CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208956Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	208956
Link to EDR	\\CDSESUB1\evsprod\NDA208956\208956.enx
Submission Date	08/29/2016
Submission Type	505(b)(1); standard review
Brand Name	TRIPTODUR
Generic Name	Triptorelin pamoate
Dosage Form and Strength	Lyophilized powder; 22.5 mg;
Route of Administration	Intramuscular (IM) injection
Proposed Indication	Pediatric patients with central precocious puberty, 2 years and older
Applicant	Arbor
Associated IND	IND 111504
OCP Review Team	*Jianmeng Chen, M.D., Ph.D.*
OCP Final Signatory	*Jayabharathi Vaidyanathan, PhD (Team Leader)*

Note – In this review, early development names Debio8206 is also used to refer to triptorelin

Table of Contents

List of Tables

List of Figures

1. EXECUTIVE SUMMARY

Triptorelin is a gonadotropin releasing hormone (GnRH) receptor agonist. Triptorelin for (b) (4) Suspension 22.5 mg is a sustained release formulation of triptorelin pamoate. This formulation was approved for treatment of advanced prostate cancer in 2010 under NDA #22-437 (Trelstar® 22.5 mg, Actavis Pharmaceuticals). A statement of cross-reference to NDA #22-437 was provided in the submission.

Arbor Pharmaceuticals submitted the NDA 208956 seeking the marketing approval for triptorelin pamoate, to be used for "the treatment of children with central precocious puberty (CPP)" in children 2 years old and above. The recommended dose is 22.5 mg administered as a single intramuscular injection once every 24 weeks.

1.1 Recommendations

The Office of Clinical Pharmacology, DCP-2 has reviewed the NDA 208956 submitted on 8/29/2016 and recommend approval. The key review issues with specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	An open label study Debio 8206-CPP-301 is the sole efficacy and safety study in the NDA program
General dosing instructions	The triptorelin 22.5mg once every 24 weeks (Q24W) dosing regimen is appropriate for pediatric CPP patients 2 years old and above
Dosing in patient subgroups (intrinsic and extrinsic factors)	The proposed dosing is acceptable. No dose adjustment is recommended for intrinsic or extrinsic factors.
Labeling	See section 2.4 for labeling.
Other (specify)	None

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Triptorelin, like other GnRH agonists, has a short half-life in vivo (t½~5 hours). Therefore, sustained-release dosage forms for intramuscular administration (IM) have been developed by (b) (4) (b) (4)

PK for Triptorelin 6-month (22.5 mg) sustained-release IM formulations in adults have been submitted and reviewed under NDA #22-437. In this submission, the pharmacokinetics and pharmacodynamics were evaluated in 44 pediatric patients (2-9 years old) with CPP in the pivotal study Debio 8206-CPP-301.

- For all study participants, mean triptorelin serum concentrations at Months 1, 2, 3, 6, 9, and 12 showed that following the first triptorelin injection, geometric mean serum levels were 0.11 and 0.17 ng/mL, respectively, for the first two months, then remained at 0.03 to 0.05 ng/mL over the remainder of the dosing period.

- In the PK subset of 8 patients, serum triptorelin concentration vs. time profiles showed that release of triptorelin consists of two distinct phases, a burst phase followed by a maintenance phase. Following each triptorelin injection, the triptorelin serum concentrations peaked at a median of 4 hours post-dose for both first and second doses, with a geometric mean Cmax of 39.9 ng/mL and 36.5 ng/mL after the first and second injections, respectively. No significant accumulation was detected after the second triptorelin injection, based on a geometric mean accumulation ratio of 0.91 for Cmax.

- Comparable triptorelin concentrations were observed across weight tiers and age groups following the 22.5mg Q24W dosing regimen in CPP patients 2-9 years old (Figure 1). Therefore, dose adjustment based on weight or age is not necessary.

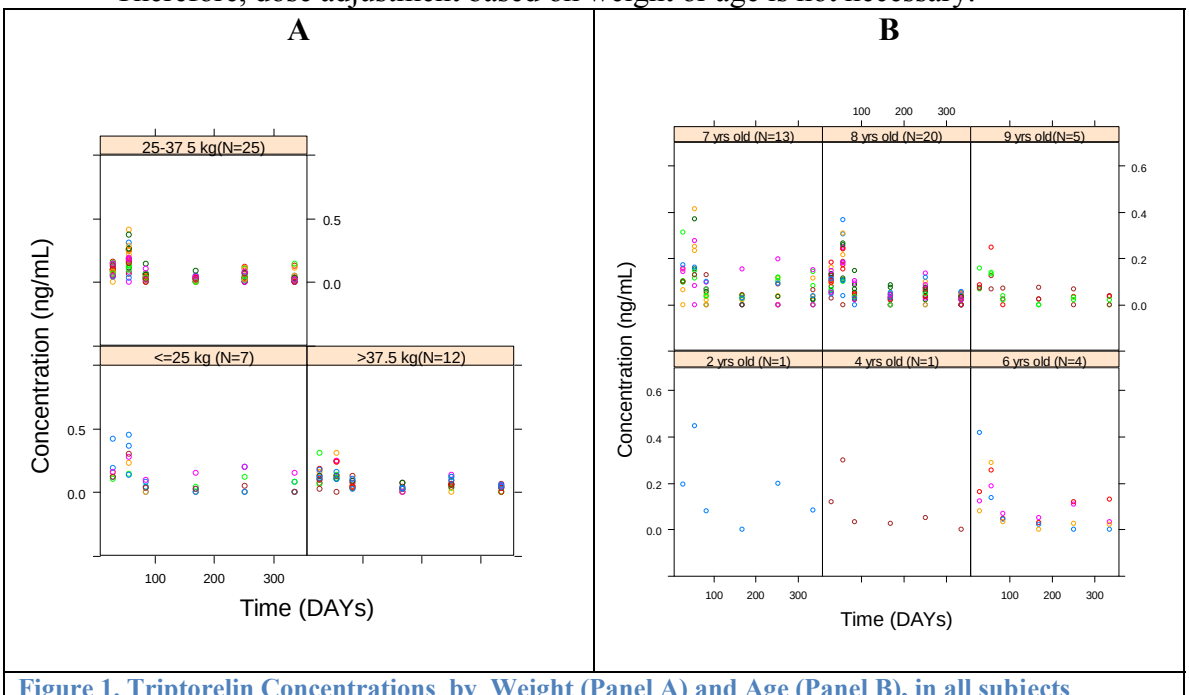

Figure 1. Triptorelin Concentrations by Weight (Panel A) and Age (Panel B), in all subjects

(Source: Reviewer analysis)

- Comparable pharmacodynamic effect on LH, FSH, Estradiol and testosterone were observed across age groups following the 22.5mg Q24W dosing regimen in CPP patients 2-9 years old (Figure 2).

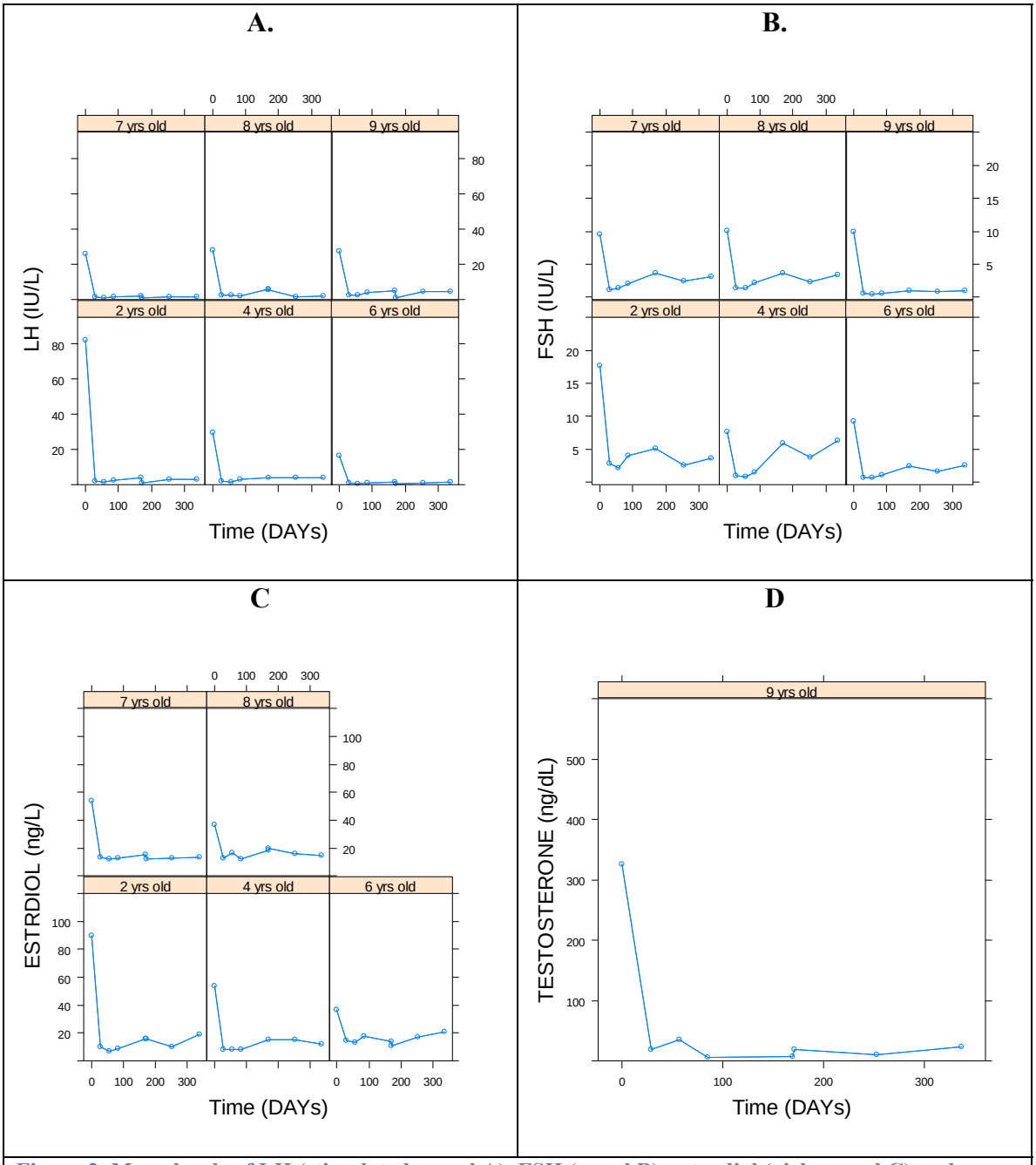

Figure 2. Mean levels of LH (stimulated, panel A), FSH (panel B), estradiol (girls, panel C) and testosterone (boys, panel D) by age

(Source: Reviewer analysis)

- Cross study comparison showed that the Cmax of triptorelin after first injection was similar in pediatric CPP patients (~39.9 ng/mL) and adult prostate cancer patients (~44.1 ng/mL).

