CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208956Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA, via 505(b)(1) pathway
Application Number(s)	208956
Priority or Standard	Standard
Submit Date(s)	8/29/2016
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PDUFA Goal Date	June 29, 2017
Division/Office	Division of Metabolism and Endocrinology Products (DMEP)
Reviewer Name(s)	Shannon Sullivan, MD, PhD
Review Completion Date	
Established Name	Triptorelin pamoate for (b) (4) suspension
(Proposed) Trade Name	Triptodur
Applicant	Arbor Pharmaceuticals, LLC
Formulation(s)	Powder, lyophilized, for suspension
Dosing Regimen	22.5 mg administered as a single intramuscular injection once every 24 weeks
Applicant Proposed Indication(s)/Population(s)	Treatment of central precocious puberty in pediatric patients
Recommendation on Regulatory Action	APPROVAL (pending labeling agreement)
Recommended Indication(s)/Population(s) (if applicable)	Pediatric patients (b) (4) with central precocious puberty

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Glossary

AC	advisory committee
AE	adverse event
AOC	acute-on-chronic phenomenon
BA/CA	bone age to chronological age ratio
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
E2	estradiol
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FSH	Follicle Stimulating hormone
GCP	good clinical practice
GnRH	gonadotropin releasing hormone
GnRHa	GnRH agonist
GRMP	good review management practice
HPG	hypothalamic-pituitary-gonadal
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness

ISS	integrated summary of safety
ITT	intent to treat
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
T	total testosterone
TEAE	treatment emergent adverse event
TSI	tracked safety issue

1 Executive Summary

1.1. Product Introduction

Triptorelin pamoate for (b) (4) suspension is a synthetic decapeptide analogiue of naturally-occurring gonadotropin releasing hormone (GnRH) and is under development by Arbor Pharmaceuticals ('Arbor,' 'Sponsor') for treatment of children with central precocious puberty (CPP). The proposed proprietary name for triptorelin under the CPP indication is Triptodur. The drug is formulated as a lyophilized powder for suspension and is administered as a single intramuscular (IM) injection of 22.5 mg once every 24 weeks under physician supervision. The lyophilized powder is to be reconstituted in its vial using a sterile water pre-filled syringe that is provided in the product kit.

A 1-month formulation of triptorelin pamoate was initially approved for use in the United States (U.S.) in 2000 for palliative treatment of advanced prostate cancer under the proprietary name Trelstar 3.75 mg (NDA 20715). For the same indication (palliative treatment of prostate cancer), a 3-month formulation was approved in 2001 (Trelstar 11.25 mg, NDA 21288), and a 6-month formulation was approved in 2010 (Trelstar 22.5 mg, NDA 22437). The 22.5 mg 6-month formulation of Trelstar is the same triptorelin pamoate formulation that was used in the pivotal Phase 3 clinical trial in children with CPP to support the present NDA. The Sponsor holds the rights of reference to Trelstar NDA 20715, NDA 21288, and NDA 22437; therefore, the present NDA (208956) for Triptodur is submitted via the 505(b)(1) pathway. Currently, the triptorelin pamoate 1-month and 3-month formulations are approved in several non-US countries for treatment of CPP.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The submitted data provide substantial evidence to support the efficacy of triptorelin 22.5 mg (b) (4) for the treatment of central precocious puberty in children. Specifically, in a single pivotal, open-label, 50 week trial, treatment with triptorelin 22.5 mg every 24 weeks decreased LH to pre-pubertal levels in 93% of children with CPP at 6 months and 98% of children at 12 months. Additionally, triptorelin suppressed levels of gonadal hormones (estradiol in girls and testosterone in boys) in ≥80% of patients at all timepoints during the study, decreased clinical signs of puberty in ~90% of patients at months 6 and 12, and suppressed bone age advancement in 96% of patients at month 12.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Triptorelin 22.5 mg (b) (4) is a long-acting GnRH agonist that was initially approved for palliative treatment of advanced prostate cancer in 2010 and is currently being developed for treatment of CPP in children. CPP is a rare disorder affecting approximately 1 in every 5,000 to 10,000 children, with an estimated ratio of girls to boys of ~20:1. CPP is characterized by early onset of pubertal development, defined as prior to age 8 in girls and age 9 in boys. CPP is diagnosed by a GnRH agonist-stimulated LH in the pubertal range. GnRH agonist-stimulated LH levels are also used during treatment to monitor a child's response to therapy. Early puberty often causes extreme psychological distress and social isolation for patients, which may improve with treatment. Additionally, CPP promotes bone age advancement and consequently, leads to diminished final adult height if not treated. GnRH agonist therapy, which reversibly suppresses the hypothalamic-pituitary-gonadal (HPG) axis (resulting in reversible suppression of pubertal development and slowing of bone age advancement), is considered the gold standard of care for children with CPP. Currently, there are three GnRH agonist formulations approved for CPP in the U.S.: Lupron Depot Ped (leuprolide, NDA 20263)), Supprelin (histrelin, NDA 22058), and Synarel (nafarelin, NDA 20109).

The applicant demonstrated in a single pivotal study—Debio-8206-CPP-301, an open-label, single arm study in 44 children between aged 2-9 years—the safety and efficacy of triptorelin 22.5 mg (b) (4) administered every 6 months for treatment of CPP.

In the primary efficacy analysis, 93% of patients (41/44; 95% CI: 81.3% to 98.6%) achieved GnRH agonist-stimulated LH levels in the pre-pubertal range at month 6, i.e., after a single triptorelin dose. Secondary efficacy outcomes were similarly favorable, further supporting the efficacy of triptorelin for the treatment of CPP. Secondary efficacy outcomes demonstrated that 100% of patients maintained LH suppression from month 6 to month 12; ≥95% achieved LH suppression at months 1, 2, 3, 9, and 12; ≥80% achieved pre-pubertal levels of estradiol (girls) and testosterone (boys) at months 1, 2, 3, 6, 9, and 12; ~90% had suppression of pubertal development at months 6 and 12; and 96% achieved stabilization of bone age to chronological age ratio (BA:CA) at month 12. Notably, the efficacy of triptorelin in the treatment of CPP was similar to that of the three marketed GnRH agonists currently approved for the CPP indication.

Data from pivotal study Debio-8206-CPP-301 also provide substantial evidence supporting the safety of the triptorelin 22.5 mg 6-month formulation in the treatment of children with CPP. Administration of triptorelin was well tolerated, and the safety risks of triptorelin were comparable to other approved sustained-release GnRH agonist formulations. The most common adverse reactions associated with the triptorelin 22.5 mg 6-month formulation in this clinical development program were injection site pain, menstrual bleeding, and an initial increase in signs and symptoms of puberty (due to initial stimulatory effect on the HPG axis). After the second triptorelin dose, 14% of patients experienced acute-on-chronic (AOC) effect, a transient stimulation of the HPG axis in the setting of chronic suppression. These adverse

reactions are all expected with use of an intramuscular GnRH agonist in children with CPP based on the drug's mechanism of action and route of administration and can be easily monitored.

Post-marketing experience with triptorelin in non-US countries has identified additional potential adverse reactions: hypersensitivity reactions including anaphylaxis, hypertension, and convulsions. These adverse reactions have also been seen with other sustained-release GnRH agonist formulations approved for CPP; however, none were seen in the clinical development program for triptorelin 22.5 mg (b) (4)

In conclusion, the safety and efficacy data from the single pivotal open-label phase 3 trial conducted to support approval of triptorelin 22.5 mg (b) (4) for treatment of CPP demonstrate that the benefits of triptorelin outweigh the potential risks. Further, the safety and efficacy profile of triptorelin 22.5 mg (b) (4) is similar to that of the other GnRH agonist formulations previously approved for treatment of CPP (Lupron Depot-PEDS, Supprelin, Synarel).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• CPP is a rare disorder affecting approximately 1 in every 5,000 to 10,000 children, with an estimated ratio of girls to boys of ~20:1. CPP is characterized by early onset of pubertal development, prior to age 8 in girls and age 9 in boys.	
Current Treatment Options	• Current standard of care for treatment of CPP is with GnRH agonists, which suppress the HPG axis and thus suppress pubertal development as long as treatment is ongoing. • Other GnRH agonists currently approved in the U.S. for treatment of CPP in children are: i) Lupron Depot-Ped (leuprolide acetate for depot suspension, NDA 20263), ii) Supprelin LA subcutaneous implant (histrelin acetate, NDA 22058), and iii) Synarel nasal spray (nafarelin acetate, NDA 020109).	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The primary efficacy endpoint (% of patients with pre-pubertal levels of GnRH-stimulated LH at month 6) was achieved in 93% of patients; all patients who achieved LH suppression at month 6 maintained LH suppression at month 12. • At month 6, 79% of girls and 100% of boys achieved pre-pubertal gonadal hormone levels, and at month 12, 79% of girls and 80% of boys achieved pre-pubertal gonadal hormone levels.	The study protocol was agreed upon between the Sponsor and the Agency in a Special Protocol Assessment (SPA)-Agreement letter issued in October, 2011.
Risk	• The most common adverse reactions were injection site pain and menstrual bleeding, both expected AEs with use of an intramuscular formulation of a GnRH agonist. • Post-marketing experience with Triptorelin use for CPP in non-US countries has identified additional potential adverse reactions: *hypersensitivity reactions including anaphylaxis, hypertension, convulsions, and vision changes*.	The risk of triptorelin 22.5 mg (b) (4) in children with CPP is low and is similar to the risk with other approved GnRH agonist formulations. *Convulsions* and *psychiatric AEs* have been seen with other approved GnRH agonist formulations for the CPP indication, thus Tracked Safety Issues and Supplemental Labeling Changes have been issued for these AEs for all GnRH agonists approved for CPP. A requirement for Enhanced Pharmaco-vigilance (ePV) documenting post-marketing cases of vision changes will be issued upon approval.
Risk Management	• Labeling will be used to mitigate the risks associated with Triptorelin use. • No risks identified require risk management beyond labeling to warrant consideration of a REMS.	Safety information will be adequately relayed to patients and providers in product labeling. No REMS will be issued.

2 Therapeutic Context

2.1. Analysis of Condition

Central (GnRH dependent) precocious puberty affects approximately 1 out of every 5,000 to 10,000 children (1), with a typical age of onset between 2 and 8 years of age. CPP is more common in girls, with a reported ratio of affected boys to girls of between 1:3 and 1:23 (1). The gold standard therapy for CPP is chronic GnRH agonist therapy, which suppresses the reproductive axis. The gold standard diagnostic test for CPP is a GnRH stimulation test, in which the luteinizing hormone (LH) response to an immediate-release (rather than sustained-release) GnRH agonist is determined. An LH response to GnRH agonist stimulation that is in the pubertal range, typically defined as LH ≥ 6 IU/L, is diagnostic for CPP. The GnRH stimulation test is similarly used during GnRH agonist therapy to assess response to treatment. A GnRH agonist-stimulated LH in the pre-pubertal range, typically defined as LH ≤ 5 IU/L, is the goal of treatment because it indicates sufficient HPG axis suppression.

Clinically, CPP is defined by pubertal development prior to age 9 years in boys or age 8 years in girls that is due to premature activation of the HPG axis, and which is *not* caused by primary adrenal or gonadal steroid hormone over-production (known as peripheral precocious puberty). Physiologically, CPP occurs due to premature activation of the GnRH pulse generator in the hypothalamus. This results in increases in both the frequency and amplitude of pulsatile GnRH release, which in turn leads to increased pulsatile release of the pituitary gonadotropins, LH and follicle stimulating hormone (FSH). Such signaling from the pituitary drives the gonads (testes in boys and ovaries in girls) to produce pubertal levels of gonadal sex steroids, which induce early development of secondary sexual characteristics. CPP also leads to accelerated growth velocity and premature bone maturation due to increased estradiol levels (directly from the ovaries in girls and indirectly via conversion from testosterone in boys), which ultimately results in premature fusion of ephiphyseal growth plates and diminished adult height (1).

Although a *pulsatile* signal from GnRH is required to stimulate pituitary gonadotropin secretion and thus drive gonadal hormone production and accompanying pubertal changes, it has been long recognized that a *continuous* GnRH signal suppresses the HPG axis, resulting in a hypogonadal state (2). For this reason, drugs in the GnRH agonist class are the standard of care for treating children

with CPP (3). GnRH agonists, when used chronically, effectively suppress the prematurely activated HPG axis and halt pubertal development until a child reaches an appropriate age for pubertal development to begin. At that time, the GnRH agonist can be discontinued, removing suppression of pulsatile GnRH release and allowing puberty to proceed.

2.2. Analysis of Current Treatment Options

GnRH agonist drug development started in the 1980s with formulations that required daily subcutaneous (SC) injections. These drugs included triptorelin, leuprorelin, buserelin, and deslorelin. Since then, alternative GnRH agonist formulations have been approved for treatment of CPP in the U.S., including sustained-release intra-muscular and subcutaneous implantable formulations, as well as an intra-nasal formulation. These newer GnRH agonist formulations have largely replaced daily SC GnRH agonist formulations due to greater ease of use. Currently, three GnRH agonist formulations are approved and marketed in the U.S. for the CPP indication: Lupron Depot PED (leuprolide) 7.5, 11.25, and 15 mg 1-month intramuscular formulations and 11.25 and 30 mg 3-month intramuscular formulations (NDA 020263, AbbVie); Supprelin LA Implant (histrelin), 50 mg yearly SC implant (NDA 22058, Endo Pharmaceuticals); and Synarel (nafarelin) intra-nasal spray, 1600-1800 µg (8-9 sprays)/day (NDA 020109, Pfizer)(**Table 1**).

Although the gold standard treatment for CPP is GnRH agonist therapy, adjuvant drugs are occasionally used off-label to help improve final height, a major concern for children with CPP. That said, experience with off-label use of adjuvant drugs in the treatment of CPP is limited and large, randomized studies have not been performed to determine efficacy or safety in this setting. Adjuvant therapies include oxandrolone, a non-aromatizable androgen; recombinant growth hormone (rGH); aromatase inhibitors (AI), which inhibit conversion of testosterone to estrogens; selective estrogen receptor modulators (SERMs); and spironolactone in boys. A small non-randomized study of ten children with CPP demonstrated a possible benefit to final adult height when oxandrolone was used along with GnRH agonist therapy (4). Statistically significant improvement in final adult height has also been seen in several small, non-randomized studies in which children with CPP were treated with rGH in addition to GnRH agonist therapy (5-8). Small non-randomized studies have shown that suppressing estrogen with aromatase inhibitors slows acceleration of bone age and improves final adult height in children with precocious puberty due to McCune Albright Syndrome (MAS) (9,10). A study of effects of the SERM tamoxifen in 25 girls with precocious puberty due to MAS demonstrated decreased skeletal maturation and reduced growth velocity, although only four of the girls in this study had gonadotropin-dependent (central) precocious puberty, and those girls were also being treated with GnRH agonist therapy (11). Finally, a small non-randomized study showed improvement in

final height in boys treated with both spironolactone and the AI testolactone (12,13). Overall, however, the efficacy and safety of these adjuvant therapies have not been studied in well-designed trials in children with CPP, and it is evident from the limited available data that efficacy is far inferior to that of the GnRH agonist drug class.

Major safety concerns related to GnRH agonists as a class include injection site reactions, rare immune-allergic reactions, side effects due to an initial increase in gonadal hormone production at the initiation of treatment (e.g., vaginal bleeding in girls), and side effects related to HPG axis suppression during chronic therapy (e.g., hot flashes).

Table 1. Summary of Available GnRH Agonists Approved for Treatment of Central Precocious Puberty in the U.S.

