U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 213150
Supplement #:	NA
Drug Name:	Leuprolide acetate for injection suspension, 45 mg
Indication(s):	Central Precocious Puberty
Applicant:	Tolmar
Date(s):	Date submitted: July 2, 2019
	PDUFA due date: May 20, 2020
Review Priority:	Standard
Biometrics Division:	II
Statistical Reviewer:	Jiwei He, PhD
Concurring Reviewers:	Feng Li, PhD (Acting statistical team leader)
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Keywords:

Central Precocious Puberty, Single Arm

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1. EXECUTIVE SUMMARY

Tolmar has developed leuprolide acetate for injectable suspension, 45 mg (proposed name FENSOLVI®) as a treatment for children with central precocious puberty (CPP). My statistical review of the efficacy results suggests support for the CPP claim. This NDA is approvable from statistical and efficacy point of view.

This application contains one uncontrolled, open-label phase 3 study TOL2581A. The primary efficacy endpoint was suppression of stimulated serum luteinizing hormone (LH) concentrations to <4 IU/L, 30 minutes following an abbreviated GnRHa stimulation at Week 24 (Month 6). It was pre-specified that the primary endpoint would be met if there were greater than 80% responders. Subjects in the study were required to have pubertal-type LH response (>5 IU/L) after a GnRHa stimulation test before treatment initiation.

The primary endpoint was met: 54/62 (87.1%) of the patients in the intent-to-treat (ITT) population achieved serum LH concentrations <4 IU/L at 30 minutes post GnRHa simulation at Week 24, with 95% CI of 76.2%-94.3%. Results from the secondary endpoints were also supportive.

Although study TOL2581A did not have a placebo control, we are not very concerned about its impact on the conclusion of efficacy, since all except one of the 62 subjects in the ITT population had reduction in LH level from screening, and many had fairly large reduction. The extent of LH suppression cannot possibly be achieved by placebo effect alone. Refer to Section 5.1 for details on minor statistical issues in this study.

2. INTRODUCTION

2.1 Overview

Tolmar has developed leuprolide acetate for injectable suspension, 45 mg (proposed name FENSOLVI®) as a treatment for children with central precocious puberty (CPP). This submission contains one uncontrolled, open-label phase 3 study.

2.2 Data Sources

The data and final study report were submitted electronically. The submission was under the network path location: \\CDSESUB1\evsprod\NDA213150\0001. The applicant later resubmitted the datasets containing a revised ITT population, following FDA's advice in the 74-day letter. The revised datasets are under the network path location: \\CDSESUB1\evsprod\NDA213150\0005. My review used adsl, adlb, adef, adef2 and advs ADAM datasets.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Datasets were provided in both STDM and ADAM format and appeared to be in good quality. Define file and reviewer's guide were provided. I did not refer to the applicant's SAS programs for the simple analyses required for this NDA.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study TOL2581A was a multi-center, open-label, single-arm 12-month study. Subjects in the study were required to have a pubertal-type LH response (i.e., >5 IU/L) after a GnRHa stimulation test conducted before treatment. Treatment was given twice at the start of the study and at Week 24 (6-month). Screening was within 28 days from start of the study. There was no additional baseline measurement for LH suppression and other laboratory measurements other than the ones at screening.

The efficacy analysis population was intent-to-treat (ITT) population, defined as subjects providing consent/assent who received at least one dose, fulfilled protocol eligibility criteria, and provided at least one PD laboratory assessment post dosing. The safety population was all subjects providing consent/assent and who received at least one dose of the study drug.

The primary objective was to determine the effectiveness of leuprolide acetate 45 mg for injectable suspension for the treatment of children with CPP. The primary efficacy endpoint was suppression of stimulated serum LH concentrations to <4 IU/L 6 months after the first injection. The secondary endpoints included:

- Percent change from baseline in height

- Growth velocity of height in cm/year (change from baseline/time from baseline)
- Ratio of bone age to chronological age
- Percent change from baseline in LH, FSH, Testosterone, and Estradiol
- Baseline to end-of-study shifts for each Tanner category
- The percent change from baseline in systemic leuprolide concentration

3.2.2 Statistical Methodologies

There was no formal statistical testing for this study. The SAP stated that the primary endpoint would be met if greater than 80% of the subjects in the ITT population demonstrated this level of LH suppression 30 minutes after an abbreviated GnRHa stimulation test at Week 24. The sample size was planned to rule out a lower limit of 70% for the primary endpoint. The Clopper Pearson Exact method was used to compute the 95% confidence interval (CI) for the binomial proportion in the statistical reviewer's analysis.

Since all the secondary endpoints were considered exploratory, there was no multiplicity adjustment.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient dispositions were presented in Table 1. There were 62 subjects in the ITT population, which was used for efficacy analyses. Refer to Section 5.1.1 for details on the revision history for this analysis population. All the 62 subjects had response status for LH suppression at Week 24, the primary endpoint. Refer to Section 5.1.2 for missing data handling.

Patient demographics were presented in Table 2. All but 2 of the subjects were female. Around half of the subjects were white, and around half of the subjects were from USA. Most of the subjects aged 7-8 (Figure 1).

All patients in the ITT population had a post-GnRHa LH > 5 IU/L at screening. About 90% of the patients had screening LH level in the range of 5.1 to 53.5 IU/L, with a few patients having extremely high LH level at screening (Figure 2).

