CLINICAL REVIEW

Application Type	505 (b) (2)
Application Number(s)	NDA 213150
Priority or Standard	Standard
Submit Date(s)	July 2, 2019
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Division/Office	DGE/ODEII/OND
Reviewer Name(s)	William Lubas MD PhD
Review Completion Date	April 2, 2020
Established/Proper Name	Leuprolide acetate
(Proposed) Trade Name	Fensolvi
Applicant	Tolmar Inc.
Dosage Form(s)	Injectable suspension for subcutaneous use
Applicant Proposed Dosing Regimen(s)	45 mg is administrated subcutaneously every 6 months
Applicant Proposed Indication(s)/Population(s)	Treatment of pediatric patients 2 years of age and older with central precocious puberty
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Pediatric patients 2 years of age and older with central precocious puberty

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BA:CA	difference in bone age relative to chronological age
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
CPP	central precocious puberty
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
GCP	good clinical practice
GnRH	gonadotropin releasing hormone
GnRHa	gonadotropin releasing hormone agonist
GRMP	good review management practice
HPG axis	hypothalamic pituitary gonadal axis
ICH	International Council for Harmonization
IND	Investigational New Drug Application
IRB/IEC	Institutional Review Board/Independent Ethics Committee
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 or package insert
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	testosterone
TEAE	treatment emergent adverse event
TSI	tracked safety issue

1. Executive Summary

1.1. Product Introduction

Tolmar, Inc has submitted this 505(b)(2) new drug application for Fensolvi (leuprolide acetate) seeking an indication for treatment of pediatric patients 2 years of age and older with central precocious puberty. Fensolvi is an injectable suspension of a synthetic nonapeptide of naturally occurring gonadotropin releasing hormone that, when given continuously, inhibits pituitary gonadotropin secretion and suppresses testicular and ovarian steroidogenesis. Fensolvi is to be administered as a 45mg single subcutaneous injection once every six months. It consists of two syringes that are mixed together prior to administration to produce a homogenous reconstituted drug product. The product is identical to Tolmar's Eligard (leuprolide acetate) 45mg injectable suspension approved for the palliative treatment of advance prostate cancer, except for the indication and labeling.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The submitted data provide substantial evidence to support the efficacy of Fensolvi 45 mg single subcutaneous injection every six months for the treatment of central precocious puberty in children. In the pivotal open-label, 48-week trial, treatment with Fensolvi 45 mg every 24 weeks decreased LH to pre-pubertal levels in 87% of children with CPP at 24 weeks and 86% of children at 48 weeks. Consistent with suppression in LH, estradiol levels were decreased to prepubertal levels in 98% and 100% of girls at 24 and 48 weeks, respectively, and testosterone was decreased to prepubertal levels in the two boys in the study at 24 weeks, although one boy had an increase in testosterone to just above the prepubertal level at week 48. In addition, growth velocity, which is accelerated in CPP, was consistently decreased from baseline at both 24 and 48 weeks and there was limited maturation as measured by Tanner staging in both girls and boys.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Fensolvi 45 mg subcutaneous injection is a long-acting GnRH agonist that is approved under the trade name Eligard (NDA 21731) for palliative treatment of advanced prostate cancer and is currently being developed for the treatment of children with central precocious puberty (CPP). CPP is a rare disorder affecting approximately 1 in every 5,000 to 10,000 children, with an estimated ratio of up to 23:1 in girls vs. boys. CPP is characterized by early onset of pubertal development, in girls ages under 8 years and boys ages under 9 years. CPP is diagnosed by measuring GnRH agonist-stimulated luteinizing hormone (LH) levels to determine if they are in the pubertal range. Measurement of GnRH agonist-stimulated LH levels is also used during treatment to monitor a child's response to therapy. Early puberty often causes extreme psychological distress and social isolation for patients as they undergo physical body changes well ahead of their peers in school. CPP also promotes bone age advancement, which initially makes the children appear taller than their peers but eventually leads to early closure of epiphyseal plates in their long bones and diminished final adult height if not treated. GnRH agonist therapy reversibly suppresses the hypothalamic-pituitary-gonadal (HPG) axis, resulting in reversible suppression of pubertal development and slowing of bone age advancement and is considered the gold standard of care for children with CPP. Currently, there are four GnRH agonist formulations approved for CPP in the U.S.: Lupron Depot-Ped (leuprolide, NDA 20263)), Supprelin (histrelin, NDA 22058), Synarel (nafarelin, (b) (4)) and Triptodur (triptorelin pamoate for depot suspension, NDA 208956).

The applicant has demonstrated the safety and efficacy of Fensolvi 45mg subcutaneous injection in a single pivotal study TOL2581A- an open label, single arm, 48-week study of 64 children with CPP treated with Fensolvi every 24 weeks.

In the primary analysis, 87% of patients achieved pre-pubertal levels of GnRH-stimulated LH (< 4 IU/L) at 24 weeks, and a similar level of LH suppression (86%) was also seen at 48 weeks. Secondary efficacy endpoints supported the primary endpoint findings. Consistent with suppression of LH, estradiol levels were decreased to prepubertal levels in 98% and 100% of girls at 24 and 48 weeks, respectively, and testosterone was decreased to prepubertal levels in the two boys in the study at 24 weeks, although one boy had an increase in testosterone to just above the prepubertal level at week 48. In addition, growth velocity, which is accelerated in CPP, was consistently decreased from baseline at both 24 and 48 weeks and there was limited further pubertal maturation as measured by Tanner staging in both girls and boys. The efficacy of Fensolvi in the treatment of CPP was similar to that of the other marketed GnRH agonists currently approved for the CPP indication.

Data from the single pivotal study TOL2581A also provide substantial evidence supporting the safety of Fensolvi 45 mg subcutaneous injection with 24-week dosing in the treatment of children with CPP. Administration of Fensolvi was well tolerated, and the safety risks of this formulation were comparable to other approved sustained-release GnRH agonist formulations. The most common adverse reactions were

related to injection site reactions including (30%) injection site pain, (9%) erythema, (3%) bruising, (3%) induration, (2%) nodule, and (2%) swelling. After the second injection, up to 8% of patients experienced acute-on-chronic (AOC) effect, a transient stimulation of the HPG axis in the setting of chronic suppression. This consisted of adverse reactions including (n=2) hot flushes, (n=1) nausea, (n=1) headache, and (n=1) fatigue observed during the two weeks following the second dose. The AOC effect is expected with the use of sustained-release GnRH agonists 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 leuprolide and other sustained-release GnRH agonists has identified additional potential adverse reactions, such as hypersensitivity reactions including anaphylaxis, seizures/convulsions and emotional lability/suicidal ideation. There were two cases of rash, and one case each of urticaria and hypersensitivity in the safety population but no cases of anaphylaxis. There was no evidence of seizures/convulsions in the Nervous System Disorder SOC, but patients with a history of seizure disorder or taking medications associated with seizures were excluded from the trial, so it is not possible to assess whether there could be an effect on seizure threshold. There were three adverse events in the Psychiatric Disorders SOC including irritability, emotional disorder and insomnia (each in one patient), but there was no evidence for suicidal ideation. These potential adverse reactions can be adequately addressed in labeling.

In conclusion, the safety and efficacy data from the single pivotal open-label phase 3 trial conducted to support approval of Fensolvi 45 mg subcutaneous injection for the treatment of CPP demonstrate that the benefits of Fensolvi outweigh the potential risks. Further, the safety and efficacy profile are similar to that of the other GnRH agonist formulations previously approved for treatment of CPP (Lupron Depot-PEDS, Supprelin, Synarel and Triptodur).

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Central precocious puberty (CPP) is a rare disorder affecting approximately 1 in every 5,000 to 10,000 children, with an estimated ratio of up to 23:1 in girls vs. boys. • CPP is characterized by early onset of pubertal development, in girls ages under 8 years and boys ages under 9 years.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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: 1) Lupron Depot-Ped (leuprolide acetate for depot suspension, NDA 20263), 2) Supprelin LA subcutaneous implant (histrelin acetate, NDA 22058), 3) Synarel nasal spray (nafarelin acetate, NDA 020109) and 4) Triptodur (triptorelin pamoate for depot suspension, NDA 208956)	
• Benefit	• 87% of patients achieved pre-pubertal levels of GnRH-stimulated LH (< 4 IU/L) at 24 weeks, the primary efficacy endpoint, and a similar level of LH suppression (86%) was also seen at 48 weeks. • At 24 weeks, 98% of girls and 100% of boys achieved pre-pubertal gonadal hormone levels, and at 48 weeks, 100% of girls and 50% of boys achieved pre-pubertal gonadal hormone levels.	The study protocol and endpoints were agreed to in meetings between the Applicant and the Agency.
Risk and Risk Management	• The most common adverse reactions were related to injection site reactions including (30%) injection site pain, (9%) erythema, (3%) bruising, (3%) induration, (2%) nodule and (2%) swelling, which can be expected from subcutaneous injection. • Labeling will be used to mitigate the risks associated with Fensolvi use. • No risks identified require risk management beyond labeling to warrant consideration of a REMS.	The risk of Fensolvi 45 mg 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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		Safety information will be adequately relayed to patients and providers in product labeling. No REMS will be required.

2. Therapeutic Context

2.1. Analysis of Condition

Central precocious puberty results from premature activation of the hypothalamic-pituitary gonadal (HPG) axis. Central precocious puberty is an orphan disease with an estimated prevalence of 1 in 5,000-10,000 children, girls age under 8 years and boys age under 9 years. Girls are much more commonly affected with estimates of up to 23:1 vs. boys [1].

Early onset of puberty has significant psychosocial and long-term health implications. Girls enter menarche early and show signs of early breast development, and while children appear to grow faster than their peers early on, they eventually end up shorter than their predicted height due to premature bone maturation and earlier closure of their epiphyseal plates.

Treatment involves tonic activation of the HPG axis with gonadotropin releasing hormone (GnRH) agonists, which initially may appear to accelerate puberty over the first few weeks, but eventually down-regulate receptors, suppressing the pulsatile GnRH signal needed for continued gonadal hormone production [2, 3].

2.2. Analysis of Current Treatment Options

There are currently 4 approved and marketed newer GnRH agonist treatments in the US that have replaced the earlier daily subcutaneous injections of triptorelin, leuprorelin, buserelin and deslorelin. These include a nasal formulation for daily administration (Synarel [4]), intramuscular injections approved for use at 1, 3 and 6-month intervals (Lupron Depot-Ped [5], Triptodur [6]) and a subcutaneous implant for 12-month administration (Supprelin LA [7]).

- SYNAREL® (nafarelin acetate) nasal solution 2 mg/mL (daily administration)
  - Mean GnRHa-stimulated LH was reduced from 78-113 mIU/mL pre-treatment to 7-11 mIU/mL post-treatment (100% suppressed at 12 months)
  - Mean E2 decreased from 27-72 pg/mL pre-treatment to 8-9 pg/mL post-treatment
  - Mean T decreased from 295-339 ng/dL pre-treatment to 14-34 ng/dL post-treatment

- LUPRON DEPOT-PED® (leuprolide acetate for depot suspension) intramuscular injection 7.5 mg, 11.25 mg, 15 mg (1-month administration); 11.25 mg and 30 mg (3-month administration)
  - LH suppression at week 8-24: 78-96%
  - % girls with pre-pubertal E2 at weeks 4-24: 93-100%
  - % boys with pre-pubertal T at weeks 4-24: 67-100%

- Tanner stage decreased or stabilized at 24 weeks:
  - Girls—67-91%
  - Boys—40-100%
- BA:CA stable or decreased at 24 weeks: 75-90%

• TRIPTODUR® (triptorelin) for extended release injectable suspension, intramuscular injection 22.5 mg (6-month administration)

- LH suppression at 1 to 12 months: 93-98%
- % girls with pre-pubertal E2 at months 1 to 12: 79-92%
- % boys with pre-pubertal T at months 1 to 12: 80-100%
- Tanner stage decreased or stabilized at months 6 to 12:
  - Girls—69-77%
  - Boys—100%
- BA:CA stable or decreased at months 6 to 12: 64-95%

• SUPPRELIN LA® (histrelin acetate) subcutaneous implant 50 mg (12-month administration)

- LH suppression at week 4-52: 100%
- % girls with pre-pubertal E2 at week 4-36: 100%
- % boys with pre-pubertal T at week 4-52: 100%
- Tanner stage decreased or stabilized: not assessed
- ΔBA:CA in treatment naïve patients: -0.08±0.08
- ΔBA:CA in previously-treated patients: -0.09±0.06

Major safety concerns related to GnRH agonists as a class include injection site reactions, rare immune-allergic reactions/anaphylaxis, 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., vasomotor symptoms due to hypoestrogenism). Psychiatric and psychological symptoms, and convulsions also have been reported.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This product is identical to Tolmar's currently marketed ELIGARD injectable suspension for the palliative treatment of advanced prostate cancer. ELIGARD is available in doses of 7.5, 22.5, 30 and 45 mg that release the drug over 1, 3, 4, and 6 months, respectively. ELIGARD has been marketed for nearly 20 years in the US and is available in more than 92 other countries.

3.2. Summary of Presubmission/Submission Regulatory Activity

The applicant, Tolmar Inc, submitted a Pre-IND meeting request July 30, 2014. The Agency responded with a letter containing written responses to their questions dated September 29, 2014. Major points addressed in the letter include:

1) No further nonclinical studies were necessary prior to the proposed clinical trial.
2) The primary endpoint of LH suppression to less than 4 IU/L at 6 months after the first injection was considered acceptable for the pivotal phase 3 trial.
3) The secondary endpoints for the pivotal phase 3 trial were considered acceptable. The Agency also asked for an analysis of physical signs of puberty, height velocity and bone age relative to chronological age at 6 and 12 months.
4) The study was to be performed in treatment-naive patients.
5) The Agency asked the sponsor to characterize the initial burst in leuprolide concentrations and to explore the PK/PD relationship.
6) The clinical study should include "acute-on-chronic" symptom evaluation at the 6-month dose.

The clinical program was conducted under IND 123631, which was opened February 6, 2015. The clinical protocol for study 2581A was reviewed as part of the original IND submission and found to be acceptable with non-hold issues that were adequately addressed in protocol amendment 1. There was no special protocol agreement (SPA) for this application.

Tolmar, Inc submitted a Pre-NDA meeting package on December 12, 2018, and the Agency responded with written responses in a letter dated January 23, 2019. Major points addressed in the letter include:

1) Impairment of fertility information was understandably lacking in the current label for Eligard for the treatment of advanced prostate cancer, but it was felt that such information was pertinent to an adolescent CPP population and should be included in the drug label for a product with this indication.

While CPP is an orphan disease, and Lupron Depot-Ped has orphan drug designation for example, this applicant did not apply for orphan drug designation.

3.3. Foreign Regulatory Actions and Marketing History

Not applicable.

