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APPLICATION NUMBER:

208956Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	6/26/2017
From	Marina Zemskova, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	208956
Applicant	Arbor Pharmaceuticals, LLC
Date of Submission	8/29/2016
PDUFA Goal Date	6/29/2017
Proprietary Name / Established (USAN) names	Triptodur/ Triptorelin pamoate for (b) (4) suspension
Dosage forms / Strength	Powder, lyophilized for suspension/ 22.5 (b) (4)
Proposed Indication(s)	Treatment of children (> 2 years) with central precocious puberty.
Recommended:	Approval

1. Introduction

On August 29, 2016 Arbor Pharmaceuticals submitted a New Drug Application (NDA) for Tritpodur (triptorelin pamoate for (b) (4) suspension, 22.5 mg; triptorelin) under Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act.

Triptorelin pamoate is a synthetic GnRH agonist that has been approved in the United States for the treatment of advanced prostate cancer as Trelstar (b) (4) (Sponsor: Allergan Sales LLC). FDA-approved formulations for prostate cancer indication include a 1-month formulation approved in 2000 under NDA 20715 (3.75 mg), a 3-month formulation approved in 2001 under NDA 21288 (11.25 mg), and a 6-month formulation approved in 2010 under NDA 22437 (22.5 mg). The Sponsor has obtained the rights of reference to all three Trelstar NDAs.

This NDA proposes a new indication for the currently approved 6-month 22.5 mg triptorelin pamoate formulation (under NDA 22437):

treatment of children (> 2 years) with central precocious puberty.

2. Background

Central precocious puberty (CPP) is a rare disease with an estimated incidence of 1 in every 5,000 to 10,000 children.

Precocious puberty is often identified when sexual development is observed before the age of 8 years in girls and 9 years in boys. CPP results from premature activation of the hypothalamic-pituitary-gonadal axis (HPG). The increase in amplitude and frequency of GnRH release from the hypothalamus stimulates the release of gonadotropins, LH and FSH, from the pituitary. The gonadotropins subsequently stimulate gonadal steroid production, resulting in the development of secondary sexual characteristics. A variety of CNS disorders including inflammation, structural defects, or chemotherapy may contribute to the development of CPP; however, in many cases, no cause is identified (idiopathic). Premature sexual development includes early thelarche and menarche in girls, increased testicular and penile growth in boys, premature bone maturation and accelerated linear growth with possible premature fusion of epiphyseal growth plates and reduced final height. Other consequences of precocious puberty include psychological impact and social stigmatization.

GnRH agonist analogs are the standard of care for children with CPP. Drugs in this class bind to and activate GnRH receptors on pituitary gonadotrophs; this activation results in an initial stimulation of gonadotropin release and a possible exacerbation of clinical presentations. Subsequently, the prolonged activation of these receptors leads to desensitization and suppression of gonadotropin secretion to prepubertal levels, thereby arresting further production of gonadal sex steroids. Currently available GnRH agonists approved for CPP include nafarelin acetate (Synarel, intranasal spray, NDA 020109), leuprolide acetate (Lupron, 1-month and 3-month injectable formulations in different strengths, NDA020263) and histrelin acetate (Supprelin, s.c. implant, NDA (b) (4)).

Triptorelin pamoate for (b) (4) suspension is a synthetic decapeptide analogue of naturally-occurring gonadotropin releasing hormone (GnRH). As stated above, three formulations of triptorelin pamoate have been approved in the US for the treatment of advanced prostate cancer. Triptorelin pamoate 3-month formulation and triptorelin acetate 3-month formulation are registered for the treatment of CPP in Europe. Similar to other synthetic GnRH analogs, triptorelin suppresses LH to prepubertal levels; this constitutes the physiologic rationale for triptorelin pamoate use in the treatment of CPP. (b) (4)

Regulatory Background

The following are the major regulatory interactions that took place between DMEP and the Sponsors (Debiopharm International SA, and later Arbor Pharmaceuticals) regarding the pediatric Triptodur development program for the precocious puberty indication:

1) Debiopharm International SA submitted a new IND (111504) on 5/18/2011 with a protocol for a Phase 3 clinical trial to evaluate efficacy and safety of a 6-month 22.5 mg formulation of

Triptodur, a triptorelin formulation already approved for the treatment of prostate cancer, in patients with CPP. In the IND, the Sponsor indicated that they plan to submit a Special Protocol Assessment (SPA) once the IND review has been completed.