Table 1 Patient Dispositions

Dispositions	**Study TOL2581A**
Screen Failure	50
ITT Population[1]	62
Safety Population[2]	64
Completed Trial[3]	60 (93.8)
Early Termination[3]	4 (6.3%)
Lack of Efficacy	1
Required Concomitant Medication	1
Protocol Deviation	1
Withdrawal by Parent/Guardian	1

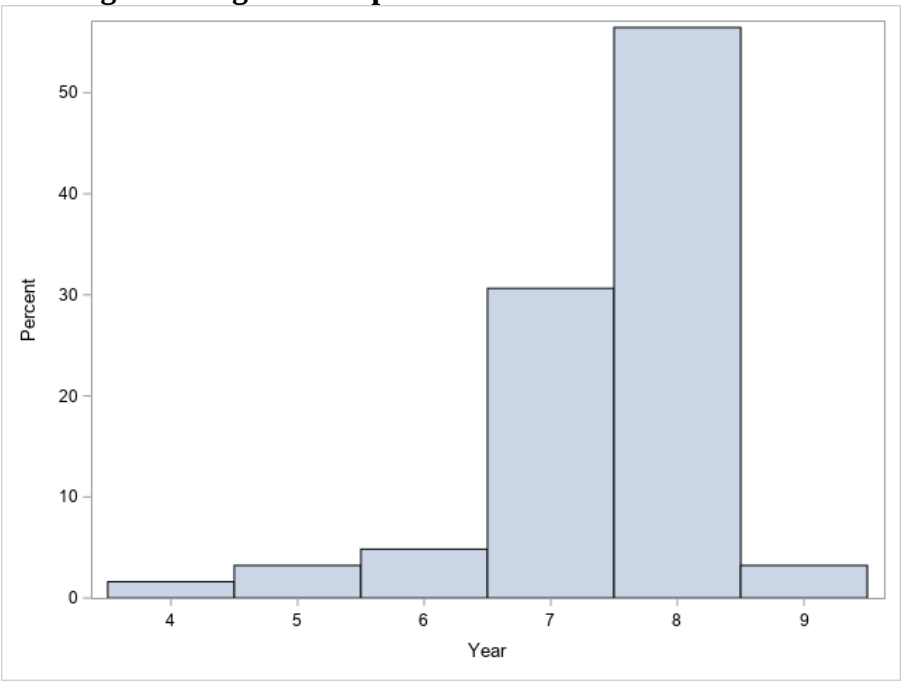
Source: Statistical Reviewer's Analyses

Table 2 Patient Demographics-ITT Population

Characteristics	ITT Population (N=62)
Age	
Mean (SD)	7.5 (0.90)
Min, Max	4, 9
Sex, n(%)	
Male	2 (3.2%)
Female	60 (96.8%)
Race, n(%)	
American Indian Or Alaska	5 (8.1%)
Asian	3 (4.8%)
Black Or African American	15 (24.2%)
Native Hawaiian Or Other	1 (1.6%)
White	32 (51.6%)
Unwilling to Provide	1 (1.6%)
Other	5 (8.1%)
Ethnicity, n(%)	
Hispanic Or Latino	35 (56.5%)
Not Hispanic Or Latino	27 (43.5%)
Country, n(%)	
USA	29 (46.8)
Non-USA	33 (53.2)

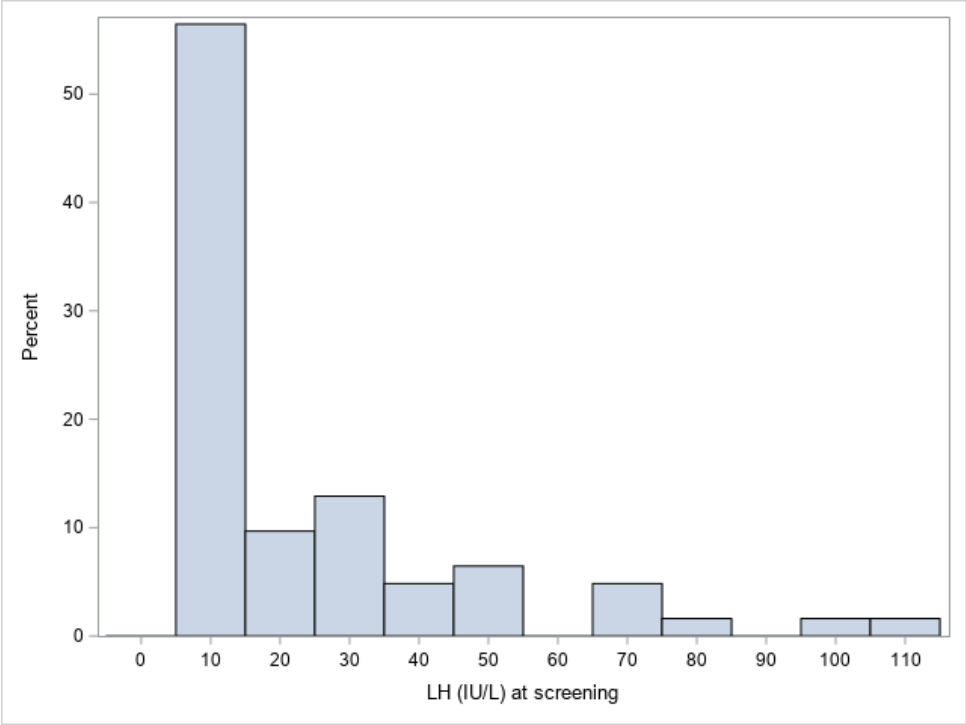
Source: Statistical Reviewer's Analyses

Figure 1 Histogram of age-ITT Population



Source: Statistical Reviewer's Analyses

Figure 2 Histogram of Luteinizing Hormone Level at Screening-ITT population



Source: Statistical Reviewer's Analyses

3.2.4 Results and Conclusions

54/62 (87.1%) patients achieved serum LH concentrations <4 IU/L at 30 minutes post GnRHa simulation at Week 24, with 95% CI (Clopper Pearson Exact CI) of 76.2%-94.3%. Since the percent of responders was higher than 80%, the primary endpoint was met.