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

4.1. Office of Scientific Investigations (OSI)

The inspection for this new drug application consisted of two domestic clinical sites and one foreign clinical site. The inspections of two of the sites found regulatory deficiencies, but the findings were not considered significant. In general, based on the inspections of the three clinical sites, the inspectional findings support validity of the data reported by the applicant under this NDA.

4.2. Product Quality

Fensolvi is an injectable suspension that includes the GnRH agonist, leuprolide acetate, in a polymer matrix to permit slow continuous release over time. The same formulation is currently approved as the subcutaneous injectable, Eligard, indicated for the palliative treatment of adult men with advanced prostate cancer at the same dose, 45mg, and for the same dosing interval, every 6 months.

4.3. Clinical Microbiology

Refer to CMC review for complete details. The applicant revised the endotoxin specification to meet USP <85> recommendations for the pediatric population and provided details for the Non-Inhibitory Dilution and Maximum Valid Dilution associated with revised endotoxin limits, as requested by the Agency. Sterility was determined to be adequate.

4.4. Nonclinical Pharmacology/Toxicology

Refer to Nonclinical Pharmacology/Toxicology review for more details. No new nonclinical studies were submitted to support NDA 213150. The applicant is relying upon the Agency's findings of safety and effectiveness for Eligard (NDA 21731) and Lupron Depot-PED (NDA 20263) for the nonclinical information needed to support approval of Fensolvi.

4.5. Clinical Pharmacology

Refer to Clinical Pharmacology review for more details.

4.5.1 Mechanism of Action

Leuprolide acetate, a GnRH agonist, in a sustained release formulation acts as a potent inhibitor of gonadotropin secretion [e.g., luteinizing hormone (LH) and follicle stimulating hormone (FSH)]. Following initial stimulation of GnRH receptors, chronic administration of leuprolide acetate results in down-regulation of GnRH receptors and reduction in release of LH and FSH, resulting in suppression of gonadal sex steroid production (e.g., estradiol and testosterone). This effect is reversible upon discontinuation of drug therapy.

4.5.2 Pharmacodynamics

In study TOL2581A, following the first dose of leuprolide acetate injectable suspension, LH concentrations increased 12-fold from baseline at 4 hours and FSH increased 7-fold to a maximum at 6 hours. Sustained exposure to leuprolide from administration of leuprolide acetate injectable suspension reduced mean basal levels of LH and FSH at the first measurement at week 4 and for the rest of the 24-week treatment period. After a second injection at week 24, levels of LH and FSH remained suppressed out to week 48. Pharmacodynamic effects on the gonads resulted in temporary increases in estradiol and testosterone levels at approximately 6 hours after injection. Thereafter, mean basal estradiol levels fell rapidly by week 4 as serum leuprolide concentrations remained relatively constant through week 48. Testosterone levels in the two boys in study TOL2581A showed a similar profile, with a substantial reduction in mean basal levels through Week 48 (Table 1).

Table 1. Serum Concentrations of Leuprolide, LH, FSH, Estradiol and Testosterone

Time Point	Leuprolide (ng/mL)	Luteinizing hormone (IU/L)	Follicle-stimulating hormone (IU/L)	E2 (pmol/L)	E2(HS) (pmol/L)	Testosterone (nmol/L)[a]
Screening	-	1.84	4.10	107.0	102.3	4.15
Basal	BLQ[b]	3.44	3.91	104.5	92.5	9.90
Week 4	0.627	0.79	0.99	58.7	54.2	0.85
Week 12	0.353	0.60	1.44	43.7	38.9	0.55
Week 20	0.372	0.62	1.37	45.7	38.7	0.80
Week 24	0.309	0.51	1.14	43.3	36.9	0.65
Week 36	0.317	0.53	1.44	43.1	37.6	0.40
Week 44	0.411	0.56	1.43	43.1	40.2	0.40
Week 48 (end of treatment)	0.177	0.65	1.45	44.4	37.8	0.60

[a] n=2
[b] 0.0250 ng/mL is the lower limit of detection for this assay.
Abbreviations: BLQ, below the limit of quantitation E2=estradiol results from the chemiluminescent immunoassay, E2(HS)=estradiol results from the high-sensitivity assay,
Source: Table 14.4.1.1.2 and Table 14.4.2.1.2 in the CSR

Source: Table 1 applicant's Clinical Overview

4.5.3. Pharmacokinetics

Cmax was observed at a median of 4 hours post the first dose. The initial burst in leuprolide concentration (39.7day*ng/mL) over the first six hours after dosing represented only a small portion (1.5%) of the AUC over the next 24 weeks (2,719 day*ng/mL)(Table 2).

Table 2. PK Parameters for Leuprolide in Study TOL2581A

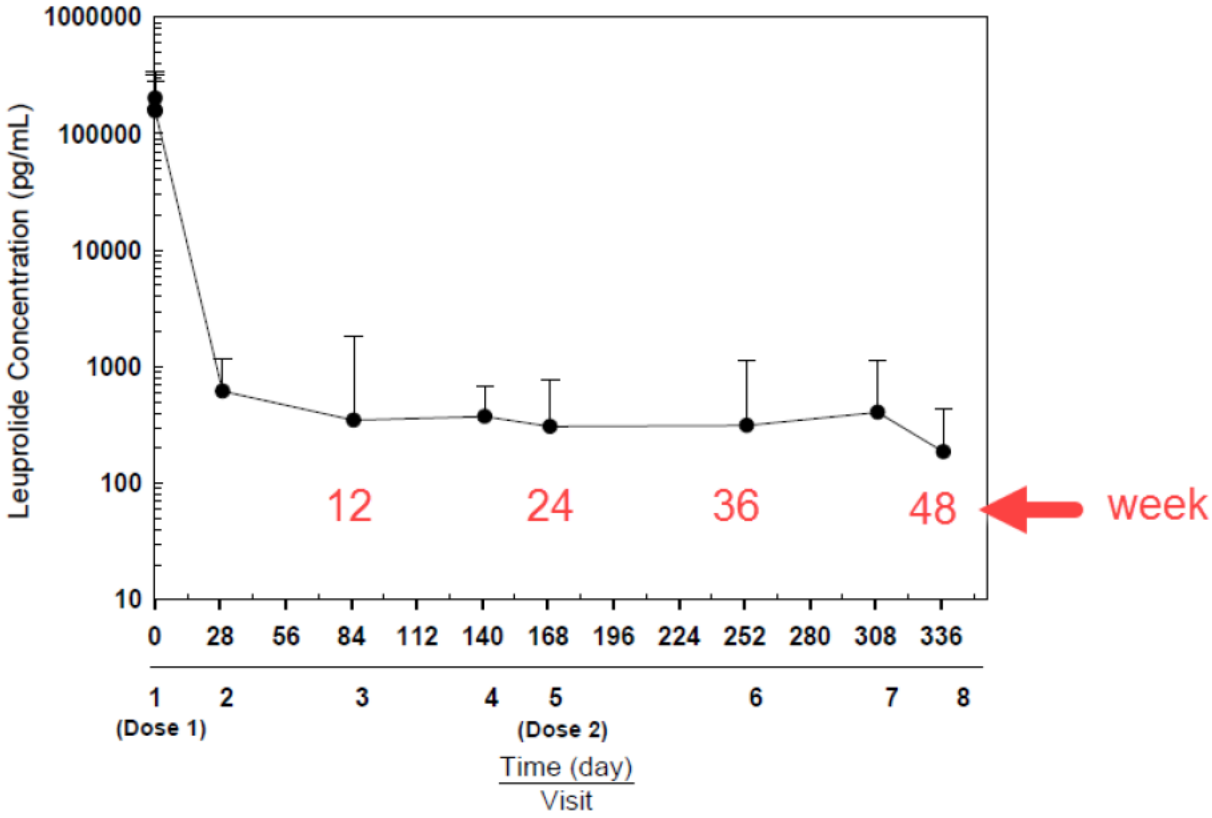
Leuprolide Mean (SD), n			
Parameter / **Time Frame**	**C_{max} (ng/mL)**	**T_{max}[d] (hr – Burst) (day – all other)**	**AUC (day•ng/mL)**
Injection 1[a]	215.739 (163.2432), 58	4.0 (1, 6), 58	
AUC 0-6 hr[a]			39.706 (29.5378), 58
AUC 0-169 days[b]			2719.541 (2601.8202), 59
AUC Day 7-6 mo[c]			1770.545 (2054.9172), 59
AUC 0_inf			2945.264 (1942.3468) 5

[a] During burst
[b] After the first dose
[c] Without burst (ie, Day 0 to Day 7)
[d] Median (min, max)
Abbreviations: AUC, area under the time-concentration curve; SD, standard deviation; hr, hour; mo, month; inf, infinity.
Data source: Table 14.4.2.2.2 in the CSR. Data converted to ng/mL.

Source: Table 2 Summary of Pharmacology Studies

Following the initial burst in leuprolide levels immediately after the injection on day 1, levels remained relatively constant from week 4 through 48 (see Figure 1). The 24-week time point measurement did not demonstrate the burst in levels expected immediately after injection due to sparse sampling to minimize blood draws.

Figure 1. Serum Leuprolide Concentrations after Subcutaneous Injection of 45mg Fensolvi by Study Day



The Week 12 time point for subject [redacted] (b) (6), and the Week 36 time point for subject [redacted] (b) (6) were excluded due to improbable concentration values.
Source: Table 14.4.2.1.2

Source: Fig. 2 Clinical Study Report for TOL2581A

4.6. Devices and Companion Diagnostic Issues

The combination product was reviewed by CDRH and found to be approvable with no further comments to be conveyed to the review team. See Shanly M. Chen's Consult review loaded into DARRTS by Jennifer Johnson 3/26/2020.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Study Number	Trial Design	Regimen/ schedule/route	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
TOL2581A	Open-label, single-arm, uncontrolled, unblinded, multi-center study	45 mg injected subcutaneously once every 6 months	12 months (2 treatment cycles)	64	Children with CPP (n=62 girls and 2 boys), ages 4-9 years	9 US 3 Chile 2 Canada 1 Argentina 1 Mexico 1 New Zealand

5.2. Review Strategy

This submission contains a single 12-month multicenter pivotal study, TOL2581A, performed at 25 sites across 6 countries, with about half of the patients from the US. Data from this pivotal study are the focus of the efficacy and safety review. The statistical reviewer was consulted in the efficacy analyses to perform a responder analysis for the primary and secondary endpoints. In general, however, the statistical and clinical reviewers performed separate analyses documented in their individual clinical reviews. The applicant was asked to reanalyze their data using a new ITT population after the statistical reviewer noted at the time of the filing meeting that subjects had been inappropriately excluded from the original efficacy analysis because they were discontinued from the study after only a single injection. The revised analysis was submitted to the NDA as supporting document number (SDN) 5. Both the statistical review and this medical review were able to confirm that the applicant's revised efficacy dataset supported the efficacy of the current product. This medical review focuses on JMP analyses performed by this reviewer using the datasets submitted by the applicant in the original submission (SDN1) and revised datasets submitted in the follow up submission (SDN5). The safety review included a review of the data from study TOL2851A as well as post-marketing data from other currently approved GnRH agonists, some of which also included the same active ingredient, leuprolide.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1.

Study TOL2581A: Open-label, Single Arm, Multicenter Study on the Efficacy, Safety, and Pharmacokinetics of Leuprolide Acetate 45 mg for Injectable Suspension Controlled Release in

6.1.1. Study Design

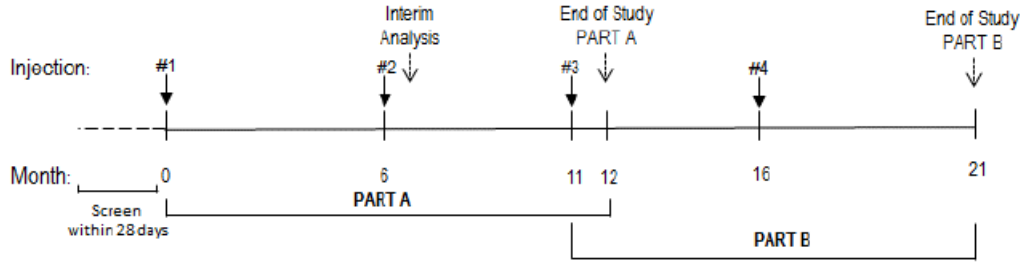
Overview and Objective

TOL2581A was designed to assess the safety, effectiveness and tolerability of leuprolide acetate 45 mg injectable suspension, in the treatment of children with central precocious puberty (CPP), with efficacy defined as suppression of post GnRHa-stimulated serum LH concentration to levels <4 IU/L at 6 months after injection.

Trial Design

TOL2581A was a multicenter, multinational, open-label, single-arm, 12-month study in children with central precocious puberty from the US (n=31), Argentina (n=13), Chile (n=9), Mexico (n=7) Canada (n=2), and New Zealand (n=2). The study incorporated an adaptive design protocol with a scheduled interim analysis after 16 subjects (40% of a planned 40 subjects) had completed their 6-month assessment to determine the dosing interval (5 or 6 months) at which leuprolide acetate was able to suppress LH concentration to <4 IU/L. As 14/16=88% of the subjects showed suppression at 6-months in Part A of the study, which was greater than the pre-specified 85% requirement, there was no need to invoke Part B of the study designed to look for efficacy at the shorter duration of treatment of 5-months in case efficacy at the 6-month measurement was inadequate. The Part B extension would have included two additional study drug injections and overall study extension to 21 months (Figure 2).

Figure 2. Study Design of the Pivotal Study TOL2851A



Subjects would only receive Injections #3 and #4 if Part B was conducted, based on Part A interim data.

Source: Fig. 1 Clinical Study Report

Medical officer's comment-The single-arm, open-label study was typical of studies in this clinical area, as it would be unethical to include a placebo group, and there was no need for a control group to demonstrate efficacy as individual CPP patients would not be expected to show LH suppression or a delay in progression of puberty without effective treatment. The primary diagnostic criterium, prepubertal-type LH response <4 IU/L following an abbreviated GnRH agonist stimulation test, used to identify patients with

CPP was appropriate, and similar to the cut-off point used for the approval of Supprelin LA and for Lupron Depot-Ped, although it was more conservative than the cut-off point of ≤5 IU/L used for the recent approval of Triptodur.