Product (s) Name	Relevant Indication	Sponsor/ Year of Approval	Dosing/ Administration	Efficacy Information (from FDA labels)
Lupron Depot PED (leuprolide acetate) (14,15)	CPP Total patients across all dose groups: 139 (n=125 F, 14 M)(97 treatment-naïve, 42 pre-treated)	AbbVie/ 1-month formulations: 1993 (7.5 mg), 1994 (11.25 and 15 mg) 3-month formulations: 2011 (11.25 and 30 mg)	7.5 mg, 11.25 mg, and 15 mg, 1-month formulations; 11.25 mg and 30 mg 3-month formulations	(b) (4)

Supprelin (histrelin) (16)	CPP Pivotal Phase 3 study included 36 patients (n=33F, 3M) (20 treatment-naïve, 16 pre-treated)	Endo Pharma-ceuticals/ 2007	50 mg implant, placed once every 12 months (52 weeks)	(b) (4)
Synarel (nafarelin) (17)(NDA 20109, (b) (4)	CPP 2 Pivotal Phase 3 studies included 126 patients with CPP (n=107F, 19M)	Pfizer/1992	1600-1800 µg/day (2 sprays into each nostril bid (8 sprays/day) or 3 sprays into alternating nostril tid (9 sprays/day))	(b) (4)

				(b) (4)

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Sponsor is developing triptorelin 22.5 mg (b) (4) for the treatment of children with CPP, to be administered every 24 weeks (168 days). This product, currently marketed in the U.S. as Trelstar 6-Month by Watson Laboratories, Inc., was initially approved in 2010 for palliative treatment of advanced prostate cancer under NDA 22437 in the Division of Oncology Products 1. Triptorelin for treatment of CPP is not currently marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

The triptorelin 22.5 mg (b) (4) drug development program was conducted under IND 111504, Sponsor Debiopharm, which opened in May, 2011. Sponsorship was transferred to Arbor Pharmaceuticals upon submission of this NDA.

Clinical Review
Shannon Sullivan, MD, PhD
NDA 208956
Triptodur (triptorelin pamoate for [redacted] suspension)

A clinical Special Protocol Assessment (SPA) request was submitted by the Sponsor on June 17, 2011, and a SPA-No Agreement letter was issued by the Agency on August 4, 2011. The SPA-No Agreement letter outlined the following recommendations regarding the originally proposed SPA (*Refer to IND 111504, COR-INDSPA-04 dated 8/4/2011 in DARRTS*):

1. extend the proposed study period from 6 to 12 months given that the program is for development of a 6-month triptorelin formulation,
2. evaluate for Acute-on-Chronic (AOC) effect in a subset of patients after the second triptorelin dose,
[redacted]
4. modify the Intention-to-treat (ITT) population to include only subjects who have been enrolled, treated at baseline, and who have at least one post-treatment assessment of LH suppression status,
5. modify the modified ITT (mITT) population such that subjects who discontinue from the study prior to the month six assessment for any reason or who otherwise do not provide an assessment of LH suppression at month 6 be classified as "not suppressed" with respect to the primary endpoint,
6. primary analysis of LH endpoints should reference the mITT population,
7. classify subjects who withdraw for any reason or who otherwise do not provide LH data at month 3 or month 6 as "not suppressed" with respect to the endpoint maintenance of LH suppression from month 3 to month 6,
8. perform a secondary analysis based on LH suppression of ≤4 IU/L 30 minutes after GnRH agonist stimulation,
9. provide descriptive statistics by time point for GnRH-stimulated LH levels, basal estradiol (in females) and testosterone (in males), including change from baseline,
10. characterize C_{max} in a subset of subjects and assess triptorelin levels after drug doses,
11. calculate study size based on a one-tailed α of 0.025 and a null percentage of LH suppression of 80%, and
12. provide individual patient profile plots that depict the time course of LH and either estradiol or testosterone for each patient from baseline to month 6.

The SPA was revised and resubmitted by the Sponsor on September 2, 2011, and a SPA-Agreement letter was issued by the Agency on October 21, 2011 (*Refer to IND 111504, COR-INDSPA-05, dated 10/21/2011 in DARRTS*). In the SPA resubmission, all of the above recommended modifications were implemented with the exception of [redacted]

(b) (4)
(b) (4) All other details of the revised SPA were acceptable to the Agency, including the proposed sample size (n=44, with a minimum of 4 boys), primary and secondary endpoints, statistical analysis plan, and inclusion of a PK subset of 8 children for measurement of triptorelin C_{max} and T_{max} following the first and second doses.

Orphan drug designation was granted to this product and indication on August 20, 2012 (Designation request #12-3760).

A pre-NDA meeting between the Sponsor and the FDA occurred on December 3, 2015. Major points of discussion during the pre-NDA meeting included the following (*Refer to IND 111504, COR-MEET-03 (Meeting Minutes) dated 12/30/15 in DARRTS*):

1. clarification from the Agency that results from the pivotal study Debio-8206-CPP-301, which had been agreed upon under the SPA agreement (October, 2011), would support filing of the NDA for the 6-month triptorelin formulation for CPP,
2. clarification from the Sponsor that the NDA would be submitted via the 505(b)1 regulatory pathway and that literature submitted with the application would be supportive only,
3. clarification by the Agency that pharmacovigilance (PV) data from GnRH agonists as a class and from use of triptorelin outside of the U.S. for treatment of children with CPP should be included in labeling, with a clear rationale for inclusion of any such supportive safety data,
4. clarification from the Sponsor that the 3-month triptorelin formulation will not be referenced in the NDA for the 6-month formulation,
5. clarification by the Agency that for CPP labeling, PK/PD data from children with CPP will be sufficient, and
6. clarification by the Agency that at the time of NDA submission, the application should be complete, as the Agency may not be able to review data that is submitted during the review cycle. Specifically, the Agency stated that lack of information on a diluent/ injection kit to be used with the drug product would be considered a filing deficiency, and that submission of new Chemistry, Manufacturing, and Control (CMC) data to a Drug Master File during the review process may be considered a major protocol amendment and thereby extend the review clock.

3.3. Foreign Regulatory Actions and Marketing History

The triptorelin 22.5 mg (b) (4) formulation is not currently marketed in any non-U.S. country for the CPP indication. Refer to Sections 1.1, 6.1.2 (Secondary efficacy analysis, #7), and 8.9 regarding foreign use of Triptorelin 1-month and 3-month formulations for treatment of CPP.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

A total of thirteen study sites enrolled patients into the Phase 3 trial, Debio-8206-CPP-301. Two study sites were selected for OSI audit: Site #81 (Dr. Fernando Cassorla, IDIMI, Santiago, Chile), which enrolled 15 subjects, and Site #25 (Dr. Joshua Yang, Arnold Palmer Pediatric Endocrinology Practice, Orlando, Florida), which enrolled five subjects. These sites were selected based on high numbers of patients enrolled (15 for the Chilean site and 5 for the US site). Site #81 in Chile underwent an inspection by the National Drug Agency, Public Health Institute of Chile on March 19-21, 2013, and an audit by Debiopharm's Regulatory Compliance Group on October 16-18, 2013. Site 25 did not undergo an internal regulatory audit initiated by the Sponsor during the study period.

Name of PI **Address** **Site #**	**Number of Subjects enrolled**	**Reason for inspection**	**Classification**
Dr. Fernando Cassorla IDIMI – Instituto de InvestigacionesMaterno Infantil Santa Rosa 1234 Santiago de Chile 836016 Site #81	15	Site with highest enrollment	NAI

Dr. Joshua Yang Arnold Palmer Pediatric Endocrinology Practice Arnold Palmer Hospital For Children 89 West Copeland Street, 2nd Floor Orlando, Florida 32806-1134 Site #25	5	High U.S. enroller; not audited during the study by the Sponsor	VAI

Significant findings of the OSI audits include no regulatory violations for Site #81 (Dr. Cassorla), which was given the classification of No Action Indicated (NAI) by OSI, and minor regulatory violations at Site #25 (Dr. Yang), which was classified as Voluntary Action Indicated (VAI) by OSI. The regulatory violations at Site #25 included use of whiteout on several source documents, missing laboratory values for five subjects at a total of five study timepoints, use of a prohibited concomitant medication by one subject during the study (intravenous heparin to flush a PICC line), a total of six individual data points in source documents that did not match the eCRF in three subjects. Overall, OSI determined that the violations at Site #25 were minor and unlikely to significantly impact safety or efficacy analyses; therefore, the reliability of data from Site #25 was determined to be acceptable for use in support of the drug's proposed indication (see CONSULT REV-DSI-02 (Clinical Inspection Summary) dated 4/19/17 in DARRTS for complete details).

In conclusion, the overall integrity and submission quality of the data from the two sites that were inspected were found to be adequate to support the current NDA.

4.2. Product Quality

Refer to the CMC Review for complete details regarding product quality.

The chemical name for triptorelin pamoate drug substance is L-pyroglutamyl-L-histidyl-L-trytophyl-L-seryl-L-tyrosyl-Dtryptophyl-L-leucyl-L-arginyl-L-prolylglycinamide, pamoate salt. The drug product is manufactured as microgranules and will be provided in a kit with sterile water for reconstitution and injection of single doses. The formulation (b) (4) (b) (4)

(b) (4) The drug product used in the clinical development program for CPP (study Debio 8206-CPP-301) is the same as the to-be-marketed product.

All product quality data for triptorelin pamoate 22.5 mg (including manufacturing process and controls, materials, critical steps and intermediates, process validation and evaluation, manufacturing process and development, elucidation of structure, impurities, stability, and container closure system) are derived from (b) (4) Drug Master File (DMF) No. (b) (4) and Debiopharm's DMF No. (b) (4) (for batch formulation).

All product quality data for Sterile Water For Injection (WFI) and the container closure system are derived from (b) (4) DMF No. (b) (4) DMF No (b) (4), respectively.
WFI (Ph.Eur./USP) is provided in a single use pre-filled (b) (4) (b) (4) glass syringe. (b) (4) (b) (4) mL WFI/prefilled syringe); WFI will be provided in a kit for reconstitution of triptorelin pamoate microgranules 22.5 mg vial, and the primary container/closure is a (b) (4) (b) (4) syringe that consists of a syringe barrel, sterilized stopper, and a (b) (4) cap with a luer-lock (refer to DMF (b) (4)).

Biopharmaceutics:
The triptorelin formulation used in study Debio 8206-CPP-301 is identical to the formulation approved for treatment of men with advanced prostate cancer under NDA 22437. The *in vitro* dissolution profiles obtained for batches of triptorelin 22.5 mg (b) (4) manufactured to date show consistency of performance across batches used in the pivotal prostate cancer study, the pivotal CPP study (Debio 8206-CPP-301), and batches distributed commercially worldwide.

4.3. Clinical Microbiology

Refer to the CMC Review for complete details.

From CMC review of NDA 22437, triptorelin 22.5 mg for treatment of advanced prostate cancer (the same triptorelin formulation being reviewed here for treatment of CPP), microbiological attributes of the drug product were determined to be acceptable. The CMC review concluded that the current sterility test is sufficient in that triptorelin 22.5mg is (b) (4). Further, the

(b) (4) procedure was determined to be sufficient based on exposure time, process validation and historical experience with triptorelin 3.75mg and 11.25 mg formulations.

4.4. Nonclinical Pharmacology/Toxicology

Please refer to the Pharmacology/Toxicology primary review for more details.

PK/PD of triptorelin was extensively characterized under NDA 20715. No new non-clinical PK/PD studies were conducted under this NDA.

Pharmacology:
Studies in mice and rats evaluating potential side effects of triptorelin on the cardiovascular, central nervous, digestive, and renal systems demonstrated no safety findings that are of concern for human use.

Although triptorelin is more resistant to enzymatic cleavage than endogenous GnRH, like other peptides, the metabolism of triptorelin involves degradation to smaller peptide fragments and individual amino acids; therefore, hepatic microsomal enzymes are unlikely to be involved in triptorelin metabolism. *In vitro* studies were performed to assess the effects of triptorelin on induction of CYPs 1A2 and 3A4/5 in human hepatocytes, on inhibition of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5 in human microsomes, and on interactions with p-glycoprotein (P-gP). Altogether, these studies showed that drug-drug interactions with triptorelin are unlikely to occur. Further, in pharmacovigilance since 1986, no significant drug-drug interactions with triptorelin have been reported, supporting the *in vitro* data. Consistent with regulatory guidance, no additional metabolism studies were performed for triptorelin, since the metabolic pathways for peptides are generally understood *(ICH Guidance S6; EMEA Guideline CHMP/EWP/89249/2004)*.

Pharmacodynamic (PD) studies of the triptorelin 6-month formulation were done in rats. After IM injection, testosterone levels decreased rapidly and remained at a low level plateau for 24 weeks. Slight increases in testosterone levels were seen at 26 weeks, coincident with decreased serum triptorelin levels. Serum triptorelin levels peaked within one day post-administration, then progressively decreased over the next 4 weeks, followed by a second increase and finally a plateau until week 20. Triptorelin levels then gradually decreased until week 24. Triptorelin release was consistently correlated with a low mean serum testosterone value.

Reviewer Comment: Results from safety pharmacology studies showed no findings which might cause concern for use in humans.

Toxicology:
In single dose toxicity studies in mice and rats, no clinical symptoms were observed in either mice or rats with single doses up to 10 mg/kg triptorelin, which is about 7000 times the daily therapeutic dose intended for humans. In sub-chronic and chronic toxicity studies in rats, dogs, and monkeys, the only effects observed were expected based on the physiologic mechanism of GnRH agonists. At doses of the daily and 1-month sustained release formulations that effectively suppressed gonadal hormones and LH, and that were up to 500 times the doses intended for human use, spermatogenic arrest and atrophy of the testes and accessory sex organs were seen in males; inhibition of estrus and atrophy of the ovary and accessory sex organs were seen in females; and decreased weight of reproductive organs was seen in both sexes. All of the changes in reproductive organs were reversible with cessation of therapy, seen along with reversal of hormonal suppression. Pituitary focal hyperplasia or microadenoma developed in male rats after 6 months of treatment (a common occurrence in rats in the setting of an altered hormonal milieu), but not in other species; pituitary effects in male rats did not reverse with treatment cessation.

Regarding developmental toxicity, there were no maternal, fetal, embryonic, or teratogenic toxicities when pregnant female mice were treated with daily subcutaneous injections of 2 to 200 mcg/kg triptorelin or when pregnant female rats were treated with 10 mcg/kg daily from gestational day 6 through day 15. Reduced maternal weight gain and increased uterine resorption were seen in pregnant female rats treated with 100 mcg/kg triptorelin on gestational days 6-15.

Mutagenicity
Triptorelin showed no mutagenic or clastogenic activity against Salmonella strains, Chinese Hamster Ovary cells, or mouse lymphoma cells. In *in vivo* mouse micronucleus assays, there was no increase in micronucleus frequency in triptorelin-treated animals compared to negative controls and micronucleus frequency was significantly lower than the frequency in a positive control (cyclophosphamide).

Oncogenicity/Carcinogenicity
Carcinogenicity testing, done in mice and rats, showed no oncogenic effects in mice treated with 120 to 6000 mcg/kg triptorelin every 28 days for 18 months; however, rats treated with 120 to 3000 mcg/kg triptorelin every 28 days for 23 months developed posterior pituitary adenomas that resulted in premature death. Rats also developed benign adenomas or focal hyperplasia of the anterior pituitary, changes thought to be due to the pharmacologic action of GnRH agonists and species-specific, thus not applicable to human use.

Reviewer Comment: Pituitary toxicities of triptorelin seen in rats are species-specific and are expected findings in rat models. These toxicities are thus not relevant to human use of triptorelin at clinically recommended doses.

Local Tolerance:
In healthy adult female rats, tissue reactions at the injection site 24 hours after IM injection of triptorelin were histologically characteristic of the mild inflammatory reaction seen with repairing tissue damage, including infiltration of lymphocytes, plasma cells, and histiocytes, which was most prevalent around muscle fibers that were damaged during the injection. There was also a fibrous connective tissue reaction and an accumulation of inflammatory cells (indicative of a foreign body reaction) around each injected triptorelin microgranule.

Reviewer Comment: In summary, the non-clinical Pharmacology/Toxicology program, including the demonstrated mechanism of action, safety profile, and pharmacokinetic profile of the triptorelin pamoate 6-month formulation, supports its use in humans.

4.5. Clinical Pharmacology

Refer to Clinical Pharmacology review for detailed review.

4.5.1. Mechanism of Action

Triptorelin pamoate is a synthetic decapeptide analog of endogenous GnRH. Triptorelin is a sustained-release GnRH agonist which acts to suppress endogenous release of the pituitary gonadotropins, LH and FSH, and thereby decreases downstream gonadal sex steroid production. It is well established that continuous (rather than pulsatile) GnRH signaling suppresses (rather than activates) the HPG axis (2). Physiologically, chronic GnRH agonists lead to down-regulation of pituitary GnRH receptors, resulting in suppression of pituitary gonadotropin release and ultimately, indirectly inhibit of gonadal hormone production.

4.5.2. Pharmacodynamics

From the small PK subset in Debio-8206-CPP-301 (n=8), triptorelin PK/PD relationships could not be evaluated. However, the PK/PD relationship has been evaluated in men with prostate cancer; this relationship is non-linear and time-dependent due to pituitary desensitization, which, once achieved, is maintained with very low levels of circulating triptorelin (*see NDA 22437, Clinical*

Pharmacology review, dated 6/30/2009 in DARRTS).