2) Debiopharm International SA submitted a request for a special protocol assessment (SPA) of the Phase 3 study protocol (Debio 8206-CPP-301) on June 17, 2011.
The Division issued an agreement letter on October 21, 2011. Some of the trial design attributes required for the agreement were:

- the study will be a single arm, open-label study
- the duration of the study will be 12 months with a demonstration of lack of an "acute over chronic" effect
- the proposed primary endpoint will be a percentage of patients who achieve suppression of LH levels to prepubertal levels (defined as < 5IU/L 30 minutes after GnRH agonist stimulation) at 6 months
- the proposed secondary endpoints will be the change in estradiol and testosterone levels from baseline, percentage of children maintaining LH suppression at Month 1,2,3, and 6, change in height, growth velocity, bone age, etc.
- the selected patient population will be girls 2-8 years old and boys 2-9 years old with onset of precocious puberty (defined as onset of puberty before age 8 and 9 in girls and boys, respectively) at least 18 months prior to the treatment with trip[torelin and with LH level > 6 IU/L following GnRH agonist stimulation test.
- the sample size of 46 patients is acceptable
- the primary analysis will be conducted on Intent to Treat (ITT) population and patients with missing primary endpoint data at 6 month will be considered as treatment failures.

3) Triptodur was granted Orphan Drug designation for the treatment of CPP on 8/20/2012 by the Office of Orphan Products Development.

4) Pre-NDA meeting (December 3, 2015).
The Division and the Sponsor agreed that NDA will be filed under 505 (b) (1). The Agency clarified that expected class effects for GnRH agonists should be included in the labeling. The Agency also clarified that all data including CMC information have to be included in new NDA at time of submission. The meeting also focused on NDA's content and format and the completeness of the different NDA modules.

5) Sponsorship of Orphan Drug Designation #123760 (Tritpodur for the treatment of CPP) was transferred to Arbor Pharmaceuticals from Debiopharm International SA on 2/12/2016.

6) NDA submission: 8/ 29/ 2016.

3. CMC/Device

The CMC reviewers recommend approval of this application (refer to Dr. Tran's executive summary). There are no outstanding issues that preclude approval. All facilities inspections have been completed and the Office of Pharmaceutical Quality and Office of Compliance has determined these facilities are acceptable (refer to review in Panorama dated 5/30/2017).

There are no new chemistry data submitted with this application.

The drug substance is triptorelin pamoate, a small synthetic peptide of naturally occurring GnRH.

The CMC reviewer indicates that the Sponsor obtained right of reference to NDA 22437 (the same 22.5 mg 6-month triptorelin formulation approved for prostate cancer) and to the relevant DMF ((b) (4)) for all CMC information on the drug substance and drug product. This information was reviewed and found to be acceptable.

DMF (b) (4) s referenced for all CMC information on the co-packaged pre-filled syringe containing 2 mL of Sterile Water for Injection USP for reconstitution. The manufacturer/DMF holder is different from the one supporting the referenced NDA 22437. CMC reviewer confirmed that this DMF is currently adequate for CMC information on the diluent.

CDRH
This is a drug-device combination product. Each Triptodur kit contains one single-dose vial with triptorelin pamoate microgranules, one sterile glass syringe prefilled with (b) (4) ml Water for Injection, 2 sterile 21 gauge, 1½" needles (thin-wall) with safety cover and one syringe plunger. CDRH reviewer Dr. Rong Guo reviewed the device constituent part of the combination product (pre-filled syringe) and recommended approval.

Dr. Guo reviewed essential performance elements of this kit, i.e. dose accuracy and functionality of the syringe and confirmed that functionality of syringe and dose accuracy are acceptable. The shelf life for this combination product is restricted by 36 months. The kit should be stored at 20-25°C (68-77°F).

4. Nonclinical Pharmacology/Toxicology

Dr. Federica Basso and pharmacology/toxicology supervisor, Dr. Ron Wange, deem the nonclinical data acceptable in support of approval of Triptodur for the treatment of CPP in children and labeling changes provided labeling accurately reflects the nonclinical findings and their recommendations on use of the product. Please see Dr. Federica Basso review dated

5/25/2017, for the details of the nonclinical program supporting approval of Triptodur 6-month formulation for the treatment of CPP in children.

No new nonclinical studies were conducted. The same formulation, triptorelin pamoate 22.5 mg 6-month formulation is approved for the palliative treatment of prostate cancer under NDA 22437. Thus, all required studies (including single dose toxicology studies, in vitro mutagenicity studies, reproductive and developmental toxicity studies) were conducted and reviewed previously under NDAs 20715, 21288, and 22437 (triptorelin 1-, 3--, and 6-month formulations for the treatment of prostate cancer) to which the Sponsor obtained right of reference.

Pharmacodynamic and pharmacokinetics studies in rats showed that intramuscular injection of the triptorelin pamoate 6-month formulation resulted in a rapid decrease of testosterone levels which remained at castrate levels for at least 6 months. No safety signals were identified following acute administration of triptorelin in a standard battery of safety pharmacology studies.