Inclusion Criteria-including but not limited to:

- Females 2 to 8 years of age or males 2 to 9 years of age
- Confirmed diagnosis of CPP within 12 months of Baseline Visit (Day 0) but without prior GnRH agonist treatment for CPP
- Pubertal-type LH response >5 IU/L following an abbreviated GnRHa stimulation test (CPP diagnostic criterion)
- Clinical evidence of puberty, Tanner stage ≥2 for breast development (females) or testicular volume ≥4 mL (males)
- Difference between bone age and chronological age of ≥ 1 year
- Signed assent by one or both parents, custodial parent or legal guardian and subjects as per IRB/IEC requirements

Exclusion Criteria-including but not limited to:

- Gonadotropin-independent (peripheral) precocious puberty: extra-pituitary secretion of gonadotropins or gonadotropin-independent gonadal or adrenal sex steroid secretion
- Prior or current GnRH treatment for CPP
- Non-progressing isolated premature thelarche
- Presence of an unstable intracranial tumor or an intracranial tumor requiring neurosurgery or cerebral irradiation. Subjects with hamartomas not requiring surgery were eligible.
- Any other condition, chronic illness or treatment that might have interfered with growth or other study endpoints (e.g., chronic steroid use, renal failure, diabetes, moderate to severe scoliosis, previously treated intracranial tumor)
- Prior or current therapy with medroxyprogesterone acetate, growth hormone or insulin-like growth factor-1 (IGF-1)
- Diagnosis of short stature (2.25 standard deviations below the mean height for age)
- Known history of seizures, epilepsy, and/or central nervous system disorders that may have been associated with seizures or convulsions
- Prior (within 6 months of Baseline (Day 0)) or current use of medications that have been associated with seizures or convulsions

The study drug was administered in a 45 mg extended-release formulation as a subcutaneous injection into the abdominal area. Each subject was to receive a total of two single doses of the study drug over the 12-month study period in Part A of the study. The two injections of the study drug were administered at 6-month intervals: one at Baseline (Day 0) and one at Visit 5, Week 24 (Month 6).

Medical officer's comment-The choice of study dose was appropriate as Eligard (leuproplide acetate) 45mg, which contains the same drug product as Fensolvi 45mg, is currently approved for every 6-month palliative treatment in adult patients with advanced prostate cancer. Slightly lower doses of 30mg of leuprolide acetate had previously been shown to be effective with once every 3-month dosing in children with CPP (Lupron Depot-Ped 2017 PI), and the study was designed to see if 5 or 6 months was the appropriate dosing interval for the 45mg dose in children with CPP.

The study was unblinded.

Medical officer's comment-Lack of study blinding is less likely to affect the primary endpoint, the abbreviated GnRHa stimulation test or the secondary endpoints of hormonal and systemic leuprolide concentrations as these involve objective clinical laboratory measurements. It is possible that unblinding bias could affect the secondary endpoints of growth velocity, bone age and Tanner staging, as they involve human measurements and interpretation of clinical data.

Subjects were considered to have completed the trial if they received both study injections at baseline and 6 months. Of the 64 study subjects who received at least one dose of drug, 60 (94%) were considered study completers.

Table 3. Schedule of Study Assessments for Study TOL2851A

Part A	Screening	Injection #1					Injection #2				End of Treatment	Unscheduled Visit (PI discretion)
Visit Number:		Visit 1	Telephone Contact 1	Visit 2	Visit 3	Visit 4	Visit 5	Telephone Contact 2	Visit 6	Visit 7	Visit 8	
Scheduled Day/Week	Within 28 days	Baseline (Day 0)	Week 2 ±2 days	Week 4 ±7 days	Week 12 ±7 days	Week 20 ±7 days	Week 24 ±7days	Week 26 ±2 days	Week 36 ±7 days	Week 44 ±7 days	Week 48 ±7 days	
Scheduled Month (approximate)		–		~Month 1	~Month 3	~Month 5	~Month 6		~Month 9	~Month 11	~Month 12	
Written Informed Consent / Assent [1]	X											
Inclusion/Exclusion Criteria Review	X	X										
Demographics	X											
Medical History	X											
Complete Physical Examination	X										X	X
Query Subject: How have you felt in the last 2 weeks?			X	X	X	X	X	X	X	X	X	X
Directed Physical Examination		X		X	X		X		X			
Prior or Concomitant Medication Review / Medical Procedures	X	X		X	X	X	X		X	X	X	X
Tanner Stage	X				X		X		X		X	X
Vital Signs [2]	X	X		X	X	X	X		X	X	X	X
Weight	X	X		X	X	X	X		X	X	X	X
Height	X	X		X	X	X	X		X	X	X	X
Hand and Wrist X-ray	X						X				X	
Urine Pregnancy Test—females only		X					X				X	X
Urinalysis	X			X			X				X	X
Hematology	X			X			X				X	X
Chemistry	X			X			X				X	X
Hepatitis B antigen/Hepatitis C antibody	X											
Serum lipids - fasting	X	X										
LH and FSH samples (basal)	X	See Table 2		X	X	X	X		X	X	X	X
Testosterone/estradiol samples (basal)	X	See Table 2		X	X	X	X		X	X	X	X
Serum Leuprolide samples (basal) [3]	X	See Table 2		X	X	X	X		X	X	X	X
GnRHa Stimulation (SC leuprolide acetate) [4]	X				X		X		X		X	X
LH and FSH samples 30 ± 5 min AFTER GnRHa stimulation	X				X		X		X		X	X
Testosterone/estradiol samples 30 ± 5 min AFTER GnRHa stimulation	X				X		X		X		X	X
Study drug (leuprolide acetate) SC injection [5]		X					X					
Adverse Events Assessment		X		X	X	X	X		X	X	X	X
Schedule/Confirm Next Visit	X	X		X	X	X	X		X	X		(X)

[1] Informed Consent/Assent could have been signed within 28 days prior to the Baseline visit

[2] Vital signs were to be measured before any blood draws

PI=principal investigator

[3] Blood samples for leuprolide serum concentrations had to be collected before the GnRHa stimulation test.
PI=principal investigator

[4] GnRHa (SC) stimulation was to be performed AFTER a blood sample had been collected for measurement of basal LH, FSH AND testosterone/estradiol concentrations and prior to study drug injection. Blood samples for LH, FSH and testosterone/estradiol concentrations was to be obtained again 30 ± 5 minutes after SC administration of GnRHa.

[5] Local or topical anesthetic could be used at the discretion of the Investigator, prior to study drug administration. Name of the anesthetic used, route, and time of dose was to be recorded.

Source: Table 1 Clinical Study Report

Table 4. Blood Sampling Times by Parameter for Visit 1 in Study TOL2851A

Visit Number—Part A	Visit 1			
Scheduled Day/Month	Baseline (Day 0)			
	Time relative to injection			
	≥30 min prior	1 hr (±5 min)	4 hr (±10 min)	6 hr (±15 min)
LH and FSH samples	X	X	X	X
Testosterone/estradiol samples	X	X	X	X
Serum Leuprolide	X	X	X	X

Vital signs were to be measured before any blood draws
min=minutes, hr=hour, LH=luteinizing hormone, FSH=follicle stimulating hormone

Source: Table 2 Clinical Study Report

Study Endpoints

Primary efficacy endpoint

The percentage of subjects with serum LH concentrations <4 IU/L was assessed 30 minutes following an abbreviated GnRH agonist stimulation test at Visit 5, Week 24 (Month 6). Leuprolide acetate for injectable suspension, 45 mg, was considered effective for the treatment of children with CPP if ≥80% of subjects exhibited LH suppression <4 IU/L at Visit 5, Week 24 (Month 6).

Secondary efficacy endpoints

- The percentage of subjects with serum LH concentrations <4 IU/L at 30 minutes following an abbreviated GnRH agonist stimulation test for any available measurement other than the measurement constituting the primary outcome variable (see above)
- The percent change from baseline in height at each available post-baseline measurement. Percent change was defined as [(change from Baseline)/(Baseline)] x 100. Standing height was recorded with a calibrated stadiometer that has increments in millimeters and a functional Frankfort Plane perpendicular to the standing surface. It was suggested that repetitive measurements of a subject would be done using the same stadiometer by the same health care provider trained in the use of the stadiometer.
- The growth velocity of height in cm/year at each available post-baseline measurement. Growth velocity was defined for each visit as (change from Baseline)/(number of weeks since Baseline)/52
- The ratio of bone age at each given measurement point to chronological age at the same measurement points
- Baseline to end-of-study stage shifts for each Tanner category
- The percent change from baseline in hormonal concentration (LH, FSH, testosterone, and estradiol) at each available post-baseline measurement. Percent change was defined as [(change from baseline)/(baseline)] x 100
- The percent change from baseline in systemic leuprolide concentration at each

available post-baseline measurement. Percent change was defined as [(change from baseline)/(baseline)] x 100

Safety endpoints
- Vital signs
- Weight
- Physical examination
- Clinical laboratory assessments
- Pregnancy test
- Adverse events
- Serious adverse events

PK endpoints
- Visit 1 (baseline, 1 hour, 4 hours, 6 hours): concentration value at each time point, AUC over 6 hours, Cmax over 6 hours, Tmax over 6 hours
- Basal Measurement over Study Period (Screening, first Visit 1 measurement, Visit 2 and greater): concentration value at each visit, AUC (over study period (i.e., 0 to infinity)), AUC (over set time periods (e.g., 0 to 6 hours, 0 to 6 months, Day 7 to 6 months)), Cmax (post each treatment administration), Tmax (post each treatment administration)
- Post GnRH agonist stimulation (screening; Visits 3, 5, 6 and 8): concentration value of LH post 30 minutes of test initiation

The GnRH agonist stimulation test, which measures serum LH, is considered the gold standard for diagnosis of CPP. The choice of the cut-off of < 4 IU/L is considered conservative, as levels ≥ 5 IU/L were shown to give 98.4% sensitivity and 100% specificity [8] and (b) (4) has defined >8 IU/L as a pubertal response [9]. The GnRH agonist stimulation test used in TOL2581A was modeled on a published, abbreviated procedure in which levels of gonadotropins were measured 30 minutes after subcutaneous administration of a 20 µg/kg dose of an aqueous solution of leuprolide acetate. Standard doses of 20 µg/kg body weight or 500 µg are supported by literature as being sufficient and clinically qualified for use in the test to make a diagnosis of CPP [10, 11].

Statistical Analysis Plan

Please refer to the statistical review for a detailed analysis of the Statistical Analysis Plan (SAP). There was no formal statistical testing for the primary endpoint in this study. The SAP stated that if ≥85% of the first 16 subjects to be evaluated at month 6 are found to demonstrate LH suppression to < 4 IU/L, that Part B of the study would not be invoked as part of the adaptive design and efficacy would be determined if ≥80% of subjects meet the primary endpoint, LH suppression to < 4 IU/L at week 24. If, however, < 85% of the first 16 subjects evaluated at month 6 are found to demonstrate LH suppression to < 4 IU/L, the study will be adapted and

Part B will be invoked. In that case efficacy would be determined if ≥80% of subjects meet the primary endpoint, LH suppression to < 4 IU/L at month 21. The sample size determination used a one-sided lower confidence limit of 70% for the primary endpoint. All the secondary endpoints were considered exploratory, as there was no multiplicity adjustment to control for Type I error. Statistical analyses for all secondary and exploratory endpoints in this study consisted of descriptive statistics presented over time or at pre-designated time points of special interest.

Protocol Amendments

There were two protocol amendments that incorporated the following changes to the original study protocol.

Amendment 01-including but not limited to:
Exclusion criteria were added for history of seizure or use of medications that have been associated with seizures.

Secondary Objectives were changed to include:
(1) Assess percent changes in height velocity and bone age progression after the first administration
(2) Assess changes in physical signs of puberty as measured by changes in Tanner stages or changes in onset of menses.

Secondary endpoints were changed to include:
(1) Changes in height velocity (growth rate) and bone age advancement relative to chronological age from baseline to end of study.
(2) Change in physical signs of puberty as measured by changes in Tanner Stages from baseline to end of study.

Exploratory endpoints were changed to include:
(1) Descriptive statistics will be used to describe changes in physical signs of puberty as measured by changes in Tanner stages at each assessed timepoint.
(2) Changes in Tanner staging will be described for each individual and for the ITT and PP population over the entire treatment period.

Schedule of Assessments was updated to include telephone contact within 2 weeks of dosing, and specific query questions were included asking about injection site reactions, hot flashes, bone pain, difficulty with urination, allergic symptoms, and weakness or muscle symptoms.

Information about sample size determination was updated to include the conditions that would invoke the adaptive design to Part B of the study and how efficacy would be determined in Parts A and B.

(b) (4)

6.1.2. Study Results

Compliance with Good Clinical Practices

The study was conducted in accordance with International Conference on Harmonization (ICH) E6, Good Clinical Practice (GCP): Consolidated Guideline and the principles of ICH E8: General Considerations for Clinical Trials. The ICF and Assent Form used for the study complied with the applicable local and federal laws and regulations and ICH E6 GCP: Consolidated Guideline and was approved by the applicant or designee prior to review by the IRB/IEC. Subjects and the legal guardian(s) were informed about all aspects of the clinical study that were necessary to make the decision to participate in the clinical study. Subjects and the parent/guardian(s) were informed that participation was voluntary and that they could withdraw from the study at any time, without prejudice. Documentation of the discussion, the study personnel who managed or administered the ICF, and the date of informed consent were recorded in the source documentation. Parent/guardian(s) of subjects gave informed consent in writing and each subject signed the Assent Form, as required.

Financial Disclosure

The applicant provided form FDA 3454 to certify that no financial arrangements had been made with any investigators in the pivotal study TOL2581A.

Patient Disposition

A total of 114 children were screened. Of these, 64 subjects received study drug and were included in the safety population, and 60 completed the study and were included in the Intent to Treat (ITT) population as part of the original submission (SDN1). However, as part of the 74-day letter, the statistical reviewer asked for clarification surrounding the reasons certain patients were excluded from the ITT population, as subjects who simply did not complete the study should not have been excluded from the efficacy analyses. In response to the information request, the applicant revised the ITT population upward to 62, in the November 15, 2019 submission (SDN 5), and reanalyzed the data using the new ITT population. Of the original 64 patients, only two, (b) (6) and (b) (6), who did not meet the inclusion/exclusion criteria were excluded from the final ITT population. Subject (b) (4) was excluded due to a history of seizures and subject (b) (4) due to less than a one-year difference between bone age and chronological age. Three subjects had early withdrawal from the study but were included in the 24-week efficacy endpoint. They include: Subject (b) (4) who withdrew on Study Day 170 (wk 24) not due to disease progression as originally reported but because she required an additional

concomitant medication that was exclusionary per protocol (final LH=1.7 IU/L); Subject (b) (4) who withdrew on Study Day 169 (wk 24) due to parental withdrawal of consent (final LH=3.2 IU/L); and subject (b) (6) who withdrew on Study Day 93 (wk 13) due to lack of efficacy (final LH=48.1 IU/L).

Protocol Violations/Deviations

Two critical protocol deviations were reported for two subjects:

(b) (6) had a history of seizures controlled with medication, which was an exclusionary criterion and should not have been admitted to the study. The site did not realize that any history of seizure was exclusionary to enrollment and she was discontinued from the study on (b) (6) when the seizure history was noted (final LH=2.1 IU/L).

(b) (6) had a 10-month difference in bone age and chronological age, which did not meet the inclusion criteria of >1 year (final LH=0.1 IU/L).

