CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213150Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	April 28, 2020
From	Shannon Sullivan, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	213150
Applicant	Tolmar
Date of Submission	July 2, 2019
PDUFA Goal Date	May 2, 2020
Proprietary Name	Fensolvi
Established or Proper Name	Leuprolide acetate
Dosage Form(s)	Injectable suspension for subcutaneous use
Applicant Proposed Indication(s)/Population(s)	Treatment of central precocious puberty (CPP) in pediatric patients 2 years of age and older
Applicant Proposed Dosing Regimen(s)	45 mg subcutaneously every 6 months
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	Treatment of central precocious puberty (CPP) in pediatric patients 2 years of age and older
Recommended Dosing Regimen(s) (if applicable)	45 mg subcutaneously every 6 months

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Fensolvi 45 mg subcutaneous injection is a long-acting gonadotrophin releasing hormone (GnRH agonist) that is approved for palliative treatment of advanced prostate cancer (Eligard, NDA 21731, approved 2004) 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 ~23:1 in girls vs. boys. CPP is characterized by early onset of pubertal development, in girls ages 2 to 8 years and boys ages 2 to 9 years. CPP is diagnosed by a pubertal LH response to a short-acting GnRH agonist (GnRHa) stimulation test. GnRHa-stimulated LH levels are also used during treatment to monitor response to therapy. Early puberty may cause psychological distress and social isolation because patients undergo physical body changes ahead of their peers. CPP also promotes bone age advancement, which leads to early closure of epiphyseal plates and diminished final adult height if not treated. GnRH agonists are considered the gold standard of care for children with CPP, as these drugs reversibly suppresses the hypothalamic-pituitary-gonadal (HPG) axis, resulting in suppression of pubertal development and slowing of bone age advancement. 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, NDA 20109) and Triptodur (triptorelin pamoate for depot suspension, NDA 208956).

The applicant has demonstrated the safety and efficacy of Fensolvi 45mg subcutaneous injection administered every 24 weeks in a single pivotal study, TOL2581A, an open-label, single-arm, 48-week study in 64 children (62 girls and 2 boys) with CPP.

In the primary analysis, 87% of patients achieved pre-pubertal levels of GnRHa-stimulated LH (< 4 IU/L) at 24 weeks; a similar level of LH suppression (86%) was seen at 48 weeks. Secondary efficacy endpoints supported the primary efficacy findings: consistent with suppression in LH, estradiol levels were decreased to pre-pubertal levels in 98% and 100% of subjects at 24 and 48 weeks, respectively, and testosterone was decreased to pre-pubertal levels in the two boys in the study at 24 weeks, although one boy had an increase in testosterone to just above the pre-pubertal 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 every 24-weeks in the treatment of children with CPP. Administration of Fensolvi was overall 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 injection site pain (30%), erythema (9%), bruising (3%), induration (3%), nodule (2%) and swelling (2%), which are expected ARs from a subcutaneous injection. After the second injection, 8% of patients experienced symptoms of acute-on-chronic (AOC) effect, a transient stimulation of the HPG axis in the setting of chronic suppression. Reported potential AOC symptoms included hot flushes reported in two patients during the two weeks following the second dose. Symptoms of AOC effect are expected with the use of sustained-release GnRH agonists in children with CPP based on the drug's mechanism of action 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. In Study TOL2581A, 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, however, 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 (n=1 each), 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 of Fensolvis is 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 ~23:1 in girls vs. boys. • CPP is characterized by early onset of pubertal development, <8 years of age in girls and <9 years in boys.	
Current Treatment Options	• GnRH agonists are considered standard of care treatment for CPP, as these drugs reversibly suppress the HPG axis and thus pubertal development. • 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)	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• For the primary efficacy endpoint, 87% of patients achieved pre-pubertal levels of GnRH-stimulated LH (< 4 IU/L) at month 6, and a similar level of LH suppression was seen at month 12 (86%). • At month 6, 98% of girls and 100% of boys achieved pre-pubertal gonadal hormone levels, and at month 12, 100% of girls and 50% (1 of 2) of boys achieved pre-pubertal gonadal hormone levels.	The product is clearly efficacious in suppressing the HPG axis and puberty in children with CPP, with a safety profile that is similar to other approved GnRH agonists in children. No new safety signals were identified. The less frequent dosing of this product at once every 6 months compared to other injectable GnRH agonist formulations that are dosed at 1 or 3-month intervals, and the subcutaneous rather than intramuscular method of administration, may provide clinical benefit with respect to improved compliance and fewer adverse injection site reactions.
Risk and Risk Management	• The most common adverse reactions were related to injection site reactions including injection site pain (30%), erythema (9%), bruising (3%), induration (3%), nodule (2%) and swelling (2%), which is expected from a drug delivered by subcutaneous injection. • Overall, 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. Safety information for this product will be adequately communicated in product labeling. No REMS or Post-Marketing Requirements are necessary.