Triptorelin mimics endogenous GnRH in its effects on the HPG axis; that is, chronic GnRH agonist signaling suppresses pituitary gonadotropin production, which in turn results in pre-pubertal or castrate levels of gonadal sex hormones (estradiol and testosterone). In the pivotal phase 3 study for this application, the primary PD efficacy endpoint, suppression of LH at month 6 to a pre-pubertal level, was achieved in 93% of study patients. Further, all patients (100%) who achieved LH suppression at month 6 maintained LH suppression at month 12. Upon initiation of GnRH agonist therapy, a transient stimulation of the HPG axis may occur, in which pituitary gonadotropin production is increased, resulting in a transient increase in the production of gonadal sex hormones and worsening of puberty symptoms. This transient HPG axis stimulation may also occur in the setting of chronic GnRH agonist therapy when subsequent doses are given; this is known as acute-on-chronic (AOC) phenomenon. In Debio-8206-CPP-301, a subset of 22 patients was assessed for evidence of AOC phenomenon after the second (month 6) triptorelin dose. Eighty-six percent (19/22) of patients demonstrated *absence* of AOC phenomenon following the second triptorelin dose. Two of the subjects with evidence of AOC effect did not in fact experience true AOC phenomena because neither achieved complete LH suppression at month six.

4.5.3. **Pharmacokinetics**

Triptorelin pharmacokinetics in children with CPP were established by measuring serum triptorelin levels at months 1, 2, 3, 6 (prior to dosing), 9 and 12, and by measuring triptorelin C_{max} and T_{max} in a subset of 8 patients (the 'PK subset') following both the first and second triptorelin injections. Significant drug accumulation was not seen after the second triptorelin injection (mean accumulation ratio of 0.91 for C_{max}).

From the PK subset, two distinct phases of triptorelin release were demonstrated, a burst phase followed by a maintenance phase. After each triptorelin dose, serum triptorelin concentrations peaked at a median of 4 hours post-dose (mean C_{max} 39.9 ng/mL and C_{max} 36.5 ng/mL after the first and second injections, respectively). Mean serum triptorelin levels were 0.11 and 0.17 ng/mL, respectively, at months 1 and 2 after the first triptorelin injection, then remained at 0.03 to 0.05 ng/mL over the remainder of the dosing period, i.e., through month 6 (

Figure 1).

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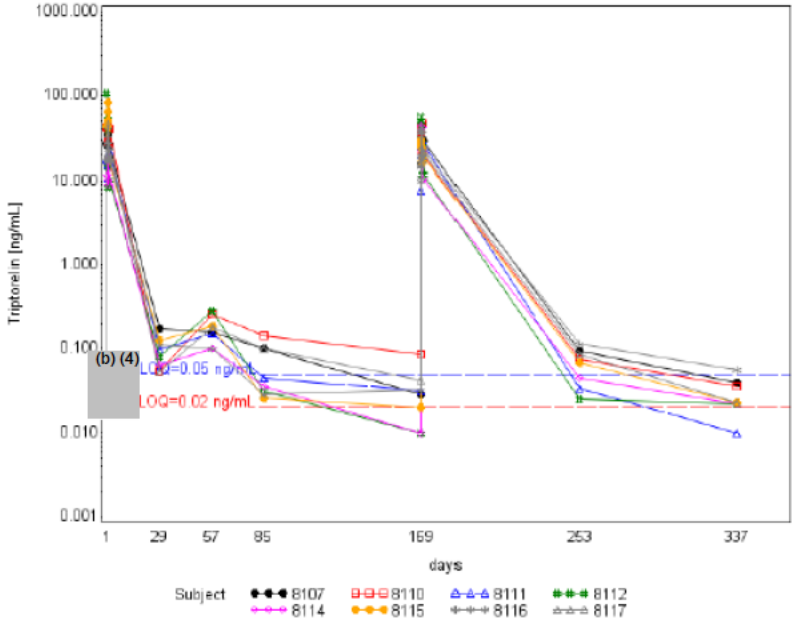
Figure 1. Triptorelin individual serum levels--PK subset (log(10)/linear axes)[#]

[#]*Source: Figure 11.4-4 in original NDA 208956*



(b) (4) (b) (4) LOQ=limit of quantification

4.6. Devices and Companion Diagnostic Issues

The drug product triptorelin pamoate microgranules 22.5 mg will be provided in a kit with Sterile Water for Injection (SWI) used for reconstituting the lyophilized microgranules. SWI is packaged in a (b) (4) (b) (4) glass syringe which is sealed with a (b) (4) stopper and (b) (4) and luer-lock adaptor. Triptorelin pamoate microgranules 22.5 mg is packaged in a (b) (4) (b) (4) glass vial with a 20 mm closure fitted with a 20 mm (b) (4) stopper. The primary container-closure system is sealed with an (b) (4) flip-off (b) (4). The drug product vial is placed in a kit

with a pre-filled syringe containing SWI. In addition, two commercially available 21-gauge 1.5" needles are provided in the kit as specified in the package insert and kit labeling.

The device was reviewed by the Center for Devices and Radiological Health (CDRH) and was found to be acceptable (*see Consult review from CDRH dated 6/1/17 in DARRTS*).

4.7. **Consumer Study Reviews**

Not applicable.

5 Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2. Clinical Trials Relevant to this NDA

Trial Identity	Trial Design	Regimen/ schedule/route	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Debio 8206-CPP-301	Open-label, single-arm, uncontrolled, unblinded, multi-center	Triptorelin 22.5 mg IM every 6 months (2 total doses)	12 months (2 treat-ment cycles)	44	Children with CPP (n=39 girls and 5 boys), ages 2-9 years	11 US 1 Mexico 1 Chile

Δ=change E2=estradiol T=testosterone

5.2. Review Strategy

Data from the pivotal open-label, multi-center phase 3 study Debio-8206-CPP-301 are the focus of both the efficacy and safety reviews. This review contains the applicant's analyses of efficacy and safety, which were confirmed by this medical reviewer and by the Division's Statistical review team (*refer to Biometrics Primary Review dated 5/19/17 in DARRTS*), as well as this medical reviewer's commentary regarding both efficacy and safety of triptorelin 22.5 mg for the treatment of CPP. In review of results from Debio-8206-CPP-301, this reviewer specifically considered the efficacy and safety goals outlined *a priori* in a SPA agreement between the Agency and the Sponsor (*refer to IND 111504, SD-4, SPA resubmission, received 9/6/2011 in DARRTS*).

This reviewer also reviewed the published medical literature describing clinical experience with the GnRH agonist drug class in the treatment of CPP, and compared efficacy and safety findings of other GnRH agonist formulations used to treat CPP to the efficacy and safety of the triptorelin 22.5 mg (b) (4) formulation. Literature reviewed included clinical trials evaluating efficacy and safety of Lupron-depot PEDS (14), Supprelin LA (16), Synarel (17; NDA 20109, SD-1 dated 8/30/1990 in DARRTS), and triptorelin 11.25 mg 3-month formulation (18).

6 Review of Relevant Individual Trials Used to Support Efficacy

6.1. **Debio 8206-CPP-301:** An open-label, non-comparative, multicenter study on the efficacy, safety, and pharmacokinetics of triptorelin pamoate 22.5 mg 6-month formulation in patients suffering from central (gonadotropin-dependent) precocious puberty**.**

6.1.1. Study Design

Overview and Objective

Study Debio 8206-CPP-301 was designed to assess the efficacy and safety of 12 months of treatment with triptorelin 22.5 mg (b) (4) suspension in children with CPP. The open-label, uncontrolled trial design in a single pivotal phase 3 study was similarly used for Agency approval of all other GnRH agonists currently marketed in the U.S. for treatment of CPP. Primary and secondary hormonal endpoints were assessed by standardized laboratory measurements of HPG axis hormone levels during the study. The key protocol elements, including the study design, patient population, primary and secondary safety and efficacy endpoints, and literature-based comparator studies of other sustained-release GnRH agonists, were agreed upon between the Sponsor and the Agency in a Special Protocol Assessment Agreement in

October 2011 (*see letter in DARRTS dated October 21, 2011*). As part of the SPA, it was determined that Debio 8206-CPP-301 could be the sole phase 3 efficacy study in the development program if all efficacy and safety endpoints were achieved. The triptorelin formulation used in Debio 8206-CPP-301 is the same 6-month sustained release formulation approved for use in men with advanced prostate cancer under NDA 22437 (Trelstar 22.5 mg).

Trial Design

Study Debio 8206-CPP-301 is a multi-center, open-label, uncontrolled phase 3 study assessing the safety and efficacy of Triptorelin 22.5 mg (b) (4) in the treatment of children with CPP. This was the sole efficacy and safety study in the NDA program. The study was performed at 11 centers in the U.S., 1 center in Mexico, and 1 center in Chile.

Debio 8206-CPP-301 included 44 children (39 girls and 5 boys) with CPP. Study subjects were treated with triptorelin 22.5 mg (b) (4) IM every 24 weeks (study days 1 and 169) for a total of 2 doses. The study duration of two treatment cycles was chosen to enable assessment of the duration of response, completeness of desensitization of pituitary gonadotropins to GnRH, and potential accumulation of triptorelin after repeat dosing. For each child, the total study duration was a maximum of 50 weeks. This included a 2 week screening period and a 48 week treatment period, during which each subject had a maximum of 11 study visits including the screening visit (see

Figure 2. Schedule of Study Procedures). Compliance with study medication was ensured for all subjects because all triptorelin doses were administered by study personnel at study visits on day 1 and day 169.

Unstimulated and GnRH agonist-stimulated LH and FSH levels were measured at screening and at months 1, 2, 3, 6, 9, and 12. Unstimulated gonadal hormones—estradiol in girls and total testosterone in boys—were measured at baseline and at months 1, 2, 3, 6, 9, and 12. Clinical outcome measures, assessed at months 6 and 12, included height (z-score and percentile for age), growth velocity, bone age (by the Greulich & Pyle method), pubertal stage (by Tanner Staging), uterine length in girls (measured by transabdominal ultrasound), and testis volume in boys (measured with an orchidometer).

Standardized GnRH agonist stimulation testing was performed by treating patients with leuprolide acetate 20 µg/kg SC at baseline and measuring serum LH and FSH 30 minutes later. GnRH agonist stimulation testing with leuprolide was performed in all children at screening and at months 1, 2, 3 6, 9, and 12.

Assessment for acute-on-chronic (AOC) phenomenon was performed in a randomly-selected subset of children (50%, n=22) by measuring basal LH and estradiol (girls) or testosterone (boys) 48 hours after the second triptorelin dose at month 6.

Triptorelin pharmacokinetics were established by measuring serum triptorelin levels in all patients at months 1, 2, 3, 6, 9, and 12, and by measuring triptorelin C_{max} and T_{max} in a subset of 8 patients (the 'PK subset') following the first and second triptorelin doses (see **Table 3. Pharmacokinetic Assessments**).

Table 3. Pharmacokinetic Assessments[1]

	TRIPTORELIN SERUM LEVELS ALL CHILDREN	TRIPTORELIN SERUM LEVELS SUBSET OF 8 CHILDREN
Day 1	Pre-triptorelin injection (ie, 0 h pre-dose)	1, 2, 3, 4, 8, 12 h post-dose
Day 2		24 h post-dose
Month 1 (Day 29)	Pre-leuprolide stimulation	
Month 2 (Day 57)	Pre-leuprolide stimulation	
Month 3 (Day 85)	Pre-leuprolide stimulation	
Month 6 (Day 169)	Pre-leuprolide stimulation test and triptorelin injection (ie, 0 h pre-dose)	1, 2, 3, 4, 8, 12 h post-dose
Day 170		24 h post-dose
Month 9 (Day 253)	Pre-leuprolide stimulation	
Month 12 (Day 337)	Pre-leuprolide stimulation test and triptorelin/other GnRH agonist injection (ie, 0 h pre-dose)	

[1]Source: Original NDA 208956

Inclusion criteria:
1. Onset of secondary sexual development prior to age 8 in girls and age 9 in boys (defined by breast development in girls or testicular enlargement in boys per the Tanner puberty staging method), and eligible to receive 12 months of GnRH agonist therapy.
2. Girls ages 2-8 and boys ages 2-9 at study initiation.
3. Initiation of study drug ≤ 18 months after onset of CPP.
4. Difference between bone age and chronological age ≥ 1 year at baseline (BA:CA ≥ 1 year).
5. GnRH agonist-stimulated LH ≥ 6 IU/L at baseline (CPP diagnostic criterion).
6. Clinical signs of puberty at baseline: Tanner stage breast development ≥ 2 (girls) or testicular volume ≥ 4 mL (boys).
7. Appropriate parental informed consent or assent for children ≥7 years.

Exclusion criteria:
1. Gonadotropin-independent (peripheral) precocious puberty.
2. Non-progressing isolated premature thelarche.
3. Presence of an unstable intracranial tumor or an intracranial tumor requiring surgery or irradiation. Children with non-surgical hamartomas were eligible.
4. Renal or hepatic impairment, defined as serum creatinine >2x the upper limit of normal (ULN) and bilirubin or AST >3x ULN, respectively.
5. Any other condition, chronic illness, or ongoing treatment possibly interfering with growth or other study endpoints, such as chronic steroid use, renal failure, diabetes, scoliosis, or pan-hypopituitarism.
6. Prior or current therapy with a GnRH agonist, medroxyprogesterone acetate, recombinant growth hormone, or IGF-1.

7. Major medical or psychiatric illness that may interfere with study visits.
8. Short stature, defined as height >2.25 standard deviations below mean height for age.
9. Positive pregnancy test.
10. Known hypersensitivity to GnRH agonist.
11. Use of anticoagulant medication.
12. Any treatment or procedure with an effect on the metabolism or secretion of gonadotropins (LH, FSH) or gonadal steroids (estradiol, testosterone) was prohibited during the study.

A screening visit occurred for all subjects within 14 days of triptorelin initiation. At the screening visit, children underwent a physical exam, including Tanner staging, height and weight, and vital signs assessments; medication history; baseline safety laboratory testing and baseline hormonal laboratory testing, including basal LH, FSH, and estradiol or testosterone, GnRH agonist-stimulated LH and FSH, and serum pregnancy test in girls; left hand and wrist x-ray to assess bone age; brain CT or MRI if not done in the prior 3 months; trans-abdominal ultrasound in girls to assess uterine length; testes measurement in boys; and AE assessment.

Figure 2. Schedule of Study Procedures#

	SCREENING	12-MONTH TREATMENT PERIOD										
D = DAY M = MONTH	D1 – 14 to D1 – 1	D1	D2 ± 3	D29 ± 3 (M1)	D57 ± 3 (M2)	D85 ± 3 (M3)	D169 ± 3 (M6)	D170 ± 3	D171 ± 3	D253 ± 3 (M9)	D337 ± 3 (M12)
INFORMED CONSENT/ASSENT	X										
VERIFICATION INCLUSION/NON-INCLUSION CRITERIA	X										
DEMOGRAPHIC DATA	X										
MEDICAL AND MEDICATION HISTORY	X										
PHYSICAL EXAMINATION	X										
BODY HEIGHT, WEIGHT AND BMI (= kg/m²)	X						X				X
VITAL SIGNS (BP/HR)	X[1]	X[3]		X[1]	X[1]	X[1]	X[3]			X[1]	X[3]
BLOOD AND URINE SAFETY LABORATORY PARAMETERS[5]	X[1]						X[3]				X[3]
FSH AND LH SERUM LEVELS	X[2]			X[2]	X[2]	X[2]	X[2]		X[7,8]	X[2]	X[2]
E_2 AND TESTOSTERONE SERUM LEVELS	X[1]			X[1]	X[1]	X[1]	X[1]		X[7,8]	X[1]	X[1]
TRIPTORELIN SERUM LEVELS (ALL CHILDREN)		X[3]		X[1]	X[1]	X[1]	X[3]			X[1]	X[3]
TRIPTORELIN SERUM C_{MAX} AND T_{MAX} (SUBSET)		X[9]	X[10]				X[9]	X[10]			
GNRH STIMULATION TEST	X			X	X	X	X			X	X
X-RAY LEFT HAND AND WRIST	X						X				X
TRANSABDOMINAL US IN GIRLS ONLY	X						X				X
PUBERTY STAGING AS PER TANNER AND TESTICULAR VOLUME MEASUREMENT	X						X				X
SERUM HCG PREGNANCY TEST IN GIRLS	X										
CT SCAN OR MRI BRAIN (IF APPLICABLE)	X										
TRIPTORELIN INJECTION[6]		X[6]					X[6]				
CONCOMITANT MEDICATION MONITORING		X	X	X	X	X	X	X	X	X	X
ADVERSE EVENT MONITORING	X	X	X	X	X	X	X	X	X	X	X
TOLERANCE AT INJECTION SITE MONITORING		X[4]					X[4]				

1 Pre-GnRH stimulation test leuprolide acetate 20 µg/kg SC
2 a) At time 0 = pre-GnRH stimulation test and b) 30 minutes post-GnRH stimulation test
3 Pre-GnRH stimulation test and/or pre-triptorelin injection or compassionate GnRH injection on Day 337
4 To be assessed a) immediately after triptorelin injection and b) 2 h post-triptorelin injection
5 Fasting (= before breakfast or after 4 hours fasting if not sampled in the morning)
6 Use green 21G 1½" [= 0.8 x 40 mm] needle with thin wall to inject the child
7 **Basal LH, estradiol (girls), and testosterone (boys) assessment at 48 h post-dose in subset of 22 children**
8 **Repeat basal LH, estradiol (girls), and testosterone (boys) assessment at 2 weeks post-dose if estradiol/testosterone or LH values were not suppressed**
9 In subset of 8 children at 1, 2, 3, 4, 8, 12 h post-dose
10 In subset of 8 children at 24 h post-dose

#Source: Original NDA 208956

Study Endpoints

Primary efficacy endpoint: Percentage of children with LH suppression to a pre-pubertal level at month 6, defined as GnRH agonist-stimulated LH ≤ 5 IU/L.