Figure 3 shows the median post GnRHa LH level at each analysis visit. The error bars represent interquartile range (IQR). The median LH level decreased sharply from screening to Week 12 and maintained low until Week 48. Figure 4 shows the trajectories from individual patients. Consistent with Figure 2, the subjects had a wide range of post GnRHa LH level at screening, but most of them decreased to around threshold level (4 IU/L) by Week 12. Figure 5 highlighted the 10 subjects who either did not reach post GnRHa LH < 4 IU/L at Week 24 or discontinued the study before Week 24. Among them, one subject showed obvious lack of efficacy and discontinued early around 100 days. Two subjects discontinued close to Week 24 and their end-of-treatment (EoT) LH levels were below the threshold 4 IU/L. Figure 6 shows change in GnRHa LH level from screening to Week 24 in individual patients. All except one subject had reduction in LH from screening and many had fairly large reduction. In overall, the treatment effect of the drug was clear.

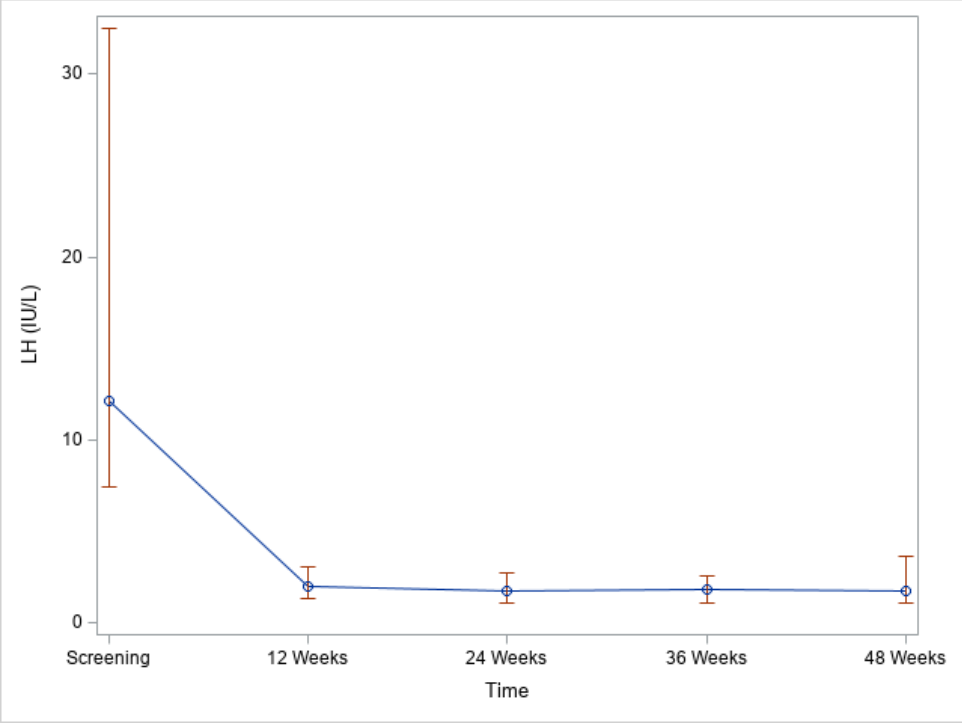
Results from a few secondary endpoints were also supportive (Table 3):

- All except one (98.3%) female patient reached Estradiol level < 73.4 pmol/L at Week 24 (Figure 7).

- The 2 male patients both reached Testosterone level < 1 nmol/L at Week 24 (Figure 8).
- Most patients showed reduction in FSH level from screening to Week 24, but there appeared to be some slight increase after Week 24 (Figure 9, Figure 10). 66.1% reached FSH Levels < 2.5 IU/L at Week 24.
- Most of the patients had no increase in the ratio of bone age to chronological age from baseline: 72.6% at Week 24 and 91.5% at Week 48 respectively.

The first measurement for growth velocity was conducted at Week 4. There was no consistent trend among the patients in terms of change in growth velocity since Week 4 (Figure 11, Figure 12). Since there was lack of baseline measurement, it is difficult to conclude about the effect of the drug on growth velocity.