- Based on *in vitro* studies, drug-drug interactions with triptorelin are unlikely.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dosage of TRIPTODUR is 22.5 mg given as a single intramuscular injection once every 24 weeks.

2.2.2 Therapeutic individualization

No dose adjustment is required for weight, or population with hepatic or renal impairment.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The revised labeling language shown below. Based on the clinical pharmacology review, most revisions were on drug-drug interactions and recommendations to update the label to reflect triptorelin PK in pediatric CCP patients.

7 DRUG INTERACTIONS

7.1 Drug-Drug Interactions

(b) (4)

Results of (b) (4) *in vitro* studies (b) (4) show that drug-drug interactions with triptorelin are unlikely [*see Clinical Pharmacology (12.3)*]. However, in the absence of relevant data and as a precaution, hyperprolactinemic drugs should not be used concomitantly with triptorelin since hyperprolactinemia reduces the number of pituitary GnRH receptors.

7.2 Drug-Laboratory Test Interactions

Administration of TRIPTODUR ~~22.5 mg~~ results in suppression of the pituitary-gonadal system. Therefore, diagnostic tests of pituitary gonadotropic and gonadal functions conducted during treatment or after discontinuation of treatment may be affected.

(b) (4) The effect of TRIPTODUR usually (b) (4) disappeared within six to twelve months after treatment discontinuation.

8 USE IN SPECIFIC POPULATIONS

8.6 Renal Impairment

TRIPTODUR has not been studied in children with renal impairment. Adult subjects with renal impairment had higher exposure than young healthy adult males *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

TRIPTODUR has not been studied in children with hepatic impairment. Adult subjects with hepatic impairment had higher exposure than young healthy adult males *[see Clinical Pharmacology (12.3)]*.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4)

12.2 Pharmacodynamics

Following the first administration, there is a transient surge in circulating levels of LH, FSH, testosterone, and estradiol *[see Warnings and Precautions (5.2)]*. After chronic and continuous administration, by 4 weeks after initiation of therapy, a sustained decrease in LH and FSH secretion and marked reduction in sex steroids are observed. (b) (4)

12.3 Pharmacokinetics

(b) (4)

Absorption

After an initial intramuscular TRIPTODUR 22.5 mg injection and a second 22.5 mg intramuscular injection 24 weeks later in children 2 to 9 years old with CPP, triptorelin peaked 4 hours postdose with a geometric mean C_{max} of 39.9 and 36.5 ng/mL, respectively. No apparent accumulation of triptorelin occurred after the second injection. Absorption occurred in two phases, a burst phase followed by a maintenance release phase. In children with CPP, following the burst phase after the first 22.5 mg injection, geometric mean serum triptorelin levels were 0.11, 0.17, 0.05 and 0.03 ng/mL at Months 1, 2, 3, and 6, respectively.

Distribution

(b) (4)

There is no evidence that triptorelin, at clinically relevant concentrations, binds to plasma proteins.

Elimination

Metabolism

The metabolism of triptorelin in humans is unknown, but is unlikely to involve hepatic microsomal enzymes (cytochrome P450). Thus far no metabolites of triptorelin have been identified. Pharmacokinetic data suggest that C-terminal fragments produced by tissue degradation are either completely degraded in the tissues, or rapidly degraded in plasma, or cleared by the kidneys.

Excretion

Triptorelin is eliminated by both the liver and the kidneys. Following intravenous administration of 0.5 mg triptorelin peptide to six healthy male volunteers with a creatinine clearance of 149.9 mL/min, 41.7% of the dose was excreted in urine as intact peptide with a total triptorelin clearance of 211.9 mL/min. This percentage increased to 62.3% in patients with liver disease who have a lower creatinine clearance (89.9 mL/min). It has also been observed that the nonrenal clearance of triptorelin (patient anuric, $Cl_{creat} = 0$) was 76.2 mL/min, thus indicating that the nonrenal elimination of triptorelin is mainly dependent on the liver.

Specific Populations

(b) (4)

Renal Impairment

After intravenous bolus injection of 0.5 mg triptorelin in adults, the two distribution half-lives were unaffected by renal impairment. However, renal insufficiency led to a decrease in total triptorelin clearance proportional to the decrease in creatinine clearance as well as increases in volume of distribution and consequently, an increase in the elimination half-life. Adult male subjects with moderate or severe renal impairment had approximately 2-fold higher exposure (AUC values) than young healthy adult males (see Table 1) *[See Use in Specific Populations (8.6)]*.

Hepatic Impairment

After intravenous bolus injection of 0.5 mg triptorelin in adults, the two distribution half-lives were unaffected by hepatic impairment. In adult males with hepatic insufficiency, triptorelin clearance was reduced and exposure (AUC) was increased 3.7-fold compared to young healthy adult males (Table 2) *[See Use in Specific Populations (8.7)]*.

Table 2 Pharmacokinetic Parameters (Mean ± SD) in Healthy Adults, Adults with Renal Impairment, and Adults with Hepatic Impairment Following an I.V. Bolus of 0.5 mg Triptorelin in Solution[50]

Group	C_{max} (ng/mL)	AUC_{inf} (h·ng/mL)	Cl_p (mL/min)	Cl_{renal} (mL/min)	$t_{1/2}$ (h)	Cl_{creat} (mL/min)

6 healthy male volunteers	48.2 ±11.8	36.1 ±5.8	211.9 ±31.6	90.6 ±35.3	2.81 ±1.21	149.9 ±7.3
6 males with moderate renal impairment	45.6 ±20.5	69.9 ±24.6	120.0 ±45.0	23.3 ±17.6	6.56 ±1.25	39.7 ±22.5
6 males with severe renal impairment	46.5 ±14.0	88.0 ±18.4	88.6 ±19.7	4.3 ±2.9	7.65 ±1.25	8.9 ±6.0
6 males with liver disease	54.1 ±5.3	131.9 ±18.1	57.8 ±8.0	35.9 ±5.0	7.58 ±1.17	89.9 ±15.1

Drug-Drug Interactions

In Vitro Assessment of Drug Interactions

Drug Metabolizing Enzyme Inhibition

Triptorelin did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19 or 2D6. (b) (4)

Drug Metabolizing Enzyme Induction

In fresh human hepatocytes from three human donors, triptorelin did not induce CYP1A2 or CYP3A4/5 activity.

Transporters

Triptorelin was a poor P-gp substrate and had no inhibitory effect toward P-gp.

(b) (4)

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Triptorelin is a synthetic decapeptide agonist analog to the naturally occurring GnRH. Triptorelin is a decapeptide (MW 1699.9 Da, 1311.5 (triptorelin) + 388.4 (pamoate)) whose major structural difference with GnRH is the substitution of the amino acid D-tryptophan (D-Trp) at position 6 by L-glycine (L-Gly). Triptorelin retains those parts of the native decapeptide responsible for its biological activity. Triptorelin pamoate is soluble in N,N-dimethylformamide (DMF) and pyridine; practically insoluble in water.

	1 2 3 4 5 6 7 8 9 10
GnRH (pyro)	Glu-His-Trp-Ser-Tyr- Gly -Leu-Arg-Pro-Gly-NH2
Triptorelin	(pyro) Glu-His-Trp-Ser-Tyr- D-Trp -Leu-Arg-Pro-Gly-NH2

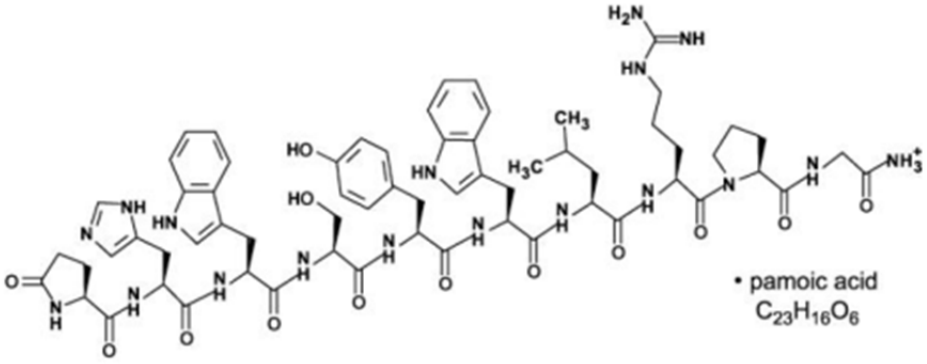

Figure 3. Molecular structure of triptorelin pamoate

Drug product: Triptorelin pamoate microgranules 22.5 mg is a sterile, lyophilized, biodegradable microgranule formulation supplied as a single-dose vial for treatment of central precocious puberty. The proposed formulation is currently approved for a different indication, palliative treatment of advanced prostate cancer, under NDA 022437 held by Actavis Laboratories UT. The triptorelin pamoate microgranules 22.5 mg vial will be provided in a kit that contains Sterile Water for Injection for reconstitution. The Sterile Water for Injection is provided in a pre-filled syringe. The commercial formulation was used in the pivotal Phase 3 Study 301, therefore, there was no need to conduct a formal bioequivalence study to compare between the product used in the clinical study and the one proposed for marketing.

Regulatory history:

Triptorelin for (b) (4) Suspension 22.5 mg was approved by FDA in 2010 for palliative treatment of men with advanced prostate cancer under NDA #22-437 (Trelstar 22.5 mg, Actavis Laboratories, Inc). The approved triptorelin 6-month sustained-release formulation was used for the pivotal study in this submission.