Secondary efficacy endpoints:

1. Percentage of children with GnRH agonist-stimulated LH≤ 5 IU/L at months 1, 2, 3, 9, and 12.
2. Percentage of children with maintenance of LH suppression (defined as GnRH agonist-stimulated LH≤ 5 IU/L) from month 6 to month 12.
3. Percentage of children with GnRH agonist-stimulated LH≤ 4 IU/L at months 1, 2, 3, 6, 9, and 12.
4. Percentage of children with maintenance of LH suppression, defined as GnRH agonist-stimulated LH≤ 4 IU/L, from month 6 to month 12.
5. Changes in GnRH agonist-stimulated LH and FSH levels from baseline at months 1, 2, 3, 6, 9, and 12.
6. Changes in GnRH agonist-stimulated gonadal hormone levels (estradiol in girls and testosterone in boys) from baseline at months 1, 2, 3, 6, 9, and 12.
7. Percentage of children with pre-pubertal estradiol (<20 pg/mL) or testosterone (<30 ng/dL) levels at months 1, 2, 3, 6, 9, and 12.
8. In a subset of 22 children ('AOC subset'), the percentage with absence of basal LH>5 IU/L and estradiol >20 pg/mL (girls) or testosterone >30 ng/dL (boys) at 48 hours after the second triptorelin dose.
9. Change in height (z-score and percentile height-for-age), growth velocity, and bone age (Greulich and Pyle method) at months 6 and 12.
10. Percentage of children in whom BA:CA ratio did not rise relative to baseline at months 6 and 12.
11. Percentage who achieved stabilization of sexual maturation by Tanner stage at months 6 and 12.
12. Percentage of girls with regression in uterine length at months 6 and 12.
13. Percentage of boys with absence of progression of testes volume at months 6 and 12.

Safety endpoints:

1. Assessment of adverse events at each study visit.
2. Evaluation of local tolerance at the injection site immediately and 2 hours after each triptorelin injection (days 1 and 169). Of note, the injection volume required per dose is 2 mL. To avoid increased risk of injection site reactions due to the volume of injections, children less than 2 years of age were excluded.
3. Change in vital signs (HR and BP) at day 1 and months 1, 2, 3, 6, 9, and 12 prior to leuprolide and/or triptorelin injections.
4. Changes in body weight, height and BMI at months 6 and 12.
5. Changes in safety laboratory assessments: complete blood count (CBC), serum chemistries (glucose, calcium, BUN, creatinine, AST, ALT, bilirubin, albumin, total protein, alkaline

phosphatase (ALK), phosphorous, lactate dehydrogenase (LDH), uric acid, total cholesterol), and urinalysis for ketones, glucose, protein, nitrites, leukocytes, pH and blood, with reflex urine microscopy for any abnormal values.

Any safety laboratory value outside of the normal range and any laboratory value that significantly changed from baseline was reviewed and, if the abnormality or change was considered to be possibly related to triptorelin, the value was followed up with retesting until a return to normal or to a level close to baseline. All critical lab values were reported to the Sponsor.

PK endpoints:
1. Serum triptorelin levels in all children at day 1 and months 1, 2, 3, 6, 9, and 12.
2. Triptorelin C_{max} and T_{max} over 24 hours post-injection in a subset of 8 children.

The safety profile was developed using data from Debio-8206-CPP-301, as well as from the entire triptorelin pharmacovigilance database regardless of the indication of use or the age or gender of patients. This included a total of 5,448 cases.

In phase 2 studies in healthy adults and in phase 3 studies in men with prostate cancer, triptorelin C_{max} during the initial burst and maintenance phases following administration of the 6-month formulation were similar to or less than triptorelin initial burst and maintenance C_{max} levels following administration of the 11.25 mg 3-month formulation (burst C_{max} 40 and 36 ng/mL, and maintenance C_{max} 180-460 and 500-710 pg/mL for 6-month and 3-month formulations, respectively), thus no safety concerns when treating children with CPP with the 6-month formulation were anticipated.

Only PK assessments from children enrolled in Debio-8206-CPP-301 were used to characterize the PK profile of the triptorelin 22.5 mg formulation for the CPP indication.

Laboratory analyses were done with appropriate and validated assays: radioimmunoassay was used for measurement of serum estradiol, immune-metric assays for serum FSH and LH, and liquid chromatography/ tandem mass spectrometry (LC-MS/MS) for serum testosterone. Serum triptorelin levels were quantified using a validated solid phase extraction and LC-MS/MS analysis, and if necessary when concentrations were below the assay detection limit (0.05 ng/mL), levels were re-analyzed using a more sensitive solid phase extraction and LC-MS/MS assay (detection limit of 0.02 ng/mL).

Hand and wrist x-rays for determinations of bone age were reviewed and evaluated by two independent reviewers, with adjudication by an independent expert in cases of disagreement between the two reviewers. Bone age was determined by the Greulich and Pyle Method (19).

Statistical Analysis Plan

Please refer to the statistical review for detailed evaluation of the Statistical Analysis Plan (SAP).

Sample size
The null hypothesis as outlined in the SPA agreement to support approval is that the null proportion of patients with LH suppression to pre-pubertal levels at month 6 (i.e., after one triptorelin dose) is 80%. Based on this null hypothesis, a sample size of 41 was calculated to provide a power of 0.853 (using a one-tailed α of 0.025) when the true proportion of responders is 95%. A drop-out rate of 5 was assumed, thus 44 patients were enrolled to achieve 41 subjects for the Intention-to-Treat (ITT) population. All 44 subjects who enrolled completed the trial. No interim analysis was done.

Missing data
There was no imputation of missing efficacy, safety, or PK data. Of note, imputation of missing LH data (primary efficacy data) was pre-specified in the Statistical Analysis Plan: missing LH data were to be treated as *non-responses* (i.e., as non-suppression of GnRH agonist-stimulated LH). However, there were no missing LH data in Debio-8206-CPP-301, thus imputation of LH data was not required.

*Analysis populations (***Table 4***)*
The *efficacy population* was based on *intention-to-treat* and included all patients who were treated with triptorelin at baseline and had at least one assessment of LH suppression. The primary efficacy analysis was done using the ITT population.

The *safety population* included all patients who received at least one dose of triptorelin and had any safety data; the safety population was used to conduct all safety analyses.

The *Per Protocol (PP) population* included the ITT population after exclusion of children who violated inclusion/exclusion criteria, used prohibited concomitant medications during the study, and/or missed assessment of LH at month 6.

The *Acute-On-Chronic (AOC) population* included a subset of 22 patients who underwent evaluation for AOC phenomenon after the month 6 triptorelin dose; the AOC population was used to determine the prevalence of AOC effect.

The *PK population* included all patients who received at least one dose of triptorelin and had any PK data; the PK population as well as a smaller *PK subset population* (n=8), which underwent more complete PK evaluation, were used to perform PK analyses.

Statistical Analyses
Continuous variables were analyzed using descriptive statistics, and categorical data was presented in contingency tables including absolute and relative frequencies. Efficacy results

from Debio-8206-CPP-301 were also compared descriptively (not statistically) with published data for triptorelin 1-month and 3-month formulations in children with CPP and with other GnRH agonist formulations used to treat CPP.

Protocol Amendments

No protocol amendments were made during the course of the trial or during statistical analysis of study results.

After Agency approval of the SPA in October 2011 but before the study start, the Sponsor submitted two protocol amendments, the first in November, 2011 and the second in January, 2012. Protocol amendment #1 specified the following changes: i) study centers were allowed to purchase leuprolide acetate from any supplier due to a shortage of leuprolide in the U.S. market and minor specific details pertaining to the original supplier were removed, ii) CT or MRI of the brain was allowable within three months of the first triptorelin dose, iii) contact person for reporting SAEs to the Sponsor and procedure for reporting SAEs of early discontinuation were modified. Protocol amendment #2 specified the following changes: i) blood volume for checking hormone levels post-leuprolide stimulation was changed from 1 mL to 2 mL, and ii) inclusion criteria were changed to allow parental signature of informed consent as per local requirements.

Data Quality and Integrity: Sponsor's Assurance

(b) (4) oversaw the general management and monitoring of the pivotal study Debio-8206-CPP-301. (b) (4) reviewed patient electronic case report forms (eCRFs) and related source documents (office, hospital, clinic, and laboratory records) at pre-arranged visits to the study sites. At study completion, all study drug was accounted for and (b) (4) reviewed study drug dispensing records.

Patient identity was protected according to local and national laws during the study.

The following sites underwent audits/inspections during the study:

i) Site 81 (Dr. Fernando Cassorla, IDIMI, Santiago, Chile) underwent a routine inspection by the National Drug Agency, Public Health Institute of Chile on March 19-21, 2013, and an audit by Debiopharm's Regulatory Compliance Group on October 16-18, 2013.

ii) Site 4 (Dr. Karen Klein, Rady Children's Hospital, San Diego, CA) underwent an audit by Debiopharm's Regulatory Compliance Group on December 10-11, 2013.

Audit certificates for both study sites were provided by the Sponsor.

Data entry was performed at the site level using the internet-based electronic data capture system 'Clinsight' (version 6.2.400), and locked data were extracted directly into SAS for statistical analyses. Data were password-protected, entered only by trained site users, and checked against source data by clinical research associates. All eCRFs were electronically signed by each site's Principal Investigator (PI) prior to database lock. All data modifications requiring dataset unlocking and re-locking were documented in an audit trail file.

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant attests that study Debio-8206-CPP-301 was performed in accordance with local regulations, Good Clinical Practice (GCP), International Conference on Harmonization (ICH) notes for GCP, and ethical principles of the Declaration of Helsinki. Written approval of the study design and informed consent documents was obtained from independent ethics committees (IEC) or institutional review boards (IRBs) affiliated with each study site prior to study initiation. For each study participant, signed parental informed consent was obtained from one or both parents (as per local requirements) prior to any study related procedures, and signed assent was obtained from children age 7 or older.

Financial Disclosure

The Applicant certified that, based on information obtained from the Sponsor and from the participating clinical investigators, none of the clinical investigators for study Debio-8206-CPP-301 participated in a financial arrangement with the Sponsor whereby compensation to the investigator could be affected by the outcome of the study, none of the clinical investigators had proprietary interest in the product or significant equity interest in the Sponsor, and none of the clinical investigators was the recipient of significant payments of other sorts from the Sponsor.

Patient Disposition

Forty-four patients between ages 2 and 9 with CPP were enrolled in and completed the pivotal study Debio-8206-CPP-301. All 44 patients received two doses of triptorelin 22.5 mg (b) (4) intramuscularly at six month intervals and attended all study visits, thus all 44 patients were included in the primary efficacy (ITT) and safety analyses. The last patient completed the study in July 2014.

The primary efficacy analysis was conducted in the ITT population, which included all 44 patients. The Safety population in which safety analyses were done also included all 44 patients. One patient was excluded from the PP population due to a major protocol violation (subject 0104, see details below); therefore, the PP population included only 43 children. Secondary efficacy analyses were conducted in both the ITT population and the PP population. All 44 children were included in the PK population for PK analyses. The PK Subset population included 8 randomly-selected patients; all 8 were included in the PK Subset analysis. The AOC population included a subset of 22 randomly-selected patients; all 22 were included in the AOC analysis (**Table 4**).

Table 4. Study Populations

ITT	Safety	PP	PK	PK Subset	AOC
44	44	43	44	8*	22

*All girls

Protocol Violations/Deviations

Protocol violations that could potentially affect an efficacy outcome were considered major and resulted in exclusion of the patient from the affected analysis populations. One major protocol violation occurred during the study, involving patient 0104. Patient 0104 performed the 6 month (day 169) study visit on day 183, 14 days after the scheduled date. Patient 0104 was therefore excluded from the PP population, but not from the safety or ITT populations. Patient 0104 was not in the PK or AOC subsets, so these analyses were not affected by this major protocol violation. Despite the major protocol violation, patient 0104 achieved the primary efficacy endpoint of LH suppression at month 6; therefore, this protocol violation did not affect the primary efficacy endpoint analyzed in the ITT population.

Protocol violations that did not lead to patient exclusion from an analysis population were considered minor. There were 41 minor protocol violations in Debio-8206-CPP-301. Most minor protocol violations were slight deviations from the scheduled time of study visits: 13 patients had more than 14 days

between screening and the day 1 study visit, 22 patients had an on-treatment study visit > 3 days from the planned time of the visit, and 1 patient had the day 171 study visit 6 days later than scheduled. Other minor protocol violations included prior or concomitant use of unallowable medications: one patient (Subject 2401) took fluticasone/salmeterol (Advair) via inhalation from day -5 to day -1, two patients took short courses of oral glucocorticoids for upper respiratory infections prior to triptorelin dosing (Subject 2501, from day -18 to day -14 and Subject 8112, from day -1 to day 1). Two patients had age at onset of development of secondary sexual characteristics (i.e., age of onset of CPP) outside of the accepted limit of age 8 or younger in girls and age 9 or younger in boys. Both of these children were boys (subjects 0411 and 8105) diagnosed with CPP at ages 9.4 and 9.04 years, respectively. Two patients had duration of disease prior to the start of triptorelin treatment that slightly exceeded the acceptable limit, defined as ≤ 18 months in inclusion criteria. These two patients (subjects 0407 and 2405) were diagnosed with CPP 18.1 and 18.5 months prior to the start of triptorelin treatment, respectively. Finally, one patient had a difference in BA - CA outside of the acceptable limit of ≥ 1 year. This patient (subject 2401) had BA – CA of only 8 months at the start of the study.

Reviewer Comment: The minor protocol violation of BA-CA would reduce the potential efficacy of triptorelin treatment on deceleration of bone age advancement, thus I agree that this protocol violation would not significantly alter the overall analysis of triptorelin's effects on bone age. Regarding timing of disease onset, some error may be expected due to uncertain exact dates of some subjects' initial diagnosis of CPP, in which case only the month and year of diagnosis were recorded. Overall, the minor protocol violations observed were very slight deviations and were unlikely to have altered efficacy, safety, or PK outcomes.

Table of Demographic Characteristics

The Debio-8206-CPP-301 study population consisted of 44 children between 2 and 9 years of age. The majority of patients were girls (39/44, 89%), consistent with the predominant female prevalence of CPP in the general population (1). Among all study participants at baseline, median (range) age was 8.0 (2.0-9.0) years, median height was 137 (103-155) cm, median weight was 34 (15-54) kg, and median BMI was 18 (12-24) mg/kg.[2] Regarding race, 59% of children were white, 27% were black, 5% were Asian, and 9% were described as "other" races (**Table 5**). Overall, baseline demographics of Debio-8206-CPP-301 study patients are similar to demographic characteristics of subjects in development programs for other GnRH agonist formulations approved for treatment of CPP.