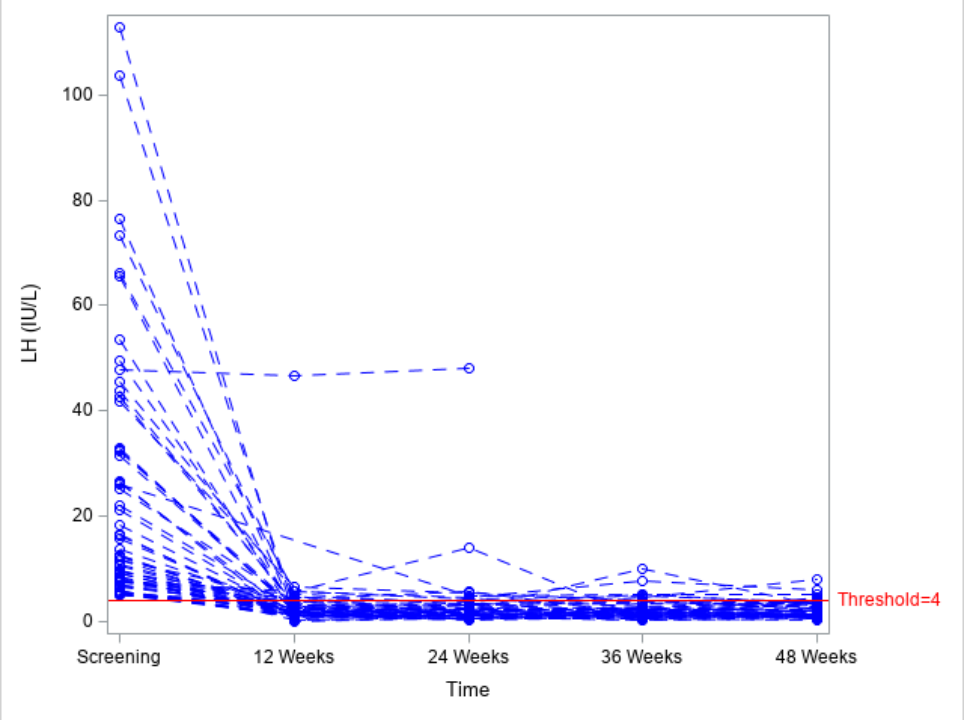
Figure 3 Median (IQR) Post-GnRHa LH Level Over Time[1] - ITT Population



1. Analysis visits

Source: Statistical Reviewer's Analyses

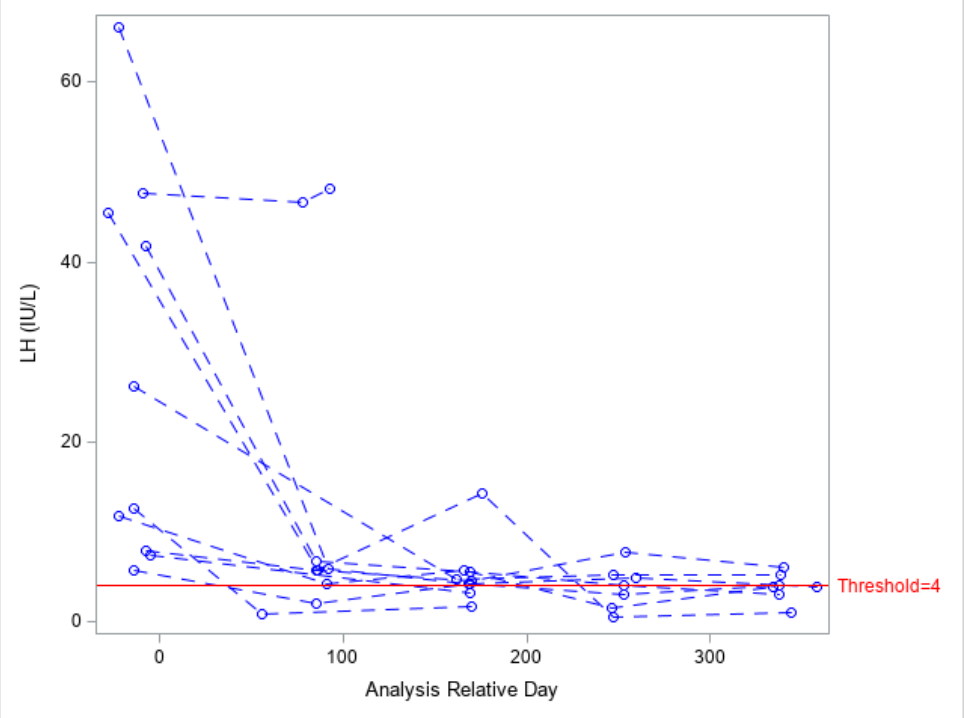
Figure 4 Post-GnRHa LH Level Over Time[1] in Individual Patients - ITT Population



1. Analysis visits

Source: Statistical Reviewer's Analyses

Figure 5 Post-GnRHa LH Level Over Time in 10 Subjects in ITT Who Did Not Reach < 4 IU/L at Week 24 or Discontinued Study



Source: Statistical Reviewer's Analyses

Figure 6 Change in Post-GnRHa LH Level from Screening to Week 24 in Individual Patients – ITT population