Eighty-two major protocol deviations were reported in 25 subjects, and 75 minor protocol deviations were reported in 34 subjects. Sixty-four of the major protocol deviations had to do with dosing during the GnRH agonist stimulation testing. Some of the study centers administered the abbreviated GnRH agonist stimulation test using a dose of 500 mcg regardless of body weight based on local standard of care instead of the protocol-specified dose of 20 mcg/kg body weight. Standard doses of 500 mcg would still be expected to provide adequate stimulation and should not have affected the study results significantly [10, 11]. The other major deviations were reviewed in Listing 16.2.2.2.2 and consisted primarily of (1) sampling problems such as lost samples or out of window sample measurements that dealt primarily with screening or baseline visits and resulted in retraining at the study sites, (2) out of window study visits and (3) problems with adequate signatures on the informed consent and assent forms.

Medical officer's comments- Standard doses of 500 mcg during the GnRH agonist stimulation testing would still be expected to provide adequate stimulation and should not have affected the study results significantly. A review of protocol deviations at study visit 5, week 24, at the time of the primary endpoint measurement, identified three patients, (b) (6) *, that were tested 2 to 7 days after the study visit window of ±7days and three patients,* (b) (6) *that had the measurement obtained at -1, + 5 and +7 minutes outside the stimulation test window of 30 to 35 minutes. Also, subject* (b) (6) *was dosed with Fensolvi 34 minutes after reconstitution during the initial injection instead of 30 minutes as per the study protocol, to allow the product to come to room temperature for easier mixing and administration. These minor differences should not have significantly affected the primary endpoint measurement in these patients.*

Table 5. Summary of Demographic Characteristics for Study TOL2851A

	Safety Population (N=64)	ITT Population (N=62)	Per Protocol Population (N=43)
Age (Years) [1]			
n	64	62	43
Mean ± SD	7.5 ± 0.89	7.5 ± 0.90	7.3 ± 0.97
Median	8.0	8.0	8.0
Min, Max	4, 9	4, 9	4, 9
Sex, n (%)			
Male	2 (3.1%)	2 (3.2%)	1 (2.3%)
Female	62 (96.9%)	60 (96.8%)	42 (97.7%)
Ethnicity, n (%)			
Hispanic Or Latino	36 (56.3%)	35 (56.5%)	22 (51.2%)
Not Hispanic Or Latino	28 (43.8%)	27 (43.5%)	21 (48.8%)
Unwilling to Provide	0	0	0
Race, n (%) [2]			
American Indian Or Alaska Native	5 (7.8%)	5 (8.1%)	5 (11.6%)
Asian	3 (4.7%)	3 (4.8%)	2 (4.7%)
Black Or African American	15 (23.4%)	15 (24.2%)	11 (25.6%)
Native Hawaiian Or Other Pacific Islander	1 (1.6%)	1 (1.6%)	1 (2.3%)
White	34 (53.1%)	32 (51.6%)	18 (41.9%)
Unwilling to Provide	1 (1.6%)	1 (1.6%)	1 (2.3%)
Other	5 (7.8%)	5 (8.1%)	5 (11.6%)

[1] Age is calculated at date of first injection.
[2] Subjects were allowed to select more than one race. Therefore, percentages can add up to more than 100% in each treatment group.

Source: SDN 5 Table 14.1.2.1.2

Children ages 2 to 9 years were screened but only girls age 4 to 8 (n=62) and boys age 9 years (n=2) were treated.

Medical officer's comments- The study enrolled primarily female subjects (97%). While it is known that CPP is more common in girls than boys (e.g., up to 23:1), boys are clearly underrepresented in this study. The two boys in this study showed evidence of efficacy and safety. Given what is known about the efficacy and safety of other shorter lasting leuprolide containing products for the treatment of CPP, it is this medical reviewer's assessment that despite the limited efficacy and safety data in boys that the general results seen in girls can be extrapolated to boys as well.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

All 64 enrolled subjects diagnosed with CPP had a pubertal-type LH response (>5 IU/L) in the abbreviated GnRH agonist stimulation test before treatment initiation. All 62 enrolled girls had a Tanner stage of ≥2 for breast development and the two boys in the study had a Tanner stage of 3 for development of external genitalia at baseline. All subjects, except for (b) (6), who was excluded from the ITT analysis, had ≥1-year difference between bone age and chronological age.

Thirty-six subjects had 121 ongoing medical conditions. Subject (b) (6) had a history of seizures that was ongoing, which was a major protocol deviation and was excluded from the ITT analyses. Two subjects (b) (6) and (b) (6)) had medical histories of pituitary adenomas, which did not affect subject's responsiveness to the stimulation test and were included in the ITT population. One subject (b) (6)) had a history of Hashimoto's thyroiditis and thyromegaly but was excluded from the ITT population because she did not meet the bone age inclusion criteria.

The most frequently reported ongoing medical conditions were asthma (n=7), constipation (n=6), headache (n=5), seasonal allergy (n=5) and eczema (n=4).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All study drug doses were administered at the study site to ensure compliance.
Fifty (83%) subjects took at least one concomitant medication. Administration of a local anesthetic (n=23, 38%), ibuprofen (n=20, 33%), antihistamines (n=17, 28%), and paracetamol (n=16, 27%) were the most frequent concomitant medications, which were usually administered at the time of the study drug injection (see Clinical Study Report Table 14.1.5.1.2). Subjects did not receive any prohibited medications including GnRH agonists, or hormone therapies (excluding levothyroxine, n=2 (3%)), or medications that have been associated with seizures or convulsions or would put the child at risk of seizures or convulsions.

> *Medical officer's comment- There was adequate compliance. Concomitant medications were primarily used to treat injection site reactions and were unlikely to affect the safety of the subjects or the results of the study.*

Efficacy Results – Primary Endpoint

A total of 54 out of the 62 subjects in the ITT population, or 87%, had serum LH concentrations <4 IU/L assessed 30 minutes following an abbreviated GnRH agonist stimulation test at Visit 5, Week 24 (Month 6). It was prespecified that Leuprolide acetate for injectable suspension, 45 mg, would be considered effective for the treatment of children with CPP if ≥80% of subjects

exhibited LH suppression <4 IU/L at Visit 5, Week 24 (Month 6). Therefore, there was no reason to invoke Part B of the study, which included two additional study drug injections and overall drug treatment out to 21 months.

Table 6. Percentage of Patients who Achieved Efficacy Endpoints in Study TOL2851A (ITT)

	ITT Population (N=62)		Per Protocol Population (N=43)	
	Number Assessed	n (%)	Number Assessed	n (%)
Visit 3, Week 12				
Serum LH Suppression	60	51 (85.0%)	42	35 (83.3%)
Serum FSH Suppression	60	37 (61.7%)	42	27 (64.3%)
Serum Estradiol Suppression	58	58 (100.0%)	41	41 (100.0%)
Serum Oestradiol (HS) Suppression	57	56 (98.2%)	41	40 (97.6%)
Serum Testosterone Suppression	2	2 (100.0%)	1	1 (100.0%)
Visit 5, Week 24				
Serum LH Suppression*	62	54 (87.1%)	43	37 (86.0%)
Serum FSH Suppression	62	41 (66.1%)	43	27 (62.8%)
Serum Estradiol Suppression	60	59 (98.3%)	42	42 (100.0%)
Serum Oestradiol (HS) Suppression	60	58 (96.7%)	42	41 (97.6%)
Serum Testosterone Suppression	2	2 (100.0%)	1	1 (100.0%)

Source: SDN 5 Table 14.2.1.1.2

The two subjects were excluded from the ITT population because they did not meet the inclusion criteria, (b) (6) due to a history of seizures and (b) (6) due to < 1-year difference between bone age and chronological age. Both showed evidence of LH suppression from week 12 to end of treatment (see Table 7).

Table 7. LH Suppression in the Two Subjects Excluded from ITT Analysis in Study TOL2851A

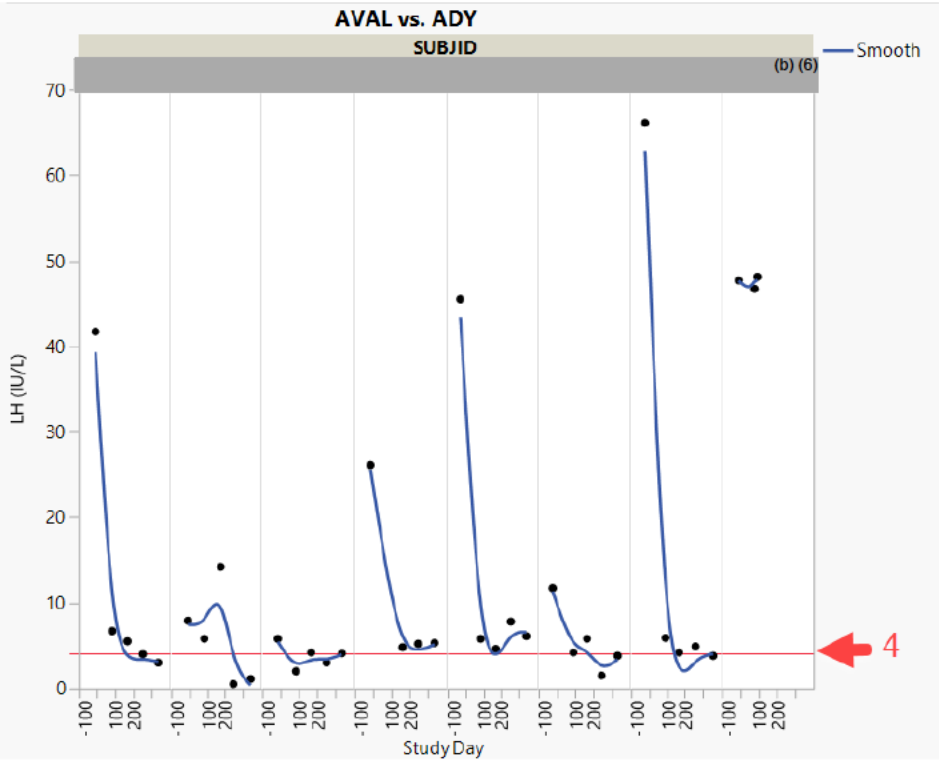
SUBJID	Country	Age (yrs)	Gender	LH (IU/L)	Visit
(b) (6)	USA	8	F	175.2	Screening
				3.3	Visit 3, Week 12
				2.1	EOT, Week 48
(b) (6)	USA	7	F	22.9	Screening
				1.8	Visit 3, Week 12
				0.9	Visit 5, Week 24
				1.4	Visit 6, Week 36
				0.1	EOT, Week 48

Source: JMP analysis- SDN 5, 5.3.5.1, Analysis Dataset Adam, ADLB dataset, PARAMCD=LH, LBTPT=Post GnRHa, ITT2FL=no, SUBJID/COUNTRY/AGE/SEX/AVAL/VISIT

Most of the patients that missed the LH < 4 IU/L cut-off at week 24 still had LH values < 10 IU/L, and 5 out of these 8 subjects went on to have later values < 4 IU/L during the subsequent 24

weeks of the study. Only one patient (b) (6) with an end of treatment LH value of 48.1 IU/L was clearly out of range, while end of treatment/week 48 LH values for the other two week 24 non-responders were 5.3 IU/L (b) (6) and 6.1 IU/L (b) (6) (see Figure 3).

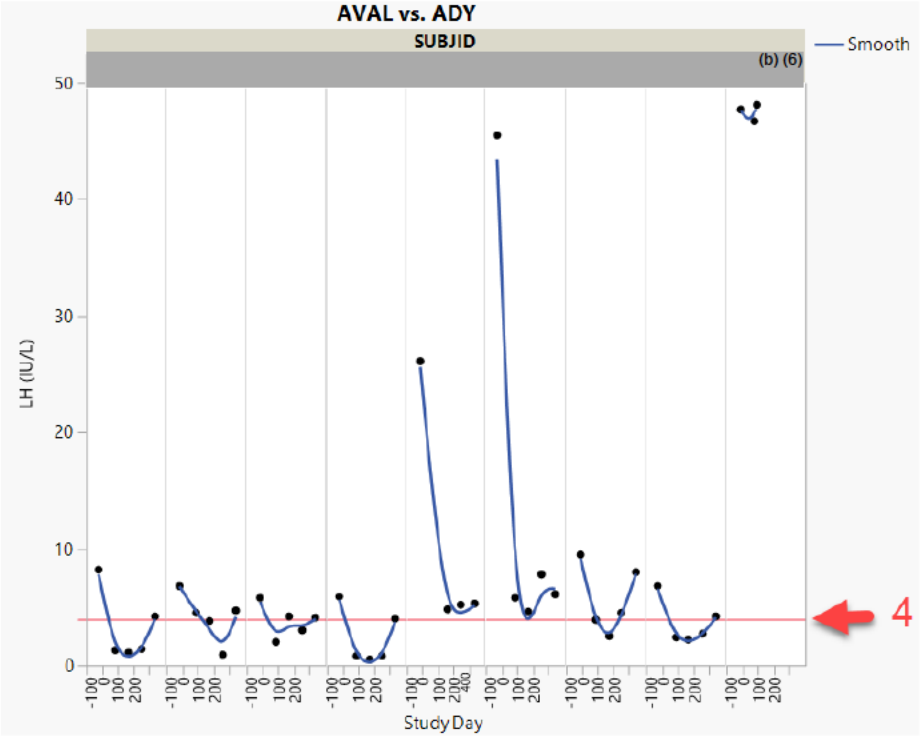
Figure 3. LH Serum Concentrations in 8 Non-responders at Wk 24 TOL2851A



Source: JMP Analysis- SDN 5, 5.3.5.1, Data Listing Data, ADLB dataset, PARAMCD=LH, LBTPT=Post GnRHa, VISIT= (Visit 5, Week 24), ITT2FL=yes, SUBJID/ AVAL/ADY/Efficacy formula (AVAL) LH<4=yes

Medical officer's comment- The applicant met the prespecified treatment goal of 85% LH suppression to < 4 IU/L with 54/62=87% at week 24 demonstrating clinical efficacy. In addition, 5 out of the 8 patients not reaching LH suppression to < 4 IU/L at week 24 demonstrated LH suppression with levels < 4 IU/L following the second injection at some point during the next 24 weeks. However, some subjects with LH suppression at week 24 went on to have LH values slightly higher than 4 IU/L at week 48 or end of the treatment (EOT). So, efficacy at week 48/EOT was essentially similar at 52/61=85%. There were 9 non-responders at week 48/EOT (see Figure 4*). Subject* (b) (6) *had evidence of LH suppression (e.g., LH < 4) at weeks 12, 24 and 36, but did not have a value reported at week 48/EOT so was not included in the 61 ITT subjects with week 48/EOT data. Three subjects discontinued the study early and had an EOT measurement prior to week 48, two with LH suppression and one without. Excluding these subjects and so looking only at subjects with 48-week data, the responder rate would be similar (50/58=86%).*

Figure 4. LH Serum Concentrations in 9 Non-responders at Wk 48 or End of Treatment in Study TOL2851A



Source: JMP Analysis- SDN 5, 5.3.5.1, Data Listing Data, ADLB dataset, PARAMCD=LH, LBTPT=Post GnRHa, VISIT= (End of Treatment, Week 48), ITT2FL=yes, SUBJID/ AVAL/ADY/Efficacy formula (AVAL) LH<4=yes

Initial PK values for 0 to 6 hours post dose were available for 60 patients and are graphed in Figure 5. The 8 non-responders at week 24 are identified with red arrows and bolded dots. Subject (b) (6) with the highest LH level of 48.1 IU/L at end of treatment is labeled in the figure. Both subjects (b) (6) and (b) (6) had very low leuprolide drug levels initially after dosing at 6,899 day*pg/mL and 1,422 day*pg/mL, respectively, which may explain their lack of efficacy. It should be noted that the other 6 non-responders had leuprolide serum levels during the first 6 hours post dose that were in a similar range as the responders, so pharmacokinetics alone may not explain the lack of efficacy in these patients.