Table 5: Baseline Demographic Characteristics of Children with CPP Enrolled in Debio-8206-CPP-301 and Included in the Intention-to-Treat Analysis

Demographic Parameters	Total (N=44) n (%)
Sex, n (%)	
Female	**39 (89%)**
Male	**5 (11%)**
Age (years)	
Mean (SD)	**7.4 (1.3)**
Median	**8.0**
Min, max	**2.0-9.0**
Weight (kg)	
Mean (SD)	**32.8 (8.4)**
Median	**34.0**
Min, max	**15.3, 54.0**
Height (cm)	
Mean (SD)	**134.8 (10.9)**
Median	**137.0**
Min, max	**103.0, 155.0**
BMI (mg/kg²)	
Mean (SD)	**17.8 (2.7)**
Median	**18.0**
Min, max	**11.8, 23.8**
Race, n (%)	
White	**26 (59.1%)**
Black or African American	**12 (27.3%)**
Asian	**2 (4.5%)**
Other[1]	**4 (9.1%)**
Geographic region	
US	**28**
Mexico	**1**
Chile	**15**

Reviewer Comment: There are no missing demographic data.

Other Baseline Characteristics: Disease Characteristics and Concomitant Drugs

Baseline disease-related demographics and baseline hormone levels for the safety/ITT population are summarized in **Table 6**.

All patients were treatment-naïve with respect to treatment of CPP at study entry. Regarding baseline Tanner staging, six children (14%) had a baseline Tanner score of 2, 29 (66%) had a baseline Tanner score of 3, and 9 (21%) had a baseline Tanner score of 4.

Table 6. Baseline Disease-Related Characteristics of Children in the ITT and Safety Populations

	Mean (SD)	Range	Outliers (Subject ID (outlying value))
Age at CPP diagnosis (years)	7 (1.4)	1.3-9.4	0411 (9.4 years)[1] 8105 (9.0 years)[1]
Duration of disease (months)	11.9 (4.4)	2.6-18.5	0407 (18.1 months)[2] 2405 (18.5 months)[2]
Bone age (months)	133 (18)	94-162	n/a
Chronological age (months)	95 (16)	31-118	n/a
BA:CA	1.4 (0.3)	1.1-3.0	2401 (BA – CA = 8 months)[3]
Uterine length (cm)	4.6 (1.1)	2.3-7.5	n/a
Testis volume (mL)	10.4 (3.5)	6-15	n/a
Baseline Hormonal Measures[4]			
LH (IU/L)	27.2	6.3-91	n/a
FSH (IU/L)	10.0	4.0-24.0	n/a
Estradiol (ng/L)	44.8	10-117	n/a
Testosterone (ng/dL)	326	142-573	n/a

[1]outside acceptable limit of <9 years
[2]outside acceptable limit of ≤18 months
[3]outside acceptable limit of ≥1 year
[4]GnRH agonist-stimulated LH and FSH; basal estradiol and testosterone

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance with study medication was ensured for all patients due to the fact that both triptorelin doses were administered by study personnel at the day 1 and day 169 study visits. Patient adherence to the treatment schedule was overall acceptable.

In the safety/ITT population, attendance rates to study visits within the allowable ±3-day time frame for the 6-month and 12-month study visits were 77% and 82%, respectively. Among all study visits for all patients combined, there were only three protocol violations (one major and two minor) for patients who attended study visits outside of the allowable time window (see Protocol Violations/ Deviations, **Section 6.1.2**).

In the safety/ITT population, there were 72 concomitant medical conditions not related to CPP among 33 children (75%). The most common concomitant medical conditions were seasonal allergy (5 patients), asthma (4 patients) and history of adeno-tonsillectomy (3 patients).

Other than leuprolide for GnRH agonist stimulation testing, the 44 children enrolled in Debio-8206-CPP-301 used a total of 89 concomitant medications during the study, most of which do not affect levels of HPG axis hormones. The most common concomitant medications were propionic acid derivatives (anti-inflammatory) used by 11 (25%) patients, anilides (acetaminophen) used by 8 (18%) patients, penicillins used by 6 (14%) patients, and beta-2-receptor agonists (for asthma) used by 5 (11%) patients. Prior or concomitant medications used by study subjects that *may* alter HPG axis hormone levels (although which are unlikely to do so when used for short durations only) were systemic glucocorticoids used by two patients (Subject 8112 took prednisone from study day -1 to day 1 for acute bronchitis and Subject 2501 took methylprednisolone from day -18 to day -14 for an upper respiratory infection), intranasal corticosteroids used by two patients (Subject 2502 took mometasone (Nasonex) on an *as needed* basis for treatment of seasonal allergies and Subject 2401 took fluticasone + salmeterol (Advair) from day -5 to day -1 for asthenia), and a potent topical corticosteroid used by one patient (Subject 6301 used topical barmetasone + clotrimazole + gentamycin cream (Barmicil) every other day for treatment of a genital rash). No rescue medications for treatment of CPP (i.e., additional doses of long-acting GnRH agonist) were taken by any patient during the study.

Reviewer Comment: The concomitant medications of systemic, intranasal, and topical glucocorticoids used by five patients are unlikely to have affected study results given that none of these medications were used chronically in high doses to result in HPG axis suppression.

Efficacy Results – Primary Endpoint

Primary efficacy analysis:
The pre-specified primary efficacy endpoint required for approval of the triptorelin 22.5 mg formulation for the CPP indication was LH suppression to pre-pubertal levels at month 6 in ≥80% of subjects (lower 95% confidence interval). LH suppression was defined as LH≤ 5 IU/L 30 minutes after GnRH agonist stimulation with 20 µg/kg leuprolide acetate. The primary efficacy endpoint was achieved in 41 of 44 subjects in the ITT population (93%; 95% CI: 81.3% to 98.6%).

A total of three patients did not meet the primary efficacy endpoint: Subject 0802 (a 9 year-old black boy), Subject 0803 (a 9 year-old Asian boy), and Subject 2404 (an 8 year-old black girl). Patient 0802 did not achieve LH suppression at month 6 or month 12. Patient 0803 had a borderline LH at month 6 (5.1 IU/L) that did not meet the primary efficacy endpoint; however, this patient achieved LH suppression at month 12 (3.2 IU/L). According to the Sponsor, patient 2404 experienced a technical difficulty with the first triptorelin injection, possibly resulting in lack of LH suppression due to insufficient drug levels. In support of this, after the first injection, serum triptorelin levels were below the LOQ in 2 of 4 serum samples, and after her second triptorelin dose, which was uncomplicated, her

GnRH agonist-stimulated LH was suppressed (LH 3.6 IU/L at month 12).

Reviewer Comment: Patient 0803 also had one minor protocol violation at study visit 4 (day 57) of more than 3 days deviation from the planned on-treatment visit (visit 4 occurred on day 61). This minor protocol violation did not affect the primary efficacy outcome for this patient given that it did not impact results at the month 6 study visit.

The Sponsor has provided good evidence that lack of LH suppression at month 6 in patient 2404 was due to a technical difficulty with her first triptorelin injection, which resulted in serum drug levels insufficient to achieve LH suppression. This patient then achieved LH suppression after the 2nd dose of study drug, which was administered without complications.

Conclusion of Primary Efficacy Endpoint:
The study met the primary efficacy endpoint, with a percentage of responders of 93.2% (95% CI, 81.3-98.6%). Therefore, the null hypothesis, that the proportion of responders would be ≤ 80%, was rejected.

Reviewer Comment: These data support the efficacy of triptorelin 22.5 mg (b) (4) 6-month formulation in the treatment of CPP.

Data Quality and Integrity – Reviewers' Assessment

*Reviewer Comment: This medical reviewer agrees with OSI's assessment of the clinical inspection sites (see **Section 4.1**). In summary, the applicant's monitoring for data quality and integrity was acceptable.*

Efficacy Results – Secondary and other relevant endpoints

Secondary efficacy analyses:
Pituitary and Gonadal hormone levels—
1. Percentage of children with LH suppression (LH ≤ 5 IU/L) at months 1, 2, 3, 9, and 12:
In both the ITT and PP populations, 95% (42/44, ITT and 41/43, PP) of children achieved suppression of GnRH agonist-stimulated LH to ≤5 IU/L at months 1, 2, 3, and 9, and 98% (43/44, ITT and 42/43, PP) achieved LH suppression at month 12. In both the ITT and PP populations, 93% (41/44, ITT and 40/43, PP; 95% CI: 81 to 99%, ITT and PP) maintained suppression from month 6 to month 12.

2. Percentage of children with LH suppression (LH ≤ 4 IU/L) at months 1, 2, 3, 6, 9, and 12:
In both the ITT and PP populations, 95% of children achieved LH suppression to ≤ 4 IU/L at months 1 and 2, 93% achieved LH suppression to ≤ 4 IU/L at months 3 and 9, 91% achieved LH suppression to ≤ 4 IU/L at month 6, and 98% achieved LH suppression to ≤ 4 IU/L at month 12. In both the ITT and PP analyses, 91% (95% CI: 78 to 97%) maintained LH suppression to ≤ 4 IU/L from month 6 to month 12.

Overall, using this stricter definition of LH suppression (i.e., GnRH agonist-stimulated LH ≤ 4 IU/L), only one additional patient failed to achieve LH suppression at month 6 (Subject 8105, a 9 year old white boy). This patient also failed to maintain LH suppression to ≤ 4 IU/L from months 6 to 12. Of note, this patient had borderline LH values of 4.1 IU/L at month 6 and month 9.

3. Changes in levels of LH, FSH, estradiol (girls) and testosterone (boys) at months 1, 2, 3, 6, 9, and 12. In order to suppress puberty, chronic GnRH agonist therapy must inhibit the release of pituitary gonadotropins with resultant reductions in the downstream production of gonadal steroid hormones, primarily estradiol and testosterone. Secondary efficacy analyses thus included comparisons of mean LH, FSH, estradiol, and testosterone at baseline with mean levels while on treatment. GnRH agonist-stimulated LH and FSH levels and basal (i.e., unstimulated) estradiol and testosterone levels were used for comparisons. In the ITT population, mean LH decreased from 27.2 IU/L at baseline to levels ranging from 2.0 IU/L to 4.2 IU/L on-treatment (**Figure 3** and **Figure 4**). Mean FSH decreased from 10.0 IU/L at baseline to levels ranging from 1.2 IU/L to 3.3 IU/L on-treatment.

For girls, mean serum estradiol decreased from 44.8 ng/L at baseline to levels ranging from 12.7 ng/L to 16.6 ng/L on-treatment, and for boys, mean serum testosterone decreased from 326 ng/dL at baseline to levels ranging from 7 ng/dL to 35 ng/dL on-treatment (**Figure 3** and **Figure 4**). Similar results were obtained in the PP population.

In the ITT population, 79% (31/39) of girls achieved pre-pubertal estradiol levels (<20 pg/mL) at both month 6 and month 12, and 100% (5/5) and 80% (4/5) of boys achieved pre-pubertal testosterone levels (<30 ng/dL) at month 6 and month 12, respectively. At all other time-points tested (months 1, 2, 3, and 9), gonadal hormone suppression to pre-pubertal levels was similarly as prevalent: during the 12 month treatment period, the percentage of girls with pre-pubertal estradiol levels ranged from 79.5% to 92.3%, and the percentage of boys with pre-pubertal testosterone levels ranged from 80% to 100%.

Figure 3. Mean±SD levels of LH and estradiol in girls in the ITT population during 12 months of Triptorelin 22.5 mg (b) (4) treatment. *Dotted lines indicate pre-pubertal cutoff levels*

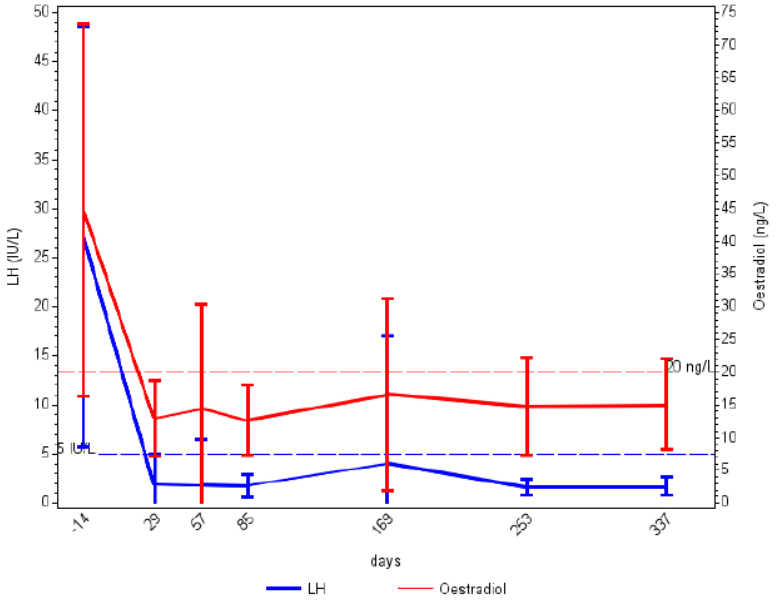
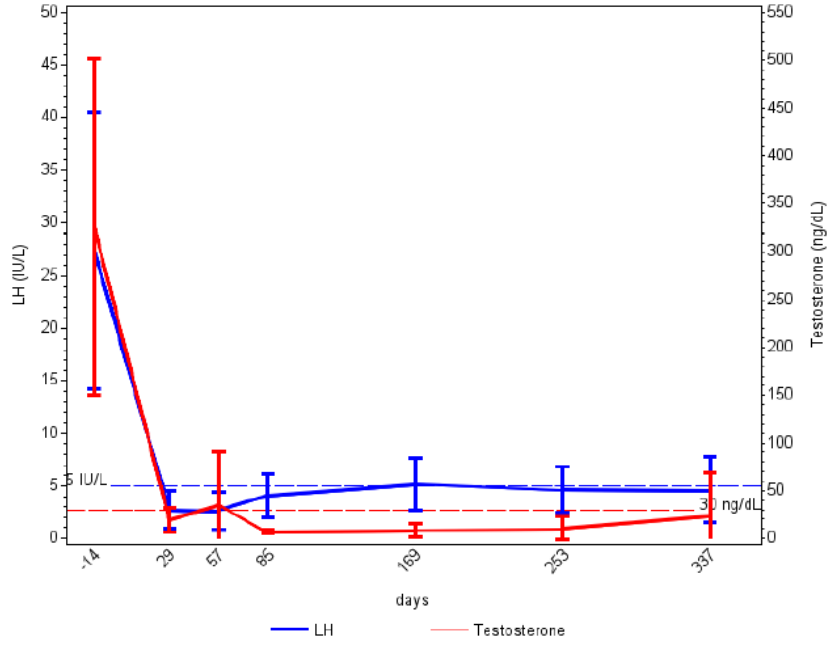


Figure 4. Mean±SD levels of LH and testosterone in boys in the ITT population during 12 months of Triptorelin 22.5 mg (b) (4) treatment. *Dotted lines indicate pre-pubertal cutoff levels*



4. *Acute-on-chronic phenomenon*

A subset of children (22/44, all girls) were assessed for development of acute-on-chronic (AOC) phenomenon after the second triptorelin dose. An AOC event was defined as basal LH > 5 IU/L *or* serum estradiol > 20 pg/mL 48 hours after the second triptorelin dose. Nineteen of the twenty-two patients evaluated had no biochemical evidence of an AOC event (86%, 95% CI: 65-97%) and three patients had biochemical evidence of an AOC event (13.6%, 95% CI: 3-35%). *Of the three children with biochemical*

evidence of an AOC event, two had not achieved pre-pubertal LH or estradiol levels after the first triptorelin dose, therefore, these cases were determined not to be true AOC events.

Reviewer Comment: I agree with the Sponsor's assessment that 2 of the 3 patients meeting diagnostic laboratory criteria for AOC phenomenon did not in fact experience true AOC events due to lack of LH or estradiol suppression at the time of testing.

5. Growth

CPP advances bone age resulting in diminished final adult height, thus one goal of GnRH agonist therapy is to reduce growth velocity and bone maturation so that growth rate reverts to a normal rate for chronological age and final adult height potential is preserved. Secondary endpoints related to growth included i) changes in height (z-score and percentile) and growth velocity at month 6 and month 12, and ii) percentage of patients with no increase in BA:CA ratio at month 6 and month 12 compared to screening. In the ITT population, the mean change in height-for-age Z-score was +0.1 at month 6 and +0.0 at month 12, while the corresponding mean change in height-for-age percentile was +1.0 at month 6 and +0.9 at month 12, suggesting a slowing down of growth velocity while on-treatment. In the ITT population, mean (SD) growth velocity (cm/year) was 6.8 (2.3) and 6.1 (1.7) at month 6 and month 12, respectively, both close to the normal growth velocity of 5-6 cm/year for children between 4 and 10 years of age (20). Sixty-four percent (28/44, 95% CI: 48-78%)) of children had a stabilization of BA:CA at month 6, and 95% (42/44, 95% CI: 85-99%)) achieved BA:CA ratio stabilization at month 12.