The toxicology profile observed with triptorelin in animals is consistent with drug pharmacology: decrease in serum LH and testosterone levels and suppression of testicular and ovarian function at the clinical dose. All changes but testicular changes were reversible at dose cessation. Testicular changes in rats (tubular atrophy, mineralization, and maturation arrest) were partially reversible.

Triptorelin was not genotoxic in *in vitro* or *in vivo* testing.

In a carcinogenicity study in rats only, increased incidence of pituitary adenoma and carcinoma was observed. No tumors were observed in mice at doses up to 4 fold the clinical dose. Dr. Federica Basso concluded that pituitary tumors were species-specific and that "limited data from rat study and complete data from the mouse study were considered sufficient to support the safety profile of triptorelin".

No adverse effect on fertility was observed in female animals treated with triptorelin for two months. Embryofetal development studies showed maternal toxicity (decrease in maternal weight) and embryotoxicity (pre-implantation loss, increased resorptions, and reduced number of viable fetuses) in rats at 8-fold the clinical dose. None of these effects were apparent in mice at the same doses. Triptorelin was not teratogenic in mice or rats.

I concur with Drs. Basso's and Wange's assessment. There does not appear to be any nonclinical issue that would preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review was completed by Drs. Jianmeng Chen and Jayabharathi Vaidyanathan. Both reviewers recommended approval of Triptodur for the treatment of CPP. For detailed discussion, please refer to their Clinical Pharmacology review in DARRTS (5/25/2017).

Reviewers concluded that the PK/PD data submitted in this application supports the proposed dose of 22.5 mg in children with CPP and provides acceptable PK data for labeling purposes.

PK parameters

- The Sponsor did not conduct any clinical studies to investigate the distribution, metabolism or excretion of Triptodur; this data has been submitted and reviewed under NDAs 22314, 20715, and 21288 to which the Sponsor obtained rights of reference
- PK parameters in children with CPP (from the Sponsor's study Debio 8206-CPP-301):
  - Following the first injection: geometric mean Triptodur serum concentrations were 0.11 and 0.17 ng/mL at the first and the second month, respectively. Thereafter, mean Triptodur levels decreased and remained at 0.05 -0.03 ng/mL over the remainder of the dosing period.
  - Following each injection, the release of Triptodur was bi-phasic and consisted of a burst phase with median Tmax of 4 hours followed by a maintenance phase.
  - Geometric mean Cmax is 39.9 ng/mL and 36.5 ng/mL after the first and second injections, respectively. No significant accumulation was detected after the second Triptodur injection.
  - Comparable Triptodur concentrations were observed across weight and age groups (refer to Clin.Pharm review, figure 2). Therefore, dose adjustment based on weight or age is not necessary.
  - Pediatric PK data was comparable to adult PK data. Cmax of Triptodur was similar after the first injection in adults and children (39.9 ng/ml and 44.1 ng/ml, respectively).

Pharmacodynamic

Following the first administration, there was a transient surge in circulating levels of LH, FSH, testosterone, and estradiol. After chronic and continuous administration, in 4 weeks after initiation of therapy, a sustained decrease in LH and FSH secretion and marked reduction in gonadal steroids was observed.

The reviewers also confirmed that ≥93% of patients maintained LH suppression and > 80% of children maintained suppression of gonadal steroids at each time point during 12 months of treatment (refer to efficacy section below). Dr. Chen also confirmed "once the effect is achieved, the suppression is maintained even at very low triptorelin plasma concentrations" (refer to Clinical Pharmacology review, figure 7).

Based on the available data from the Sponsor's study and data from the literature, Dr. Chen concluded that the exposure-response for efficacy and safety supports the dosing recommendation.

The reviewers also indicated that based on *in vitro* studies, drug-drug interactions with Triptodur are unlikely.

There do not appear to be any Clinical Pharmacology issues that would preclude approval. I agree with reviewers' conclusion.

6. Clinical Microbiology

Quality microbiology data was reviewed by Dr. Denise A. Miller on April 6, 2017 and by Dr. Neal J. Sweeney on May 17, 2017. No concerns were identified and the reviewers recommended approval.

7. Clinical/Statistical- Efficacy

This memorandum will focus on the design and the results of a single Phase 3 study evaluating efficacy and safety of Triptodur to treat CPP in the intended population. As stated above, the design (exclusion and inclusion criteria, endpoints, size of the study and analysis plan) for this pivotal study was agreed upon under a special protocol assessment agreement issued on 10/21/2011.

Study Debio 8206-CPP-301 (referred to as study in this review)
This study was an open label, single arm multicenter (11 sites in US), 12-month study that investigated the use of Triptodur for the treatment of CPP in pediatric patients.

As Dr. Sullivan noted, the approval of other GnRH agonists for the treatment of CPP was based on data obtained from the trials with similar design, i.e. open-label, single arm, small trials.