Source: Statistical Reviewer's Analyses

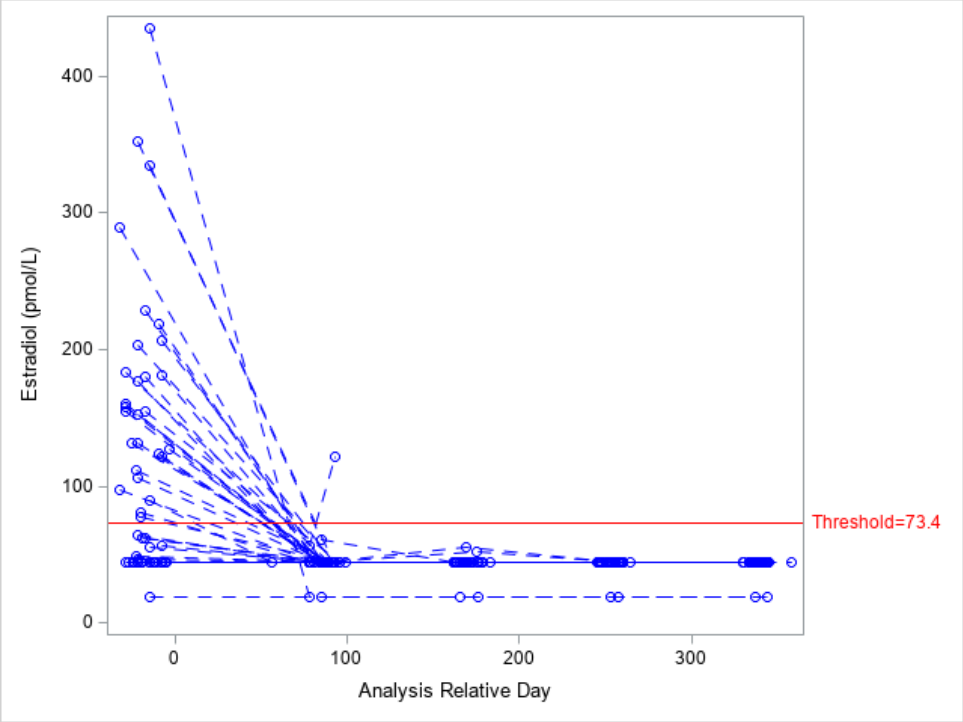
Table 3 Efficacy Results of FENSOLVI 45 mg– ITT population

Endpoints	n/N (%) of Children Achieving Endpoints[3]			
	Week 12	Week 24	Week 36	Week 48
Post GnHRa LH Levels < 4 IU/L	51/60 (85)	54/62 (87.1)	50/59 (84.8)	50/58 (86.2)
Estradiol Levels < 73.4 pmol/L (<20 pg/mL)	58/58 (100)	59/60 (98.3)	57/57 (100)	56/56 (100)
Testosterone Levels < 1 nmol/L (<28.4 ng/dL)	2/2 (100)	2/2 (100)	2/2 (100)	1/2 (50)
FSH Levels < 2.5 IU/L	37/60 (61.7)	41/62 (66.1)	26/59 (44.1)	32/58 (55.2)
With no Increase in BA/CA[1] Ratio vs. Baseline[2]	NA	45/62 (72.6)	NA	54/59 (91.5)
With no Increase in Tanner Stage vs. Baseline[2]				
Boys – Development of External Genitalia	2/2 (100)	2/2 (100)	2/2 (100)	2/2 (100)
Girls – Breast Development	56/59 (94.9)	58/60 (96.7)	55/57 (96.5)	55/57 (96.5)
Boys and Girls – Public Hair	49/61 (80.3)	49/62 (79.0)	47/59 (79.7)	48/59 (81.4)

Source: Statistical Reviewer's Analyses

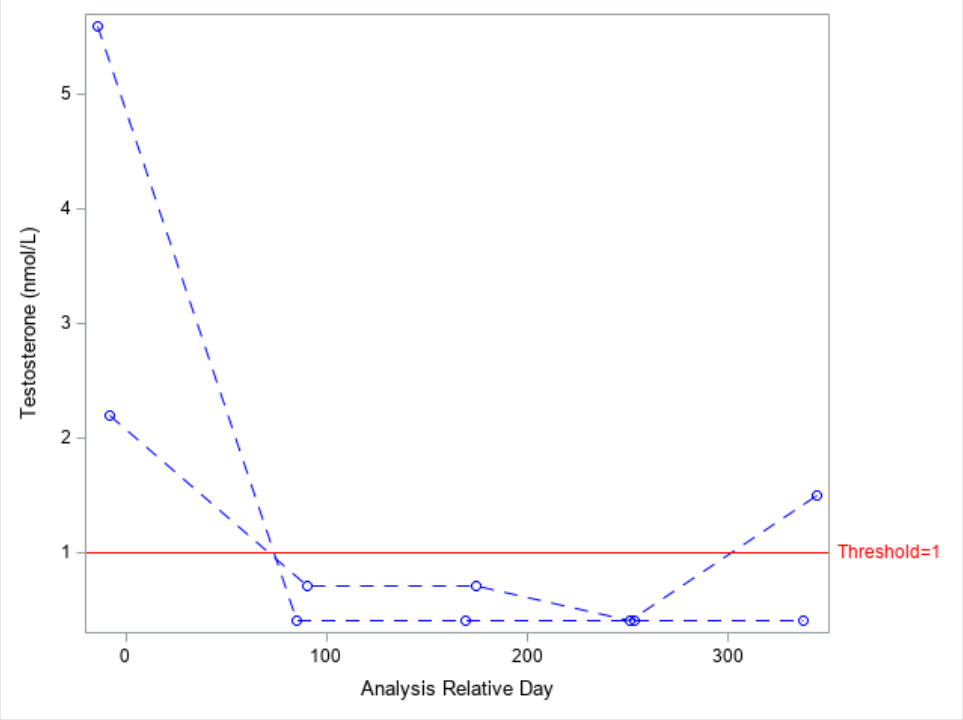
1. Bone Age/Chronological Age
2. Baseline here refers to Screening
3. A few subjects had missing measurements at Week 12, 36 or 40 and were not included in the calculation for percentage.

