CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208956Orig1s000

STATISTICAL REVIEW(S)

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 208956
Drug Name:	Triptorelin pamoate for (b) (4) Suspension 22.5 mg
Indication(s):	For treatment of children with central precocious puberty (CPP)
Applicant:	Arbor Pharmaceuticals, LLC
Date(s):	Date submitted: August 29, 2016 PDUFA due date: June 29, 2017 Review due date: May 25, 2017
Review Priority:	Standard
Biometrics Division:	II
Statistical Reviewer:	Jiwei He, PhD
Concurring Reviewers:	Jennifer Clark, PhD, Acting Team Leader
Medical Division:	Metabolism and Endocrinology Products
Clinical Team:	Shannon Sullivan, MD, Medical Reviewer Marina Zemskova, MD, Medical Team Leader Jean-Marc Guettier, MD, Division Director
Project Manager:	Jennifer Johnson

Keywords: NDA review, clinical studies, central precocious puberty

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1. Executive Summary

Arbor Pharmaceuticals LLC proposes triptorelin for (b) (4) Suspension 22.5 mg, for treatment of children with central precocious puberty (CPP). Triptorelin is a gonadotropin releasing hormone (GnRH) agonist. Based on the proportion of children achieving luteinizing hormone (LH) suppression to prepubertal levels, the applicant claims triptorelin for (b) (4) Suspension 22.5 mg is effective in treating children with CPP. My review of the statistical evidence in efficacy suggests support for this claim. This NDA is approvable from statistical and efficacy point of view.

Debio 8206-CPP-301 was the sole efficacy and safety study in the NDA program. It has single-arm, open-label, non-comparative study design and enrolled 44 children with CPP. The primary efficacy endpoint was the proportion of children achieving LH suppression to prepubertal levels ($\leq$ 5 IU/L) 30 minutes after leuprolide stimulation at Month 6.

The primary endpoint was met with 93.2% children achieving LH suppression at Month 6 (95% CI: 81.3% to 98.6%). The null hypothesis, that the proportion of responders would be $\leq$ 80%, was rejected. The supportive secondary endpoints appeared to be consistently favorable. There was no missing data for the primary endpoint. No statistical issue was identified in this submission.

2. Introduction

2.1 Overview

2.1.1 Class and indication

Triptorelin is a GnRH agonist. Arbor Pharmaceuticals LLC proposes triptorelin for (b) (4) Suspension 22.5 mg, for treatment of children with CPP. Central (GnRH dependent) CPP is defined by puberty development occurring before age of 8 in girls and of 9 years in boys, which is not secondary to exposure to sex steroids of adrenal or gonadal origin.

2.1.2 History of drug development

Triptorelin for (b) (4) Suspension 22.5 mg was approved by FDA in 2010 for palliative treatment of men with advanced prostate cancer under NDA 22437 (Trelstar 22.5 mg, Actavis Laboratories, Inc). The approved triptorelin 6-month sustained release formulation was used for the efficacy and safety study Debio 8206-CPP-301. The protocol was performed under FDA Special Protocol Agreement (SPA) (Agreement letter dated 2011/10/21). FDA stated agreement on the study design, patient population, sample size and method of handling with missing data in the letter.

2.1.3 Specific studies reviewed

Debio 8206-CPP-301 was the sole efficacy and safety study in the NDA program and is the focus of this review. It had single-arm, open-label, non-comparative study design.

2.2 Data sources

The data and final study report were submitted electronically. The submission was archived under the network path location <\\CDSESUB1\evsprod\NDA208956\208956.enx>. The information needed for this review was contained in Module 1 FDA Regional Information (cover letter, meeting correspondence, and labeling), Module 2.5 Clinical Overview, Module 2.7 Clinical Summary, and Module 5 Clinical Study Report. This review focused on documents submitted to serial number 0000.

3. Statistical evaluation

3.1 Data and analysis quality

This submission is in electronic common technical document (eCTD) format with xml backbone. All required materials that are necessary for statistical review were submitted.

Study datasets are provided as SAS XPORT transport files version 5. Both tabulation and analysis datasets are provided. Tabulation datasets include the source data without any derivations or enrichments, whereas analysis datasets also include derived and enriched data (such as formatted variables, populations, derived endpoints). The tabulation and analysis datasets are joinable by the unique record identifier (USUBJID). SAS code for the primary analysis was also provided. This review covered datasets from study Debio 8206-CPP-301 and mainly used analysis datasets.