There have been several interactions between Agency and Sponsor to discuss the clinical pharmacology program of the proposed product. The key Clinical Pharmacology agreements are summarized in Table 1. Triptorelin pamoate was granted FDA Orphan Drug Designation on Aug 20, 2012 for the "treatment of children with central precocious puberty". The NDA review is under standard review timelines.

Table 1. Summary of Regulatory history relevant to clinical pharmacology

PNDA (Dec 2015)	• Agree that the PK, PD assessment are adequate to support NDA filing
FDA Special Protocol – Agreement (Oct 2011)	• Agreed with phase 3 study design, primary endpoint, etc. • Agreed with PK assessment plan (assess serum triptorelin levels in all patients at Months 1, 2, 3, 6, 9, and 12 and to assess triptorelin Cmax (and Tmax) in a subset of eight patients) • Recognize sponsor's intention to market only the 6-month triptorelin formulation, which is evaluated in the phase 3 study, for the treatment of central precocious puberty. Clarify that sponsor is not seeking approval of triptorelin 3-month or 1-month formulation for treatment of CPP based on the phase 3 study (Study 301).

(Source: Reviewer summary)

3.2 General Pharmacology and Pharmacokinetic Characteristics

GnRH agonists have been the standard of care for children with CPP for almost 30 years. An international consensus conference concluded in 2008 that all available GnRH agonists are effective for the treatment of CPP despite their different routes of administration, dosing, and duration of action and that sustained-release preparations are preferred because of improved compliance.

The following drugs are approved in the US for treatment of CPP:

- Lupron Depot Ped (leuprolide acetate for depot suspension)
- Supprelin LA (histrelin acetate) subcutaneous implant
- Synarel (nafarelin acetate) nasal spray

Mechanism of Action

Triptorelin is a gonadotropin releasing hormone (GnRH) agonist. An acute injection of GnRH agonist such as triptorelin induces a marked and prolonged release of LH and FSH. However, continuous stimulation of LH secretion by a long-acting GnRH agonist results in "desensitization" of gonadotroph cells and suppression of gonadotropin secretion, gonadal suppression, and a marked decrease in testosterone production in boys and estradiol production in girls.

Triptorelin for (b) (4) Suspension 22.5 mg is proposed to be indicated for the treatment of children with central precocious puberty (CPP).

Pharmacokinetics of Triptorelin

The pharmacokinetics (PK: triptorelin) and pharmacodynamics (PD: LH, FSH, testosterone/ estrogen) were evaluated in 44 pediatric patients 2-9 years old with CPP in the pivotal study Debio 8206-CPP-301.

Triptorelin serum concentrations vs time profiles were determined in all children at Day 1 and at Months 1, 2, 3, 6, 9, and 12 (Days 29, 57, 85, 169, 253, and 337). Triptorelin Cmax and Tmax

were assessed from serum concentration vs time profiles over 24 hours post-triptorelin injection in a subset of 8 children, as indicated in the table below:

Table 2: Pharmacokinetic assessments

	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)	

(Source: Table 9.5-2, study report 301)

Sparse PK in all patients (n=44)

For all 44 study participants, mean triptorelin serum concentrations by time point during the maintenance phase are summarized in Table 3. Following the first triptorelin injection, geometric mean serum levels were 0.11 (range 0.03 to 0.42) ng/mL and 0.17(range 0.00 to 0.45) ng/mL at the first and second month post-first injection, respectively. Thereafter, similarly for both injections, triptorelin decreased to mean levels of 0.05 ng/mL and 0.03ng/mL at 3 and 6 months post-dose, respectively.

Table 3: Triptorelin Serum Concentrations* (ng/mL) by Time Point in Children with CPP Participating in Study Debio 8206-CPP-301

	Day 1 (pre-dose)	Month 1 (Day 29)	Month 2 (Day 57)	Month 3 (Day 85)	Month 6 (Day 169 pre-dose)	Month 9 (Day 253)	Month 12 (Day 337)
N	44	43	44	44	40	43	42
Mean (SD)	0.00 (0.00)	0.12 (0.07)	0.20 (0.10)	0.05 (0.03)	0.03 (0.03)	0.06 (0.05)	0.04 (0.04)
Min-Max	0.00 - 0.00	0.03 - 0.42	0.00 - 0.45	0.00 - 0.15	0.00 - 0.15	0.00 - 0.20	0.00 - 0.15
Geometric mean*	0.03*	0.11	0.17	0.05	0.03	0.05	0.03
Geometric CV%	0%	52%	73%	56%	68%	78%	79%
Geometric 90% CI		0.10 - 0.12	0.14 - 0.20	0.04 - 0.05	0.02 - 0.03	0.05 - 0.06	0.03 - 0.04

CI: confidence interval; CV: coefficient of variation; SD: standard deviation

(Source: Table 2, summary of clin pharm)

Graphic displays of triptorelin levels at Day 1 and Months 1, 2, 3, 6, 9, and 12 vs time curves in the PK population are presented in Figure 4 as geometric means ± SD in log10/linear scales. The continuous line reflects changes in triptorelin serum concentration measured 1 to 6 months after each administration (triptorelin IM dosing on Days 1 and 169) and illustrates that triptorelin

serum levels were overall maintained at around 0.03-0.05 ng/mL. Of note, the peak in triptorelin serum concentration (Cmax) that occurs shortly after dosing ("burst" phase) is not captured by this figure.

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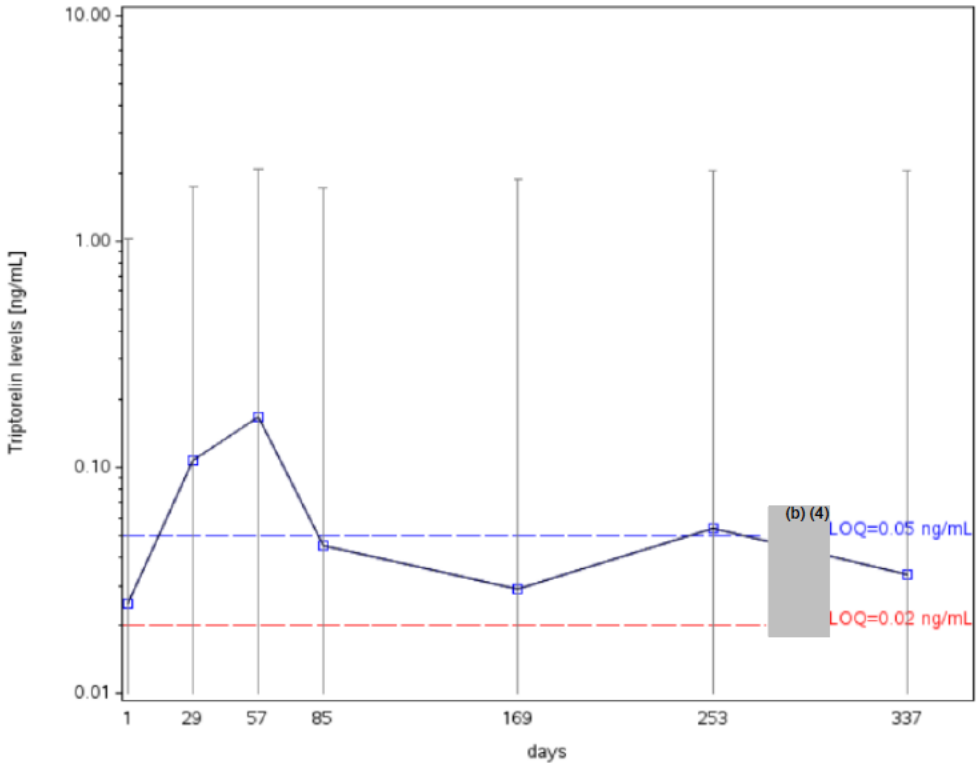

Figure 4. Geometric mean ± geometric SD triptorelin serum levels - PK population (log10/linear axe) ((b) (4) and (b) (4) are two bioanalytical methods used for Study 301, with lower limit of quantitation at 0.05 ng/mL and 0.02 ng/mL respectively. Refer to appendix 4.1 for details)

(Source: Figure 11.4-3, Study report 301)

Intensive PK in PK subset (n=8)

Triptorelin PK parameters Cmax and Tmax following the 1st and the 2nd triptorelin injection (on Days 1 and 169, respectively) were assessed in a PK subset of 8 patients.

Accumulation ratio on Cmax between the first and the second triptorelin injection was calculated as Cmax (Day 169)/Cmax (Day 1). The geometric mean Cmax was 39.9 ng/mL after the 1st triptorelin injection and 36.5 ng/mL after the 2nd triptorelin injection. The median Tmax was 4 hours after both the 1st and the 2nd triptorelin injection (Table 4). The geometric mean of the Cmax accumulation ratio was 0.9 with a 90% CI including "1"; there was therefore no statistically significant accumulation of triptorelin between the 1st and the 2nd injection (Table 5).

Table 4: Triptorelin serum pharmacokinetic parameters

INJECTION	STATISTIC	C_{max} [ng/mL]	t_{max} [h]
1st	N	8	8
	Geometric mean	39.89	-
	90% CI of geometric mean	(25.98;61.24)	-
	Median	-	4.00
	90% non-parametric CI of median	-	(2.00;8.00)
2nd	N	8	8
	Geometric mean	36.48	-
	90% CI of geometric mean	(29.81;44.65)	-
	Median	-	4.00
	90% non-parametric CI of median	-	(3.00;12.00)

(Source: Table 11.4-23, summary of clin pharm)

Table 5: Triptorelin Cmax accumulation ratio and Tmax difference following the second vs the first injection

	C_{max} ACCUMULATION RATIO	t_{max} MEDIAN DIFFERENCE [h]
N	8	8
Geometric mean of the ratio	0.91	
90% CI of geometric mean of the ratio	(0.63; 1.33)	
Median difference		-0.50
Non-parametric 90% CI of difference		(-4.00; 2.00)

(Source: Table 11.4-24, summary of clin pharm)

Individual Days 1 and 169 triptorelin levels vs time curves in the PK subset are presented in Figure 5. In all patients of the PK subset, triptorelin concentration vs time profiles showed that the release of triptorelin consisted of two phases, a "burst" phase followed by a maintenance release phase. Triptorelin serum concentration peaked on the day of dosing and then decreased to mean levels of 0.09, 0.17, 0.05, 0.06 and 0.03 ng/mL at 1, 2, 3 and 6 months post-dose, respectively (Figure 6).