2. Background

On July 2, 2019, Tolmar submitted NDA 213150 for leuprolide acetate (LA) 45 mg for subcutaneous injection (trade name, 'Fensolvi') under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for treatment of central precocious puberty (CPP) in children >2 years of age. The proposed product is the same as Tolmar's currently marketed leuprolide acetate 45 mg 6-month formulation (NDA 021731, ELIGARD), approved in 2004 for palliative treatment of advanced prostate cancer. Tolmar has right of reference to NDA 021731 and will use non-clinical and CMC information from ELIGARD to support the current application. In addition, Tolmar is referencing NDA 020263 (Lupron Depot-Ped, 7.5 mg, 11.25 mg, and 15 mg for 1-month administration and 11.25 mg or 30 mg for 3-month administration formulations, approved 1993) for additional non-clinical information that is relevant to the pediatric CPP indication. Tolmar has thus identified NDA 020263 as the RLD for this 505(b)(2) NDA.

CPP is a rare disease afflicting 1 in every 5,000 to 10,000 children that is characterized by early sexual development (prior to age 8 years in girls and age 9 years in boys) due to premature activation of the hypothalamic-pituitary-gonadal (HPG) axis. Importantly, if left untreated, premature puberty can result in premature closure of the epiphyseal growth plates, resulting in reduced final adult height, and may have significant psychological ramifications as patients enter puberty much earlier than their peers. GnRH agonists are considered standard of care for patients with CPP because these drugs reversibly suppress the HPG axis. At the initiation of treatment, GnRH agonists bind and activate pituitary GnRH receptors, resulting in an initial transient stimulation of gonadotropin release, followed by receptor desensitization and suppression of gonadotropin secretion to pre-pubertal levels. Effects are completely reversible following drug discontinuation, thus treatment to suppress puberty is typically continued until the average age of normal puberty and then discontinued to allow endogenous puberty to progress at an appropriate age. The Applicant believes the reduced injection frequency and the subcutaneous (rather than intramuscular) mode of administration of the proposed leuprolide acetate formulation will improve compliance and reduce the frequency of injection site reactions compared to other available GnRH agonist formulations.

Regulatory Backgound

Major regulatory interactions between DGE (formerly DMEP) and the Applicant regarding the development program for the CPP indication are discussed below.

On July 31, 2014, the Applicant requested a pre-IND meeting, for which the Division agreed to provide written responses only (WRO). On September 29, 2014, the Division sent the Applicant final responses regarding the design and conduct of a pivotal phase 3 trial to support approval of the leuprolide acetate 45 mg 6-month formulation for the CPP indication (including the planned patient

population, criteria for diagnosing CPP, primary and secondary efficacy endpoints, and pharmacokinetic assessments), request for waiver of studies in patients under two years of age, and the appropriate regulatory pathway through which to submit an NDA. It was communicated to the Applicant at that time that although no new non-clinical data would be needed to support the CPP indication, information on impairment of fertility, which is not present in the ELIGARD (NDA 021731) label, should be included in section 8.1 of a label for treatment of CPP.

On February 6, 2015, IND 123631 was opened to initiate Study TOL2581A, an open-label, single arm, phase 3 pivotal trial investigating the efficacy, safety and pharmacokinetics of leuprolide acetate 45 mg for injectable suspension in treatment-naïve girls 2-8 years of age and boys 2-9 years of age with CPP. The Division provided non-hold comments to the Applicant at that time.

On December 24, 2014, the Applicant submitted an initial Pediatric Study Plan (iPSP) requesting a waiver for studies in children under 2 years of age. This iPSP was found to be acceptable by the Division and the Pediatric Review Committee (PeRC) after minor revisions (submitted 6/3/2015), and an Agreed iPSP was communicated to the Applicant on 10/9/2015.

The proposed proprietary name for this product ('Fensolvi') was found to be conditionally acceptable by the Division of Medication Error Prevention and Analysis on 6/8/2018.