Figure 7 Post-GnRHa Estradiol Level Over Time in Individual Female Patients in ITT (N=60)



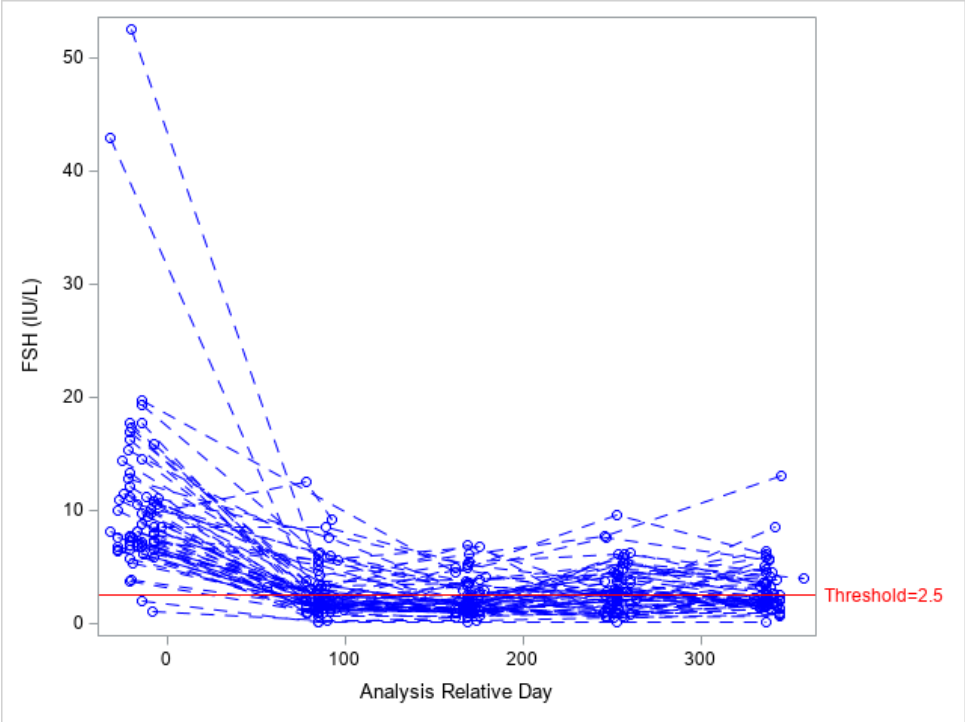
Source: Statistical Reviewer's Analyses

Figure 8 Post-GnRHa Testosterone Level Over Time in Individual Male Patients in ITT (N=2)