The datasets have a coherent organization. Variables in study datasets have a clear description in the Define.pdf file. The reported analysis results are in good quality. I was able to reproduce the results on the primary endpoint and the secondary efficacy endpoints included in the proposed product label.

3.2 Evaluation of efficacy

3.2.1 Study design and endpoints

Debio 8206-CPP-301 was the sole efficacy and safety study in the NDA program. It was a multicenter, non-comparative, open-label single arm study. **The primary objective** was to evaluate the efficacy of triptorelin pamoate (b) (4) 22.5 mg 6-month formulation IM in achieving LH suppression to prepubertal levels (defined as serum LH ≤ 5 IU/L 30 minutes after SC leuprolide stimulation [leuprolide acetate 20 μg/kg SC]) at Month 6 (Day 169) in children

with CPP. The subjects were given two intramuscular injections of Triptorelin for (b) (4) Suspension 22.5 mg at an interval of 24 weeks (Day 1 and Day 169). LH and FSH serum levels were measured prior to and 30 minutes after GnRH agonist stimulation at screening and at Months 1, 2, 3, 6, 9, and 12.

The primary efficacy endpoint was the proportion of children achieving LH suppression to prepubertal levels (≤ 5 IU/L) 30 minutes after leuprolide stimulation at Month 6.

Secondary endpoints in the proposed product label included:

- % of children with prepubertal LH at Month 1, 2, 3, 9 and 12
- % of girls with prepubertal estradiol at Month 1, 2, 3, 6, 9 and 12
- % of boys with prepubertal testosterone at Month 1, 2, 3, 6, 9 and 12
- % of children with no increase in bone age/chronological age (BA/CA) ratio versus baseline at Month (b) (4) 6, (b) (4) and 12
- % of children achieving stabilization of sexual maturation at Month 6 and 12
- % of girls with regression of uterine length at Month 6 and 12
- % of boys with no progression in testis volumes at Month 6 and 12

The applicant stated that the open-label non-comparative study design is justified because the primary endpoint as well as secondary hormonal efficacy endpoints were assessed by objective measurements. Additionally, all GnRH agonists previously approved by FDA for treatment of CPP were based on open-label, non-comparative studies using similar endpoints.

3.2.2 Statistical methodologies

The primary analysis was pre-specified by the applicant in the protocol:

The proportion of children with LH suppression at Month 1, 2, 3, 6, 9 (Days 29, 57, 85, 169, 253 and 337), as well as the proportion of children who maintained the LH suppression from Month 6 to Month 12 will be presented in contingency tables including the 95% CI (exact binomial).

The primary analysis population was the patients who had been enrolled, treated at baseline, and who had at least one on-treatment assessment of LH suppression status. The applicant termed this the intent-to-treat (ITT) population.

All the secondary endpoints were considered supportive. No tests were pre-specified. No multiplicity adjustment was performed.

The applicant pre-specified the method of handling missing data for the primary endpoint. In the ITT population, patients who discontinue from the study for any reason or who have missing data at the last planned visit(s) will be classified as "not suppressed" for the corresponding missing data visit(s). One missing data between 2 visits where LH is suppressed will be considered as missing for that particular visit, and considered as maintaining LH suppression.

The sample size calculation was based on the alternative hypothesis that the percentage of LH suppression at 6 months with the test product would be at least 95%. With 44 subjects, the study would have reasonable statistical power to rule out a percentage of LH suppression of 80% or less (one-sided α of 0.025; power of 82% from exact binomial test of a proportion). A minimum of 4 boys would be included.

3.2.3 Patient disposition, demographic and baseline characteristics

All the 44 enrolled patients received the scheduled treatment and completed the study. No major protocol violation was reported.

The demographic characteristics of the subjects in Study Debio 8206-CPP-301 were shown in Table 1. 26 (59.1%) of the subjects were white and 39 (88.6%) where female. The applicant stated that the low number of boys is consistent with studies published on the treatment of CPP and therefore the study population is representative of the target population to be treated.

All the enrolled patients had LH > 5 IU/L at baseline. 90% of the patients had baseline LH level in the range of 6.3 to 51 IU/L, with a few patients having extremely high baseline LH level (Figure 1).