On 10/16/2018, the Applicant requested a Type B, Pre-NDA meeting for guidance on administrative, regulatory, statistical, labeling, and human factors questions related to submission of an NDA. A teleconference was granted and cancelled due to inclement weather, and written responses were provided to the Applicant on 1/9/2019 and 1/23/2019. The Division agreed that it was acceptable to submit a new NDA via the 505(b)(2) pathway with clinical data from Study TOL2581A and to cross-reference NDA 021731 (ELIGARD) for non-clinical and CMC information.

NDA 213150 was submitted on July 2, 2019.

On September 13, 2019 (at the time of filing), the Applicant was sent an Information Request (IR) requesting that they reanalyze the efficacy data using a new ITT population after the statistical reviewer noted that subjects who had discontinued from the study after only a single injection were inappropriately excluded from the original efficacy analyses. This re-analysis was submitted to the NDA as supporting document number (SDN) 5 on November 15, 2019. Both the statistical and clinical reviewers (Drs. He and Lubas, respectively) confirmed that the Applicant's revised efficacy dataset supported the efficacy of the current product. Therefore, this CDTL review will discuss only the data as it pertains to the revised ITT population submitted in SDN5.

3. Product Quality

No new CMC information was submitted for this application; all CMC information is cross-referenced from NDA 021731. Fensolvi (45 mg, leuprolide acetate for injectable suspension) is a polymeric matrix formulation of leuprolide acetate intended for subcutaneous injection once every 6 months. The Fensolvi 45 mg drug product consists of a two-syringe mixing system and a sterile needle. One syringe contain (b) (4) mg of a sterile, polymeric solution of (b) (4) % 85:15 poly (DL-lactide-co-glycolide) (PLG) and (b) (4) % Nmethyl-2-pyrrolidone (NMP) [Atrigel]. The second syringe contains (b) (4) mg of leuprolide acetate. The two syringes are ned and the single dose product is mixed until it is homogenous prior to subcutaneous administration.

4. Nonclinical Pharmacology/Toxicology

No new non-clinical information was submitted; all non-clinical data is cross-referenced from NDA 021731 and from FDA's findings of saferty and effectiveness for Lupron Depot-PEDS (NDA 020263).

5. Clinical Pharmacology

The Clinical Pharmacology reviewer, Dr. Suryanarayana Sista, recommended approval of Fensolvi for the treatment of CPP. For a detailed discussion, refer to the Clinical Pharmacology review in DARRTS dated 3/24/20. Overall, the clinical pharmacology review team concluded that the PK/PD data submitted in this application supports the proposed dose of 45 mg subcutaneously administered every 6 months in children with CPP and provides acceptable PK data for labeling purposes.

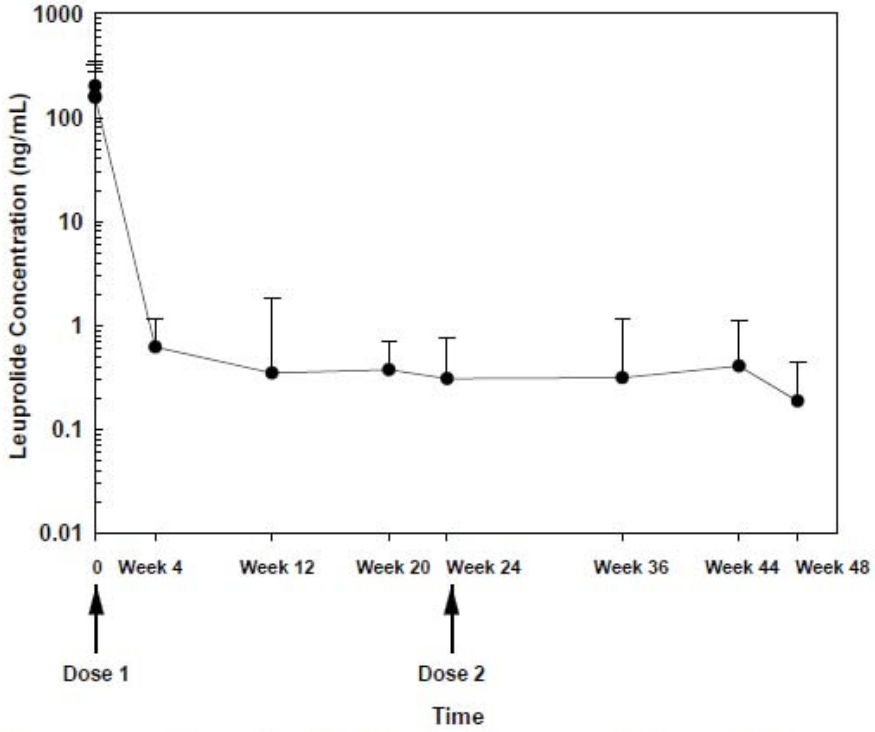
The ITT population was used for PK analyses and included 62 subjects who received at last one dose of study drug. PK/PD analyses in the pivotal phase 3 trial included characterization of the PK for 6 hours after the first dose (described as the 'burst' kinetics) and characterization of the PK/PD relationship of leuprolide serum concentrations to concentrations of serum LH, FSH, and testosterone(T)/estradiol (E2) over 2 dosing intervals.