Figure 5. Leuprolide AUC 0-6 hrs Post Dose for 8 Non-responders at Wk 24 in Study TOL2851A

Source: SDN 5, 5.3.5.1, Data Listing Data, PP dataset PPSCAT=AUC 0-6 HRS, **bolded** USUBJID=8 Non-Responders PPSTRESN vs. USUBJID

The study enrolled more patients from the US, 31/64=48%, than any other country, so there was sufficient US data to look for potential geographical differences.

Table 8. Subjects with LH<4 IU/L at Week 24 by Study Country in Study TOL2851A

Efficacy LH<4 IU/L	Country	ITT Pts N=62	% total	% no efficacy N=8	% efficacy N=54
no	ARG	1	1.6	12.5	-
no	CHL	1	1.6	12.5	-

Efficacy LH<4 IU/L	Country	ITT Pts N=62	% total	% no efficacy N=8	% efficacy N=54
no	USA	6	9.7	75.0	-
yes	ARG	12	19.4	-	22.2
yes	CAN	2	3.2	-	3.7
yes	CHL	8	12.9	-	14.8
yes	MEX	7	11.3	-	13.0
yes	NZL	2	3.2	-	3.7
yes	USA	23	37.1	-	42.6
Totals		62	100	100	100

Source: JMP Analysis- SDN 5, 5.3.5.1, Data Listing Data, ADLB dataset, PARAMCD=LH, LBTPT=Post GnRHa, ITT2FL=yes, SUBJID/COUNTRY/AVAL/VISIT=Visit 5, Week 24/Efficacy formula (AVAL) LH<4=yes

Medical officer's comment- Efficacy at the 24-week time point was slightly lower in the US ITT population (23/29=79%) compared to the overall population at 87%. Of the 6 US subjects who did not have LH suppression to < 4 IU/L at week 24, two went on to show suppression at the end of treatment/week 48 visit for an adjusted rate of 86%, and all but one had LH levels of 6.1 IU/L or less at the end of treatment visit (see Table 9 *).*

Table 9. LH Levels at Week 24 and End of Treatment/Week 48 in the 6 United States Non-responders

SUBJID	LH (IU/L)	Week 24 or EOT/Week 48
(b) (6)	4.2	Visit 5, Week 24
	4.1	End of Treatment, Week 48
	4.8	Visit 5, Week 24
	5.3	End of Treatment, Week 48
	4.6	Visit 5, Week 24
	6.1	End of Treatment, Week 48
	5.8	Visit 5, Week 24
	3.8	End of Treatment, Week 48
	4.2	Visit 5, Week 24
	3.8	End of Treatment, Week 48
	48.1	End of Treatment, Week 48

Source: JMP Analysis- SDN 5, 5.3.5.1, Data Listing Data, ADLB dataset, PARAMCD=LH, LBTPT=Post GnRHa, ITT2FL=yes, SUBJID/AVAL/VISIT=Visit 5, Week 24 or End of Treatment, Week 48/Efficacy formula (AVAL) LH<4=no

Data Quality and Integrity

Two domestic and one foreign site were inspected. The inspections of the sites found regulatory deficiencies, but the findings were not considered significant. In general, based on

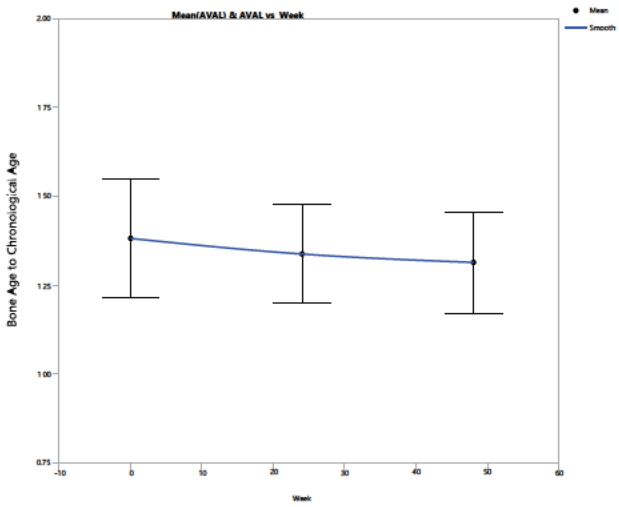
the inspections of the three clinical sites, the inspectional findings support validity of data as reported by the applicant under this NDA.

Efficacy Results – Secondary and other relevant endpoints

The secondary endpoints were not controlled for Type I error and multiplicity, so only selective endpoints will be reviewed.

Growth velocity is accelerated in children with CPP due to premature bone maturation. Treatment with GnRH agonists is expected to slow the course of bone maturation and slow growth velocity. The ratio of bone age to chronological age at the time of the measurement is plotted below. There is a clear trend for a decrease in bone age over the course of the study, but the changes were within the standard deviation of the measurements (Figure 6).

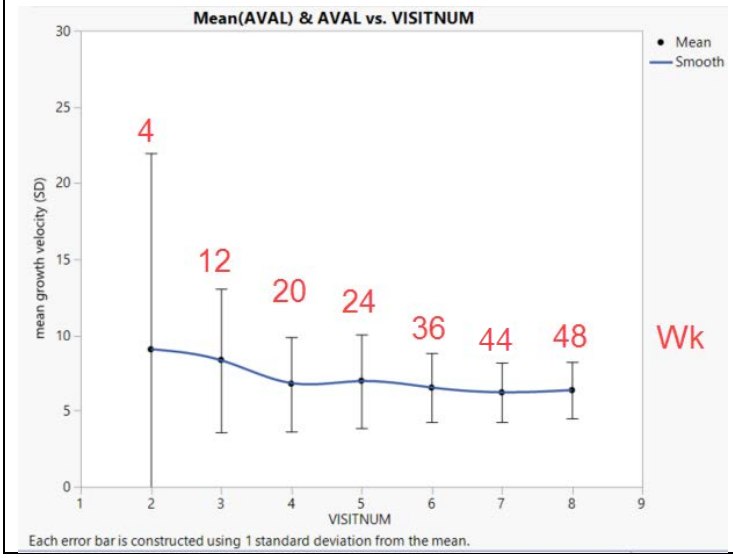
Figure 6. Ratio of Bone Age to Chronological Age Over Time in Study TOL2581A (ITT)



Source: SDN 5 ADEF dataset plotted as AVAL vs. Week
Each error bar is constructed using 1 standard deviation from the mean.

Growth velocity over the course of the trial is plotted in Figure 7. Growth velocity decreases from baseline to week 20 and then starts to go up slightly prior to the next injection at week 24. Similarly, growth velocity again continues to decrease from weeks 24 to week 44 and then starts to go up slightly prior to the next injection at week 48. The slight increase in growth velocity at the last 4 weeks prior to each injection suggests that efficacy is starting to wear off just prior to the next injection. Similar trends were seen when median (IQR) growth velocity was plotted over time (see Fig. 12 in the Final Statistical Review).

Figure 7. Growth Velocity by Study Visit in Study TOL2581A (ITT)

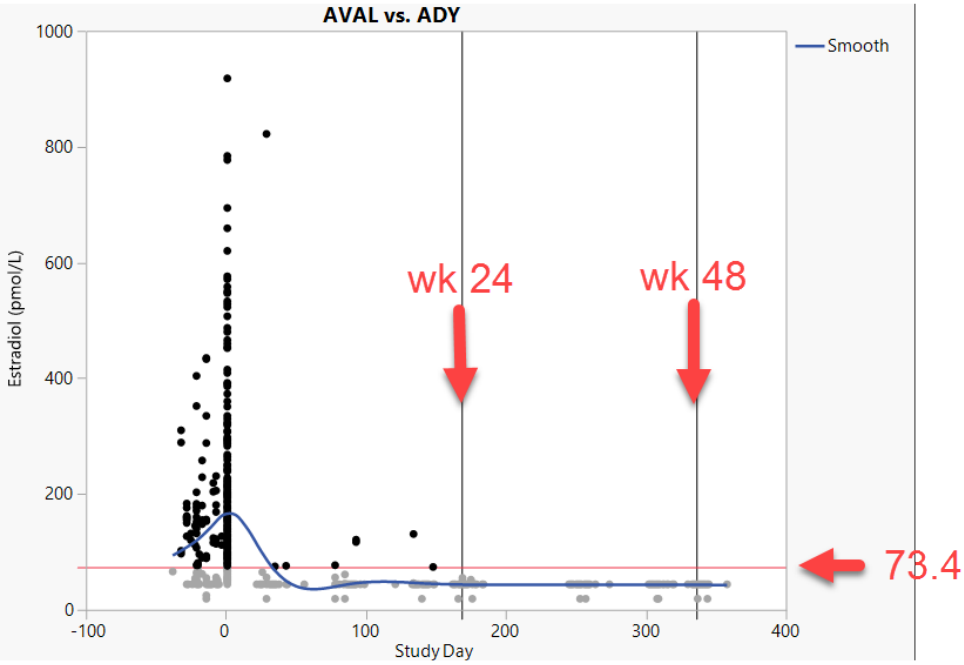


Growth Velocity (cm/year)
Mean ± SD
Wk 04 9.02 ± 12.9
Wk 12 8.32 ± 4.75
Wk 20 6.77 ± 3.13
Wk 24 6.96 ± 3.10
Wk 36 6.51 ± 2.26
Wk 44 6.20 ± 1.94
Wk 48 6.34 ± 1.85

Source: SDN 5 ADEF2 dataset plotted as AVAL vs. VISITNUM

Estradiol levels in girls were plotted by study day in Figure 8. Values above the prepubertal level of 73.4 pmol/L are bolded in the figure. There are a handful of girls with levels above 73.4 pmol/L, but most subjects showed clear evidence of efficacy after about 12 weeks after the initial injection.

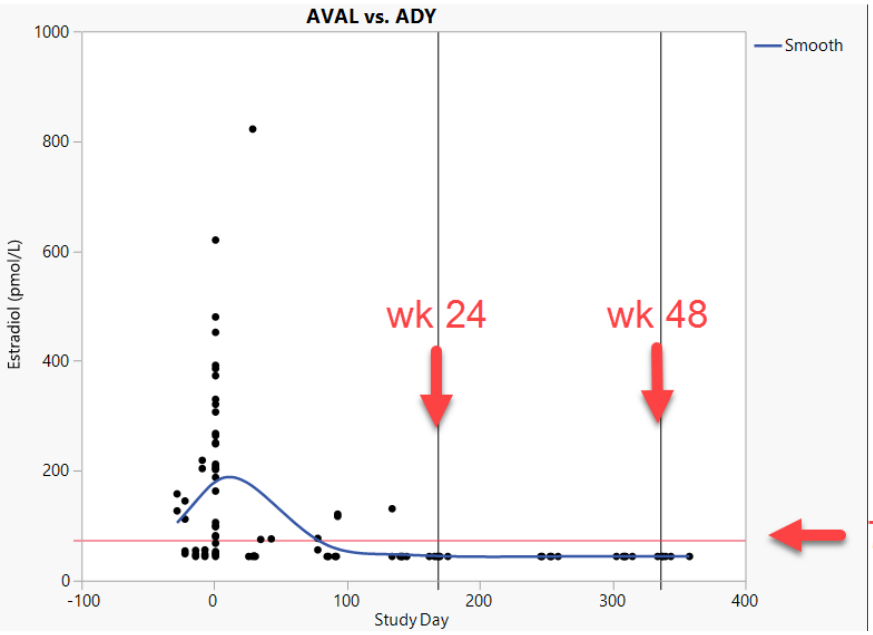
Figure 8. Serum Estradiol Concentration in Girls by Study Day in Study TOL2581A (ITT)



Source: SDN 5 ADLB dataset PARAM=Estradiol (pmol/L), Study Day=ADY, AVAL vs ADY

The estradiol values in the 8 LH non-responders at week 24 are bolded in Figure 9 below. There are 7 values above 73.4 pmol/L between the initial injection on day 1 and day 134, but all of the LH non-responders that were still in the study after week 24 had estrogen values below the pubertal level following the second injection. Note subject (b) (6) discontinued from the study on study day 93, and so did not receive a second injection.

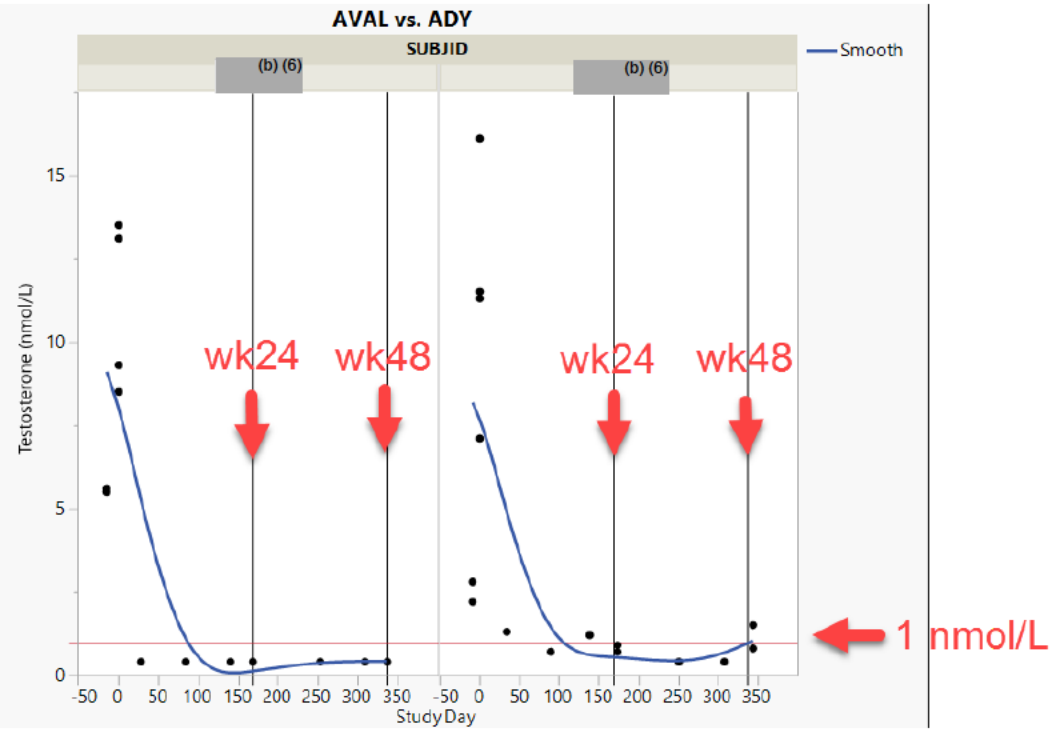
Figure 9. Serum Estradiol Concentration by Study Day in Study TOL2581A in the 8 Non-responders at Wk 24



Source: SDN 5 ADLB dataset PARAM=Estradiol (pmol/L), Study Day=ADY, SUBJID=8 non-responders, AVAL vs ADY

Testosterone levels were measured in the two boys treated in the study. Most values were below the pubertal level of 1nmol/L, as shown in Figure 10 below. However, one of the boys, subject (b) (6), had a value of 0.8 nmol/L before the GnRH agonist stimulation test and a value of 1.5 nmol/L after the GnRH agonist stimulation test at the end of treatment/week 48 visit, which is slightly above the pubertal level of 1nmol/L.