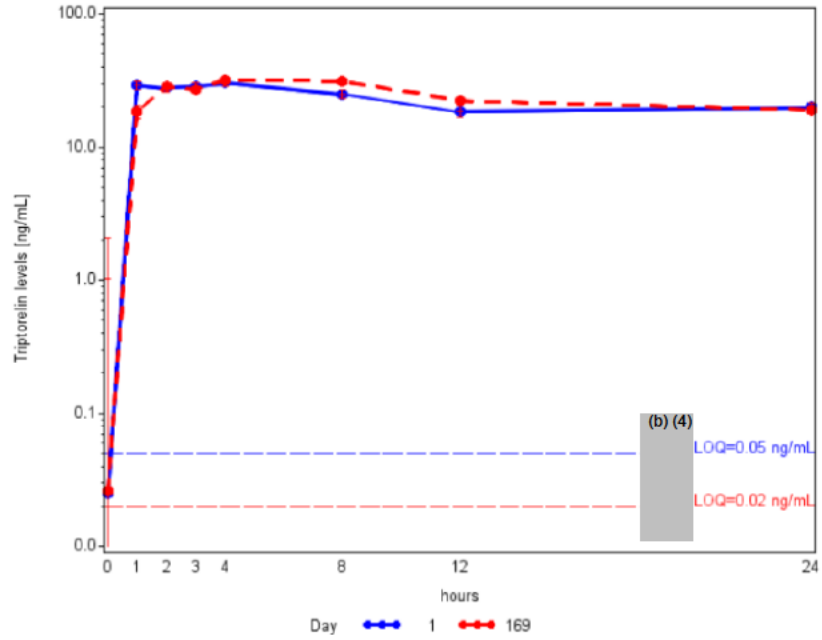

Figure 5. Geometric mean ± geometric SD Day 1 and Day 169 triptorelin serum levels – PK subset (log10/linear axes) (b) (4) are two bioanalytical methods used for Study 301, with lower limit of quantitation at 0.05 ng/mL and 0.02 ng/mL respectively. Refer to appendix 4.1 for details)

(Source: Figure 11.4-5, study report 301)

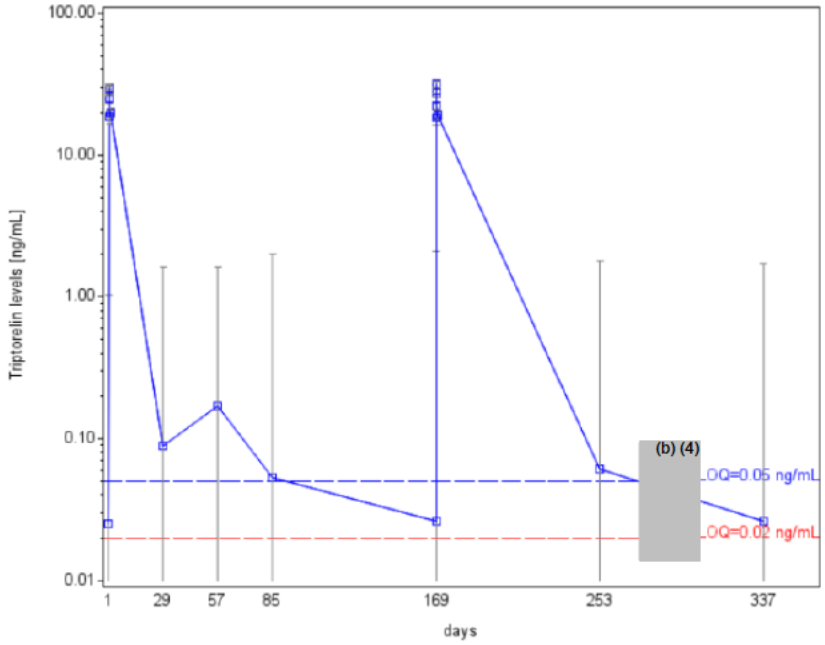

Figure 6. Geometric mean ± geometric SD triptorelin serum levels - PK subset (log10/linear axes) (b) (4) (b) (4) are two bioanalytical methods used for Study 301, with lower limit of quantitation at 0.05 ng/mL and 0.02 ng/mL respectively. Refer to appendix 4.1 for details)

(Source: Figure 11.4-6, study report 301)

Absorption

- For all study participants, mean triptorelin serum concentrations at Months 1, 2, 3, 6, 9, and 12 showed that following the first triptorelin injection, geometric mean serum levels were 0.11 and 0.17 ng/mL, respectively, for the first two months, then remained at 0.03 to 0.05 ng/mL over the remainder of the dosing period.

- In the PK subset of 8 patients, serum triptorelin concentration vs. time profiles showed that release of triptorelin consists of two distinct phases, a burst phase followed by a maintenance phase. Following each triptorelin injection, the triptorelin serum concentrations peaked at a median of 4 hours post-dose for both first and second doses, with a geometric mean Cmax of 39.9 ng/mL and 36.5 ng/mL after the first and second injections, respectively. No significant accumulation was detected after the second triptorelin injection, based on a geometric mean accumulation ratio of 0.91 for Cmax.

Please refer to the original NDA 22-314, 20-715 and 21-288 submissions for the following issues

Distribution

Metabolism

Elimination

Pharmacodynamics

Following the first administration, there is a transient surge in circulating levels of LH, FSH, testosterone, and estradiol. After chronic and continuous administration, by 4 weeks after initiation of therapy, a sustained decrease in LH and FSH secretion and marked reduction in sex steroids are observed. In 44 children with CPP receiving two injections of TRIPTODUR 22.5 mg at 24-week intervals, longitudinal assessments of LH, FSH, estradiol (in 39 girls) and testosterone (in 5 boys) at Months 1, 2, 3, 6, 9 and 12 showed that at each time point ≥93% of CPP patients achieved LH suppression to prepubertal levels (GnRH agonist-stimulated LH ≤5 IU/L); ≥79% of girls achieved prepubertal levels of estradiol (<20 pg/mL); and ≥80% of boys achieved prepubertal levels of testosterone (<30 ng/dL) (Table 10).

Table 6: Longitudinal Pharmacodynamic Effects of Triptorelin for Depot Suspension 22.5mg in Children with CPP (Pivotal Study Debio 8206-CPP-301 – Intent-to-Treat Analysis)

Pharmacodynamic Measure	Screening	Day 29 (Mo 1)	Day 57 (Mo 2)	Day 85 (Mo 3)	Day 169 (Mo 6)	Day 253 (Mo 9)	Day 337 (Mo 12)
Primary Efficacy Endpoint							
% Patients with pre-pubertal LH (GnRH-stimulated LH≤5 IU/L)					93%** (41/44)		
Secondary Efficacy Endpoints							
% Patients with pre-pubertal LH (GnRH-stimulated LH≤5 IU/L)	none*	95% (42/44)	95% (42/44)	95% (42/44)		95% (42/44)	98% (43/44)
Mean GnRH-stimulated LH level (IU/L)	27.2	2.00	1.96	2.04	4.16	1.97	2.06
Mean basal LH level (IU/L)	2.13	0.68	0.60	0.36	0.59	0.36	0.42
Mean GnRH-stimulated FSH level (IU/L)	10.01	1.16	1.20	1.88	3.34	2.14	3.02
Mean basal FSH level (IU/L)	4.40	0.83	0.90	0.94	1.59	1.06	1.49
% with pre-pubertal estradiol (<20 pg/mL, girls)	(not reported)	87% (34/39)	89% (34/38)	92% (36/39)	79% (31/39)	82% (32/39)	79% (31/39)
Mean estradiol level (ng/L)	44.8	13.0	14.5	12.7	16.6	14.7	15.1
% with pre-pubertal testosterone (<30 ng/mL, boys)	(not reported)	80% (4/5)	80% (4/5)	100% (5/5)	100% (5/5)	80% (4/5)	80% (4/5)
Mean testosterone level (ng/dL)	326	19.0	35.3	6.8	8.4	10.5	24.1

* Protocol inclusion criteria specified GnRH-stimulated LH ≥6 IU/L

**Primary efficacy endpoint; result of 93% (95%CI: 81.3 %-98.6%) rejected the null hypothesis of ≤80% responders

***% with pre-pubertal testosterone should have cut off at 30 ng/**dL,** and the sponsor table had a typo and list it as 30 ng/mL. The label was also corrected for this typo.

(Source: Table 3, summary of clin pharm)

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

NDA 208956 consists of 3 in vitro studies with human materials (Table 7), and one Phase 3 study (Study 301, Table 8). Only one dosing regimen (22.5 mg Q4W) was assessed for the proposed indication.

Table 7. Triptorelin in Vitro Studies Using Human Biomaterials

ADME	Objective	Study/Report
DDI potential	In Vitro Evaluation of the Possible Induction of CYP1A2 and CYP3A4/5 by Debio 8206 Using Fresh Human Hepatocytes	XT083051
	Determination of the IC50 Values and Time-dependent Inhibitory Properties of Debio 8206 for the Cytochrome P450 Isoenzymes 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A Using Human Liver Microsomes	XT083091
Transporter	Evaluation of Triptorelin as a Potential P-gp Substrate and Inhibitor Using a Caco-2 Cell Monolayer System	8DEBIP2R1

(Source – reviewer summary)

Table 8: Clinical studies

Study	Objective	Population	Formulation
301	Efficacy, Safety and PK	44 CPP subjects, 2-9 yrs old	22.5 mg , to-be marketed formulation

(Source: Reviewer summary)

Endpoint: In the phase 3 study 301, the pre-specified primary efficacy endpoint was percentage of children with LH suppression to prepubertal levels (serum LH ≤ 5 IU/L 30 minutes after leuprolide [leuprolide acetate 20 μg/kg SC] stimulation) at Month 6 (Day 169). Additional endpoints were also assessed, such as LH, FSH, estradiol (in girls) and testosterone (in boys) levels at Months 1, 2, 3, 6, 9, and 12 (Days 29, 57, 85, 169, 253, and 337).