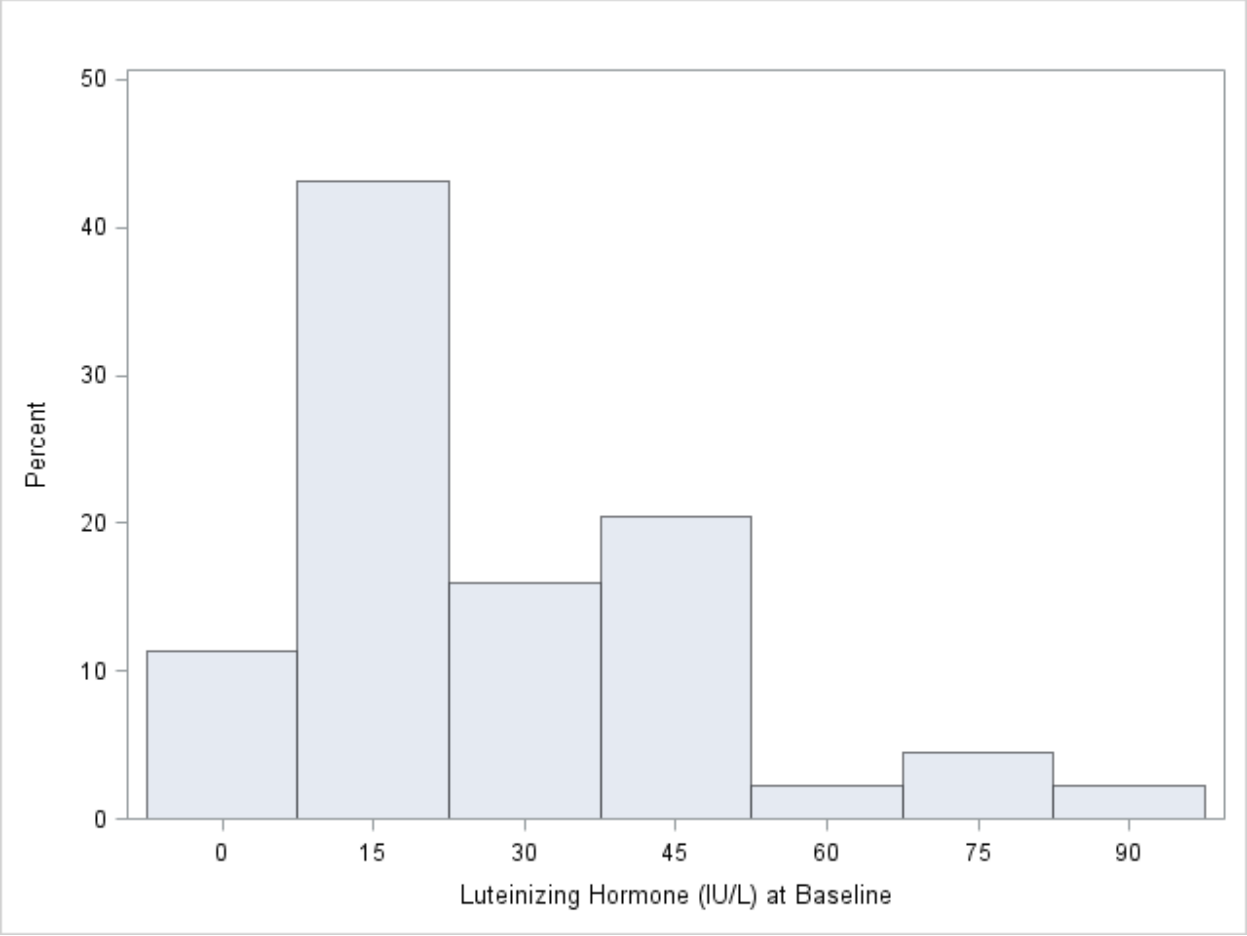
Table 1 Summary of patient demographic information

	Triptorelin (N=44)
Sex	
n(%) Girl	39 (88.6%)
n(%) Boy	5 (11.4%)
Age, years	
Mean (SD)	7.4 (1.3)
Median	8.0
Range	2.0 - 9.0
Race, n (%)	
White	26 (59.1%)
Black	12 (27.3%)
Asian	2 (4.5%)
Other	4 (9.1%)
Country, n (%)	
US	28 (63.64%)
Chile	15 (34.1%)
Mexico	1 (2.3%)

Weight, kg	
Mean (SD)	32.8 (8.4)
Range	15.3 - 54.0
Height, cm	
Mean (SD)	134.8 (10.9)
Range	103.0 - 155.0
BMI, kg/m^2	
Mean (SD)	17.8 (2.7)
Range	11.8 - 23.8
Baseline LH, IU/L	
Mean (SD)	27.3 (20.6)
Range	6.3 – 91.0

Source: adapted from Table 3 of Summary of Clinical Efficacy

Figure 1 Histogram of baseline luteinizing hormone level in the ITT population



3.2.4 Results and conclusions

I verified the sponsor's results of the primary endpoint. 41 out of 44 children in the ITT population had LH suppression to prepubertal levels at Month 6. The proportion of children with LH suppression to prepubertal levels at Month 6 was 93.2% with 95% CI of [81.3%, 98.6%]. The lower bound of the 95% CI was greater than 80%. The null hypothesis, that the proportion of responders would be ≤ 80%, was rejected.