Reviewer Comment: Baseline growth velocity was not assessed, thus changes in growth velocity on-treatment could not be determined.

6. Sexual maturation

Secondary endpoints relating to sexual maturation included i) percentage of children achieving stabilization of Tanner pubertal stage at month 6 and month 12, ii) percentage of girls with regression of uterine length at month 6 and month 12, and iii) percentage of boys with no progression in testis volumes at month 6 and month 12 compared to baseline. In the ITT population, 91% (40/44, 95% CI: 78-97%) had stable or reduced Tanner puberty staging at month 6 and 89% (39/44, 95% CI: 75-96%) exhibited stabilization of Tanner stage at month 12. In girls, regression of uterine length was seen in 69% (27/39, 95% CI: 52-83%) at month 6 and 77% (30/39, 95% CI: 61-89%) at month 12. In boys, no progression in testis volumes was seen in 100% (5/5, 95% CI: 48-100%)) at months 6 and 12.

7. Efficacy comparison between triptorelin 22.5 mg (b) (4) and approved GnRH agonists

Descriptive comparisons were made between efficacy findings from Debio-8206-CPP-301 and those of currently marketed sustained-release GnRH agonist formulations approved for the treatment of CPP in the U.S. and Europe. The percentage of patients achieving LH suppression to pre-pubertal levels with the triptorelin 22.5 mg formulation was similar to the percentage of children achieving LH suppression with the triptorelin 11.25mg 3-month formulation (86%-100% at months 6-12)(18,21), the triptorelin 3.75 mg 1-month formulation (100% at months 6-12) (22-25), Supprelin LA implant (100%, months 1-12)(16), Lupron Depot PED 7.5 mg, 11.25 mg, and 15 mg 1-month formulations (96%, week 4; 89%,

week 12; 94%, week 48)(15,26) and Lupron Depot PED 11.25 mg or 30 mg 3-month formulations (79%-95%, months 2-6)(14,26).

Compared to the triptorelin 22.5 mg formulation, previously approved GnRH agonist formulations also have similar effects on gonadal hormone levels, pubertal development, and growth:

Gonadal hormones
In Debio-8206-CPP-301, 79% of girls and 80-100% of boys had suppressed gonadal hormones (E2 in girls and T in boys) to pre-pubertal levels at months 6-12. In studies using the triptorelin 11.25 mg 3-month formulation, 98-100% of girls and 50-70% of boys had suppressed gonadal hormone levels at months 6-12 (18). When reported in studies using the triptorelin 3.75 mg 1-month formulation, 100% of children achieved pre-pubertal gonadal hormone levels at months 2-12 (23,24). In the pivotal phase 3 trial that supported approval of Supprelin LA implant, 100% of children had suppressed gonadal hormone levels from months 1-12 (16). In studies of Lupon Depot PED 11.25 mg and 30 mg 3-month formulations, 93% and 100% of all children, respectively, achieved gonadal hormone suppression at months 1-6 (14).

Pubertal development
In Debio-8206-CPP-301, ~90% of children had stabilized or reduced pubertal stage at months 6-12, 77% of girls had regression in uterine length at month 12, and 100% of boys had stable or reduced testis volumes at month 12. When assessed in clinical trials investigating other GnRH agonists, rates of suppression of pubertal development and/or secondary sexual characteristics were similar: 94-100% of children with the triptorelin 11.25 mg 3-month formulation (18) and the triptorelin 3.75 mg 1-month formulation (24), and 67-91% of girls and 40-100% of boys with the Lupron Depot PED 1-month or 3-month formulations (14, 26).

Growth
In Debio-8206-CPP-301, mean growth velocity decreased from month 6 to month 12 (6.8 cm/year to 6.1 cm/year), and BA:CA ratio stabilized or decreased in 64% of children at month 6 and 95% at month 12. Studies of the triptorelin 11.25 mg 3-month and 3.75 mg 1-month formulations, Supprelin LA, and Lupron Depot PED also showed reductions in growth velocity, reduced or stabilized BA:CA ratios, and/or increases in predicted adult height in treated children (1,18, 21, 23-25, 27-35).

Dose/Dose Response

Debio-8206-CPP-301 was a single dose study, thus there is no dose response data.

Durability of Response

Furthermore, two of the three children who did not achieve LH suppression at month 6 went on to achieve LH suppression at month 12.

Persistence of Effect

In Debio-8206-CPP-301, no patient developed tolerance to triptorelin during the course of the study, as evidenced by escape from LH suppression. Additionally, several reports in the literature found no evidence of clinical or biochemical escape from HPG axis suppression after 2-5 years of treatment with triptorelin (30,39,40).

Also refer to **Durability of Response**, above.

Additional Analyses Conducted on the Individual Trial

Not applicable.

7 Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Efficacy of Triptorelin was studied in a single pivotal trial. Refer to **Section 6** for primary efficacy results.

7.1.2. Secondary and Other Endpoints

Secondary study endpoints are outlined in detail in **Section 6.**

7.1.3. Subpopulations

Subgroup analyses of primary efficacy endpoint:

Sex: Among the 39 girls in the study, 38 (97%) achieved the primary efficacy endpoint. Only 1 girl (2.6%, Subject 2402), did not achieve the primary efficacy endpoint. Subject 2402 experienced a technical error with the first triptorelin injection, resulting in serum triptorelin levels below the LOQ in 2 out of 4 samples, and likely resulting in her failure to achieve LH suppression at month 6.

Among the 5 boys in the study, 3 (60%) achieved the primary efficacy endpoint and 2 (40%) failed to achieve the primary efficacy endpoint. Regarding the 2 patients who failed to achieve the primary efficacy endpoint, one patient (Subject 0802) had a non-suppressed LH at both month 6 and month 12. The second patient (Subject 0803) had a borderline LH (5.1 IU/L) at month 6, and went on to achieve LH suppression at month 12 (LH 3.2 IU/L).

Race/ethnicity: The primary efficacy endpoint was achieved in all white patients (26/26, 100%), 83% of black patients (10/12), 50% of Asian patients (1/2), and all patients of other races (4/4, 100%). When grouped by ethnicity, 22 out of 22 (100%) Hispanic or Latino patients and 19 out of 22 (86%) non-

Hispanic or -Latino patients achieved the primary efficacy endpoint.

Subgroup analyses of the secondary efficacy endpoint of LH suppression (≤5 IU/L) at months 1, 2, 3, 9, and 12:

Sex: Among girls, 97-100% achieved LH suppression at months 1, 2, 3, 9, and 12. Among boys, 60-80% achieved LH suppression at months 1, 2, 3, 9, and 12.

Race/ethnicity: All 26 white patients (100%) achieved LH suppression at months 1, 2, 3, 9, and 12. Among the 12 black patients, 83-92% achieved LH suppression at all time-points. Among the 2 Asian patients, 1 patient did not achieve LH suppression at Month 9; at all other timepoints, both Asian patients (100%) achieved LH suppression. All 4 patients of other races (100%) achieved LH suppression at all time-points. All 22 Hispanic or Latino patients (100%) achieved LH suppression at all time-points. Among the 22 non-Hispanic or -Latino patients, 91-96% achieved LH suppression at all time-points.

Reviewer Comment: Based on subgroup analyses of the primary and major secondary efficacy endpoints, there is no evidence of differential effectiveness of triptorelin between sexes, races, or ethnicities.

7.1.4. Dose and Dose-Response

Not applicable.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

In the majority of patients, triptorelin effectively suppressed clinical and biochemical signs of precocious puberty at the earliest time point in which testing was performed (either month 1 or month 6) for each efficacy endpoint. Similarly, clinical and biochemical HPG axis suppression was maintained in the vast majority of patients throughout the 12 month study period. Regarding LH suppression to pre-pubertal levels, 95% achieved pre-pubertal LH levels at month 1, and at all other study time-points, LH suppression was achieved in ≥95% of patients. Of the patients who achieved LH suppression at month 6, 100% maintained suppression at month 12. Regarding suppression of gonadal steroid hormone production, estradiol was suppressed to pre-pubertal levels in 79-92% of girls at all study time points (including month 1), and testosterone was suppressed in 80-100% of boys at all study time points (including month 1). Tanner puberty stage regressed in 91% of patients at month 6 and 89% of patients at month 12. Reductions in height velocity were seen as early as month 6, when 64% of patients achieved reduced or stabilized BA:CA. By month 12, BA:CA was reduced or stabilized in 95% of patients.

Reviewer Comment: Effects of triptorelin to suppress the HPG axis, as indicated by significant changes in both biochemical and clinical signs of puberty, were evident within 1 month after a single injection and persisted throughout the duration of the 12 month study period. Changes in bone age were evident by month 6 (the earliest on-study assessment) and further improved by month 12.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

This Reviewer did not identify any potential post-marketing efficacy issues to consider regarding future use of this product in children with CPP.

7.2.2. Other Relevant Benefits

The less frequent dosing of this product (once every 6 months) compared to all other injectable GnRH agonist formulations approved for CPP may potentially be a benefit to patients and providers. Dosing of triptorelin 22.5 mg once every 6 months, compared to once monthly or once every 3 months for Lupron Depot-PEDS, could potentially improve patient compliance and thereby improve overall response to therapy, however, drug-drug comparisons have not been done. Additionally, less frequent dosing has the potential benefit of decreasing adverse reactions at the injection site, one of the most common adverse reactions seen with injectable GnRH agonists (26). Together, improved compliance, better response to therapy, and decreased injection site reactions could theoretically improve overall satisfaction with GnRH agonist treatment by patients, caregivers, and providers; however, these potential benefits of triptorelin have not yet been studied.

Reviewer Comment: The less frequent dosing of the triptorelin 22.5 mg formulation may be an advantage for children with CPP, possibly resulting in improved compliance and less adverse injection site reactions; however, comparisons of triptorelin to other GnRH agonist formulations have not been done.

7.3. Integrated Assessment of Effectiveness

CPP is a rare disease affecting 1 in 5,000 to 10,000 children. The gold standard and only approved treatment for CPP is chronic GnRH agonist therapy, which suppresses puberty and premature advancement of bone age. As evidenced by results of the single pivotal phase 3 study, Debio-8206-CPP-301, triptorelin 22.5 mg (b) (4) every six months is highly effective in suppressing puberty and halting bone age advancement in children with CPP. After 12 months of treatment with triptorelin 22.5 mg (2 doses), 98% of study participants achieved pre-pubertal levels of LH, 80% achieved pre-pubertal levels of gonadal hormones (estradiol in girls and testosterone in boys) , and deceleration of bone age advancement occurred in 95% of subjects. These efficacy measures, and in particular the primary efficacy endpoint of pre-pubertal LH at 6 month (i.e., after one triptorelin dose), met efficacy criteria outlined in a SPA agreement between the Sponsor and the Agency to support approval of this product for the CPP indication. In further support of its efficacy, the triptorelin 22.5 mg formulation demonstrated similar effectiveness compared to currently marketed GnRH agonists approved for CPP, using a similar development program, e.g., a single, open-label phase 3 trial.

A potential advantage of the triptorelin 22.5 mg formulation is its less frequent dosing regimen—once every 6 months compared to once monthly or once every 3 months for Lupron Depot-PEDS, the only currently approved *injectable* GnRH agonist formulation for treatment of CPP in the U.S. However, the

potential benefits of less frequent dosing of triptorelin compared to other GnRH agonist formulations have not been studied.

8 Review of Safety

8.1. Safety Review Approach

Safety data included all 44 subjects enrolled in the pivotal study Debio-8206-CPP-301 (**Table 2**). All 44 subjects were included in the safety population given that all 44 received two doses of triptorelin and completed all study visits.

In this safety review, all AEs experienced by study subjects enrolled in Debio-8206-CPP-301 were reviewed and assessed for their possible relationship to triptorelin. Specific attention was paid to AEs in the nervous system and psychiatric system SOCs due to two Tracked Safety Issues initiated by the Agency for all GnRH agonists approved for CPP: TSI 1404 (convulsions), and TSI 1405 (depression with or without suicidal ideation or attempt)(see **Section 8.5**). In addition, this safety review compared the known safety profile of triptorelin in children with CPP (including post-marketing safety data from triptorelin formulations approved outside the U.S. for the CPP indication) with the safety profiles of other currently marketed GnRH agonists approved for CPP.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The safety population consisted of all patients who received any single dose of the triptorelin 22.5 mg 6-month formulation, provided that they had any safety data. All 44 enrolled patients were included in the safety population.

All 44 children in the pivotal phase 3 study Debio-8206-CPP-301 received two doses of triptorelin. All drug doses were administered at scheduled study visits by study personnel on study days 1 and 169. There were no treatment interruptions or delays for any of the 44 enrolled patients.

8.2.2. Relevant characteristics of the safety population:

The safety population represents the entire patient population studied in Debio-8206-CPP-301 and is sufficiently representative of the overall population of children with CPP. Refer to **Table 5** and **Table 6** for baseline demographic and disease-related characteristics, respectively, of the study (safety) population.

8.2.3. Adequacy of the safety database:

The safety database is adequate and conforms to the previously agreed upon SPA Agreement between the Sponsor and the Agency to assess the safety of triptorelin 22.5 mg (b) (4) in children with CPP. All enrolled patients received the planned two doses of triptorelin and completed the 12 month trial, thus all enrolled patients were included in the safety database. Patient demographics and disease-related characteristics are representative of the U.S. target population, children with CPP (refer to **Table 5** and **Table 6**).

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The overall data integrity and submission quality were adequate to perform an effective safety review. There were no issues identified with the overall organization of the application, ease of finding information, completeness of submitted information, or identification of data relevant to site-specific analyses.

8.3.2. Categorization of Adverse Events

The applicant's definitions of **AEs** and serious adverse events (**SAEs**) in the protocol were accurate.

A **treatment emergent adverse event (TEAE)** was defined as an AE that occurred during or after the first administration of study drug, whether or not considered to be drug-related. AEs with an unknown start date were considered to be TEAEs.

The last available version of the Medical Dictionary for Regulatory Activities (MedDRA) was used to code all AEs in the pivotal study Debio-8206-CPP-301. AEs were coded per system organ class (SOC) and preferred term. Verbatim terms were included in the data files and were appropriately categorized in the AEDECOD (dictionary-derived term) data file.

Reviewer Comment: Adverse events were appropriately categorized, coded, and recorded in the protocol. The Applicant's overall approach to the safety analysis was appropriate and acceptable.

8.3.3. Routine Clinical Tests

Clinical safety laboratory and urine testing was done fasting prior to GnRH agonist stimulation testing and prior to triptorelin dosing at screening, month 6 (day 169) and month 12 (day 337). Safety laboratory assessments included:

1. Hematology: Hemoglobin (Hb), hematocrit (Hct), red blood cell count (RBC), white blood cell count (WBC), differential count, and platelets.

2. Chemistry: albumin, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, total protein, uric acid, lactic dehydrogenase (LDH), glucose, calcium, phosphorus, and total cholesterol.

3. Urinalysis: Dipstick (glucose, ketones, blood, pH, proteins, nitrites, leukocytes) with reflex

urine microscopy in cases of abnormal dipstick urinalysis.

4. Pregnancy test: serum β-hCG in all girls at screening.

Safety laboratory values that were outside normal ranges or represented a significant change from baseline (screening) were reviewed by the Investigator. Abnormal values that were considered to have a reasonable relationship to triptorelin or that were of uncertain origin were followed up by routine re-testing until the values had returned to an acceptable level compared with baseline values.

Reviewer Comment: The safety laboratory assessments were reasonable and adequate for the population and disease indication being investigated.

8.4. Safety Results

8.4.1. Deaths

There were no deaths during the triptorelin 22.5 mg (b) (4) development program for the CPP indication.