Figure 10. Serum Testosterone Concentration by Study Day in the Two Boys in Study TOL2581A



Source: SDN 5 ADLB dataset PARAM=Testosterone (nmol/L), SUBJID= (b) (6) or (b) (6), Study Day=ADY, AVAL vs ADY

A summary of efficacy endpoints by responder rate at weeks 12, 24, 36 and 48 is displayed in Table 10 below (taken from Table 3 in Dr. Jiwei He's Statistical Review). There is evidence for even greater efficacy with respect to estradiol suppression (98%) and testosterone suppression (100%) (secondary endpoints), than seen with LH suppression (87%) (the primary endpoint) at week 24. There is also evidence for no increase in Tanner stages from baseline to weeks 24 or 48 for "development of external genitalia" in boys (100%) and "breast development" in girls (97%), although evidence for no increase in "pubic hair" in boys and girls was lower (79-81%).

Table 10. Responder Rates for Primary and Secondary Endpoints in Study TOL 2581A (ITT)

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

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

Dose/Dose Response

Study TOL2581A was a single dose study so there is no dose response data.

Durability of Response

Four out of the 8 patients not reaching LH suppression to < 4 IU/L at week 24 demonstrated LH suppression with levels < 4 IU/L following the second injection at week 48, and one barely missed the cut-off with an LH value of 4.1 IU/L, demonstrating efficacy after repeat dosing. Serum estradiol and testosterone levels were maintained at prepubertal levels in most patients, starting at 4 to 12 weeks up until the end of the study at week 48 (see Figures 8, 9 and 10). However, while growth velocity decreased initially after injection, it appeared to start to go back up slightly during the last 4 weeks prior to each next injection (see Figure 7), suggesting that efficacy may be waning near the end of each 24-week treatment period.

Persistence of Effect

Study TOL2581A used an adaptive design protocol to look for efficacy at up to 6 months of treatment. No patients were followed without active treatment beyond the 6-month time

period, as it would be unethical to limit treatment in these patients.

Additional Analyses Conducted on the Individual Trial

Not applicable.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Fensolvi was studied in a single pivotal trial. Refer to Section 6 for primary efficacy results.

7.1.1. Primary Endpoints

Refer to Study Endpoints in Section 6.1.

7.1.2. Secondary and Other Endpoints

Refer to Study Endpoints in Section 6.1.

7.1.3. Subpopulations

Table 11. Efficacy in LH Suppression by Subject Age and Gender in Study TOL2581A (ITT)

Gender	Age (years)	Patient Number	Efficacy* Patient Number	
			LH < 4 (IU/L)	LH ≥ 4 (IU/L)
F	4	1	1	0
F	5	2	1	1
F	6	3	3	0
F	7	19	17	2
F	8	35	30	5
M	9	2	2	0
97% F	Mean 7.5 SD (0.9)	Total 62	54	8

*LH efficacy at week 24 or EOT if no Wk 24 data. Age at start of study
Source: JMP Analysis- SDN 5, 5.3.5.1, Data Listing Data, ADLB dataset, PARAMCD=LH, LBTPT=Post GnRHa, VISIT=Visit 5, Week 24 or EOT if no 24 Week data, SUBJID/SEX/AGE/AVAL

Given the small study size, there were no clear differences in efficacy based on age (< 8yrs, 82%; ≥8yrs, 87%), gender (Females 81%, Males 100%), race (American Indian +Asian +Native

Hawaiian, 80%; Black, 87%; White, 84%)(Table 12), or ethnicity (Hispanic or Latino, 89%; Not Hispanic or Latino, 85%)(Table 13).

Table 12. Efficacy in LH Suppression by Subject Race in Study TOL2581A (ITT)

Race	Patient number	Efficacy* Patient Number	
		LH < 4 (IU/L)	LH ≥ 4 (IU/L)
AMERICAN INDIAN OR ALASKA NATIVE	5	5	0
ASIAN	3	2	1
BLACK OR AFRICAN AMERICAN	15	13	2
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	1	1	0
OTHER	5	5	0
UNKNOWN	1	1	0
WHITE	32	27	5
TOTAL	62	54	8

*LH efficacy at week 24 or EOT if no Wk 24 data.
Source: SDN 5, 5.3.5.1, Data Listing Data, ADLB dataset, PARAMCD=LH, LBTPT=Post GnRHa, VISIT=Visit 5, Week 24 or EOT if no 24 Week data, SUBJID/RACE/AVAL

Table 13. Efficacy in LH Suppression by Subject Ethnicity in Study TOL2581A (ITT)

Ethnic	Patient number	Efficacy* Patient Number	
		LH < 4 (IU/L)	LH ≥ 4 (IU/L)
HISPANIC OR LATINO	35	31	4
NOT HISPANIC OR LATINO	27	23	4
TOTAL	62	54	8

*LH efficacy at week 24 or EOT if no Wk 24 data.
Source: SDN 5, 5.3.5.1, Data Listing Data, ADLB dataset, PARAMCD=LH, LBTPT=Post GnRHa, VISIT=Visit 5, Week 24 or EOT if no 24 Week data, SUBJID/ETHNIC/AVAL

7.1.4. Dose and Dose-Response

While there was no dose-response performed in children in this clinical program the same 45 mg dose of leuprolide acetate, under the trade name Eligard, had been shown to be effective for 6 months in adult males to block testosterone production for the palliative treatment of advanced prostate cancer. Also, doses of a similar product with a slightly different formulation,

leuprolide acetate for depot suspension (e.g., Lupron Depot-Ped) had been shown to be effective for the treatment of precocious puberty at the 30mg dose for 3 months. So, the choice of a 45 mg dose at 6 months was reasonable for this clinical program.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

There is evidence of the onset of efficacy, measured as LH suppression and decreases in estradiol or testosterone levels at the earliest measurements taken at week 4. The number of responders is greatest and consistent from weeks 12 to 24 after an injection. The decrease in growth velocity from week 20 through 24 suggests efficacy may be waning toward the end of the 24-week treatment interval, but LH suppression and estradiol and testosterone levels were still maintained at prepubertal levels in patients throughout the 24-week treatment period (see Section 6.1.2 Study Results Durability of Response and Persistence of Effect).

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

This medical reviewer did not identify any potential differences in efficacy with use in the clinical trial and how it will be used in the post-marketing setting. However, it is possible that once approved, it may be used off label, as have other GnRH agonists, in children with gender dysphoria who are not sure they wish to enter puberty with their genetic gender. Given that the future reproductive safety is not well characterized in that population, this could be considered a limitation of use.

7.2.2. Other Relevant Benefits

The less frequent dosing of this product, at once every 6 months compared to other injectables that are dosed at 1 or 3-month intervals, would be a clinical benefit with respect to improved compliance and fewer adverse injection reactions, assuming this product is not more likely than other currently approved products to produce severe injection site reactions.

7.3. Integrated Assessment of Effectiveness

Central precocious puberty is an orphan disease with an estimated prevalence of 1 in 5,000-10,000 children, girls ages under 8 years and boys ages under 9 years. This small pediatric population limits the number of new onset cases available to study this condition. Children with CPP are at risk for psychological and long-term health implications, as they enter puberty ahead of their peers and undergo premature bone maturation and earlier closure of their epiphyseal plates, resulting in decreased final adult height. The gold standard and only approved treatment for this condition is chronic GnRH agonist therapy, which inhibits pituitary gonadotropin secretion and suppresses testicular and ovarian steroidogenesis. This results in suppression of puberty and delays premature advancement of bone age. The pivotal study

TOL2581A was designed in a manner similar to previous studies used to approve GnRH agonists for treatment of CPP, as it is considered that a single adequately powered open-label study should be adequate for approval for this indication. Efficacy was determined by using LH suppression at week 24 (month 6), which is a well described surrogate for disease control in CPP. Secondary endpoints, including serum hormone levels and physical growth and maturation parameters, were used to support these findings. Fensolvi had been previously approved under the trade name Eligard at the same 45mg dose and for the same 6-month duration of therapy in adult males to limit gonadotropin-mediated testosterone production for the palliative treatment of advanced prostate cancer. Study TOL2581A was designed to determine if a similar dosing regimen would be effective in children with CPP, assuming there were no increased safety concerns with this dose in the pediatric population. At 24 weeks, Fensolvi demonstrated LH suppression to prepubertal levels in 87% of patients, and similar results were seen after 48 weeks with an 86% response rate following a second injection at week 24. Consistent with suppression in LH, estradiol levels were decreased to prepubertal levels in 98% and 100% of girls at 24 and 48 weeks, respectively, and testosterone was decreased to prepubertal levels in both boys at 24 weeks, although one boy had an increase in testosterone to just above the prepubertal level at week 48. In addition, growth velocity, which is accelerated in CPP, was consistently decreased from baseline at both 24 and 48 weeks and there was limited pubertal maturation as measured by Tanner staging in both girls and boys. The safety profile of Fensolvi in Study TOL2581A was similar to other approved GnRH agonists for the CPP indication; no new safety signals were identified. Fensolvi therefore provides an effective treatment for children with CPP, with the added potential benefit of a less frequent dosing regimen, i.e., once every six months compared to other currently marketed injectable GnRH agonists that are approved for dosing monthly or every 3 months.

8. Review of Safety

8.1. Safety Review Approach

The safety review included data on 64 subjects that received at least one injection of Fensolvi in study TOL2581A. The safety review focused on injection site reactions, which are the most common adverse reaction associated with injectable GnRH agonists. In addition, the nervous system body system or organ class (SOC) was monitored for signs of seizures/ convulsions and the psychiatric system SOC was monitored for signs of depression, emotional lability and suicidal ideation, which have been seen post-marketing with other approved GnRH agonists in children with CPP. As part of the safety review, the sponsor was also asked to perform a specific analysis looking for “acute-on-chronic” adverse reactions that could occur within the first two weeks after the second injection due to transient GnRH agonist stimulation. The safety profile of Fensolvi was also compared to 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 the 64 subjects who received at least one subcutaneous injection of Fensolvi. Three subjects were discontinued from the study prior to the second injection (see Section 6.1.2 Patient Disposition). The rest of the 61 subjects were followed for 48 weeks.

8.2.2. Relevant characteristics of the safety population:

The safety population (n=64) was essentially the same as the efficacy population (n=62) except for two patients that did not meet inclusion/exclusion criteria. Refer to Section 6.1.2, Table 5, for a summary of demographic characteristics and other baseline characteristics.

8.2.3. Adequacy of the safety database:

Medical officer's comment-The safety database was adequate for this orphan indication and conforms to what had been requested by the Agency.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Medical officer's comment- The data integrity and submission quality were adequate to perform the safety review. There were no issues with organization of the application or completeness of the safety information that affected the ability to perform an adequate review.

8.3.2. Categorization of Adverse Events

The applicant's definitions of adverse events and serious adverse events were accurate. Severity of adverse events was based on the NCI CTCAE severity grading scale, including (1) mild, (2) moderate, (3) severe, (4) life-threatening and (5) death. Treatment emergent adverse events (TEAEs) were defined as those occurring or worsening after the first study drug injection. TEAEs were categorized using MedDRA version 18.0 preferred terms or SOCs. Subjects with one or more adverse events in the same SOC or with the same preferred term were counted only once in that category. Any adverse events related to study drug were followed for 28 days or through resolution, stabilization, until deemed clinically insignificant, or until the subject was lost to follow-up. For serious adverse events, follow-up was required on an expedited timeline, within 24 hours of the initial report. Adverse event frequency was assessed per patient number and not patient-years, which was appropriate given the study duration.

Medical officer's comment- Adverse events were coded and categorized appropriately.

8.3.3. Routine Clinical Tests

Clinical safety laboratory tests, including hematology, chemistry and urine testing was performed at screening, week 4, week 24 and week 48. Hepatitis B and C and serum lipid panels were performed only at screening or baseline prior to dosing. Safety laboratory assessments included:

1. Hematology: Hemoglobin (Hb), hematocrit (Hct), red blood cell count (RBC), white blood cell count (WBC), reticulocyte count, platelets and automated differential count.
2. Chemistry: sodium, potassium, chloride, total CO2, blood urea nitrogen (BUN), creatinine, albumin, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), alkaline phosphatase (ALP), total bilirubin, uric acid, glucose, calcium, and total cholesterol.
3. Urinalysis: Dipstick (glucose, ketones, blood, protein and pH).
4. Pregnancy test: urine test in females only at day 1, week 24 and week 48.

Any abnormal hematology, serum chemistry, serum lipid, or urinalysis parameters considered clinically significant by the Investigator were to be captured as adverse events.

Medical officer's comment- The routine clinical tests were reasonable and adequate for the population and disease indication being investigated.

8.4. Safety Results

8.4.1. Deaths

There were no deaths in the Fensolvi clinical development program.

8.4.2. Serious Adverse Events

There were two CTCAE Grade 3 serious AEs observed in study TOL2581A, both in the same patient, subject (b) (6), an 8-year-old black female with a history of asthma, eczema and sensitivity to skin products. The patient had no problem with the first injection. Starting at 4 days prior to the clinic visit for a second injection, she developed a cough and was treated with OTC Triaminic syrup. On the day she returned for the second injection, she was noted to be wheezing, but the wheeze cleared with cough so the second Fensolvi injection was administered on schedule. She was referred to follow up with her pediatrician, who noted her to still be wheezing, though not in distress, and noted that she had developed a pruritic urticarial rash within 30 minutes of receiving the earlier injection. The rash was not present over the injection site. She was referred to the pediatric ER, where she was treated with inhaled albuterol and prednisone 60 mg and discharged to home on prednisone 20 mg TID, atarax 25 mg, and albuterol inhaler 2 puffs Q4hr. Mom initially delayed in filling the prescriptions and reported that the rash had progressed, and her lips became swollen. After mother filled the

prescriptions, her daughter improved and was reported as recovering.