The primary objective of the study was to evaluate the efficacy of Triptodur in achieving LH suppression to prepubertal levels (defined as serum LH ≤ 5 IU/L 30 minutes after leuprolide stimulation) at month 6 in children with CPP.

Patient population
Patients > 2 years and < 9 years (girls) or < 10 years (boys) old with CPP were eligible to participate in the study. CPP was defined as an onset of development of sex characteristics

(Tanner staging >2 for breast development in girls or testicular enlargement > 4 ml in boys) before 8 and 9 years in girls and boys, respectively, and with pubertal-type LH response to a leuprolide stimulation test (> 6 IU/L at 30 minutes). Eligible patients were also required to have advanced bone age compared to chronological age (> 1 years) and to be treatment-naïve to GnRH agonists.

The selection of patients with CPP by GnRH agonist stimulation tests is acceptable. GnRH stimulation test with immediate release GnRH agonist (Lupron) is the gold standard diagnostic test for CPP: an increase in LH ≥ 6 IU/L is diagnostic for CPP. The GnRH stimulation test is similarly used during GnRH agonist therapy to monitor a response to treatment: LH of < 5 IU/L is considered as a successful suppression of gonadotropins in the prepubertal range.

Study design

The study was comprised of a screening period and a 12-month treatment period. All patients received two doses of Triptodur 22.5 mg intramuscularly: the first dose was administered on Day 1 of the treatment period followed by the second dose at 6 months.

To evaluate the maintenance of LH and other gonadal hormones suppression, unstimulated and stimulated LH levels, testosterone and estradiol levels were measured at baseline, and at months 1,2,3,6,9, and 12. As stated above, the use of stimulated LH levels to monitor the efficacy of treatment is widely accepted in clinical practice.

Lastly, assessment of the acute-on-chronic (AOC) phenomenon (as required under SPA) was performed in 22 subjects-responders at 6 months by evaluating baseline LH and estradiol or testosterone levels in 48 hours after the second Triptodur injection.

Assessment of sexual development, uterine length and testicular volume by ultrasound were also performed during the study.

Primary efficacy outcome

The primary efficacy endpoint was a responder analysis examining the number of subjects in the Intent to Treat (ITT) population who experienced a suppression of LH to prepubertal levels defined as GnRH agonist-stimulated LH ≤ 5 IU/L at month 6.

Subjects missing 6-month stimulated LH values were classified as "not suppressed" in the primary analysis. However, Dr. He considered the method of handling missing data to be irrelevant, since there was no missing data for the primary analysis in the study.

The selection of stimulated LH levels within the prepubertal range as the efficacy endpoint and on responder analysis looking at the percentage of subjects having achieved suppressed LH levels at month 6 was agreed under SPA.

Baseline Demographics and Disposition

A total of 44 children with CPP were enrolled in this study and received two injections of Triptodur. All patients were treatment-naïve to GnRH agonists.

Of these, 39/44 (89%) patients were girls. The mean age of patients was 7.4 years (median 8 years, range 2-9 years). Overall, the demographic characteristics of the studied population match the demographic characteristics of patients with CPP in the general population. CPP is usually observed before the age of 8 years in girls and 9 years in boys and is more common in girls, with a reported ratio of boys to girls 1:3 to 1:23[1]. Dr. Sullivan noted that the baseline characteristics of patients enrolled in this study are also similar to the demographic characteristics of subjects in development programs for other GnRH agonists approved for the treatment of CPP.

All patients had confirmed diagnosis of CPP at baseline: mean stimulated LH level was 27.2 IU/L (range 6.3-9.1 IU/L), mean estradiol was 44.8 ng/L (range 10-117 ng/L), mean testosterone was 326 ng/dL (range 142-573). All children had signs of premature sexual development at baseline: Tanner score was 2 in 6 children, 3 in 29 children, and 4 in 9 children; mean uterine length was 4.6 cm (range 2.3-7.5 cm), mean testicular volume was 10.4 cm (6- 15 cm). Lastly, the majority of patients had advanced bone age (BA) at baseline: BA (months) to CA (chronologic age, months) ratio was 1.4 (range 1.1-3).

Efficacy results

The statistical review for efficacy was performed by Dr. Jiwei He. Efficacy findings were also discussed in Dr. Shannon Sullivan's review. The efficacy findings are summarized below. For a more detailed discussion of the efficacy findings, see Dr. He's review and Dr. Sullivan's review.

Dr. He verified the Sponsor's results for the primary analysis and confirmed that Triptodur effectively suppresses LH to prepubertal levels. The study demonstrated that 93.2% (41/44 children) of children (95% CI: 81.3% to 98.6%) achieved LH suppression to prepubertal levels (i.e. serum LH $\leq$ 5 IU/L 30 minutes after leuprolide stimulation) at month 6, after the first injection of Triptodur. The lower bound of the 95% CI was > 80%; null hypothesis that the proportion of responders would be < 80% was rejected.