8.4.2. Serious Adverse Events

A single SAE, rated as severe, was reported for one of the 44 patients (2.3%) enrolled in Debio-8206-CPP-301. Patient 2501, a 7 year-old girl with epilepsy, experienced an infection of a vagus nerve stimulator (device-related infection), which was surgically placed during the course of the study for treatment of her underlying seizure disorder. According to the Sponsor, the infection was *not related* to triptorelin and resolved after the vagal nerve stimulator was removed and relocated, a procedure that required hospitalization. This SAE did not interrupt the patient's triptorelin treatments or any study visits.

Reviewer Comment: This MO agrees with the Sponsor that the SAE of vagus nerve stimulator infection described above was not related to study drug.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were no dropouts or discontinuations from the study for any reason, including due to adverse events. There were no treatment interruptions or delays for any of the 44 enrolled patients.

8.4.4. Significant Adverse Events

There was one SAE rated as severe in one study patient (ID 2501), described above (**Section 8.4.2**). This SAE was not considered by the Sponsor nor by this MO to be related to triptorelin and did not lead to study termination.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

A total of 81 TEAEs were reported by 32 patients (73%) during Debio-8206-CPP-301. Seventy-two (89%) mild AEs were reported by 32 (73%) patients, 8 (10%) moderate AEs by 4 (9%) patients and one (1%) severe AE by one patient (3%). The single severe AE (device-related infection) was also an SAE and was described previously (**Section 8.4.2**).

Five events in four patients (9%) were considered by the Sponsor to be related to triptorelin. No AEs were considered to be related to short-acting leuprolide (used for GnRH agonist stimulation testing). The five AEs considered to be related to triptorelin were injection site pain of mild severity reported by one (2.3%) patient and vaginal bleeding reported four times by three patients (7%). Three of the reports of vaginal bleeding were of mild severity and one was of moderate severity. One (2.3%) patient (ID 2404) reported two episodes of vaginal bleeding, one of mild and one of moderate severity; it is noteworthy that this patient also experienced therapeutic inefficacy after the first triptorelin injection and failed to achieve the primary endpoint at month 6, which was thought to be due to a technical problem with the first triptorelin injection.

The SOCs with >10% incidence of all AEs include the following: i) infections and infestations (35 AEs in 21 patients, 48% of AEs), ii) gastrointestinal disorders (6 AEs in 5 patients, 11% of AEs), iii) general conditions and administrative site conditions (6 AEs in 5 patients, 11% of AEs), iv) nervous system disorders (8 AEs in 6 patients, 14% of AEs), and v) reproductive system and breast disorders (6 AEs in 5 patients, 11% of AEs).

The most common AEs by SOC among study participants (reported in >5% of patients) were nasopharyngitis (13.6%), headache (13.6%), upper respiratory tract infection (URI) (9.1%), gastroenteritis (6.8%), and cough (6.8%). Of note in this study of children, 35 of 81 AEs (43%) were infection-related (e.g., nasopharyngitis, URI, gastroenteritis, influenza, bronchitis, otitis media), and none of these AEs were considered to be drug related.

Three AEs were injection site reactions (one injection site pain, one pruritus, and one erythema), of which only the AE of injection site pain was considered to be study drug-related by the Sponsor. This reviewer considers it a reasonable possibility that all three injection site adverse reactions were study drug-related. Two patients reported two AEs in the vascular disorder SOC: two episodes of hot flushes, both of mild severity. The AEs of hot flushes were not considered to be triptorelin-related by the Sponsor; however, this reviewer considers it a reasonable possibility that these AEs are related to triptorelin treatment based on the mechanism of action of sustained release GnRH agonist therapy (e.g., suppression of gonadal hormone production, specifically estradiol).

This reviewer specifically reviewed all AEs in the psychiatric and nervous system SOCs given that these are SOCs of interest for all GnRH agonists approved for CPP and are being tracked under two TSIs (TSI #1404 and TSI #1405)(refer to **Section 8.5**). In the psychiatric system SOC, there were six AEs reported in two patients: one patient had five episodes of anxiety (all of moderate severity)(ID 280101) and one patient had one episode of mood altered (of mild severity)(ID 630101). Based on the limited information provided in patient narratives for these two patients, it is difficult to assess causality between the AEs of 'anxiety' and 'mood altered' and treatment with triptorelin. In patient ID 280101,

anxiety episodes occurred prior to each study visit and were treated with anxiolytic medications at each occurrence; this patient was therapeutic on triptorelin based on GnRH agonist stimulation testing. In patient ID 630101, altered mood occurred within 10 days of the final study visit and resolved without intervention; this patient was also therapeutic on triptorelin. Emotional lability is a known potential AE related to GnRH agonist treatment due to hormonal fluctuations that occur while on treatment and is included in labeling of all currently marketed GnRH agonists approved for CPP in the U.S. Therefore, this reviewer concludes that there is a reasonable possibility that the six reported psychiatric system SOC AEs were triptorelin-related. In the nervous system SOC, there were eight AEs in seven patients: 7 reports of headache and 1 report of paresthesia, all mild in severity. Of note, the nervous system SOC TSI for all GnRH agonists approved for CPP was initiated primarily out of concern for seizures (convulsions) related to GnRH agonist treatment in children. No seizures were reported in Debio-8206-CPP-301. This reviewer does not consider the nervous system SOC AEs of headache and paresthesia to be study drug-related.

When sorted by severity, there was only one severe AE. This severe AE was also considered a SAE and the only SAE reported during the study (described previously, **Section 8.4.2**). Four patients (9%) reported a total of 8 moderate AEs (5 episodes of anxiety in 1 patient, 1 episode of vaginal bleeding, and 2 episodes of respiratory infection in 2 patients), and 32 patients (73%) reported 72 mild AEs.

Local tolerance at the triptorelin injection site was specifically evaluated in all patients immediately and 2 hours after each triptorelin dose. Overall, the injections were well tolerated. *Thirty-five patients reported some form of injection site reaction: 25 patients (57%) reported pain, 6 patients (14%) reported redness, 3 patients (7%) reported swelling, and 1 patient (2%) reported bruising at the injection site.* Only one of the injection site reactions listed above was considered clinically significant by the investigators: 1 report of injection site pain by patient 0901. This was also the only injection site reaction considered to be related to study drug by the Sponsor. There were three additional AEs related to the injection site reported *after* the two hour observation period, all mild in severity: one patient had 2 reports of injection site pruritus and 1 patient had one report of injection site erythema. The investigators do not consider these AEs to be study drug-related. *However, given that none of the injection site reactions would have occurred without the intramuscular triptorelin injection, this reviewer disagrees with the Sponsor and concludes that there is a reasonable possibility that all of the reported injection site reactions are study drug-related.*

Reviewer Comments: Injection site reactions and vaginal bleeding are expected AEs with use of GnRH agonist therapy in children with CPP. This reviewer agrees with the Sponsor that the AEs of vaginal bleeding were likely related to triptorelin. However, this reviewer disagrees with the Sponsor's assessment of causality for all but one injection site reaction, which the Sponsor does not believe are study drug-related. In this reviewer's assessment, there is a reasonable possibility that <u>all</u> of the reported injection site reactions are related to triptorelin.

Based on post-marketing experience with other currently marketed GnRH agonist formulations and the drug's mechanism of action, additional AEs in which there is a reasonable possible relationship with triptorelin are the 6 AEs in the psychiatric system SOC (5 reports of anxiety and 1 report of altered mood) and the 2 AEs in the vascular system SOC (2 reports of hot flushes).

8.4.6. **Laboratory Findings**

Safety laboratory data was collected at baseline and at months 6 and 12 (screening and days 169 and 337). Safety laboratory data included serum chemistry, CBC, and urinalysis in all patients and a serum pregnancy test in female patients at screening only.

In the entire study cohort, laboratory parameters with statistically significant changes from baseline to study day 169 (month 6) and/or study day 337 (month 12) are serum ALP, BUN, creatinine, total protein, and platelets. ALP levels, a marker of bone formation, significantly decreased on-treatment relative to baseline (mean reduction -67 U/L at month 6 and -72 U/L at month 12), providing biochemical evidence that treatment with triptorelin slows accelerated bone growth in children with CPP. Mean differences in ALP were also evident when individual patient changes were assessed. Eighty-seven percent of patients (20 of 23) with high ALP levels at baseline had normal ALP levels on-treatment.

Statistically significant mean differences in BUN (mean increase +1.6 and +0.98 mg/dL at months 6 and 12, respectively), creatinine (mean increase +0.03 and +0.04 mg/dL at months 6 and 12, respectively), TP (mean increases +0.25 and +0.17 g/dL at months 6 and 12, respectively), and platelets (mean decrease -18 and -19 billions/L at months 6 and 12, respectively) were not considered to be clinically significant by the Investigator and were not reflected in individual patient responses.

Laboratory changes among individual patients from baseline to month 6 or month 12 on-treatment were assessed with shift tables using worst case on-treatment. Laboratory parameters that fluctuated from normal to outside of the normal reference range (either high or low) for >10% of patients were bilirubin (change from normal to low in 13% of patients), calcium (change from normal to high in 21%), glucose (change from normal to high in 12%), leukocytes (change from normal to low in 12%), basophils (change from normal to high in 31%), eosinophils (change from normal to high in 14%), lymphocytes (change from normal to high in 27%), monocytes (change from normal to high in 14% and change from normal to low in 17%), and neutrophils (change from normal to low in 15%). None of these changes were considered to be clinically significant by the Investigator.

> Mean laboratory values at each study time point (baseline, day 169, and day 337) for those lab parameters with fluctuations outside the normal range in >10% of patients (total bilirubin, calcium, glucose, leukocytes, basophils, eosinophils, lymphocytes, monocytes, and neutrophils) and for those lab parameters with statistically significant mean differences on treatment (BUN, creatinine, TP, and platelets) were reviewed. This reviewer agrees with the Sponsor that none of these laboratory parameters demonstrated *clinically* meaningful changes on-treatment (Table 7).

Table 7. Mean Laboratory Parameters at Each Study Time Point for Labs with Fluctuations Outside the Normal Range in >10% of Patients*

Lab parameter	Mean ± SEM	Mean ± SEM	Mean ± SEM	Maximum mean

(units)				±SEM change from baseline
	Baseline	**Day 169**	**Day 337**	
Total Bilirubin (mg/dL)	0.37±0.18	.035±0.16	0.34±0.03	-0.03±0.13
Calcium (mg/dL)	9.9±0.4	10.0±0.5	10.0±0.4	0.08±0.45
Glucose (mg/dL)	87±8	89±10	87±8	1.6±10.2
Leukocytes (billions/L)	6.3±2.5	6.3±2.1	6.0±1.6	-0.04±2.1
Basophils (billions/L)	0.8±0.4	0.8±0.4	0.8±0.3	0.07±0.5
Eosinophils (billions/L)	3.0±2.8	2.8±1.3	3.0±1.7	-0.4±2.6
Lymphocytes (billions/L)	41.1±10.9	41.2±10.4	42.2±8.7	0.83±11.3
Monocytes (billions/L)	5.7±1.8	6.0±2.0	5.3±1.6	-.037±1.6
Neutrophils (billions/L)	49.4±10.9	49.2±10.4	48.8±8.6	-0.7±11.6
BUN (mg/dL)	10.9±2.6	12.5±2.7	11.9±2.7	1.6±2.7
Creatinine (mg/dL)	0.5±0.1	0.5±0.1	0.5±0.1	0.04±0.06
Total protein (g/dL)	7.1±0.4	7.4±0.5	7.3±0.4	0.3±0.5
Platelets (billions/L)	299±63	282±56	273±54	-19±40

*Derived from NDA Table 14.5-10

The majority of patients had normal urinalysis (UA) results for the entirety of the study (70% at baseline, 64% at month 6, and 76% at month 12). Non-clinically significant abnormalities were present in 28% of patients at baseline, 34% at month 6, and 24% at month 12. One patient (ID 8103) had a clinically significant abnormal UA (positive for leukocytes, nitrite, protein, and occult blood), which was present at baseline and persisted on-treatment. Because these abnormalities were present at baseline, they were not considered to be related to treatment with triptorelin. There were no clinically significant changes in urine pH for any patient during the study.

Reviewer Comment: This reviewer agrees with the Sponsor's assessment that mean laboratory changes in BUN, creatinine, TP, and platelets on-treatment compared to baseline are not clinically relevant and do not indicate a potential safety signal. This reviewer also agrees with the Sponsor's assessment that the decrease in mean ALP levels on-treatment is not clinically relevant but suggests a positive effect of triptorelin treatment on the deceleration of bone growth in children with CPP. In evaluating individual patient changes in laboratory parameters, this reviewer agrees with the Sponsor's assessment that changes in bilirubin, calcium, glucose, and WBC differentials are not clinically meaningful. This reviewer further assessed mean values for each of these lab parameters at each study time point and found no clinically meaningful differences on-treatment compared to baseline.

8.4.7. **Vital Signs**

Vital signs (heart rate (HR), systolic (SBP) and diastolic blood pressure (DBP)) were assessed pre-study, at screening, and at each study visit. No clinically significant changes from baseline in mean vital signs measurements were seen during the study. Individual patient changes in vital signs from baseline were assessed with shift tables using worst case on-treatment. For HR, shifts of ±20 beats per minute (bpm) from baseline were considered normal, and for BP, shifts of ±20 mm Hg from baseline were considered normal. For HR, 50% of patients remained within ±20 bpm; for DBP, 73% of patients remained within ±20 mm Hg; and for SBP, 59% remained within ±20 mm Hg during the entire study period. None of the inter-individual fluctuations in HR, SBP, or DBP that were seen were clinically significant. Across the entire study population, there were no systematic trends for any vital sign change.

8.4.8. Electrocardiograms (ECGs)

Not applicable.

8.4.9. QT

Not applicable.

8.4.10. Immunogenicity

Not applicable.

8.5. Analysis of Submission-Specific Safety Issues

Across the GnRH agonist class, the Agency has initiated two Tracked Safety Issues for the CPP indication: TSI 1404 for nervous system SOC AEs, particularly non-fatal and fatal seizures, and TSI 1405, psychiatric SOC AEs, particularly new or worsening depression with or without suicidal ideation or attempt. Both TSIs were initiated due to post-marketing AE reports suggesting a possible drug class effect in children with CPP. Further, after review of all FAERS data of nervous system and psychiatric SOC AEs for the three GnRH agonists currently marketed in the U.S. for treatment of CPP (Lupron Depot-PEDs, Supprelin, and Synarel) and review of the medical literature, it was determined that labeling changes across the class to increase awareness of these potential AEs were warranted. Thus, Supplemental Labeling Change (SLC) notifications were issued in 2016 to Sponsors of all GnRH agonists approved for the CPP indication to implement the labeling changes below:

TSI 1404: Non-fatal and fatal seizures (convulsions)

1. **Section 5 *Warnings & Precautions* (PLR):**
"Postmarketing reports of convulsions have been observed in patients receiving GnRH agonists. These have included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above."

2. **Section 17 Patient Counseling (PLR)**

"Inform parents that reports of convulsions have been observed in patients receiving [name of GnRH agonist]. Patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions may be at increased risk [see Warnings and Precautions (5)]."

TSI 1405: Psychiatric SOC Adverse Events related to GnRH agonist use in children with CPP

1. Section 5 Warnings and Precautions

Psychiatric Events

"Psychiatric events have been reported in patients taking GnRH agonists. Post-marketing reports with this class of drugs include symptoms of emotional lability, such as crying, irritability, impatience, anger and aggression. Monitor for development or worsening of psychiatric symptoms during treatment with DRUG. [See Adverse Reactions (6)]"

2. Section 6.X Postmarketing

Psychiatric Disorders

"Depression, including rare reports of suicidal ideation and attempt, have been reported for GnRH agonists. Many, but not all, of these patients had a history of psychiatric illness or other comorbidities associated with an increased risk of depression."

3. **Section 17 Patient Counseling Information**

"Inform caregivers that symptoms of emotional lability, such as crying, irritability, Impatience, and anger, have been observed in patients receiving GnRH agonists. Alert caregivers to the possibility of development or worsening of psychiatric symptoms, including depression, during treatment with DRUG [see Warnings and Precautions (5.X) or Warnings, Adverse Reactions (6)]"

In addition to these labeling changes, all application holders of GnRH agonists approved for treatment of CPP have been required to create medication guides to better inform patients and caregivers of the possible risks associated with GnRH agonist use in children. Applicants are further required to carry out enhanced pharmacovigilance (ePV) for events of depression and suicidality. Specifically, for a period of 5 years, applicants must submit all cases of suicidal ideation and behavior, self-injury, or depression as 15-day alert reports, and should provide detailed analyses of such events reported from clinical study and post-marketing reports as *adverse events of special interest* in periodic safety reports.