Medical officer's comment- It is possible that the patient's bronchospasm was aggravated by the injection and the pruritic urticarial rash seems to be drug related given that it occurred so soon after the injection.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were no significant AEs that led to withdrawal from the study or stopping of the study drug, although subject (b) (6) experienced a Grade 1 "drug administration" error reported as drug interruption due to re-positioning. The AE resolved and the injection was successfully administered. Also, subject (b) (6) had a Grade 1 "drug administration interrupted" error because the syringe broke, which resulted in a delay in drug administration.

8.4.4. Significant Adverse Events

There were two Grade 3 adverse events, wheezing and rash, observed in the same patient, subject (b) (6), previously described above under section 8.4.2. There were also 23 Grade 2 adverse events in 14 patients that were considered not related to the study drug by the applicant. These included events such headache/migraine, nausea, fever, vomiting, gastritis/abdominal pain that could have been related to the trauma surrounding a painful subcutaneous injection, but only one of these, an episode of fever, was reported on the same day as study drug administration and so was temporally related. There were also 240 Grade 1 adverse events observed in 52/64=81% of the patients in the safety population following the initial drug injection. The most commonly reported Grade 1 adverse events per study subject were (n=20) injection site pain, (n=12) nasopharyngitis, (n=10) pyrexia, (n=9) headache, (n=8) cough, (n=6) injection site erythema and (n=5) abdominal pain. Of these, 16 different AEs were reported as study drug related (AEREL=related) and most dealt with injection site reactions: (n=17) injection site pain, (n=6) injection site erythema, (n=3) hot flush, (n=2) injection site induration, (n=2) injection site bruising, (n=1) injection site swelling, (n=1) injection site nodule, (n=1) drug administration error, (n=1) syringe issue, (n=1) headache, (n=1) fatigue, (n=1) irritability, (n=1) increased appetite, (n=1) emotional disorder, (n=1) condition aggravated and (n=1) nausea.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

AEs observed in 3 or more patients at any time during the open label study are included in Table 14, which was generated from the applicant's ADAE dataset by this medical reviewer. These data are consistent with the data in Table 23 of the Clinical Study Report and Table 2 in the applicant's Package Insert (PI), except that in the PI the applicant has chosen to organize the AEs in categories by higher order terms instead of sorting in order of individual preferred term frequency as reported here.

Table 14. AEs Occurring in ≥3 Subjects Treated with Fensolvi in Study TOL2581A

AEDECOD	Pt number	(n=64) %
Injection site pain	20	31
Nasopharyngitis	14	22
Pyrexia	11	17
Headache	10	16
Cough	8	13
Abdominal pain	6	9.4
Injection site erythema	6	9.4
Nausea	5	7.8
Bronchospasm	4	6.3
Constipation	4	6.3
Productive cough	4	6.3
Upper respiratory tract infection	4	6.3
Vomiting	4	6.3
Bronchitis	3	4.7
Hot flush	3	4.7
Influenza	3	4.7
Pharyngitis	3	4.7
Pharyngitis streptococcal	3	4.7
Sinusitis	3	4.7
Urinary tract infection	3	4.7

Source: SDN 1 ADAE dataset AEDECOD by SUBJID for n≥3
Pts with more than 1 AEDECOD term counted only once per term
Excluding events that occurred prior to initial injection TRTSDT > ASTDT

Given that these AEs occurred over the course of a year (with most events occurring outside the treatment window) in a pediatric population that is prone to childhood infections, this medical reviewer chose to look only at AEs that occurred within one day of either of the two subcutaneous injections. These AEs are reported in Table 15 and confirm that the AEs associated with the use of Fensolvi are primarily related to injection site reactions.

Table 15. AEs Occurring in Study TOL2581A within 1 Day of Injection with Fensolvi

AEDECOD	Pt number	(n=64) %
Injection site pain	19	30
Injection site erythema	6	9.4
Headache	2	3.1
Injection site bruising	2	3.1

AEDECOD	Pt number	(n=64) %
Injection site induration	2	3.1
Pyrexia	2	3.1
Drug administration error	1	1.6
Fatigue	1	1.6
Hot flush	1	1.6
Influenza	1	1.6
Injection site nodule	1	1.6
Injection site swelling	1	1.6
Lymphadenopathy	1	1.6
Nausea	1	1.6
Rash	1	1.6
Scoliosis	1	1.6
Skin abrasion	1	1.6
Syringe issue	1	1.6
Urinary tract infection	1	1.6
Wheezing	1	1.6

Source: SDN1 ADAE dataset ASTDT-TRTSDT=0 or 1 (First injection), or ASTDT-TRTEDT=0 or 1 (Second injection) AEDECOD by SUBJID, Pts with more than 1 AEDECOD term were counted only once per term

Medical Officer's comments-
The most frequent drug related AEs were related to injection site pain 30%, erythema 9%, headache 3%, bruising 3%, induration 3%, nodule 2%, or swelling 2%. These are similar to event rates seen with other approved GnRH agonists such as Triptodur [6]- (*injection site pain 45%, erythema 14%, pruritus 2%, or swelling 2%); and Lupron Depot-Ped [5]- (injection site pain 20%, injection site reactions including abscess 9%, or swelling 2%).*

There were 4 reports of hot flushes in 3 subjects (4.7%). Three of these were likely treatment related. One subject, (b) (6), had hot flushes reported on day 1 of the first injection and on day 4 of the second injection which resolved, and one subject, (b) (6) had hot flushes reported on day 14 after the first injection which were described as intermittent and ongoing at the end of the study. The final subject, (b) (6), had "hot flush" reported 130 days after the second injection which was likely unrelated. This event rate is similar to another approved GnRH agonist Triptodur [6] (4.5%).

Based on post-marketing experience with other currently marketed GnRH agonist formulations and the drug's mechanism of action, the SOC terms of Nervous System Disorder and Psychiatric Disorders were screened to look for evidence of seizure/convulsions or emotional lability/suicidality, respectively.

There was no evidence of seizures/convulsions in the Nervous System Disorder SOC. There were 10 patients with headache, 2 with migraine and 1 with pineal cyst. Of these events, the applicant considered only one of the cases of headache as related even though there were two patients with headaches observed on the day of the injection.

There were 3 adverse events in the Psychiatric Disorders SOC (4.7%). Of these only the events of irritability and emotional disorder were considered by the applicant to be drug related. The AE of irritability was reported as ongoing while the AE of emotional reaction was reported as resolved. There was also a case of insomnia that started on day 20 after the first injection which was ongoing, and which was not considered drug related by the applicant. This event rate is similar to what was seen with other approved GnRH agonists such as Triptodur [6]- (anxiety 2.3% and mood altered 2.3%); and Lupron Depot-Ped [5]- (emotional lability 5%).

In conclusion, there were no cases of convulsion in this study, but patients with a seizure disorder or taking concomitant medications that could predispose to seizure were excluded from the study, so the study results cannot rule out an effect on seizure threshold. Also, there were a small number of cases of emotional lability, which may be related to the study drug, but no evidence of suicidal ideation.

Acute-on-chronic response (AOC)-

Changes in behavioral or physical symptoms that may have been related to a potential acute-on-chronic response due to GnRH-stimulated increases in sex hormones occurring within 14 days after the second injection (Visit 5, Week 24) were collected via telephone contact evaluations (SDN5 ADEF dataset, VISIT=Telephone Contact #2). These telephone contacts identified 15 subjects complaining of injection site pain, 3 with injection site redness, and two with hot flushes: (b) (6). The study did not measure LH, FSH, estradiol or testosterone during this time period to confirm if they might have escaped LH and FSH suppression. This medical reviewer identified all AEs reported from day 0 to 14 after the second injection in the ADAE dataset to look for other AEs that might represent AOC response. Other AEs reported during the initial 14 days after the second injection that could have represented acute-on-chronic response include: fatigue, headache, and nausea. All of these AEs were only reported in one patient each. It appears that the hot flush reported by subject (b) (6), described in the second 14-day telephone contact ADEF dataset was not listed as a separate AE after the second injection and so was not listed in Table 16. This probably occurred because the hot flush reported by subject (b) (6), 14 days after the first injection was reported as ongoing for the rest of the trial, so it was not reported as a separate AE after the second injection.

Table 16. Reported AEs Occurring in Study TOL2581A within 14 Days after the Second Fensolvi Injection

AEDECOD	Patient number
Injection site pain	14
Injection site erythema	3
Drug administration error	1
Fatigue	1
Headache	1
Hot flush	1
Injection site induration	1
Ligament sprain	1
Nausea	1
Rash	1
Skin abrasion	1
Syringe issue	1
Wheezing	1

Source: SDN1 ADAE dataset ASTDT-TRTEDT=0 to ≤ 14 (Second injection)
AEDECOD by SUBJID, Pts with more than 1 AEDECOD term were counted only once per term

Medical Officer's comments-
A small number of patients had potential symptoms of acute-on-chronic phenomenon obtained from telephone contact information including: (n=2) hot flushes; (n=1) nausea, headache, and fatigue. However, the study did not monitor for hormone levels to identify acute-on-chronic phenomenon using laboratory criteria. While the risk appears small, it is not possible to better quantify the actual risk in Study TOL2581A.

8.4.6. Laboratory Findings

Clinical laboratory assessments (hematology, clinical chemistry, and urinalysis parameters) were assessed at screening, weeks 4, 24 and 48. No subjects had ALT or AST values > 3xULN during the trial. One subject, (b) (6) had GGT > 3xULN at 150 IU/L (3.6x ULN) on week 4, day 29. She also had an ALT value of 84 IU/L (2.4x ULN), AST of 38 (1.2x ULN) and elevated alkaline phosphatase 400 IU/L (1.3x ULN), but her total and direct bilirubin levels were normal. She was reported to have AEs of fever, vomiting and sinus infection within the week prior to the transaminase elevations, which were considered not related to the study medication according to the clinical investigator. All labs normalized and the AEs were reported as resolved by the next measurement at week 48 at end of treatment.

Table 17. Abnormal Chemistry Lab Values for Subject (b) (6)

Chemistry	Value	ULN	Day	Visit
ALP (IU/L)	447	300	-14	Screening
	400	300	29	Visit 2, Week 4
	190	300	169	End of Treatment, Week 48
ALT (IU/L)	17	35	-14	Screening
	84	35	29	Visit 2, Week 4
	27	35	169	End of Treatment, Week 48
AST (IU/L)	22	31	-14	Screening
	38	31	29	Visit 2, Week 4
	29	31	169	End of Treatment, Week 48
BILDIR (umol/L)	4	5	-14	Screening
	2	5	29	Visit 2, Week 4
	2	5	169	End of Treatment, Week 48
BILI (umol/L)	7	20	-14	Screening
	4	20	29	Visit 2, Week 4
	5	20	169	End of Treatment, Week 48
GGT (IU/L)	15	42	-14	Screening
	150	42	29	Visit 2, Week 4
	20	42	169	End of Treatment, Week 48

Source: SDN5 ADLB dataset SUBJID (b) (6) abnormal results are highlighted

Medical officer's comments-Given that the study drug injection occurred several weeks before the onset of what appears to be a viral illness, this medical reviewer agrees that this episode was likely not related to the study medication.

Subject (b) (6), who had an episode of rash and wheezing, described previously under section 8.4.2., also had moderately elevated ALT 70 IU/L (2x ULN) and AST 64 IU/L (2x ULN) noted at week 24, which probably were related to her acute illness. There were no follow up values recorded. No other subjects had significantly elevated chemistry values recorded during the study.

Urinalysis findings were normal for most patients except for a small number of girls and one boy who were noted to have blood or protein in isolated urine samples. Follow up urinalyses were normal except for two subjects in whom protein was noted only on the last visit and no follow up urinalysis was available.

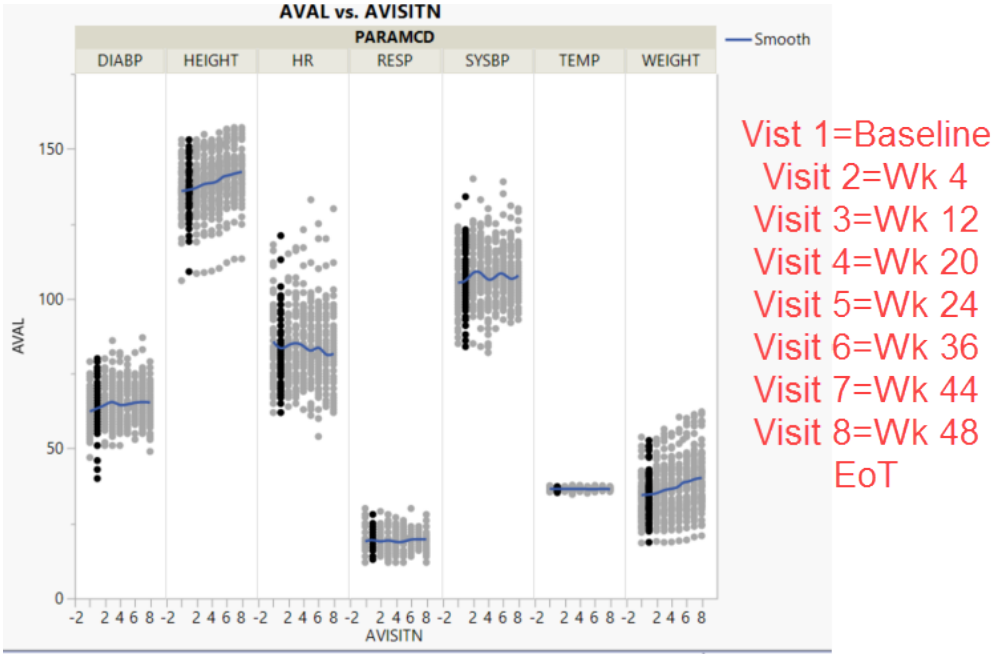
Serum lipid levels were assessed at screening or baseline only so were unrelated to the study treatment.

Hematology measurements were performed at screening, week 4, week 24 and week 48. Low WBC counts were seen in 29 subjects with values below the LLN (range 4,500 to 5,000 x10^6/L). The lowest values were seen in subject (b) (6), which ranged from 2,270 to 2.97 x10^9/L during the study but were above the screening value of 1,990 x10^6/L, so were unlikely to be due to study drug treatment. Subject (b) (6) was also the only subject to have absolute neutrophil counts below 500 x10^6/L, placing her at a higher risk of infection, but her low neutrophil counts were also seen at screening and so were unlikely to be due to the study treatment. Subject (b) (6) had a low WBC value of 2,970 x10^6/L at week 24 but did not have any subsequent hematology measurements to see if this resolved. Subject (b) (6) had a low WBC value of 3,000 x10^6/L at the week 48/end of study. All other subjects who had low WBC values had values above 3,000 x10^6/L. No subjects had WBCs above the ULN. Eight subjects had hematocrits below the LLN of 35% observed at weeks 24 and 48, but all values were above 33% and so were unlikely to be clinically relevant.