For assessment of the primary and secondary endpoint in the pivotal study, please see the clinical review by Dr. Shannon Sullivan.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing is reasonable from a clinical pharmacology perspective. The exposure response for efficacy and safety supports the dosing recommendation:

Efficacy

The limited dataset from study Debio 8206-CPP-301 did not allow PK/PD modeling. The PK/PD relationship of triptorelin has been described in the literature (Tornoe et al, 2006). Chronic administration of triptorelin causes down regulation of the pituitary GnRH receptors and suppresses gonadotropin (LH and FSH) secretion and subsequently release of gonadal sex-hormones. Once the effect is achieved, the suppression is maintained even at very low triptorelin plasma concentrations. This is consistent with observations in Study 301 (Figure 7).

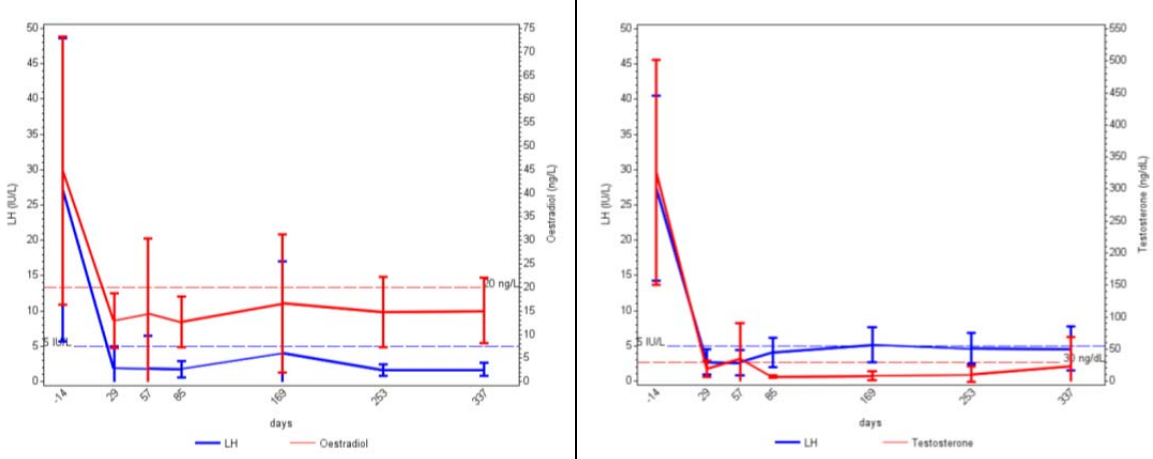

Figure 7. Mean levels of LH (stimulated, blue, reference line at 5 IU/L), estradiol (girls, panel A, red, reference line at 20 ng/L) and testosterone (boys, panel B, red, reference line at 30 ng/dL)

(Source: Figure 11.4-1, Figure 11.4-2, Study repot 301)

In the pivotal Phase 3 Study 301, all patients (n=44) had their triptorelin serum concentrations measured over the study period of 1-337 days. The relationship between LH serum levels and triptorelin serum concentrations at 6 month (Day 169) is shown in Figure 8. As shown in Figure 8, 41 out of the 44 patients achieved LH serum levels of ≤5 IU at Day 169.

The 3 non-responders appeared to have a lower exposure of triptorelin, based on the very limited data (Figure 8).

- Patient 2404, an 8-year-old girl with an LH of 83 IU/L at Month 6, encountered a technical problem with the 1st triptorelin injection. She had a successful 2nd injection at Month 6, and at Month 12 LH was suppressed to a prepubertal level (3.6 IU/L).
- Patient 0803, a 9-year-old boy had a borderline LH value of 5.1 IU/L at Month 6. At Month 12 his LH was suppressed to a prepubertal level (3.2 IU/L).
- Patient 0802, a 9-year-old overweight boy had a non-suppressed LH of 9.4 IU/L at Month 6. At Month 12 his LH was still 10.2 IU/L.

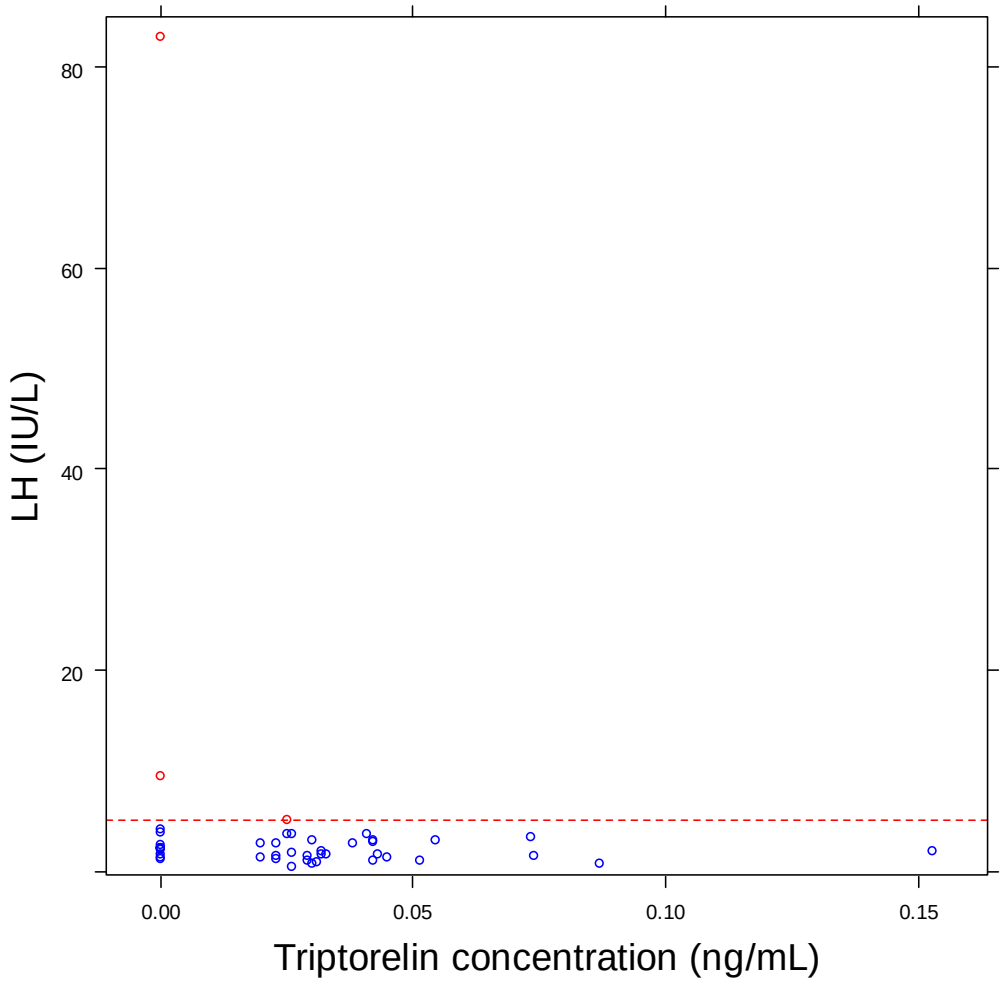

Figure 8. LH Serum Concentrations versus Triptorelin Serum Concentrations at Day 169 from Study 301. (Reference line: LH=5 IU/L, blue dots: responders, red dots: non-responders)

(Source: reviewer analysis)

Safety

Only one dose was assessed in the Phase 3 study, and no exposure-response analysis was done for safety due to the small number of patients (n=44) in the program.

Per sponsor, most treatment-emergent adverse events (TEAEs) were considered mild and moderate, as summarized in Table 9. See Dr. Shannon Sullivan's clinical review for detailed information on safety analysis.

Table 9: Treatment-Emergent Adverse Events in Study Debio 8206-CPP-301 Considered Related to Triptorelin

System Organ Class Preferred Term	Patients Experiencing Event*, n (%)			
	Total	Mild	Moderate	Severe
Any event	**4 (9.1%)**	**3 (6.8%)**	**1 (2.3%)**	-0-
General disorders & admin site conditions**	**1 (2.3%)**		-0-	-0-
Injection site pain	1 (2.3%)	1 (2.3)		
Reproductive system & breast disorders	**3 (6.8%)**	**2 (4.5%)**	**1 (2.3%)**	-0-
Menstrual disorder	1 (2.3%)	-0-	1 (2.3%)	
Vaginal hemorrhage	2 (4.5%)	2 (4.5%)	-0-	

(Source: Table 6, clinical overview)

Reviewer's comments:

During clinical development, only triptorelin 22.5 mg Q24W regimen was evaluated in the CPP patients. The sponsor planned to market only the 6-month triptorelin formulation for the treatment of central precocious puberty, and was not seeking approval of triptorelin 3-month or 1-month formulation for treatment of CPP. The division acknowledged this plan in the Special Protocol Agreement in 2011.

Phase 3 study showed that a single intramuscular injection of 22.5 mg triptorelin lowered serum LH levels to below 5 IU by 28 days post-injection, and the effect was maintained throughout the 6 months dosing interval (Figure 7). Therefore, the efficacy data supports the proposed dosing regimen. For assessment of the efficacy and safety in the pivotal study, please see clinical review by Dr. Shannon Sullivan.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

There is no dose adjustment for intrinsic factors.

Body Weight

The dosing for CPP patients was fixed dosing (22.5 mg Q24W) and not adjusted for body weight. When stratified by baseline bodyweight, the observed concentrations of triptorelin were comparable among different weight groups (Figure 9), and the proposed dosing regimen is reasonable.