I also verified the applicant's results of the secondary endpoints in the proposed product label (Table 2). Only descriptive statistics were shown for these supportive endpoints.

There was no missing data for the primary endpoint in the proposed product label. The method of handling missing data is not relevant. Among the secondary endpoints in the proposed product label, one girl had missing value for prepubertal estradiol at Month 2 visit. This subject had prepubertal estradiol < 20 pg/mL in all the other visits. It is reasonable to consider this subject as missing completely at random for this particular visit. It has little impact on the conclusions.

Table 2 Descriptive statistics of primary and secondary efficacy endpoints in the ITT population (in the proposed product label)

Efficacy Endpoints	**% (n/N) children achieving endpoint**					
	Month 1	**Month 2**	**Month 3**	**Month 6**	**Month 9**	**Month 12**
% with prepubertal LH (≤ 5 IU/L)	95% (42/44)	95% (42/44)	95% (42/44)	93%[1] (41/44)	95% (42/44)	98% (43/44)
% girls with prepubertal estradiol (<20 pg/mL)	87% (34/39)	89%[2] (34/38)	92% (36/39)	79% (31/39)	82% (32/39)	79% (31/39)
% boys with prepubertal testosterone (<30 ng/mL)	80% (4/5)	80% (4/5)	100% (5/5)	100% (5/5)	80% (4/5)	80% (4/5)
% with no increase in BA/CA ratio vs. baseline				64% (28/44)		95% (42/44)
% achieving stabilization of sexual maturation				91% (40/44)		89% (39/44)
% girls with regression of uterine length				69% (27/39)		77% (30/39)
% boys with no progression in testis volumes				100% (5/5)		100% (5/5)

1. Primary endpoint

2. One subject had missing value

Source: Table 4 of Summary of Clinical Efficacy

3.3 Evaluation of safety

Analyses on safety events were reviewed by Dr. Shannon Sullivan in the medical division.

4. Findings in special/subgroup populations

4.1 Sex, Race, Age, and Geographic Region

The primary endpoint, % with LH suppression at Month 6, was assessed in subgroups in Study Debio 8206-CPP-301, and presented as descriptive statistics in Table 3. The factors considered for subgroup analyses include:

- Sex
- Race
- Age (< 8 years, ≥ 8 years)
- Geographic Region (US, non-US)

Subjects from Chile and Mexico were grouped into the non-US category, because there was only1 subject from Mexico. The numbers in most subgroups were too small to make any meaningful conclusion ab out the differences between subgroups.

Table 3 Subgroup analysis of the primary endpoint

	% with LH suppression at Month 6
Sex, %(n/N)	
Girl	97.4% (38/39)
Boy	60% (3/5)
Race, % (n/N)	
White	100% (26/26)
Black	83.3% (10/12)
Asian	50% (1/2)
Other	100% (4/4)
Age, % (n/N)	
< 8 years (median)	100% (19/19)
≥ 8 years (median)	88% (22/25)
Country, % (n/N)	
US	89.3% (25/28)
Non-US	100% (16/16)
Baseline LH, % (n/N)	
< 20 IU/L (median)	100% (22/22)
≥ 20 IU/L (median)	86.4% (19/22)

Source: FDA statistical analysis

4.2 Other Special/Subgroup Populations

The primary endpoint, % with LH suppression at Month 6, was also assessed in subgroups by baseline LH level and presented in Table 3.

5. Summary and Conclusions

5.1 Statistical Issues

No statistical issue was identified in this submission.

5.2 Collective Evidence

The primary endpoint was met with 93.2% children achieving LH suppression at Month 6 (95% CI: 81.3% to 98.6%). The null hypothesis, that the proportion of responders would be ≤ 80%, was rejected. The supportive secondary endpoints appeared to be consistently favorable.

5.3 Conclusions and Recommendations

This review on efficacy supports the claim of using triptorelin pamoate (b) (4) 22.5 mg 6-month formulation for treatment of children with CPP. This NDA is approvable from statistical point of view.