Reviewer Comment: In the triptorelin clinical program (Debio-8206-CPP-301), no AEs of convulsion/seizure, depression, or suicidal ideation or attempt were reported during the 12 month study period. However, post-marketing experience with triptorelin formulations used for treatment of CPP in non-U.S. countries show 1 AE report of convulsion and 2 AE reports of emotional lability. Nervous system and Psychiatric SOC AEs associated with triptorelin use in children with CPP will be tracked under TSI 1404 and TSI 1405, respectively. Further, an approved triptorelin label for the CPP indication will

need to include the labeling changes implemented above for the GnRH agonist class as well as an approved medication guide.

8.6. Safety Analyses by Demographic Subgroups

Not applicable.

8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Not applicable.

8.8.2. Human Reproduction and Pregnancy

Not applicable.

8.8.3. Pediatrics and Assessment of Effects on Growth

Not applicable.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Drugs in the GnRH agonist class are not considered to have a high abuse potential, thus an assessment of abuse potential of triptorelin for use in CPP is not necessary.

There is no clinical experience with overdosage of triptorelin, however, other marketed GnRH agonists have been used in adult patients for up to 2 years at doses 20 times higher than the recommended prescribed dose without adverse effects differing from those observed with the prescribed dose.

In preclinical single dose toxicity studies, the LD_{50} of triptrolin in mice and rats was approximately 500 and 600 times, respectively, the estimated monthly human dose.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

See also Department of Pharmacovigilance (DPV) review of post-marketing safety with triptorelin (see CONSULT REV-SAFETY-03 (Post Market Safety Review) by C. Cao, dated 4/6/17 in DARRTS).

Two safety databases, (b) (4) and Debiopharm, have been established for post-marketing surveillance of triptorelin formulations approved in non-U.S. countries for treatment of CPP (triptorelin acetate and

pamoate in the (b) (4) database and triptorelin pamoate in the Debiopharm database). No new safety concerns for the GnRH agonist class have been identified in post-marketing experience with triptorelin.

Analysis of the (b) (4) post-marketing surveillance safety database for the CPP indication showed a total of 711 AEs (203 serious) in 395 patients from 1986 through March 3, 2016. The most commonly reported AEs in children with CPP were injection site pain (4.1%), inappropriate schedule of drug administration (3.8%), headache (3.4%), hypersensitivity (2.4%), and urticaria (2.4%). Of the 203 SAEs (in 91 patients), the most notable and frequent SAEs (>3% of all SAEs) were hypersensitivity (17 events), anaphylactic reactions (3 events), angioedema (7 events), urticaria (7 events), and hypertension (8 events). All of these SAEs were considered drug-related with the exception of 2 SAEs of hypertension, one of which was not considered drug-related and one of which was unassessable.

Nine AEs concerning CPP patients treated with triptorelin were retrieved from the Debiopharm database. One AE was serious. Of the 8 non-serious AEs, there were 2 injection site reactions, 1 event of lack of hormonal suppression on-treatment, and 5 reports of off-label use (inappropriate age or disease indication). The 1 serious AE was reported in a 9 year-old girl taking no concomitant medications, who was treated with various doses of triptorelin for ~2 years when she experienced severe brain infarction and cerebrovascular accident due to left carotid artery dissection. Relationship to triptorelin was unable to be assessed.

In the *entire* post-marketing triptorelin safety database for all indications and ages, major identified risks associated with triptorelin use are listed below:

1. *Hypersensitivity and related reactions:*

   -Serious hypersensitivity reaction (21 patients), angioedema (28), rash (10), urticaria (17), pruritus (12), erythema (9), circulatory collapse (2), anaphylactic shock (6), anaphylactic reaction (3), dermatitis bullous (2), and face edema (6)

   -<u>Specifically in children with CPP</u>, serious hypersensitivity reaction (13 patients), angioedema (7), urticaria (7), rash (4), anaphylactic reaction (2), erythema (2), face edema (2), pruritus (3), drug hypersensitivity (1), and anaphylactic shock (1).

2. *Bone mass changes:*

   -SAEs reported in >1 patient include wrist fracture (18 cases), osteoporosis (15), fracture (7), ankle fracture (7), foot fracture (6), osteopenia (6), hand fracture (5) , femur fracture (3), radius fracture (3), spinal compression fracture (3), pathological fracture (2) , hip fracture (2), osteoporotic fracture (2), bone density decreased (2), bone density abnormal (2), and femoral neck fracture (1). Overall, there were 87 cases of bone loss from 25 male patients and 62 female patients in which triptorelin was considered causal.

   -<u>Specifically in children with CPP</u>, 6 SAEs were reported— 1 osteoporosis, 1 osteochondritis, 1 osteoarthropathy, and 1 upper limb fracture, all reported in children; 1 joint destruction and osteoarthritis reported in an adult male; and 1 fracture and osteoporosis reported in an adult female.

3. *Slipped capital femoral epiphysis* (*SCFE)*

-1 SAE in an 11 year-old female child treated for CPP.

4. *Metabolic changes*

-The entire pharmacovigilance (PV) database includes 35 serious cases of "metabolic changes," of which 63% (22/35) occurred in men with prostate cancer and 37% (13/35) occurred in female patients with various indications, 2 of whom were children. SAEs reported in >1 patient were weight decreased (11), weight increased (6), type 2 diabetes mellitus (7), hyperglycemia (6), and type 1 diabetes mellitus (2). The 2 SAEs of type 1 diabetes mellitus were reported in children.

5. *Cardiovascular (CV) disease:*

-The entire PV database reported 204 serious CV adverse events in adults (men with prostate cancer and women with multiple indications) and 18 SAEs in 15 children with CPP (6 hypertension, 3 hot flush, 2 increased intracranial pressure, 2 pallor, 1 benign intracranial hypertension, 1 tachycardia, 1 cardiac hypertrophy, 1 myocarditis, and 1 flushing).

6. Mood changes, including depression and suicide attempts:

-The entire PV database includes 64 serious psychiatric adverse events. SAEs reported in >1 patient were: depression (39), suicidal ideation without suicide attempt (15), suicide attempt (4), mood altered (5), anxiety (5), and disturbance in sexual arousal (2). In children with CPP, 3 SAEs occurred: affective disorder and mood altered (2) and disturbance in sexual arousal (1).

7. Disease flare:

-The entire PV database includes 65 SAEs of disease flare in prostate cancer patients.
-Specifically in children with CPP, 2 SAEs were reported: breast enlargement (1) and vaginal discharge (1).

8. Convulsions:

-The entire PV database includes 6 SAEs of convulsions or seizures. Five of these cases occurred in women treated for various indications (infertility, fibroids, breast cancer). One SAE occurred in a child treated for CPP. This was a 7 year-old female who experienced partial seizures while being treated with triptorelin; the seizures were considered to be drug-related.

In summary, analysis of Debiopharm's post-marketing surveillance safety database covering the period from 1986 through March 3, 2016, showed a total of 395 AEs reported for children with CPP. The most common AEs in children with CPP were injection site pain, inappropriate schedule of drug administration, headache, hypersensitivity, and urticaria. The most serious post-marketing safety signal is the risk of hypersensitivity reactions; this risk is addressed in proposed labeling section 6.2 (Postmarketing).

After DPV review of these post-marketing data *(see CONSULT REV-SAFETY-03 (Post Market Safety*

Review) by C. Cao, dated 4/6/17 in DARRTS), it was also noted that there were 10 cases of visual disorders among children using triptorelin for treatment of CPP in the (b) (4) and Debiopharm databases. Additionally, 5 cases of visual disorders were found in the FAERS database among pediatric patients using triptorelin.

Reviewer Comment: Given the number of cases of visual disorders seen among children using triptorelin, this AE should be included in labeling. Further, enhanced pharmacovigilance (ePV) for visual disorders in the post-marketing setting will help to determine relatedness of triptorelin use in children to vision changes.

8.9.2. Expectations on Safety in the Postmarket Setting

Because of its identical mechanism of action, triptorelin is expected to have a similar safety profile to other marketed GnRH agonists approved for the CPP indication (Lupron Depot-PEDS, Synarel, and Supprelin). Regarding injection site reactions, triptorelin is expected to have a safety profile that is similar to the only currently marketed GnRH agonist formulation that is also administered intramuscularly— Lupron Depot-PEDS.

8.10. Additional Safety Issues From Other Disciplines

Not applicable.

8.11. Integrated Assessment of Safety

Triptorelin 22.5 mg IM every 6 months was well tolerated in children with CPP enrolled in the pivotal phase 3 trial Debio-8206-CPP-301. Triptorelin exhibited a safety profile consistent with other GnRH agonists approved for treatment of CPP.

All 44 patients enrolled in Debio-8206-CPP-301 completed 48 weeks of treatment and received the two planned triptorelin doses, for a total of 45 mg of triptorelin over 12 months. There were no AEs leading to treatment interruptions or delays and no deaths during the study. A total of 81 TEAEs were reported by 32 patients (73%), all of which were mild (72 AEs, 89%) to moderate (8 AEs, 10%) in severity with the exception of one SAE rated as severe during the entire trial. The single SAE (infection of a vagus nerve stimulator) was not considered related to triptorelin.

The most frequent AEs, all determined not to be related to triptorelin, were nasopharyngitis (14%), headache (14%), upper respiratory infection (9%), gastroenteritis (7%), and cough (7%). These are all common events occurring in children over the course of one year.

Per the Investigator, 5 AEs reported by 4 patients were considered to be related to triptorelin: injection site pain in 1 patient and four occurrences of vaginal (menstrual) bleeding reported by 3 patients. Additional AEs that this reviewer has determined are possibly related to triptorelin are: 3 AEs of injection site reaction in 3 patients (one injection site pain, one injection site pruritus, and one injection site erythema), 1 psychiatric SOC AE in 1 patient (altered mood), and 2 AEs in 2 patients in the vascular disorders SOC (2 reports of hot flushes). Injection site reactions, psychiatric AEs of emotional lability (including mood fluctuations), and symptoms of hypoestrogenemia (e.g., hot flushes) are not unexpected AEs based on the mechanism of action of GnRH agonists and should be included in labeling.

In Debio-8206-CPP-301, local tolerance at the injection site was assessed immediately and 2 hours after each triptorelin dose and was overall good. A total of38 patients reported mild injection site reactions during the trial: 26 patients (59%) reported pain, 7 patients (16%) reported redness, 3 patients (7%) reported swelling, and 2 patients (5%) reported bruising at the injection site.

There were no clinically significant adverse changes in clinical laboratory parameters (CBC, CMP, U/A) or vital signs (HR, DBP, SBP) during the treatment period. Serum ALP levels decreased significantly during the treatment period, which was an expected finding with GnRH agonist therapy due to slowing of accelerated bone growth. There were no unexpected changes in body weight or BMI during treatment.

Post-marketing safety data with other formulations of triptorelin approved in non-U.S. countries for treatment of CPP are similar to previous clinical experience with GnRH agonists as a class. Regarding AEs of interest with the GnRH agonist class (nervous system SOC and psychiatric SOC AEs), 2 reports of emotional lability in 2 patients (1 mood altered and 1 affective disorder) and 1 report of seizure have been reported in post-marketing data in children with CPP. One additional AE of potential interest was identified in review of the triptorelin post-marketing data—visual disorders. This AE will be included in labeling and will be the subject of ePV in the post-marketing setting.

9 Advisory Committee Meeting and Other External Consultations

Not Applicable.

10 Labeling Recommendations

10.1. Prescribing Information

1 INDICATIONS AND USAGE
Appropriate

2 DOSAGE AND ADMINISTRATION
Include the following language:

(b) (4)

(b) (4)

Delete:

(b) (4)

.

Reviewer Comment: (b) (4) (b) (4)

3 DOSAGE FORMS AND STRENGTHS

Suggest using the language below:

(b) (4)

4 CONTRAINDICATIONS

Appropriate.

5 WARNINGS AND PRECAUTIONS

Add the following language:

5.3 Psychiatric Events

Psychiatric events have been reported in patients taking GnRH agonists. Postmarketing reports with this class of drugs include symptoms of emotional lability, such as crying, irritability, impatience, anger, and aggression. Monitor for development or worsening of psychiatric symptoms during treatment with Triptodur [see Adverse Reactions (6)].

5.4 Convulsions

Postmarketing reports of convulsions have been observed in patients receiving GnRH agonists. These included patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients on concomitant medications that have been associated with convulsions such as bupropion and SSRIs. Convulsions have also been reported in patients in the absence of any of the conditions mentioned above.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Table 1 should be modified to include all AEs experienced during the trial, (b) (4)

(b) (4) The AEs of menstrual disorder and vaginal bleeding should be combined to simplify labeling, as these AEs are equivalent clinically. The percentage with AEs of menstrual disorder/vaginal bleeding should reflect the percentage of female patients only.

(b) (4)

Include the following language:

6.2 Postmarketing

Psychiatric Disorders: Depression, including rare reports of suicidal ideation and attempt, has been reported for GnRH agonists. Many, but not all, of these patients had a history of psychiatric illness or other comorbidities with an increased risk of depression.

Nervous system disorders: convulsions (b) (4)

Reviewer Comment: Labeling changes were ongoing at the time of submission of this review.

10.2. Patient Labeling

The Medication Guide for this product will be modified to reflect the above changes to USPI.

10.3. Nonprescription Labeling

Not applicable.

11 Risk Evaluation and Mitigation Strategies (REMS)

None of the currently approved GnRH agonists for the CPP indication have a REMS. The cumulative worldwide patient exposure for all triptorelin formulations and all indications is estimated at >3 million treatment-years through August 2015.

11.1. Safety Issue(s) that Warrant Consideration of a REMS

None.

11.2. Recommendations on REMS

The primary safety issues identified in this application are consistent with currently marketed GnRH agonists approved for treatment of CPP and can be adequately addressed with appropriate labeling. Therefore, a REMS is not needed for this application.

12 Postmarketing Requirements and Commitments

Based on postmarketing experience with GnRH agonist products currently marketed for the CPP indication, the following enhanced pharmacovigilance (ePV) measures for all GnRH agonists approved for use in children with CPP has been initiated:

For a period of 5 years, Sponsors should submit all cases of suicidal ideation and behavior, self-injury, or depression reported with Triptodur as 15-day alert reports, and provide detailed analyses of suicidal ideation and behavior, self-injury, or depression events reported from clinical studies and postmarketing reports as *adverse events of special interest* in periodic safety reports (i.e., the Periodic Adverse Drug Experience Reports [PADER] required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). These analyses should show cumulative data relative to the date of approval as well as relative to prior periodic safety reports. Medical literature reviews for case reports/case series of suicidal ideation and behavior, self-injury, or depression reported with Triptodur should also be provided in the periodic safety report.

13 Appendices

13.1. References

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Debio-8206-CPP-301

Was a list of clinical investigators provided:	Yes **X** ☐	No ☐ (Request list from Applicant)
Total number of investigators identified: 18		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements: **N/A**	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: **N/A**	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: **N/A**	Yes ☐	No ☐ (Request explanation from Applicant)

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/s/

SHANNON D SULLIVAN
06/02/2017

MARINA ZEMSKOVA
06/05/2017

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208956 **Applicant: Arbor Pharmaceuticals, LLC** **Stamp Date: 8/29/2016**

Drug Name: Triptorelin pamoate for (b) (4) suspension **NDA/BLA Type: 505 (b)(1)**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505 (b)(1)			
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study Debio-8206-CPP-301 A Multi-Center, Open-label, uncontrolled Study to Evaluate the Efficacy and safety of Triptrorelin 22.5 mg (b) (4) to	X			SPA agreement with Agency, Oct 2011

	Content Parameter	Yes	No	NA	Comment
	treat children with central precocious puberty (CPP)				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			SPA agreement with Agency, Oct 2011
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			SPA agreement with Agency, Oct 2011
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			Orphan designation; subject number agreed upon in SPA
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	discussions?				
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	CPP has Orphan Drug designation thus PREA requirements do not apply
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	There were no foreign-only pivotal studies. While the pivotal study was multinational, 64% (28/44) of the subjects were from US sites, so there is sufficient US data to look for potential geographical disparities
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Shannon Sullivan MD, PhD	October 24, 2016
Reviewing Medical Officer	Date
Marina Zemskova MD	October 24, 2016
Clinical Team Leader	Date

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

/s/

SHANNON D SULLIVAN
10/24/2016

MARINA ZEMSKOVA
10/24/2016