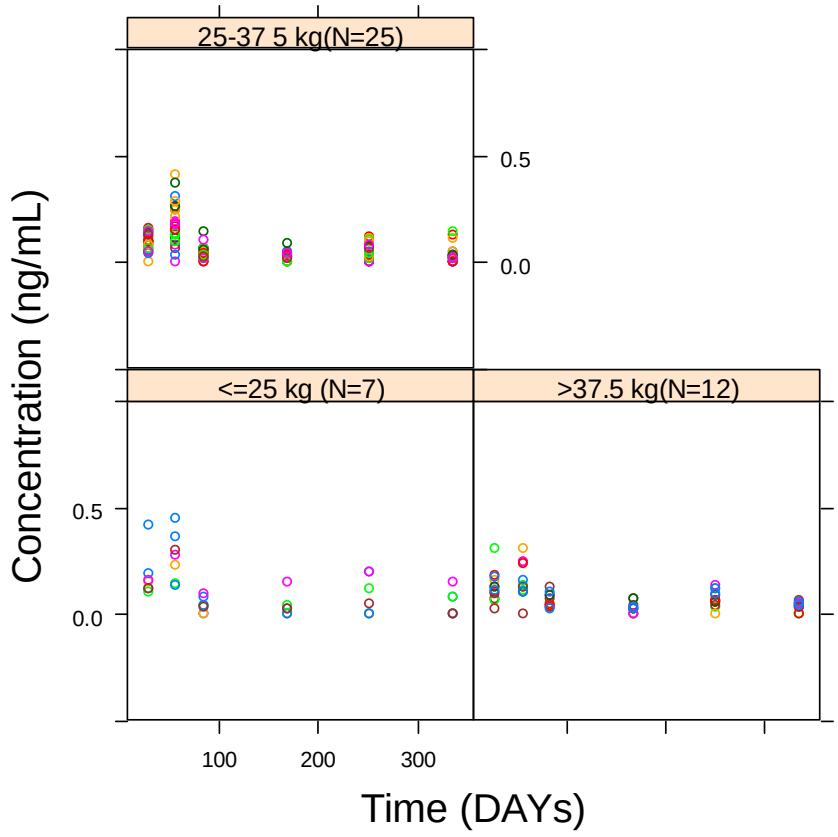

Figure 9. Triptorelin concentrations by bodyweight group in all subjects

(Source: reviewer analysis)

Age

The dosing for CPP patients 2-9 years of age was fixed dosing (22.5 mg Q24W) and not adjusted for age. The observed concentrations of triptorelin across the age range is shown in **Figure 10**. The results showed the observed triptorelin concentrations were comparable across age groups. While there are only two patients in the younger age group (2-5 yrs old), it appears that the PK of triptorelin in younger patients (2-5 yrs) is not significantly different from older patients (6-9 yrs) under the fixed dosing regimen and the proposed dosing regimen (22.5 mg Q24W) is reasonable.

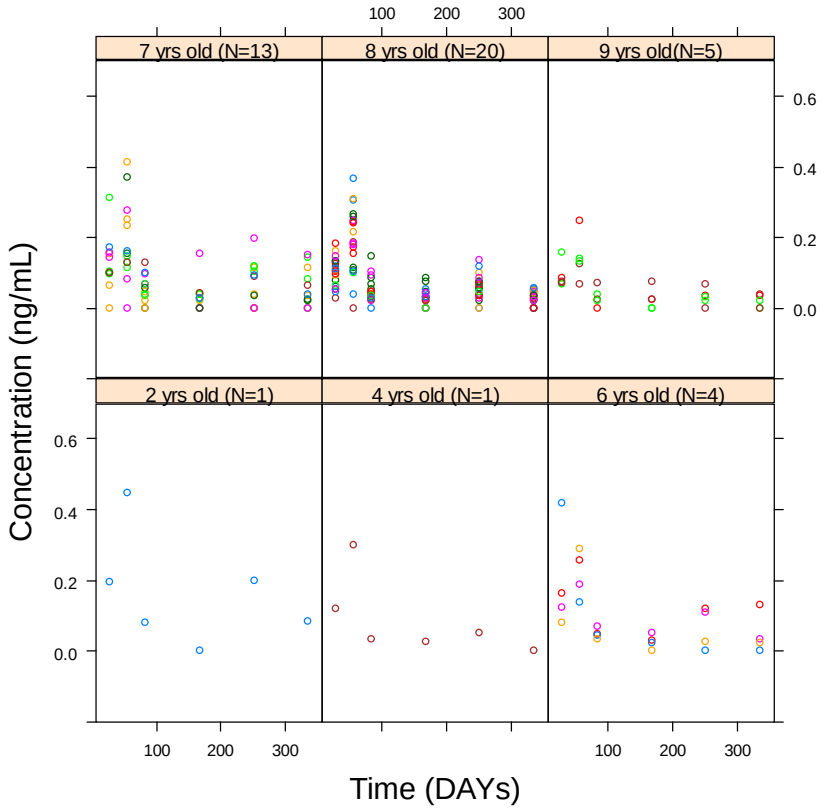

Figure 10. Triptorelin Concentrations by Age

(Source: reviewer analysis)

In patients 2-9 years old with CPP, triptorelin effectively suppressed pituitary release of LH and FSH, and consequently gonadal secretion of estradiol in girls and testosterone in boys. The effect of triptorelin is comparable across age groups (Figure 11), and supports the proposed fixed dosing regimen (22.5 mg Q24W).

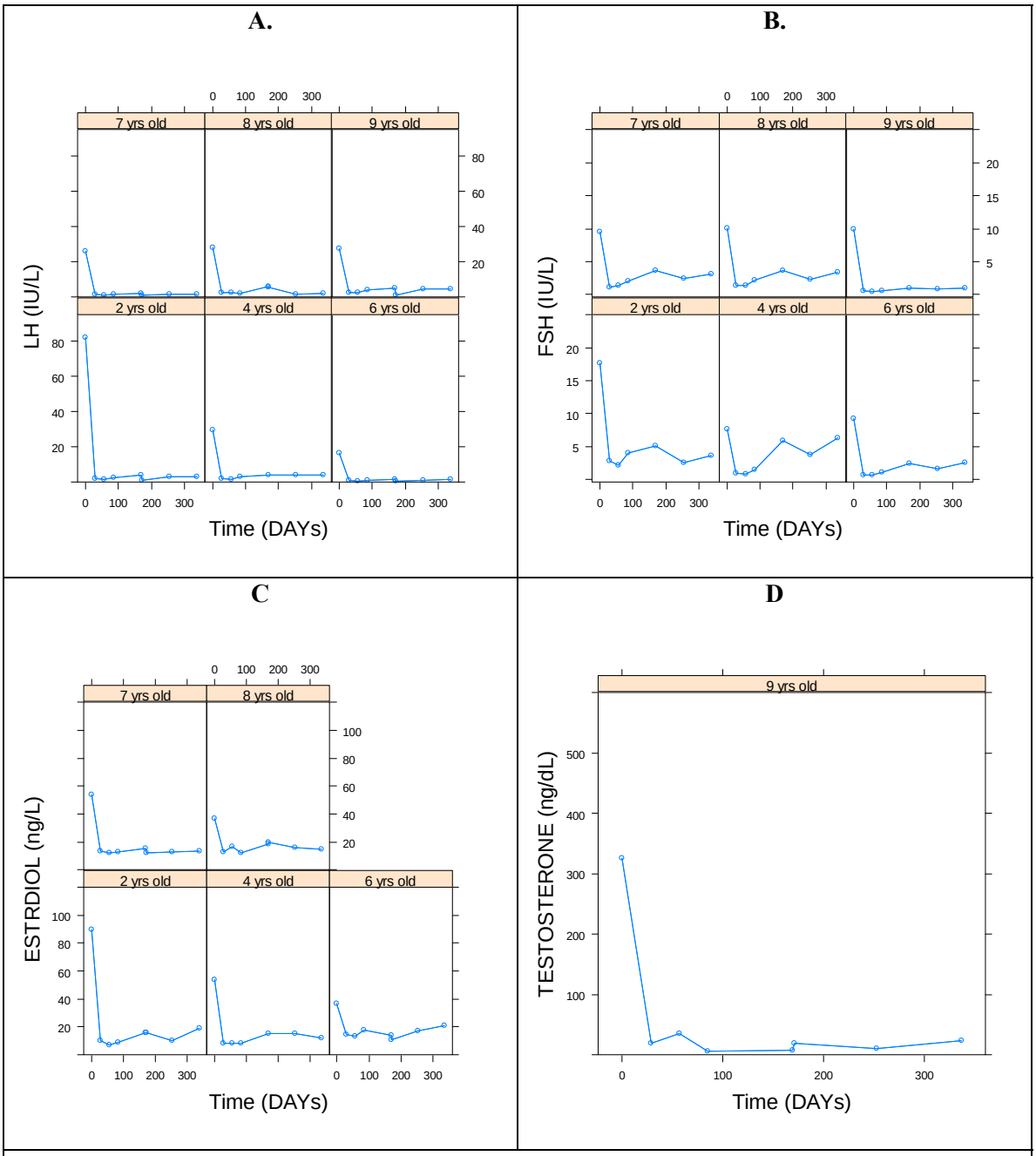

Figure 11. Mean levels of LH (stimulated, panel A), FSH (panel B), estradiol (girls, panel C) and testosterone (boys, panel D) by age

(Source: Reviewer analysis)

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

No. GnRH and/or GnRH peptide agonists are degraded by peptidases into inactive fragments and are not metabolized in liver microsomes, therefore it's unlikely that triptorelin PK would be affected by other drugs. The in vitro studies showed that drug-drug interactions with triptorelin as a perpetuator are unlikely.

In order to assess the risk of interaction of triptorelin in combination with other drug products, in vitro studies were performed to assess the effects of triptorelin on potential induction of CYPs 1A2 and 3A4/5 in human hepatocytes and on potential inhibition of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5 in human microsomes, as well as potential interactions with p-glycoprotein (P-gP). These studies were summarized in Table 10.