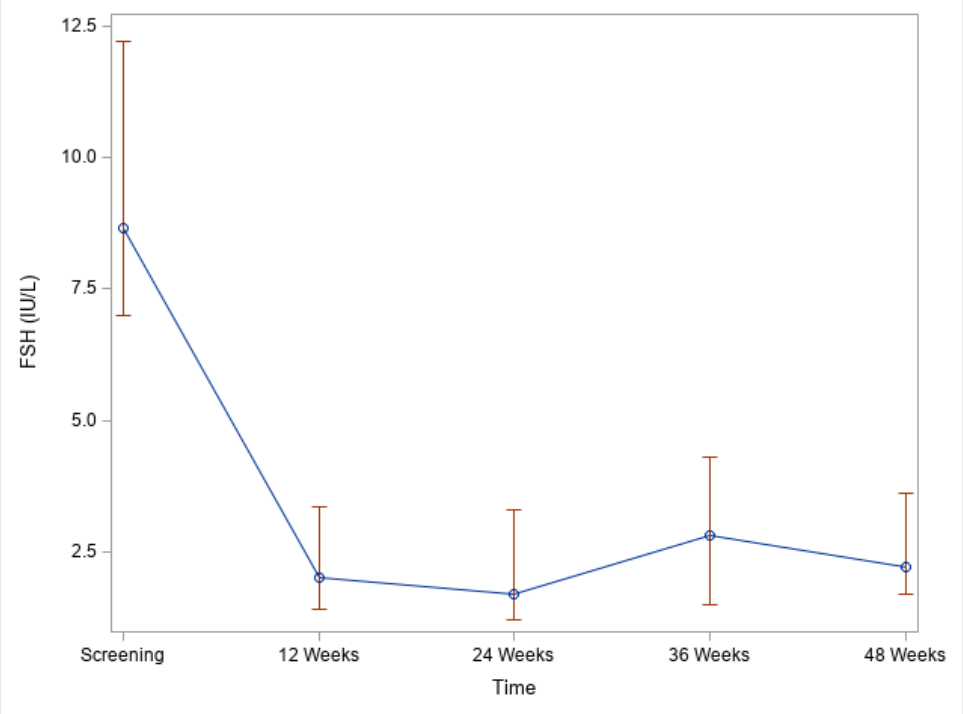
Source: Statistical Reviewer's Analyses

Figure 9 Post-GnRHa FSH Level Over Time in Individual Patients-ITT Population



Source: Statistical Reviewer's Analyses

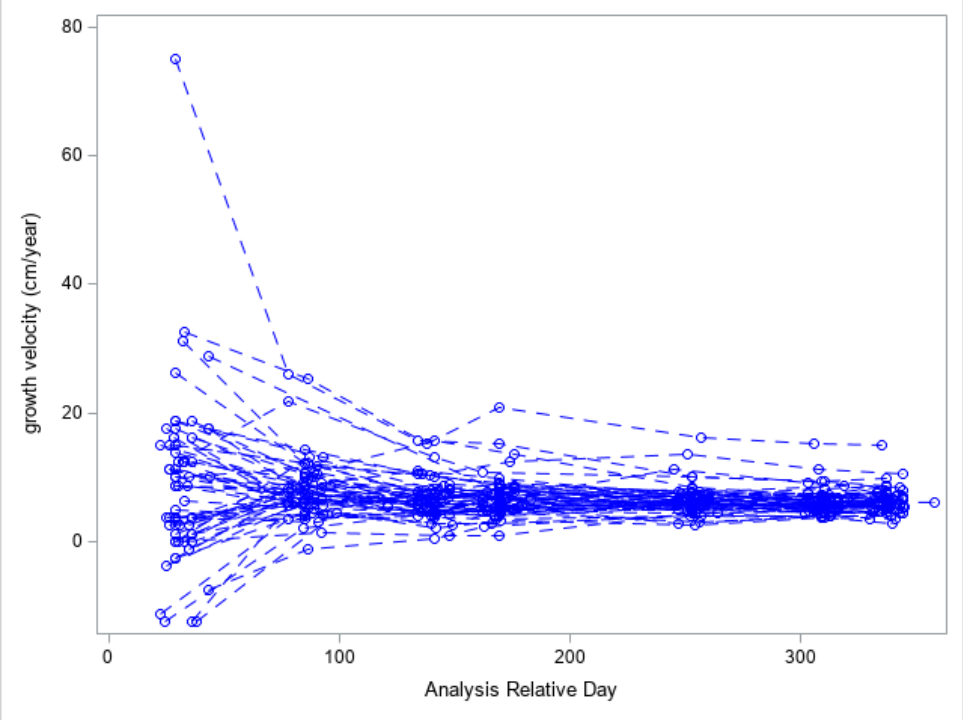
Figure 10 Median (IQR) Post-GnRHa FSH Level Over Time[1] - ITT Population



1. Analysis visits

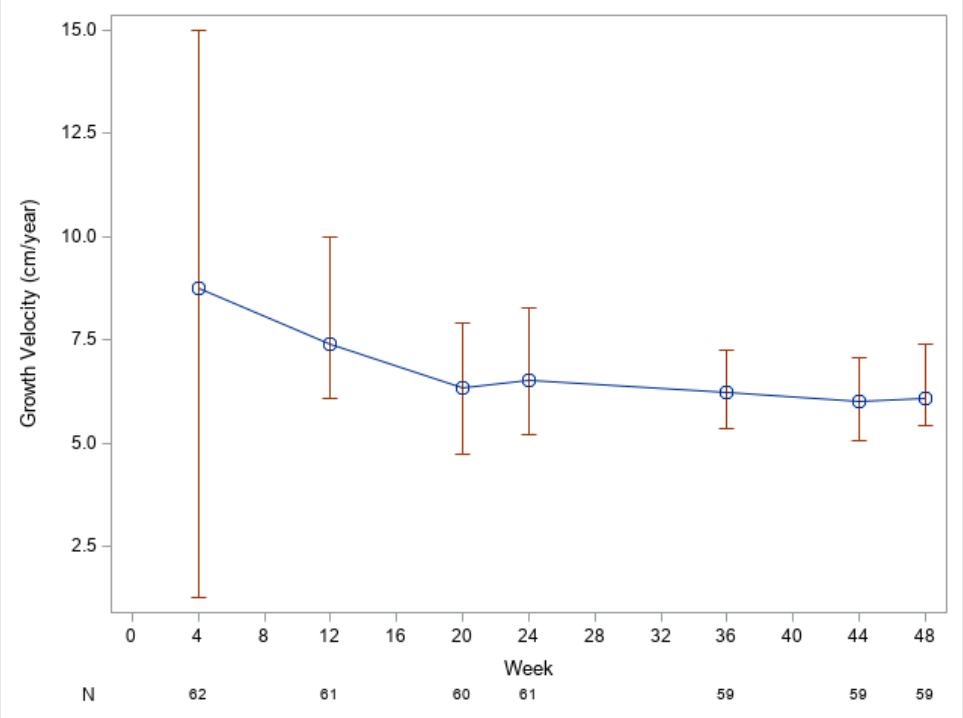
Source: Statistical Reviewer's Analyses

Figure 11 Growth Velocity Over Time in Individual Patients-ITT Population



Source: Statistical Reviewer's Analyses

Figure 12 Median (IQR) Growth Velocity Over Time[1] - ITT Population



1. Analysis visits

Source: Statistical Reviewer's Analyses

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The primary endpoint, percentage of subjects with LH suppression at Week 24, was assessed by subgroups, and presented as descriptive statistics in Table 4. The proportion of responders in the USA was slightly lower compared to that in the other countries. The proportion can have large variance for the subgroups with very few subjects and should be interpreted with caution, for instance, 66.7% (2/3) for Asian.

Table 4 Subgroup analysis of the primary endpoint

	% with LH suppression at Week 24
Sex, %(n/N)	
Girl	86.7(52/60)
Boy	100(2/2)
Race, % (n/N)	
White	84.4(27/32)
Black	86.7(13/15)
American Indian or Alaska Native	100(5/5)
Asian	66.7(2/3)
Other	100(7/7)
Age, % (n/N)	
< 8 years (median)	88.0(22/25)
≥ 8 years (median)	86.5(32/37)
Country, % (n/N)	
USA	79.3(23/29)
Non-USA	93.9(31/33)

Source: Statistical Reviewer's Analyses

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There was no major statistical issue. Some minor issues were summarized below.