[1] Antoniazzi F, Zamboni G. Central precocious puberty: current treatment options. Paediatr Drugs 2004; 6:211-231.

Dr. Sullivan further analyzed data from the three nonresponders at month 6. As per her analyses, one of the three patients had borderline LH suppression at month 6 (5.1 IU/L) and achived the full suppression at month 12 (3.2 IU/L). This patient aslo had suppressed testosterone levels to prepubertal level at month 6 and 12. In general, this patient would have been considered as a repsonder in clinical practice.The second patient had a complicated first Triptodur injection and achived full LH suppression at month 12 after the second injection. The third patient was a nonresponder at months 6 and 12. Of note, Clinical Pharmacology indicated that the absence of LH suppression in the last two patients was most likely due to "low exposure" since the Triptodur concentrations were extremly low in both patients at the time of LH eveuation.

Lastly, Dr. Sullivan also compared the efficacy of Triptodur in suppression of LH levels to the efficacy of other approved GnRH agonists observed in pivotal trials on which approval of GnRH agonists for the treatment of CPP is based and concluded that the efficacy of all GnRH agonists in suppressing LH levels to prepubertal levels was similar. For example, Lupron was associated with LH suppression in 96% of patients at week 24 and Supprelin- in 100% of patients at week 52 (refer to Dr. Sullivan's review for details).

Secondary endpoints

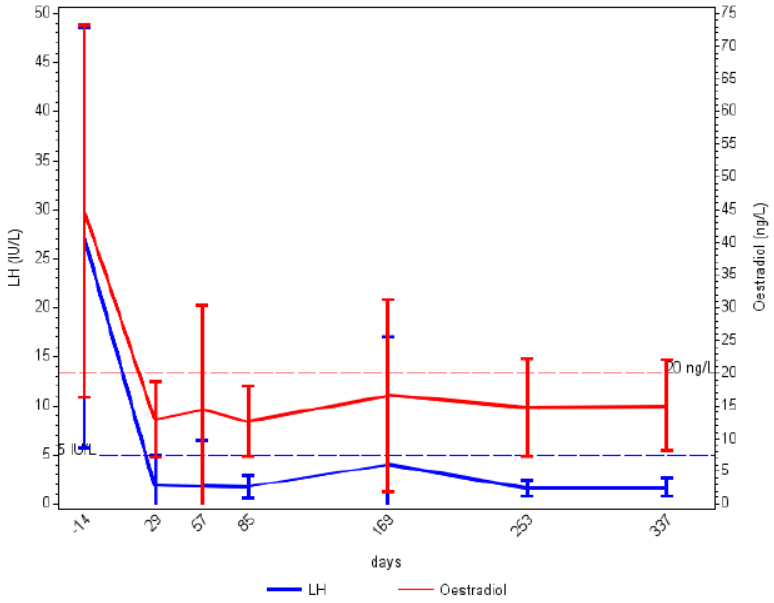
Dr. He verified the Sponsor's results of the analysis (by descriptive statistics) carried out on secondary endpoints and confirmed that the results of this analysis were supportive for the conclusion drawn from the trials' primary endpoint (Table 1).

Table 1. Descriptive statistics of secondary efficacy endpoints in the ITT population

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

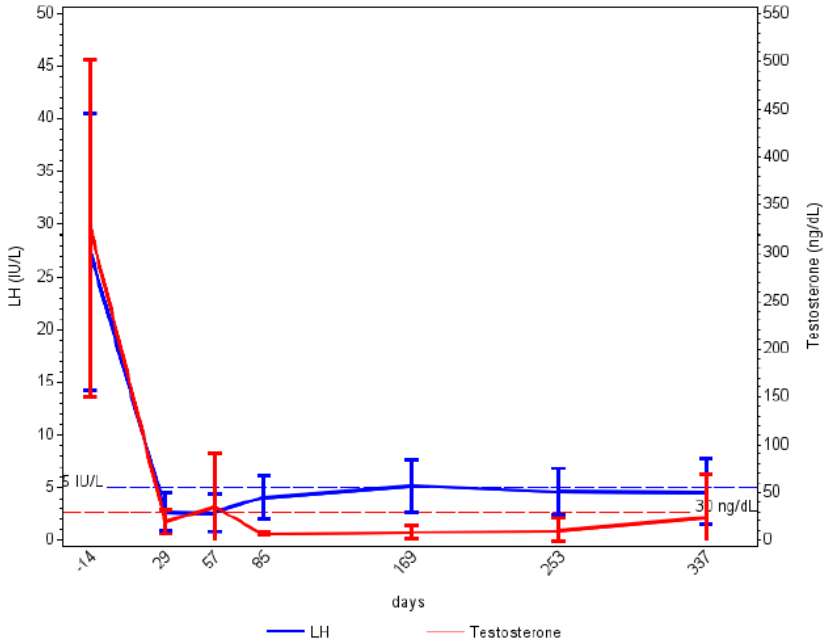
Briefly, the majority of children achieved LH suppression to prepubertal levels and maintained this suppression trough month 12. Mean LH levels decreased from 27.2 IU/L at baseline to 2 IU/L in girls and 4.2 IU/L in boys, respectively (figures 1 and 2).
The suppression of LH levels resulted in further suppression of HPG, i.e. suppression of gonadal steroid hormones to prepubertal levels in the majority of patients: all boys and approximately 80% of girls had suppressed testosterone and estradiol levels, respectively, at month 1 and effectively maintained this suppression throught the study (figures 1 and 2).