Pharmacokinetics

Mean (± s.d.) serum leuprolide acetate concentrations increased rapidly after the first dose ('burst phase'), with a Cmax of 216±163 ng/mL at 4 hours post-injection (Tmax). The area under the leuprolide concentration-time curve (AUC) during the initial burst phase ($AUC_{0–6}$ hr

after the first dose: 40 ± 30 day•ng/mL) accounted for only a small portion of the overall AUC during the first dosing interval (AUC_{0-169} days: 2,720 ± 2,602 day•ng/mL). Mean leuprolide acetate serum concentrations decreased to 0.63 ± 0.55 ng/mL at 4 weeks post-injection and to 0.35±1.5 ng/mL at 12 weeks post-injection, followed by plateaued levels until the second dose at Week 24 ('plateau phase'), indicating a constant, sustained release of leuprolide acetate over the 6-month dosing interval (Figure 1). The 24-week PK measurements did not demonstrate a burst in leuprolide acetate levels that may be expected immediately after a second injection, however, only sparse PK sampling was performed at week 24 to minimize blood draws. Mean serum leuprolide acetate concentrations during the plateau phase were similar after the second dose of study drug, indicating no accumulation after repeat administration.

Figure 1. Serum Leuprolide acetate concentrations after SC injection in subjects with CPP (n=58)



Data source: Clinical Study TOL2581A; converted to ng/mL for comparison to ELIGARD

Pharmacodynamics
During the burst phase after the first SC injection of leuprolide acetate, serum LH concentrations increased by ~12-fold above basal levels at 4 hours post-injection (mean LH: 3.4 IU/L at baseline; 43.4 IU/L at 4 hours), and serum FSH concentrations increased by ~7-fold above basal levels at 6 hours post-injection (mean FSH: 3.9 IU/L at baseline; 26.3 IU/L at 6 hours). Both LH and FSH levels decreased to suppressed (e.g., pre-pubertal) levels rapidly thereafter, such that mean basal LH levels decreased from 3.4 ± 9.7 IU/L at baseline to 0.8 ± 1.6 IU/L at Week 4 (77% decrease) and mean basal FSH levels decreased from 3.9 ± 2.5 IU/L at baseline to 0.99 ± 0.95 IU/L at Week 4 (73% decrease). In concert with the suppression of LH and FSH, serum estradiol (girls) and testosterone (boys) levels were also suppressed after sustained exposure to leuprolide acetate. At 4 weeks post-injection, mean serum estradiol levels decreased from ~95 ± 90 pmol/L to ~54 ± 94 pmol/L, and levels remained suppressed for the duration of the 24-week treatment period. Serum testosterone concentrations (n=2) exhibited a similar pattern of suppression. After a second injection at week 24, levels of LH, FSH, estradiol, and testosterone remained suppressed out to week 48.

Overall, the PK/PD profile of leuprolide acetate 45 mg is similar to that of other long-acting injectable GnRH agonist formulations approved for treatment of CPP (e.g., Lupron Depot-PEDS and Triptodur).

6. Clinical/Statistical- Efficacy

I will briefly review the design and results of Study TOL2581A, the single pivotal, open-label study evaluating efficacy and safety of Fensolvi in children with CPP. The statistical review for efficacy performed by Dr. Jiwei He confirmed the sponsor's results for the primary and secondary efficacy analyses. Efficacy findings were also confirmed by the primary clinical reviewer, Dr. Lubas, and are discussed in detail in his review. Refer to the primary clinical review by Dr. William Lubas, dated 4/15/20, and the primary statistical review by Dr. He, dated 3/25/20 in DARRTS, for additional details.