Table 10. Triptorelin in Vitro Studies Using Human Biomaterials

ADME	Conclusion	Study/Report
DDI potential	Treatment of primary cultures of human hepatocytes with triptorelin did not induce CYP1A2 or CYP3A4/5 activity levels	XT083051
	There was little or no evidence of direct inhibition of CYP enzymes with triptorelin therapeutic concentrations	XT083091
Transporter	• Since the calculated efflux ratio of triptorelin at 100 µM was less than 2, triptorelin seems to be a poor or non P-gp substrate according to the FDA draft guidance terms. • triptorelin (up to 8 µM) was not a P-gp inhibitor	8DEBIP2R1

(Source – reviewer summary)

Hyperprolactinemic drugs: hyperprolactinemic drugs should not be used concomitantly with triptorelin since hyperprolactinemia reduces the number of pituitary GnRH receptors.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

Serum samples from Study 301were first analyzed centrally by [redacted] (b) (4) (LOQ 0.05 ng/mL, [redacted] (b) (4) and 123 serum samples (not including the pre-dose baseline samples) had a concentration below the limit of quantification (LOQ) (0.05 ng/mL).

A total of 102 out of the 123 samples had a sufficient volume, were reanalyzed by Debiopharm International (LOQ 0.02 ng/mL, Switzerland) and showed detectable levels of triptorelin (i.e., ≥ 0.01 ng/mL). Of these, 90 samples were quantifiable with individual values ranging between

0.02 to 0.07 ng/mL. This more sensitive bioanalytical method was successfully cross-qualified with the above mentioned [redacted] method.

In the exploratory analysis of PK/PD, PK data from both assays were used in the analysis.

Precision and Accuracy

Primary Analytical method for triptorelin: CP115137, [redacted]

Serum samples were subjected to solid phase extraction using an Oasis MAX 96-well µ elution plate 30 µM (Waters), followed by gradient reverse phase liquid chromatography on an Equity UPLC BEH Shield RP18 column (Waters) with tandem mass spectrometric detection (positive electrospray ionization mode (ESI+), triptorelin test article transition mass over charge (m/z) 656.40 →877.50; 13C515N-triptorelin internal standard transition m/z 659.40 →883.50).

Table 11: Precision and accuracy for the assay

Calibration range (LLOQ to ULOQ)	50.0 to 5000 pg/mL (8 CS analysed in duplicate, weighting factor $1/x^2$)	
Assay volume	100 µL	
In-study assay performance	Mean determination coefficient (r^2)	0.999431
	Intra-run imprecision (as %CV)	LLOQ: <6% Other levels: <3%
	Intra-run inaccuracy (% Diff. of Mean)	LLOQ: Within ±6% Other levels: -8.86% to 2.00%
	Inter-run imprecision (as %CV)	LLOQ: <6% Other levels: <5%
	Inter-run inaccuracy (% Diff. of Mean)	LLOQ: Within ±2% Other levels: -3.71% to -1.33%
	Dilution factor	1/10
	Analyte recovery	69.50% to 72.42%
	Internal standard recovery	72.25%

(Source: summary table, study report CP115137)

Analytical method for triptorelin reassay: Debiopharm International

For 102 samples with sufficient retained serum volume, triptorelin levels were re-tested by Debiopharm International [redacted] (Lausanne, Switzerland) using a more sensitive LC-MS/MS method with a LOQ of 20 pg/mL (Debiopharm Reports REP-DEBIO8206-002 (Study REP-DEBIO8206-003; section 5.3.3.2)). Serum samples were thawed, homogenized, and centrifuged at 3500 rpm for 5 min at 4ºC. Eluates were subjected to solid phase extraction using an Oasis MAX 96-well µ elution plate 30 µM (Waters), followed by gradient reverse phase liquid chromatography on an Equity UPLC BEH Shield RP18 column (Waters) with tandem mass spectrometric detection (ESI+, triptorelin test article transition m/z 656.5 → 249.1; [13C615N]Leu7-triptorelin internal standard transition m/z 660.0 →249.1).

Table 12: Precision and accuracy for the assay

Analyte	LLOQ (pg/mL)	ULOQ (pg/mL)	Between-run %CV At LLOQ level	QCLOW,MID, HIGH Between-run %CV	|Mean % Deviation| at the LLOQ level	|Mean % Deviation| for QCLOW,MID, HIGH from Nominal Concentration
Debio 8206	20.0	1000	8.8	≤ 7.2	13.9	≤10.1

(Source – page 11, analytical report debio8206-003)

Cross-qualification: Comparison of results for 89 samples with triptorelin concentration above the LOQ at [redacted] (b) (4) (primary LC-MS/MS method) and re-tested by Debiopharm International (re-test LC-MS/MS method) showed that for 84% of samples, re-test results were within ±25% of the initial test result.

Selectivity

The selectivity of both methods was evaluated by extracting and analyzing blank human plasma from 6 individual sources. All lots were free from significant interfering peaks in the drug and internal standard regions. No peak in the blank extracts at the retention time of the analyte or internal standard (and in the relevant mass channel) interfered with the analyte and the internal standard by more than 25% of the mean analyte area ratio.

Stability

Analytical method for triptorelin: [redacted] (b) (4)

Triptorelin was stable in human serum stored frozen (At -24 ± 6ºC, or -75 ± 10ºC,) for up to 402 days. Triptorelin was stable in human serum to storage at room temperature for up to 18 hours, and was stable for at least 3 freeze-thaw cycles. Human serum sample extracts in injection solvent containing triptorelin were stable at nominal 10 °C for up to 80 hours in the autosampler. Stock solution stability was also assessed for 24 hours at room temperature and 74 days at -24°C.

Analytical method for triptorelin: Debiopharm International

Stability of triptorelin in human serum to three successive freeze-thaw cycles was determined at two concentrations (20 and 750 pg/mL) at -70°C. Mean method imprecision (CV%) was 5.2% at 20 pg/mL and 2.5% at 750 pg/mL and mean inaccuracy was 19.6% at 20 pg/mL and 8.5% at 750 pg/mL.

4.2 Summary of the pivotal study

Study Synopsis: Study 301

Study Title: An open-label, non-comparative, multicenter study on the efficacy, safety, and pharmacokinetics of triptorelin pamoate (embonate) 22.5 mg 6-month formulation in patients suffering from central (gonadotropin-dependent) precocious puberty	
Location	18 centers in USA, Mexico, and Chile
Study Dates	09.08.2012 (signature ICF 1st patient enrolled)- 14.07.2014 (Last patient out)
Study Design	International, multicenter, non-randomized, open-label, non-comparative Phase III study of two IM injections of triptorelin pamoate (embonate) 22.5 mg 6-month formulation in 44 children with CPP (minimum of 4 boys).
Population Demographics	Of the 44 patients: • The mean age was 7.4 years (range: 2 to 9 years). • Mean height was 134.8 cm (range 103.0 to 155.0 cm) • Mean weight was 32.8 kg (range 15.3 to 54.0kg) and mean BMI was 17.8 (range 11.8 to 23.8 kg/m2). • The majority of patients were white (59.1 %), and 88.6% of patients were girls.

Study Title: An open-label, non-comparative, multicenter study on the efficacy, safety, and pharmacokinetics of triptorelin pamoate (embonate) 22.5 mg 6-month formulation in patients suffering from central (gonadotropin-dependent) precocious puberty	
Inclusion criteria	Children with CPP were included into this study. The main inclusion criteria were the following: 1. Onset of development of sex characteristics before 8 and 9 years in girls and boys, respectively (breast development in girls or testicular enlargement in boys according to the Tanner method), and candidate to receive at least 12 months of leuprolide therapy after study entry. 2. Aged 2-8 years inclusive (ie, < 9 years) for girls and 2-9 years inclusive (ie, < 10 years) for boys at initiation of triptorelin treatment. 3. Initiation of triptorelin treatment at the latest 18 months after onset of the first signs of precocious puberty. 4. Difference (Δ) bone age (Greulich and Pyle method) – chronological age ≥ 1 year. 5. Pubertal-type LH response 30 minutes following a leuprolide stimulation test before treatment initiation (leuprolide acetate 20 μg/kg SC) ≥ 6 IU/L. 6. Clinical evidence of puberty, defined as Tanner Staging ≥ 2 for breast development for girls and testicular volume ≥ 4 mL (cc) for boys.
Treatment (per arm)	• Treatment arm: The treatment period lasted approximately 12 months (337 days). Two IM injections of triptorelin embonate 22.5 mg 6-month formulation were administered, one on study Day 1 and one on study Day 169. The final laboratory safety assessment was conducted on Day 337. • There is no placebo arm
Primary Endpoints	To evaluate the efficacy of triptorelin pamoate (embonate) 22.5 mg 6-month formulation IM in achieving LH suppression to prepubertal levels (defined as serum LH ≤ 5 IU/L 30 minutes after SC leuprolide stimulation [leuprolide acetate 20 μg/kg SC]) at Month 6 (Day 169) in children with CPP.
Efficacy results	• Per sponsor, the study met the primary endpoint with a percentage of responders at Month 6 of 93.2% and a lower limit of the 95% CI of 81.3% (ITT). The null hypothesis, that the proportion of responders would be ≤ 80%, was rejected. • See medical review by Dr. Shannon Sullivan for efficacy and safety assessment

Study Title: An open-label, non-comparative, multicenter study on the efficacy, safety, and pharmacokinetics of triptorelin pamoate (embonate) 22.5 mg 6-month formulation in patients suffering from central (gonadotropin-dependent) precocious puberty	
Safety Data	See medical review by Dr. Shannon Sullivan for efficacy and safety assessment.

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/s/

JIANMENG CHEN
05/25/2017

JAYABHARATHI VAIDYANATHAN
05/25/2017

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	208956	**SDN**	1
Applicant	Arbor	**Submission Date**	8/29//2016
Generic Name	Triptorelin pamoate	**Brand Name**	Triptodur
Drug Class	GnRH agonist		
Indication	Central precocious puberty		
Dosage Regimen	22.5 mg q24W		
Dosage Form	Lyophilized powder	**Route of Administration**	IM
OCP Division	DCP II	**OND Division**	DMEP
OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**	
Division	Jianmeng Chen, M.D, Ph.D	Jayabharathi Vaidyanathan, Ph.D	
Pharmacometrics			
Genomics			
Review Classification	☑ Standard ☐ Priority ☐ Expedited		
Filing Date	10/28/2016	**74-Day Letter Date**	11/10/2016
Review Due Date	5/25/2017	**PDUFA Goal Date**	6/29/2017

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

Is there a need for clinical trial(s) inspection?