Figure 1. Mean±SD levels of LH and estradiol in girls in the ITT population during 12 months of Tritodur treatment.



Dotted lines indicate pre-pubertal cutoff levels
Source: Clinical review, figure 3.

Figure 2. Mean±SD levels of LH and testosterone in boys in the ITT population during 12 months of Triptodur treatment.



Dotted lines indicate pre-pubertal cutoff levels
Source: Clinical review, figure 4.

Lastly, as expected, the majority of children also demonstrated stabilization and/or slowing of sexual maturation and advanced bone maturation (refer to Dr. Sullivan's review for details).

In conclusion, the efficacy analyses conducted in the study demonstrate that Triptodur can suppress LH levels to prepubertal levels and arrest further production of gonadal steroids and premature sexual development in patients with CPP. I agree with Drs. He's and Sullivan's conclusions that the efficacy results from this trial support the claim of using Triptodur for treatment of CPP in pediatric patients.

8. Safety

Forty-four patients were treated with Triptodur for 12 months in a single open label study; all patients received two injection 6 months apart. This level of exposure was considered to be acceptable under SPA to support chronic dosing. The Sponsor also provided the information from the pharmacovigilance database on adverse events reported in all patients treated with triptorelin regardless of the indication, country of use, formulation or age as a supportive evidence of safety (5448 cases).

There were no deaths, dropouts or discontinuation of the treatment due to adverse reactions in the Sponsor's study

Serious Adverse Events (SAE) in Debio 8206-CPP-301 study
One patient developed SAE of device-related infection: a 7-year old girl developed an infection of vagus nerve stimulator that was placed surgically for treatment of underlying seizure disorder. Dr. Sullivan reviewed the case narrative and concluded that SAE was not drug related.

Common Adverse Reactions in Debio 8206-CPP-301 study
A total of 73% of Triptodur-treated subjects developed 81 treatment-emergent adverse events. The AEs that occurred in > 5% of patients were: nasopharyngitis (13.6%), headache (13.6%), upper respiratory tract infection (9.1%), gastroenteritis (6.8%), cough (6.8%). AEs that are attributed to known GnRH activity and associated hormonal changes include four events of vaginal bleedings in 3 patients and two episodes of hot flashes in two patients.
The Sponsor concluded that the majority of AEs (e.g., nasopharyngitis, headache) may represent age-appropriate complaints/symptom and are not related to the study drug. However, the absence of a control group and a small study size severely limits the interpretation of these reports, even though the non-serious nature of these events provides some reassurance about the clinical significance of these findings. Thus, I agree with Dr. Sullivan's conclusion that all TEAEs have to be included in the labeling.

Lastly, 35 patients had injection site reactions during the study (pain, redness, swelling, bruising). However, the Sponsor considered these AEs as related to the study drug in only 3 patients. Dr. Sullivan analyzed all injection site reactions and concluded that all reactions should be considered as clinically relevant and be included in the label. I agree with Dr. Sullivan's conclusion. Injection site reactions are not unexpected events with use of any injectable drugs and none of the reactions would have occurred without Triptodur injection.

AEs of special interest

Acute-on-chronic phenomenon (AOC)

There is a known risk of AOC phenomenon that might occur with use of all GnRH agonists in patients with CPP and is caused by a transient stimulation of the HPG axis in the setting of chronic suppression when subsequent doses of GnRH agonists are given. This phenomenon is infrequent but worrisome for patients due to temporary flare of the disease (vaginal bleeding, hot flashes, etc.). Thus, the evaluation of the AOC phenomenon in a subset of patients after the second Triptodur dose was required under SPA agreement.
An AOC was defined as basal LH> 5 IU/L or serum estradiol > 20 pg/ml 48 hours after the second Triptodur dose and was evaluated in 22 patients. The Sponsor identified three children who developed AOC phenomenon after the second dose of Triptodur. However, Dr. Sullivan

re-analyzed these patients' data and concluded that only one patient had AOC phenomenon; two other patients did not achieve LH or estradiol suppression after the first dose, thus these two cases are not true AOC events. I agree with Dr. Sullivan's conclusion.