TOL2581A was a multi-center, open-label, single-arm, 12-month study evaluating the safety, efficacy, tolerability, and PK/PD of leuprolide acetate 45 mg for subcutaneous injection ('Fensolvi') in 64 treatment-naïve pediatric subjects diagnosed with CPP (n=62 girls and 2 boys, consistent with the gender distribution in the CPP population). Study TOL2581A, considered a pivotal trial to support approval, was performed at 25 sites across 6 countries, with about half of the patients from the US. Majory inclusion criteria included females age 2-8 years and males age 2-9 years; a confirmed diagnosis of CPP within 12 months of enrollment without prior GnRH agonist therapy; pubertal LH response to a standard GnRHa stimulation test (LH >5 IU/L); clinical evidence of puberty based

on Tanner staging; and bone age (BA) > chronological age (CA) by at least 1 year. Major exclusion criteria included gonadotropin-independent (peripheral) precocious puberty; prior or current GnRH agonist treatment; isolated premature thelarche; unstable intracranial tumor or intracranial tumor requiring neurosurgery or radiation; any chronic condition or treatment that may interfere with growth (e.g., chronic steroid use, renal failure, diabetes, scoliosis, etc.); prior or current treatment with medroxyprogesterone, growth hormone, or IGF-1; diagnosis of short stature (height < -2.25 SD height-for-age); and history of seizures or use of medications associated with seizures.

Subjects received study drug at the start of the study and at Week 24, and were followed for 48 weeks with assessments of safety, efficacy, and PK/PD at screening, baseline, and at Weeks 4, 12, 20, 24, 36, 44, and 48 (end of treatment). Subjects were considered to have completed the trial if they received both injections of study drug, at baseline and 6 months. Of the 64 study subjects who received at least one dose of drug, 60 (94%) were considered study completers. The ITT population included 62 subjects who received at least one dose of study drug and did not have any protocol violations/deviations. Of the original 64 patients, two subjects (601-606 and 612-602) did not meet the inclusion/exclusion criteria (considered protocol violations) and were thus excluded from the ITT population (subject 601-606 due to a history of seizures and subject 612-602 due to less than a one-year difference between BA and CA).

The primary efficacy endpoint was percentage of subjects with suppression of GnRHa-stimulated LH at Week 24. It was pre-determined with the Agency that based on response rates from other approved GnRH agonists in the CPP population, Fensolvi would be considered effective for the treatment of children with CPP if ≥80% of subjects exhibited LH suppression (defined as LH <4 IU/L) at Week 24. Secondary efficacy endpoints included changes in basal and GnRHa-stimulated serum LH, FSH, estradiol, and testosterone levels; Tanner stage; growth velocity; and ratio of bone age: chronological age.

Of the 64 patients enrolled, 62 were girls and 2 were boys, which is consistent with the gender distribution of patients with CPP in the general population. The mean (±SD) patient age was 7.5 ± 0.9 years (range 4-9 years). Thirty-four (53%) patients were white, 15 (23%) were black, and 3 (5%) were Asian. Refer to Dr. Lubas's review for details regarding subjects' co-morbid conditions and concomitant medications and major/minor protocol deviations, none of which were considered to have compromised the results of the study.

Efficacy Results

Primary endpoint

87% (54/62) of subjects in the ITT population achieved the primary efficacy endpoint of LH <4 IU/L at Week 24. Based on a pre-specified level of LH suppression of >80% of patients at week 24 to establish efficacy in the CPP population, Fensolvi 45 mg every 6 months is considered an effective treatment for this condition. The two subjects excluded from the ITT population also had LH

suppression from Week 12 to the end of treatment (Week 48). Of the 8 patients who did not achieve LH suppression < 4 IU/L at Week 24, five demonstrated LH suppression following the second injection at Week 48, for a response rate at Week 48 of 95% (59/62) in the ITT population. Overall, LH levels were suppressed in >80% of subjects in the ITT population at Weeks 12, 24, 36, and 48, indicating chronic HPG axis suppression and durability of response to the drug.

There was no difference in the primary efficacy endpoint based on age (< 8yrs, 82%; ≥8yrs, 87%), gender (females, 81%; males, 100%), race (American Indian +Asian +Native Hawaiian, 80%; black, 87%; white, 84%), or ethnicity (Hispanic or Latino, 89%; Not Hispanic or Latino, 85%).