5.4 Labeling recommendations

The proposed product label contains results from the primary endpoint and several secondary endpoints as descriptive statistics, i.e. the number and percent of subjects who met the efficacy endpoints at each visit (Table 2). All the secondary endpoints were considered as supportive. It is up to clinical judgment whether or not to include these results.

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/s/

JIWEI HE
05/19/2017

JENNIFER J CLARK
05/19/2017

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	NDA208956
Related IND #:	IND111504
Product Name:	triptorelin
Indication(s):	For treatment of children with central precocious puberty (CPP)
Applicant:	Arbor Pharmaceuticals, LLC
Dates:	Date submitted: 8/29/2016 PDUFA due date: 6/29/2017
Review Priority:	Standard
Biometrics Division:	II
Statistical Reviewer:	Jiwei He, PhD
Concurring Reviewers:	Mark Rothmann, PhD
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Medical reviewer: Shannon Sullivan, MD
Project Manager:	Jennifer Johnson

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

[*Note to reviewer: In this section provide a summary of the clinical trials that will be reviewed in your statistical assessment of the NDA/BLA. See Table 1 below for an example summary of the trials. Additional information to consider including in this section would be a discussion regarding the ability of the submitted trials to support the sponsor's proposed labeling claims and a discussion of trials that will not be reviewed and why.]*

Table : Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design	Treatment/ Sample Size	Endpoint/Analysis[1]	Preliminary Findings
Debio 8206-CPP-301	Open-Label, Non-comparative, Single-arm, Multi-center	N=44	Primary: % of children with LH suppression to prepubertal levels (≤5 IU/L) at Month 6 Secondary: include a number of hormonal and non-hormonal efficacy endpoints	41(93.2%) children achieved LH suppression to prepubertal levels at Month 6, with lower bound of 95% CI (81.3%) > 80% ⇨ Primary objective achieved

2. Assessment of Protocols and Study Reports

[*Note to reviewer: The following section should be addressed based upon review of the protocol(s) and the study report submitted for each trial referenced in Table 1 above. The reviewer is encouraged to provide details in the "Response/Comments" column of Table 2.*]

Table 2: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	**Yes (agreed upon in SPA)**
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	**Yes (agreed upon in SPA)**
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	**NA**
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	**NA**
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	**Yes (agreed upon in SPA)** Patients who discontinued from the study prior to the Month 6 assessment or who had otherwise did not provide an assessment of LH suppression at Month 6 were to be classified as 'not suppressed'

3. Electronic Data Assessment

[*Note to Reviewer: The following section is meant to document the details as they pertain to the electronic data submitted in the application.*]

Table 3: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\CDSESUB1\evsprod\NDA208956\208956.enx
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	SDTM and ADaM
Are the define files sufficiently detailed?	Yes
List the dataset(s) that contains the primary endpoint(s)	ADLB: laboratory test results (LH, LHLE5M, FSH. estradiol, testosterone) Secondary endpoints: ADMO: morphology (bone age/chronological age ratio, uterine length, testis volume) ADVS: vital signs (height, growth velocity)
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s)	Yes

Content Parameter	Response/Comments
without excess data manipulation? *	
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	No
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	NA. Debio 8206-CPP-301 is the sole efficacy and safety study.

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

[*Note to Reviewer: This information is needed or essential to be able to review the application.*]

Table 4: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	*			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)			*	Debio 8206-CPP-301 is the sole efficacy and safety study.
Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated.		*		Sponsor did not present the primary endpoint within subgroups, but they have provided relevant information so that it can be easily calculated. Geriatric subgroup is not applicable.
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	*			
Application is free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements	*			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?
Yes

5. Comments to be Conveyed to the Applicant

[*Note to Reviewer: In this section provide all comments that should be conveyed to the sponsor. Section 5.1 "Refuse-to-File Information Requests" should be based upon deficiencies identified in Section 4 of the Filing Review. Section 5.2 "Information Requests/Review Issues" should be used to*

request any additional information that would facilitate the review or to note any review issues identified by the time of filing that are meant to be conveyed to the sponsor. All comments in this section should be written in such a way that they can be copied by the project management staff.]

5.1. Refuse-to-File Issues

There is no refuse-to-file issue.

5.2. Information Requests/Review Issues

Please provide the percent of children with LH suppression to prepubertal levels within subgroups by gender, race and ethnicity. If you have already provided this, please point out where this information can be found.

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/s/

JIWEI HE
10/25/2016

MARK D ROTHMANN
10/25/2016
Concur