5.1.1 Efficacy Analysis Population

Following the initial data analysis, the applicant discovered an error in population assignment and re-classified the population assignment of several subjects. Below is a table quoted from the applicant's clinical overview that shows in the changes in the population assignment:

Table 5 Changes in the Population Assignment

Population	Original analysis	Re-analysis
PP	57	43
ITT	61	60
Safety	64	64

PP=per protocol, ITT=intent-to-treat

Source: Applicant's Clinical Overview Section 2.5.1.5.1

The numbers under “re-analysis” correspond to those in the NDA submission we received.

The applicant’s definition for safety population was all subjects providing consent/assent who received at least one dose of the study drug. We examined the 4 subjects who were in the safety population but were not included in the ITT population and noticed that 2 of the subjects with minor protocol deviations should not be excluded from the ITT population. The applicant agreed with us and submitted revised datasets and study report based on 62 subjects in the ITT population. In addition, they corrected the EoT data for another subject. As a result, the subject’s Week 24 measurement became available.

5.1.2 Missing Data

Among the 3 subjects in the ITT who discontinued the study early prior to Week 24, one subject was clearly a non-responder (Figure 4). The other two subjects discontinued close to Week 24. Therefore, it makes sense to count their EoT measurement as their Week 24 measurement. As a result, all the missing data in the primary analysis can be properly handled.

5.1.3 Lack of Comparator

There was no control arm in Study TOL2581A. For a single arm study, there is usually concern over whether the observed effect was due to treatment. However, we are not overly concerned in this case given the strong efficacy results of this drug. In Study TOL2581A, most subjects had very high post GnRHa LH levels at screening (Figure 6) and their post GnRHa LH levels were unlikely to be suppressed to < 4 IU/L without a treatment. Ultimately all except one subjects had reduction in LH from screening at Week 24 and 87.1% achieved suppression to < 4 IU/L including those starting with very high LH levels at screening (Figure 6). Such big changes in a uniform direction cannot possibly be caused by natural variation or regression-to-the-mean alone.

5.2 Collective Evidence

The primary endpoint of the study was met: 87.1% (>80%) of the patients in the ITT population achieved serum LH concentrations <4 IU/L at 30 minutes post GnRHa simulation at Week 24, with 95% CI of 76.2%-94.3%. All except one of the 62 subjects had reduction in LH from screening. Results from the secondary endpoints were also supportive.

5.3 Conclusions and Recommendations

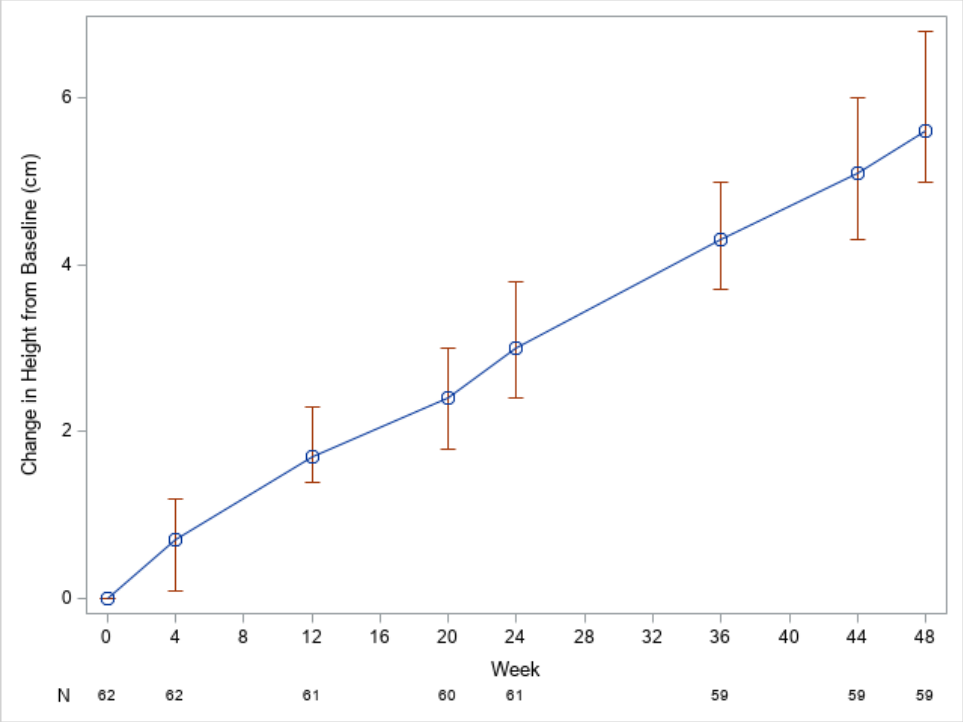
This NDA is approvable from statistical and efficacy point of view.

5.4 Labeling Recommendations

In addition to the primary endpoint, Section 14 of the proposed label also includes results for several secondary endpoints, (b) (4) Whether or not these endpoints can be included in the final label is subject to judgement the clinical reviewer and could be based on labels of approved drugs for the same indication. Labeling review is still ongoing while this review is finalized.

6. Appendix

Figure 13 Median (SD) Change in Height from Baseline Over Time[1] - ITT Population



1. Analysis visits

Source: Statistical Reviewer's Analyses

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