Secondary endpoints

Changes in secondary endpoints provided supportive data for the efficacy of Fensolvi for the treatment of CPP.

Gonadal hormone levels

At Week 24, 75% of subjects in the ITT population exhibited suppression of FSH, and serum estradiol and testosterone levels were suppressed to pre-pubertal levels in 98% of girls and 100% of boys, respectively (defined as estradiol < 73 pmol/L and total testosterone <1 nmol/L). 96% of girls maintained suppressed estradiol levels throughout the 48-week study, and both boys maintained suppressed testosterone throughout the study, except for one boy who had a total serum testosterone slightly above the pre-pubertal cutoff at Week 48 (1.5 nmol/L)(Table 1). All of the patients considered LH non-responders at Week 24 who remained in the study (7 of 8 subjects, all female) had suppressed estradiol levels after the second dose of study drug.

Table 1. Summary of hormone suppression response rates in Study TOL2581A (ITT population)

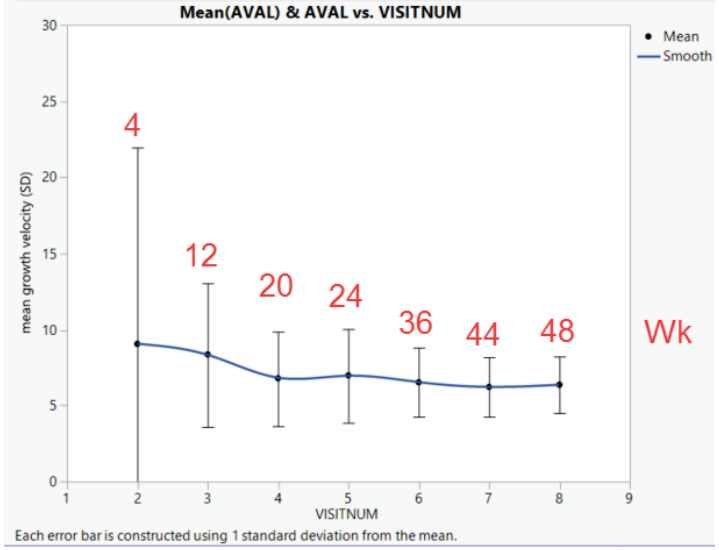
	Responders/Number Assessed (%)			
Study Visit	**FSH**	**E2**	**E2(HS)**	**Testosterone**
Visit 3 (W12)	37/59 (62.7)	57/57 (100.0)	56/57 (98.2)	2/2 (100.0)
Visit 5 (W24)	41/59 (69.5)	57/57 (100.0)	56/57 (98.2)	2/2 (100.0)
Visit 6 (W36)	26/59 (44.1)	57/57 (100.0)	56/57 (98.2)	2/2 (100.0)
EoT (W48)	32/59 (54.2)	56/57 (98.2)	55/57 (96.5)	1/2 (50.0)

Note: Response is defined as serum FSH <2.5 IU/L, E2 & E2(HS) <73.4 pmol/L, testosterone <1 nmol/L, at 30 minutes following an abbreviated GnRHa Stimulation Test.
E2=estradiol results from the chemiluminescent immunoassay, E2(HS)=estradiol results from the high-sensitivity assay, FSH=follicle stimulating hormone, W=week, EoT=end of treatment.
Source: Table 14.2.1.1.2 in the CSR

Growth velocity

Growth velocity is accelerated in children with CPP due to premature bone maturation, which ultimately leads to premature ephiphyseal fusion and reduced final adult height. Treatment with GnRH agonist therapy is expected to slow the rate of bone maturation, thereby slowing growth velocity and preserving final height. In study TOL2581A, there was a trend toward a decrease in bone age: chronological age during the course of the study. Further, growth velocity decreased from baseline to Week 20, followed by a plateau before the second dose of study drug, and then decreased again from Week 24 to Week 44, coinciding with the second dose of study drug (Figure 2).

Figure 2. Growth Velocity (cm/year) by Study Visit in Study TOL2581A (ITT population)



Source: Figure 6, Primary Clinical review, taken from SDN5 ADEF2 dataset plotted as AVAL vs. VISITNUM

Tanner Staging

There was no increase in Tanner stage from baseline for development of external genitalia in boys (100%) or breast development in girls (100%). In most patients (79%), there was no increase in Tanner stage for pubic hair from baseline.