Seizures and Psychiatric adverse events

Recently, DMEP and DPV conducted an extensive review of all postmarketing reports of seizures, depression and emotional lability in patients with CPP receiving GnRH agonists (TSI#1405 and 1404, respectively). As a result of this review, the labels for all GnRH agonists for CPP indication were updated to include new safety information regarding the risk of seizures and depression in Warning and Precaution section and regarding emotional lability in Adverse Reaction Section (refer to Division's letters of approval for NDAs 020263, 019010, 022058, 019886 from 5/19/2017 in DARRTS). The Divisions concluded that the causative role of GnRH agonists cannot be ruled out completely and may be due to the transient increase and/or fluctuations in gonadal hormone levels. The Sponsors of all GnRH agonists for CPP indication were also required to create a medication guide to inform patients and caregivers of the possible risks associated with GnRH agonist use in CPP. Lastly, the Sponsors were also required to carry out enhanced pharmacovigilance (ePV) for events of depression and suicidality for 5 years.

Thus, the Clinical Review paid special attention to the occurrence of seizures and psychiatric AEs of interest in patients treated with Triptodur.

Seizures
A single postmarketing case of convulsion was reported with triptorelin formulation used for CPP in non-US countries. No seizures were reported in Debio-8206-CPP-301 study.

Depression and emotional lability
Dr. Sullivan reviewed all AEs in the psychiatric system SOC that occurred in Debio-8206-CPP-301 study and that were reported with use of other triptorelin formulations in postmarketing settings. A total of 8 AEs of emotional lability were reported by the Sponsor: 6 events in the Sponsor's study (5 events of anxiety and one event of mood alteration occurred in 2 patients) and 2 postmarketing AEs of emotional lability. The Clinical reviewer concluded that based on the limited information provided and known mechanism of action of all GnRH agonists on gonadal hormones, the association of these events with Triptodur cannot be excluded.

Overall, I agree with Dr. Sullivan's conclusion that the overall incidence of these adverse reactions observed with Triptodur is low and do not exceed the incidence of similar AEs observed with other approved GnRH agonists. I also concur with Dr. Sullivan's recommendations to include this safety information in the label, similarly to the safety

information implemented in all other GnRH agonist labels. As required for all Sponsors of GnRH agonists for CPP indication, Arbor Pharmaceuticals should create a medication guide to inform patients and caregivers of the above risks associated with use of Triptodur and to carry out enhanced pharmacovigilance (ePV) program for events of depression and suicidality in patients with CPP treated with Triptodur.

Hypersensitivity

No hypersensitivity reactions were reported in the Sponsor's study. In the entire post-marketing triptorelin data base, serious hypersensitivity reactions were reported in patients with CPP including angioedema, urticaria, rash, anaphylactic reactions and shock, erythema, face edema, pruritus. No Stevens-Jonson syndrome or toxic epidermal necrolysis were reported with triptorelin use.

I agree that the drug has to be contraindicated in patients with known hypersensitivity to the active ingredients. Triptodur is a therapeutic peptide, thus, hypersensitivity reactions are not unexpected events and are observed with use of other GnRH agonists. All GnRH agonists are contraindicated in patients who are hypersensitive to GnRH or GnRH agonist analogs.

Eye disorders

During the review of the Sponsor's postmarketing safety analysis and FAERS data, DPV noted that there were a total of 15 postmarketing cases of visual disorders among children using triptorelin for treatment of CPP (refer to the review in DARRTS from 4/3/20177). Dr. Sullivan conducted independent analysis of the reported cases of visual changes and concluded that no causal relationship between the drug and the events can be established at this time due to the limited information provided. However, she recommended to include these AEs in the label "given the number of cases of visual disorders seen among children using triptorelin". I concur with reviewer's recommendations.

Other laboratory parameters and vital signs

There were no clinically meaningful changes from baseline to final visit in any other laboratory parameters (hematology, clinical chemistry, urinalysis, urinary calcium, phosphate, etc.) or in vital signs.

In conclusion, I concur with Dr. Sullivan that the safety observations made during the Triptodur clinical program in patients with CPP are consistent with the known safety profile established for the whole class of GnRH agonists in the intended population. No new, population specific or drug-specific, safety signals were identified in the Triptodur program.

9. Advisory Committee Meeting

No AC meeting was held.

10. Pediatrics

Triptodur has received orphan-drug designation on 8/20/2012 May 11, 2010 for the treatment of CPP. Therefore, the requirements of the Pediatric research Equity Act do not apply to this application.