8.4.7. Vital Signs

Vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate and temperature) were measured at each of the study visits at baseline and weeks 2, 4, 12, 29, 24, 36, 44 and 48/end of study. Vital signs were measured prior to any blood draws. Values for all patients at each treatment visit are plotted in Figure 11, with baseline values (Visit 1) bolded for easier comparison. There is no clear trend for changes in diastolic or systolic BP, respiratory rate or temperature. There appears to be a slight trend for decrease in heart rate over the course of the study, which may be due to less patient anxiety associated with the treatment visits. There also is a clear trend for increase in height and weight as might be expected in growing children over the course of a 48-week study.

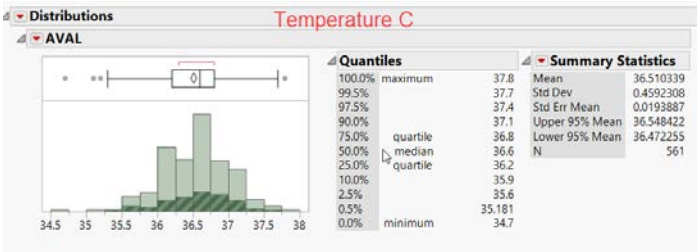
Figure 11. Safety Population Vital Signs by Study Visit in Study TOL2581A



Source: SDN5 ADVS dataset **Baseline values are bolded**, Bp is measured in mmHg, height is measured in cm, weight is measured in kg, temp in °C, and heart rate in beats/min.

There were 14 AEs of pyrexia reported, which were likely related to events outside the clinic visits as the maximal temperature at the clinic visits was 37.8 °C or 100 °F (Figure 12).

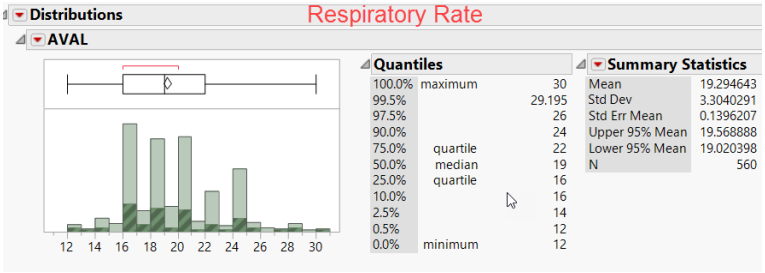
Figure 12. The Vital Sign of Temperature in Study TOL2581A



Source: SDN5 ADVS dataset **Baseline values are stippled boxes** PARAMCD=Temp

There were also 6 cases of bronchospasm and 3 cases of bronchitis reported as AEs, but the distribution of respiratory rate is similar between baseline and the course of the study (see Figure 13), with baseline and screening visits designated with the bold section of the boxes.

Figure 13. The Vital Sign of Respiratory Rate in Study TOL2581A



Source: SDN5 ADVS dataset **Baseline values are stippled boxes** PARAMCD=Resp

There were no AEs associated with changes in blood pressure (e.g., hypo or hypertension), heart rate (e.g., tachycardia, tachyarrhythmia), height or weight.

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

Not applicable.

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

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 leuprolide for use in CPP is not necessary.

In early clinical trials using leuprolide acetate in adult patients, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

In rats, subcutaneous administration of leuprolide acetate as a single dose 225 times the recommended human pediatric dose, expressed on a per body weight basis, resulted in dyspnea, decreased activity, and local irritation at the injection site. According to the applicant, there is no evidence that there is a clinical counterpart to this phenomenon.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Leuprolide is a GnRH agonist that has been previously well characterized in clinical studies. Within hours of a first administration of a GnRH agonist, there is a rapid, transient rise in gonadotropins and the gonadal hormones, estradiol and testosterone. An increase in clinical signs and symptoms of puberty may be observed during the first 2-4 weeks of therapy as gonadotropins and sex steroids rise above baseline because of the initial stimulatory effect of the drug before HPG axis suppression ensues. This may include “hot flushes” and transient increases in some symptoms of puberty such as vaginal bleeding. Outside of three events of “hot flush” that occurred within 2 weeks of drug administration, these events were not observed in the study TOL2581A.

Post-marketing reports have described convulsions or seizures in subjects receiving GnRH agonists. These reports often included patients with confounding factors such as history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients receiving concomitant medications associated with convulsions, such as bupropion and selective serotonin reuptake inhibitors. For this reason, a known history of seizures or use of medications that are associated with seizures were included as exclusion criteria in study TOL2581A. There were no adverse event safety reports of seizure or convulsion in study TOL2581A.

Psychiatric events have been reported in children taking GnRH agonists for treatment of CPP. These include emotional lability, such as crying, irritability, impatience, anger, aggression, depression, and rare reports of suicidal ideation. In TOL2581A, three subjects experienced AEs in the psychiatric system SOC. These AEs included irritability, emotional reaction and insomnia, only the first two of which were considered drug related by the applicant. The event rates were similar to what has been seen with other currently marketed GnRH agonists approved for the CPP indication.

Anaphylaxis has also been reported as a class effect. There were two cases of rash, and one case each of urticaria and hypersensitivity in the safety population, but no cases of anaphylaxis.

Injection site reactions are common with injectable GnRH agonist therapies, including rare cases of abscess formation. Reactions are likely due to the molecule, formulation, and site and route of administration. The number of injection site reactions seen in study TOL2581A was similar to what was described in the Package Inserts for other currently marketed injectable GnRH agonists, Lupron Depot-Ped and Triptodur.

8.9.2. Expectations on Safety in the Postmarket Setting

Because of its identical mechanism of action, Fensolvi is expected to have a similar safety profile to other marketed GnRH agonists approved for the CPP indication (Lupron Depot-Peds, Synarel, Supprelin LA and Triptodur). Regarding injection site reactions, Fensolvi, administered subcutaneously, might be expected to have a safety profile that is less severe than currently marketed GnRH agonist formulations that are administered intramuscularly, such as Lupron Depot-PEDS and Triptodur.

8.9.3. Additional Safety Issues From Other Disciplines

Not applicable.

8.10. Integrated Assessment of Safety

Fensolvi 45mg single subcutaneous injection every 6 months was well tolerated in children with CPP enrolled in the pivotal study TOL2581A. Fensolvi exhibited a safety profile consistent with other GnRH agonists approved for treatment of CPP. Of the 64 patients initially enrolled in the trial, there were no deaths and none withdrew due to an adverse event. Three subjects withdrew after only a single injection due to: (1) lack of efficacy, (2) withdrawal of parental consent and (3) need to take a concomitant medication that was exclusionary in the trial. The remaining 61 subjects completed the 48-week study. There were two Grade 3 severe events in a patient with ongoing bronchospasm that was exacerbated after her second injection and who developed a rash. She responded well to treatment with albuterol, prednisone and atarax. There were 23 Grade 2 moderate events in 14/64=22% of patients that included events such

headache/migraine, nausea, fever, vomiting, and gastritis/abdominal pain, all of which are common events occurring in children over the course of a year. Only one of these, an episode of fever, was reported on the same day as study drug administration and so was temporally related. Finally, there were 240 Grade 1 mild events in 52/64=81% of patients, including most commonly (n=20) injection site pain, (n=12) nasopharyngitis, (n=10) pyrexia, (n=9) headache, (n=8) cough, (n=6) injection site erythema and (n=5) abdominal pain. Of these, 16 were reported as study drug related (AEREL=related) and most dealt with injection site reactions: (n=17) injection site pain, (n=6) injection site erythema, (n=3) hot flush, (n=2) injection site induration, (n=2) injection site bruising, (n=1) injection site swelling, (n=1) injection site nodule, (n=1) drug administration error, (n=1) syringe issue, (n=1) headache, (n=1) fatigue, (n=1) irritability, (n=1) increased appetite, (n=1) emotional disorder, (n=1) condition aggravated and (n=1) nausea.

There were no clinically significant drug related adverse changes in clinical laboratory parameters, including serum chemistry, hematology or urinalysis, or in vital sign measurements, including temperature, respiratory rate, blood pressure or heart rate. WBC counts were mildly decreased in a subset of 29 patients, typically to between 3,000 $x10^6$/L and the lower limit of normal (4,5000-5,000 $x10^6$/L). Only one patient also had an absolute neutrophil count below 500 $x10^6$/L, but the low WBC and neutrophil counts had been present at screening so were unlikely to be study related.

A small number of patients had potential symptoms of acute-on-chronic phenomenon obtained from telephone contact information including: (n=2) hot flushes; (n=1) nausea, headache, and fatigue. However, the study did not monitor for hormone levels in the two weeks following the second injection to identify acute-on-chronic phenomenon using laboratory criteria. While the risk appears small, it is not possible to better quantify the actual risk.

Post-marketing safety data with other formulations of leuprolide, as well as other GnRH agonists, have identified seizures/convulsions and emotional lability/suicidal ideation as uncommon but potential class effects. There was no evidence of seizures/convulsions in the Nervous System Disorder SOC, but patients with a history of seizure disorder or taking medications associated with seizures were excluded from the trial, so the study results cannot rule out an effect on seizure threshold. There were 3 adverse events in the Psychiatric Disorders SOC (4.7%). Of these, only the events of irritability and emotional disorder were considered by the applicant to be drug related. The AE of irritability was reported as ongoing, while the AE of emotional reaction was reported as resolved. There was also a case of insomnia that started on day 20 after the first injection, which was ongoing and was not considered drug related by the applicant. There were no reports of suicidal ideation in this study. The event rate for psychiatric disorders/emotional lability seen in study TOL2581A is similar to what was seen with other approved GnRH agonists such as Triptodur [6]- (anxiety 2.3% and mood altered 2.3%); and Lupron Depot-Ped [5]- (emotional lability 5%). These GnRH agonist class safety concerns can be adequately addressed in labeling.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The PI dated 6/2019 and submitted as part of the original application SDN1 was reviewed below. The following labeling changes are recommended.

Highlights
DOSAGE AND ADMINISTRATION
Delete:

- [redacted] (b) (4)

Include the following text instead:

- Must be administered by a health care professional. (2.1)
- Administer FENSOLVI as a single subcutaneous injection of 45 mg once every six months. (2.1)
- Monitor response with LH levels after a GnRH or GnRH agonist stimulation test, basal LH, or serum concentration of sex steroid levels beginning 1 to 2 months following initiation of therapy, during therapy as necessary to confirm maintenance of efficacy, and with each subsequent dose. (2.2)
- Measure height every 3 to 6 months and monitor bone age periodically. (2.2)
- See FPI for reconstitution and administration instructions. (2.3)

Full Prescribing Information

2 DOSAGE AND ADMINISTRATION

1.2 Monitoring

Include the following text:

If the dose of FENSOLVI is not adequate, switching to an alternative GnRH agonist for the treatment of CPP with the ability for dose adjustment may be necessary.

4 CONTRAINDICATIONS

Include the following text:

- Pregnancy: FENSOLVI may cause fetal harm [see Use in Specific Populations (8.1)].

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Update text and table to round percentages and numbers to the nearest whole number.

Correct the incidence of injection site pain from (b) (4)% to (b) (4)%.

6.2 Postmarketing Experience

This information was taken from Lupron Depot-Ped PI and is out of date. Recommend updating with information from current MedWatch data. The following table was generated using Mercado Quick Search to identify post marketing reports for the active ingredient “leuprolide” or “leuprolide acetate” observed in children 1 to 17 years of age with at least seven case reports per preferred term.

Preferred Term	**Case Count**
Weight increased	47
Gait disturbance	43
Dizziness	34
Mood swings	25
Arthralgia	23
Insomnia	23
Product dispensing error	23
Dyspnoea	20
Epiphysiolysis	19
Pruritus	17
Muscle spasms	16
Vaginal haemorrhage	14
Vasodilatation	14
Asthenia	13
Myalgia	13
Oedema peripheral	13
Acne	12
Menstrual disorder	12
Back pain	11
Metrorrhagia	11

Preferred Term	Case Count
Syncope	11
Alopecia	10
Bipolar disorder	10
Breast enlargement	10
Gait inability	10
Paraesthesia	10
Bone pain	9
Decreased appetite	9
Diarrhoea	9
Fall	9
Focal nodular hyperplasia	9
Hair growth abnormal	9
Bone disorder	8
Chest pain	8
Hypertension	8
Malaise	8
Vision blurred	8
Weight decreased	8
Hallucination	7
Hyperhidrosis	7
Skin discolouration	7

8 USE IN SEPCIFIC POPULATIONS

8.1 Pregnancy

Recommend updating with correct information from the original Lupron label prior to changes made to the Lupron Depot-Ped label.

10 OVERDOSAGE

Recommend deleting text that includes (b) (4) information as it is not helpful.

(b) (4)

13 NONCLINICAL TOXICOLOGY 14 CLINICAL STUDIES

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Recommend updating with correct information from the original Lupron label prior to changes made to the Lupron Depot-Ped label.

14 CLINICAL STUDIES

Applicant needs to revise the data to correspond to the revised ITT population of 62 patients, and safety population of 64 pts.

Applicant needs to clarify estradiol data, which is referred to in this section.

Applicant needs to update LH data on 8 non-responders, not (b) (4) as currently mentioned in the text.

Recommend deleting (b) (4) data in Table 4 (b) (4) and so is misleading.

Recommend deleting (b) (4)

(b) (4)

10.2. Nonprescription Drug 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 leuprolide formulations and all indications is estimated at >3 million treatment-years through August 2015.

12. Postmarketing Requirements and Commitments

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. Based on post-marketing 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 have been initiated:

For a period of 5 years, the applicant should submit all cases of suicidal ideation and behavior, self-injury, or depression reported with Fensolvi as 15-day alert reports, and provide detailed analyses of suicidal ideation and behavior, self-injury, or depression events reported from clinical studies and post-marketing 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 Fensolvi should also be provided in the periodic safety report.

13. Appendices

13.1. References

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https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020263s042lbl.pdf

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https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022058s016lbl.pdf

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(b) (4)

10. Hernandez MI, Martinez-Aguayo A, Cavada G, Avila A, Iniguez G, Mericq V. Leuprolide acetate-stimulated androgen response during female puberty. Clin Endocrinol (Oxf). 2015 Aug;83(2):205-11.

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): TOL2581A

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 27		
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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____		

Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	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)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WILLIAM A LUBAS
04/15/2020 01:41:09 PM

SHANNON D SULLIVAN
04/15/2020 01:58:35 PM