☐ Yes

☑ No

Clinical Pharmacology Package

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies

Study Type	Count	Comment(s)
In Vitro Studies		
☐ Metabolism Characterization		
☑ Transporter Characterization	1	8DEBIP2RI, p-gp
☐ Distribution		
☑ Drug-Drug Interaction	2	XT083051, XT083091
In Vivo Studies		
Biopharmaceutics		

☐ Absolute Bioavailability			
☐ Relative Bioavailability			
☐ Bioequivalence			
☐ Food Effect			
☐ Other			
Human Pharmacokinetics			
Healthy Subjects	☐ Single Dose		
	☐ Multiple Dose		
Patients	☐ Single Dose		
	☑ Multiple Dose	1	PK information collected for study 301
☐ Mass Balance Study			
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☐ Race			
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☐ Hepatic Impairment			
☐ Renal Impairment			
☐ Genetics			
Extrinsic Factors			
☐ Effects on Primary Drug			
☐ Effects of Primary Drug			
Pharmacodynamics			
☐ Healthy Subjects			
☑ Patients			
Pharmacokinetics/Pharmacodynamics			
☐ Healthy Subjects			
☐ Patients			
☐ QT			
Pharmacometrics			
☐ Population Pharmacokinetics			
☐ Exposure-Efficacy			
☐ Exposure-Safety			

Total Number of Studies and reports	**In Vitro**	3	**In Vivo**	1
Total Number of Studies/reports to be Reviewed		3		1

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☐Yes ☐No ☑N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	The formulation was approved for treatment of prostate cancer in 2010 under NDA #22-437 (Trelstar® 22.5 mg, Actavis Pharmaceuticals). A statement of cross-reference to NDA #22-437 is provided in this 505(b)(1) submission.
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for	☑Yes ☐No ☐N/A	

not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☐Yes ☐No ☑N/A	There is no dose ranging study in this program.
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☐Yes ☐No ☑N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☐Yes ☐No ☑N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☑No ☐N/A	

Filing Memo

Submission in brief:

Indication and mechanism of action

Arbor Pharmaceuticals has submitted the NDA 208956 seeking the marketing approval for triptorelin pamoate, to be used as "the treatment of children with central precocious puberty" in children 2 years old and above.

Triptorelin is a gonadotropin releasing hormone (GnRH) receptor agonist. Recommended dose is 22.5 mg administered as a single intramuscular injection once every 24 weeks.

Formulation

Triptorelin for [redacted] Suspension 22.5 mg is a sustained release formulation of triptorelin pamoate. This formulation was approved for treatment of advanced prostate cancer in 2010 under NDA #22-437 (Trelstar® 22.5 mg, Actavis Pharmaceuticals). A statement of cross-reference to NDA #22-437 is provided in the submission.

Summary of information submitted

This supplements contain the following clinical pharmacology information:

1. Three in vitro drug-drug interaction studies (XT085091, XT083051, 8DEBIP2R1)
2. Triptorelin pharmacokinetics following administration of Triptorelin for [redacted] Suspension 22.5 mg in children with CPP was assessed in the single pivotal study, Debio 8206-CPP-301.

Mid-Cycle Deliverables

Following are the Mid-Cycle Deliverables:

1. Any approvability issues
2. Drug-drug Interaction and Extrinsic/Intrinsic Factors (age, weight)
3. Labeling

Filing slides are attached below:

Background information

1. **MOA: GnRH receptor agonist**
2. **Indicated for treatment of children (≥2yrs) with central precocious puberty (CPP)**
3. **505(b)(1)**
   - Referring NDA20715 (3.75 mg q4W), NDA21288 (11.25 mg q12W), NDA 022437 (22.5 mg q24W, advanced prostate cancer)
4. **Dosage & Administration**
   - 22.5 mg every 24 weeks IM for children ≥2, same as dose approved for prostate cancer in adults
     - Triptorelin 11.25 mg q12W by Ipsen approved in EU for CPP
     - Literature, standard dose of triptorelin in children with CPP regardless of weight
5. **Clinical pharmacology**
   - Study 301: Intensive PK (n=8); Sparse PK (n=44)
   - No Pop-PK report, PK/PD analysis not conducted

Clin Pharm Submission

- No filing issues identified
  - In vitro DDI (no DDI potential)
  - Intensive/sparse PK collected in study 301
  - PK dataset submitted
  - Label cross reference to TRELSTAR (NDA22437)
- Key review question:
  - Labeling
  - Does age impact the PK and PD of treptorelin?

PK summary (study 301*)

- Absorption*: Tmax ~4h; Cmax ~40 ng/mL, no accumulation
- Distribution: Vdss ~30-33 L
- Elimination: both liver & kidney; IV Half life ~6 min, 45 min, 3 hour (3 compartment elimination)
- Specific population: Exposure ↑ 2-4 fold with renal/hepatic impairment, no dose adjustment
- DDI unlikely

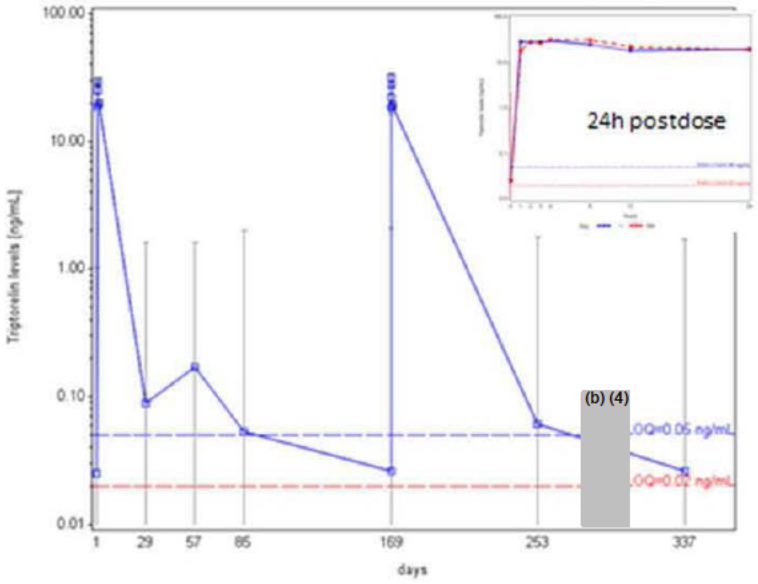
4

Study 301

- Open label, 48 week study
- Triptorelin pamoate 22.5 mg 6-month formulation (one vial) was administered by IM injection on study Day 1 and on study Day 169 at the study center.

5

Intensive PK (n=8, 6-8 yrs)



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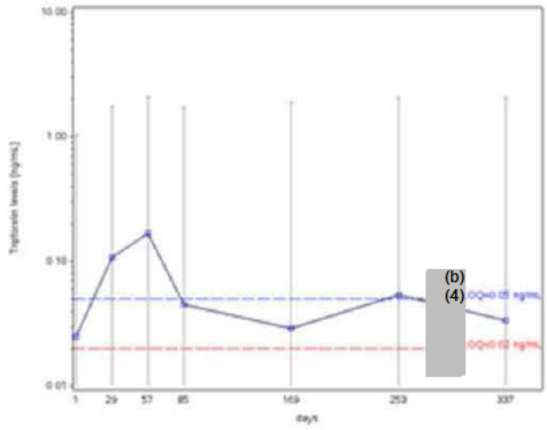
Sparse PK collected in 44 pediatric patients

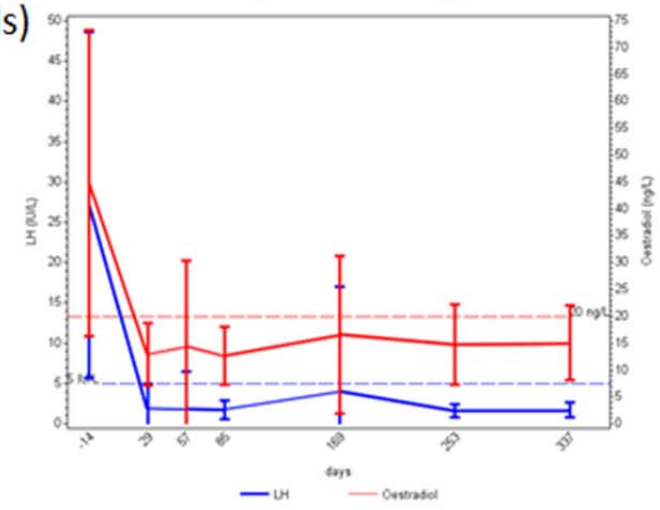
- PK datasets: children 2-9 yrs old
- Large variability; number close to LOQ



7

Pharmacodynamics

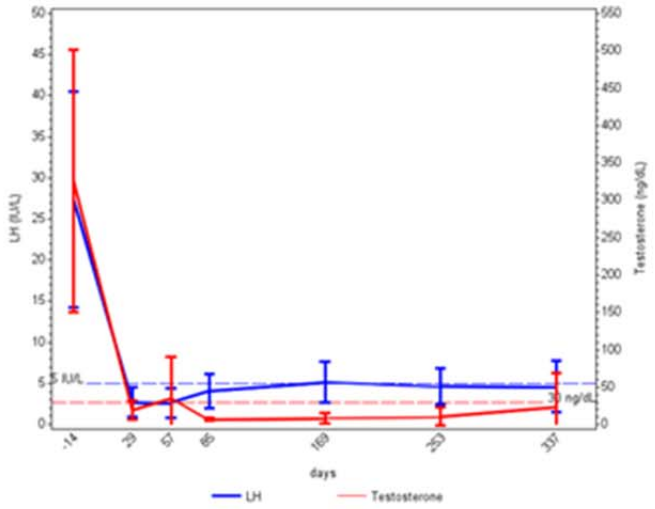
- Mean levels of LH (stimulated) and estradiol (girls)



8

Pharmacodynamics

- Mean levels of LH (stimulated) and testosterone (boys)



9

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/s/

JIANMENG CHEN
10/25/2016

JAYABHARATHI VAIDYANATHAN
10/25/2016