11. Other Relevant Regulatory Issues

OSI inspection

A clinical inspection summary was completed by Dr. Cynthia F. Kleppinger on 5/25/2017. Two principal investigators were investigated. The audit resulted in one Voluntary Action Indicated letter and one No Action Indicated decisions. The reviewer indicated that the reason for issuing Voluntary Action Indicated letter were the regulatory violations and concluded that these violations "are unlikely to significantly impact primary safety and efficacy analyses". Overall, the review concluded that "the inspectional findings support validity of the data as reported by the Sponsor under this NDA".

Financial Disclosure

FDA 3453 form was submitted confirming that the applicant of the pivotal study, Debio-8206-CPP-301 did not enter into any financial arrangement with the listed clinical investigators that could influence the outcome of the trials (refer to Dr. Sullivan's review).

12. Labeling

Proprietary name

The proposed proprietary name for triptorelin pamoate 6-month formulation is Triptodur. This was reviewed and deemed acceptable by the Office of Medication Error Prevention and Risk Management. A letter stating this was issued to the Applicant on 11/21/ 2016.

Labeling

The label was reviewed by Division of Pediatric and Maternal Health (refer to review in DARRTS from 5/26/2017) and by Division of Medication Error Prevention and Analysis (refer to review in DARRTS from 6/12/2017).

The Sponsor proposes to (b) (4) I do not agree (b) (4). (b) (4)

(b) (4)

(b) (4)

(b) (4) I also disagree with the Sponsor's plan to (b) (4)

(b) (4)

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

- Risk Benefit Assessment

The data submitted in support of Triptodur provides sufficient information to conclude that the benefits of use in patients with CPP outweigh the risk associated with the drug.

Benefit:

Study Debio 8206-CPP-301 has demonstrated that Triptodur decreased LH levels to prepubertal levels in 93% of children (41/44; 95%CI: 81.3% to 98.6%) with CPP at 6 months after a single dose; all patients maintained LH suppression for a total of 12 months (after 2 doses). The suppression of LH was maintained throughout the study as demonstrated by the suppressed LH at months 1, 2, 3, 9 and 12. Triptodur program also demonstrated that the majority of patients with suppressed LH levels had a sustained decrease in gonadal hormone levels (estradiol and testosterone) in approximately 80 % of children and suppression of clinical signs of puberty in approximately 90 % of patients. The efficacy findings from this study are consistent with the results from the pivotal trials evaluating efficacy of other approved GnRH agonists in children with CPP.

Risk:

The potential risks associated with Triptodur treatment in patients with CPP have been relatively well characterized in the Triptodur clinical program and do not outweigh the expected benefit. Overall, the safety profile of Triptodur was similar to those of other GnRH agonists currently approved for the treatment of CPP in pediatric patients. The major identified risks associated with all GnRH analogs include injection site reactions, menstrual

bleeding, and a temporary increase in signs and symptoms of puberty associated with initial stimulatory effect of GnRH agonists on the HPG axis. In this trial, 3 subjects reported 4 events of vaginal bleedings and two patients had hot flashes; all events resolved. The incidence of acute-on chronic phenomenon was low: only one patient had a transient stimulation of the HPG axis after the second injection that resolved completely. The incidence of injection site reactions was comparable to the incidence of injection site reactions seen with use of other GnRH agonists in children with CPP; injection site reactions are not unexpected events with the use of any injectable drugs.

The other recently identified adverse events associated with all GnRH agonists are depression, emotional lability and convulsions. No seizures or depression were reported in the trial, and only 2 patients reported non-serious events of emotional lability during Triptodur treatment. Postmarketing experience with triptorelin formulations approved and used in non-US countries has identified such adverse reactions, but the incidence was low. Moreover, limited information provided in all postmarketing reports and use of unapproved triptorelin formulations in unapproved doses complicate overall causality assessment of the events with the Sponsor's triptorelin formulation (Triptodur) for CPP indication.

In conclusion, the incidence of all adverse reactions observed with Triptodur was low in the clinical program and did not exceed the incidence of AEs observed with other approved GnRH agonists. More importantly, these risks can be mitigated through product labeling and medication guide, appropriate patient selection, monitoring and timely introduction of treatment.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

I am in agreement with the recommendation that an enhanced pharmacovigilance program for reports of suicidal ideation and behavior, self-injury, or depression in patients with CPP treated with Triptodur is needed. The program should include assessment and analyses of spontaneous reports of suicidal ideation and behavior, self-injury, or depression. These analyses should show cumulative data relative to the date of approval of Triptodur as well as relative to prior periodic safety reports. Medical literature reviews for case reports/case series of events of suicidal ideation and behavior, self-injury, and depression reported with Triptodur should also be provided in the periodic safety report.

- Recommended Comments to Applicant

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARINA ZEMSKOVA
06/27/2017

JEAN-MARC P GUETTIER
06/29/2017
I concur.