment by obtaining past medical histories. The primary efficacy endpoint was clinical response to treatment, classified as partial or complete response, based on criteria for bone age, growth rate and vaginal bleeding episodes. This reviewer analyzed these 3 variables as continuous measures rather than as binary variables.

Nolvadex was associated with statistically significant slowing in growth. The growth rate slowed from a mean 7.5 cm/year pre-study to 5.8 cm/yr with Nolvadex treatment ($p \leq .0046$). Nolvadex also significantly reduced the frequency of vaginal bleeding episodes from 3.6 per year pre-study to 1.7 per year during treatment based on a worst-case assessment (p=.007).

Assessing efficacy for bone age was a more complex issue than for vaginal bleeding and growth rate due to the inherent variability in the measurement and

[3] Sponsor's Table G8.1 shows duration data for all 27 patients, including patients who did not experience vaginal bleeding episodes. Patients without episodes were assigned a duration equal to zero.

to shortcomings in the quality of the pre-study data. Pre-study data for bone age were characterized by deficiencies not present for vaginal bleeding and growth: (1) bone age pre-study rates of increase were almost 5 times as variable as on-study 12-month rates; (2) there was a nontrivial percentage of missing x-rays at screening or before (>20%); and (3) the pre-study data collection process was not consistent, retrospective for some patients and prospective for others.

This reviewer examined on-study rates of increase without pre-study data. Bone age rates of increase on treatment averaged 0.72 which was statistically smaller than 1, the therapeutic goal ($p<.001$).

Although the quality of the study was diminished somewhat by the pre-study data, the statistical results were sufficiently strong so that the observed effects can reasonably be attributed to Nolvadex treatment.

8 Recommendations for labelling

- The proposed label presents response rates for bone age, growth rate and vaginal bleeding episodes. The results would be more informative and more inclusive if presented as continuous outcomes. E.g, instead of "there was a reduction in growth rare in 9 of 15 patients who exhibited excessive growth in height during the pre-study period", better language is "the average growth rate slowed from 7.5 cm/year during the pre-study period to 5.8 cm/yr with Nolvadex treatment."
- Label on-study bone age data only; not pre-study data

/S/

J. Todd Sahlroot, Ph.D.
Mathematical Statistician

Concur: Dr. Nevius

Cc:
NDA 21-109
HFD-510/MJohnson, DRoman, DOrloff
HFD-715/ENevius, TSahlroot
HFD-700/CAnello

APPENDIX – Responder (categorical) endpoints

As part of the Written Request, the sponsor was asked to evaluate response rates for the following primary endpoints:

1. Reduction of at least 50% in the number of menstrual bleeding episodes during the study period

2. Cessation of menses (no episodes in a six-month period)

3. Reduction in bone age increase to ≤6 months in a six-month period

4. Reduction of growth velocity to ≤0.8 standard deviations above normal for chronological age.

In this Appendix, summary data are presented for each major endpoint (bone age, growth rate, and vaginal bleeding episodes). Although the WR called for confidence intervals to be applied to the various response rates, they are not presented here due to the lack of reliable clinical benchmarks for comparison.

Bone age

A responder was defined as a patient whose rate of bone age increase was >1 (unfavorable outcome) pre-study and was <1 (favorable outcome) during either 6-month period while on-study. There were 13 patients whose pre-study rates of increase were >1.

Based on the above criterion, 10 of 13 patients (77%) were Nolvadex responders (Table A1). The 3 non-responders were missing 6-month data and therefore did not have bone age rates for either 6-month on-study period. Although these patients could not be classified as responders, 2 of the 3 patients had 12-month rates that were less than 1. Although Nolvadex reduced bone age rates to <1 when pre-study rates were high (>1), 7 of 9 patients with low pre-study rates (<1) had their rates increase to >1 at some time during the study (see also Figure 2).

No patient had bone age increases >1 during both 6-month periods.

Table A1. Number of patients classified by bone age response

Pre-study Rate of increase	On-study bone age rates of increase: First 6-mo rate and second 6-mo rate				
	<1 and <1	<1 and >1	>1 and <1	>1 and >1	Incomp data
<1 (n=9) [1]	2	3	4	0	0
>1 (n=13)	6 [2]	2 [2]	2 [2]	0	3

[1] Subjects with pre-study bone age increases < 1 were still eligible for enrollment in the study based on other criteria but could not be classified as bone age responders or non-responders.

[2] Responders by the criterion of the WR

Growth rate

A growth rate responder was defined as a patient whose growth rate decreased from greater than 0.8SD above the mean growth rate for a normal female of that patient's chronological age (unfavorable outcome) prior to the study to below that rate (favorable outcome) after 12 months of treatment with Nolvadex. Nine (9) of 15 patients (60%) whose pre-study growth rates were greater than 0.8SD above the mean growth rate for a normal female of the patient's chronological age were Nolvadex responders (Table A2).

Table A2. Number of patients classified by growth rate response [1]

Pre-study growth rate	On-study (12-month) growth rate		
	< normal mean + 0.8SD	> normal mean + 0.8SD	No data
< normal mean + 0.8SD (n=13) [2]	9	3	1
> normal mean + 0.8SD (n=15)	9 *	5	1

[1] A favorable clinical response is a growth rate which is less than 0.8SD above the mean growth rate for a normal female of that patient's chronological age
[2] Subjects with pre-study growth rates < normal mean + 0.8SD were eligible for enrollment in the study but could not be classified as responders or non-responders.
* Responders by the criterion of the WR

Patient 0051/0001 was a growth rate responder yet discontinued early due to disease progression related to an increased number of vaginal bleeding episodes.

Vaginal bleeding episodes

A positive response was defined in two ways: (1) a 50% percent reduction in vaginal bleeding episodes from pre-study to on-study using 12-month annualized rates and (2) cessation of bleeding episodes during treatment. The latter was defined as 0 episodes during any consecutive 180 day period.

Table A3 shows results for the 2 response criteria for the 21 patients who had at least one episode of vaginal bleeding during pre-study.

Table A3. Response rates for patients with least one episode of vaginal bleeding during pre-study (n=21)

50% reduction in episodes from pre- to on-study [1]			Cessation of bleeding episodes during on-study [2]		
Yes	No	No data	Yes	No	No data
14/21 (67%)	6/21 (29%)	1/21 [3] (5%)	13/21 (62%)	7/21 (33%)	1/21 [3] (5%)

[1] Percent reduction calculated based on 12-month annualized rates
[2] Cessation of bleeding defined as 0 episodes during any consecutive 180 day period during treatment
[3] Patient 0045/0001 had continuous intermittent bleeding so that the frequency of bleeding episodes could not be established

Not shown in the Table are 7 patients who had 0 episodes of vaginal bleeding during pre-study. The response criteria could not be applied to these patients. Five of the 7 patients had 0 episodes of vaginal bleeding during treatment, while 2 patients had new episodes during treatment (1 and 3 episodes each).

Partial and complete response

A complete responder was defined as a patient who met response criteria 2, 3 and 4 above. A partial responder was defined as a patient who met any of the criteria above (criteria 1, 2, 3 or 4). Table A4 below shows the number of patients by response category.

Table A4. Number of patients with complete, partial or no response

Complete response	Partial response	Non-responder
6/28 (21%)	18/28 (64%)	4/28 (14%)

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/s/

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Concur with review.