Overall, these secondary endpoints provide supportive data for effective HPG axis suppression by Fensolvi.

7. Safety

Major safety concerns related to GnRH agonists as a class in the CPP population include injection site reactions with injectable formulations, rare immune-allergic reactions/anaphylaxis, side effects due to transient increases in gonadal hormone production at the initiation of treatment and following subsequent doses (termed 'acute-on-chronic' effect, 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 symptoms, including depression, emotional lability, and rarely, suicidal ideation, and increased risk of seizures/convulsions have also been reported. In Study TOL2581A, subjects were monitored for injection site reactions, psychiatric system organ class (SOC) adverse events (AEs) and nervous system SOC AEs, and for 'acute-on-chronic' adverse reactions in the two weeks following the second dose of study drug.

All 64 subjects enrolled in Study TOL2581A received at least one dose of Fensolvi and were included in the Safety Population. Safety endpoints included changes in vital signs, weight, physical examination, clinical laboratory assessments (including hematology, chemistries, urinalysis, and pregnancy test in females), adverse events and serious AEs.

Serious Adverse Events (SAEs) in Study TOL2581A
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.

There were no deaths in the clinical development program for this product. There were no AEs that led to study withdrawal or study drug discontinuation.

There were two Grade 3 SAEs, all observed in the same patient, an eight year-old black girl with underlying asthma and eczema who developed wheezing and a pruritic urticarial rash within 30 minutes after receiving the second injection of study drug. The patient was sent the the ER and was treated with albuterol, prednisone, and atarax, and her symptoms subsequently improved. The pruritic rash was considered to be likely drug-related given the temporal relationship with the second injection of study drug (of note, the patient had no allergic-type reaction with the first dose).

There were 23 Grade 2 AEs in 14 patients (22%) considered not to be related to study drug by the sponsor, including headache, nausea, fever, and gastritis/abdominal pain. 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 AEs observed in 52 patients (81%) in the safety population. The most common Grade 1 AEs were injection site pain (n=20); nasopharyngitis (n=12); pyrexia, headache (n=9 each); cough (n=7); and abdominal pain (n=5). AEs associated with the subcutaneous injection (and thus considered study drug-related)

included injection site pain (n=20), injection site erythema (n=6), injection site induration and injection site bruising (n=2 each), injection site swelling (n=1), and injection site nodule (n=1). Of note, the rates of injection site reactions seen in Study TOL2581A were similar to events rates seen with other approved injectable GnRH agonists. Other Grade 1 AEs included drug administration error, syringe issue, headache, fatigue, irritability, increased appetite, emotional disorder, and nausea (n=1 each). Of the Grade 1 AEs, the following were considered study drug related: injection site pain (n=20); injection site erythema (n=6); hot flush (n=3); injection site induration and injection site bruising (n=2 each); and injection site swelling, injection site nodule, drug administration error, syringe issue, headache, fatigue, irritability, increased appetite, emotional disorder, and nausea (n=1 each). There were no reports of seizures or convulsions, however, patients with underlying seizure disorder or taking concomitant medications associated with seizure were excluded from the trial. There were two reports of mild AEs in the Psychiatric System SOC, noted above (e.g., irritability and emotional disorder, n=1 each), but no reports of depressed mood or suicidal ideation. There were also no reports of worsening of pubertal symptoms in the first 2-4 weeks after the initial dose of study drug.

Acute-on-chronic response

The sponsor assessed (via telephone contact) changes in behavorial or physical symptoms that may be related to acute-on-chronic (AOC) response within two weeks after the second dose. Two subjects reported hot flushes, and no other AOC signs or symptoms were reported. However, subjects' levels of LH, FSH, estradiol, and testosterone were not collected during this time due to sparse PK/PD sampling in a pediatric population, and therefore, whether or not potential symptoms of AOC phenomenon were due to transient increases in gonadal hormone levels cannot be confirmed. However, AOC effect is a known potential risk associated with use of GnRH agonists, and the risk appears to be low for this product in this population based on behaviorial assessments and AE reporting.

There were no clinically significant changes in safety laboratory parameters or changes in safety laboratory tests that were considered to be study drug-related. One patient had elevated LFTs (GGT 3.6xULN, ALT 2.4xULN, AST 1.2xULN, alkaline phosphatase 1.3xULN, and normal bilirubin levels) at Week 5, in association with fever, nausea, and sinus infection, none of which were considerd study drug-releated and which resolved without intervention by the next laboratory evaluation at Week 48. Low WBC counts were seen in 29 patients; however, in most cases, the low levels were seen at baseline prior to drug exposure, thus the abnormalities are not considered to be study drug-related.

There were no clinically meaningful changes in vital signs (BP, HR, RR, temperature) during the study period, and there were no AEs associated with changes in BP (e.g., hypo- or hypertension) or HR (e.g., tachycardia). 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 (100 °F); these events were not considered study drug-related.

Safety Concerns of the GnRH agonist drug class in children with CPP identified through post-marketing experience

1. *Injection Site Reactions*: Injection site reactions are common with injectable GnRH agonist therapies, including rare cases of abscess formation. The number of injection site reactions seen in study TOL2581A was similar to what is described in labeling for other currently marketed injectable GnHR agonists approved for CPP (e.g., Lupron Depot-Ped and Triptodur.

2. *Acute-on-Chronic Effect*: An increase in clinical signs and symptoms of puberty may be observed in the two weeks following subsequent doses, as gonadotropins and sex steroids may rise above baseline due to a transient stimulatory effect of the drug. Symptoms may include hot flashes and transient increases in some signs 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 Study TOL2581A.

3. *Seizures/convulsions*: Postmarketing reports have described convulsions or seizures in subjects with CPP receiving GnRH agonists. These reports often included patients with pre-disposing factors such as history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, and patients receiving concomitant medications associated with convulsions (e.g., bupropion and selective serotonin reuptake inhibitors). For this reason, a known history of seizures or use of medications 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.

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

5. *Anaphylaxis*: Anaphylaxis has been reported as a class effect. There were two cases of rash, and one case each of urticaria and hypersensitivity in the safety population in Study TOL2581A, but no cases of anaphylaxis.

In conclusion, the safety profile of Fensolvi, as demonstrated in the pivotal Study TOL2581A, is similar to the safety profiles of other approved GnRH agonists for treatment of CPP. No new safety signals were identified in the clinical development program for Fensolvi.

8. Advisory Committee Meeting

Not applicable.

9. Pediatrics

A pediatric waiver was submitted for children under 2 years of age, as the drug product is not likely to be used by a substantial number of pediatric patients in that age group. The Pediatric Review Committee agreed with a waiver of studies in children less than two years of age on April 7, 2020.

10. Other Relevant Regulatory Issues

Office of Scientific Investigations (OSI) Inspection
Three clinical sites participating in study TOL2581A were inspected by the Office of Scientific Investigations. Overall, no significant regulatory deficiencies that would put into question the validity of the study data were found.

Site 101, Mirta Graciela Gryngarten, M.D., Buenos Aires, Argentina. The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483 Inspectional Observations was issued.

Site 602, Nelly Marcus, M.D., Jacksonville, Florida. A Form FDA-483 Inspectional Observations was issued for not conducting the study in accordance to the investigational plan. as outlined in the OSI review. Although violations were noted, they are unlikely to significantly impact primary safety and efficacy analyses and the data from this site appear acceptable.

Site 612, Gad B. Kletter, M.D., Tacoma, Washington. A Form FDA-483 Inspectional Observations was issued for not conducting the study in accordance to the investigational plan. Specifically, failing to obtain screening laboratories for two subjects and failing to conduct GnRHa testing per protocol in three subjects. Dr. Kletter submitted a response to the Form FDA-483 and it was determined to be acceptable.

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.

11. Labeling

At the time of this review, labeling negotiations were ongoing.

12. Postmarketing Recommendations

This product does not require a REMS.

Based on the drug class and indication, the applicant will be asked to submit all cases of suicidal ideation and suicidal behavior, self-injury, or depression reported with Fensolvi as 15-day alert reports, and to provide detailed analyses of suicidal ideation/behavior, self-injury, or depression events reported from clinical studies and postmarketing reports as *adverse events of special interest* in periodic safety reports (i.e., the Periodic Adverse Drug Experience Reports [PADER] required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format) for a period of five years post-marketing. 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 reports.

13. Recommended Comments to the Applicant

None. The final agreed upon label will be communicated to the Applicant in the Action Letter.

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/

SHANNON D SULLIVAN
04/28/2020 03:55:49 PM

THERESA E KEHOE
04/29/2020 08:09:56 AM
I concur with Dr. Sullivan and the regulatory decision reached