Public Assessment Report for paediatric studies submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended

Triptorelin

PT/W/0003/pdWS/002

Marketing Authorisation Holder: IPSEN Pharma

Rapporteur:	**Portugal**
Finalisation procedure (day 120):	**30/06/2023**

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Decapeptyl, Diphereline, Arvekap
INN (or common name) of the active substance(s):	Triptorelin
MAH:	IPSEN PHARMA
Currently approved Indication(s)	Treatment of central precocious puberty Treatment of metastatic prostate cancer Use in endometriosis Use in female infertility as a part of an *in vitro* fertilisation programme Treatment of uterine fibromyoma prior to surgery
Pharmaco-therapeutic group (ATC Code):	L02AE04 (antineoplastic and immunomodulator)
Pharmaceutical form(s) and strength(s):	Triptorelin acetate 1-month PR formulation (3.75mg/2ml) Triptorelin pamoate 1-month PR formulation (3mg/2ml) Triptorelin acetate 3-month PR formulation. Triptorelin pamoate 3-month PR formulation (11,25mg/2ml) Triptorelin acetate 1-month IR formulation (0.1 mg/ml) Triptorelin pamoate 3-month PR formulation (22,5mg/2ml)

I. EXECUTIVE SUMMARY

Changes related to the current procedure are proposed in sections 4.8 and 5.1 of the SmPC and section 4 of the PL.

II. RECOMMENDATION

Taking into consideration the submitted data from Studies 2-54-52014-159 and D-CN-52014-243 the Rapporteur recommended an update to the SmPC and PL of all relevant formulations with an indication for CPP.

SmPC proposed changes

Section 4.8 Undesirable effects
Safety data
 Long term tolerance in children population:
• The long-term clinical trial 2-54-52014-159 (NCT00909844) included 35 patients, age ranging from 4 to 10.4 years, who had received treatment (up to 4 years) with triptorelin 11.25 mg. More than half of patients (20 patients: 57.1%) reported at least one adverse event during the study, of which the most frequent were abdominal pain (17.1%), injection site pain (11.4%) headache and hot flush (each 8.6%). Overall, the safety profile was similar as seen in the other CPP studies.

Section 5.1 Pharmacodynamic properties
Efficacy data
In the long-term clinical trial 2-54-52014-159 (NCT00909844), 34 girls and 1 boy with central precocious puberty (CPP) have been treated with triptorelin pamoate 11.25 mg every 3 months for a period of up to 4 years. Treatment ended when the investigator decided the patient had completed his/her treatment, that is to say at about 11 years in girls and 13 in boys, usually after 1-3 years of treatment. At that timepoint, 31/34 (91%) of girls had maintained stabilization or regression of Tanner breast pubertal stage.

PL proposed changes

Section 4 Possible side effects
Paediatric population
Long term trial (up to 4 years) did not bring any new and significant safety concerns.

III. INTRODUCTION

On 6.2.2023, Ipsen submitted a completed paediatric study(ies) for Triptorelin, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies do not influence the benefit risk for Triptorelin and that there is no consequential regulatory action.

IV. SCIENTIFIC DISCUSSION

IV.1 Information on the pharmaceutical formulation used in the study(ies)

- **Study 2-54-52014-159**

Triptorelin pamoate 11.25 mg prolonged release formulation administered by intra muscular injection once every three months until the end of the treatment. Eleven different batches of triptorelin 11.25 mg were used during the study: TBPQ, UBGZ, C02759, TBD9, C15526, E02910, SBLT, TBNZ, F04250, F19995, UBNX

- **Study D-CN-52014-243**

The test product was triptorelin pamoate 15 mg for injection (manufactured by Ipsen Pharma Biotech), which was created to guarantee the release of 11.25 mg of triptorelin. It was presented as a slightly yellow freeze-dried cake or powder in a glass vial. The solvent provided for injection was a 2 mL ampoule of mannitol and water for injection. The triptorelin 3-month formulation was to be administered by I.M. route only. The powder was reconstituted with the solvent for suspension and be injected immediately after preparation.
The batch numbers used in this study was U03211

IV.2 Clinical aspects

1. Introduction

The MAH submitted the final report for 2 studies:

- **Study 2-54-52014-159**
- **Study D-CN-52014-243**

2. Clinical study(ies)

STUDY 2-54-52014-159 - Follow Up of the Phase III, Multicentre, Non Comparative, One Single Group, Open Study to Assess the Long Term Efficacy and Tolerability of Pamoate of Triptorelin 11.25 mg in Children with Precocious Puberty

- **Description** – this was an open-label follow-up to Study 2-54-52014-143. The subjects included in the follow-up study were those who had a pubertal effective response to two injections of triptorelin pamoate 11.25 mg during the previous study.

- **Methods**

  - Objective(s)
    - Primary - to assess the efficacy of triptorelin pamoate 11.25 mg with respect to the proportion of children who maintain a regression or stabilisation of sexual maturity until the end of the study.

- Secondary - To assess the efficacy of triptorelin pamoate 11.25 mg at Month 12 (M12), M24, M36, M48 and Final Visit (if applicable) on:
    - Luteinizing Hormone (LH) response to GnRH tests.
    - Follicle Stimulating Hormone (FSH) response to GnRH tests.
    - Levels of oestradiol in girls or testosterone in boys, both measured by RIA.
    - Bone maturation.
    - Growth velocity.
    - Uterine length
- To assess the variation of predicted adult height at M12, M24, M36, M48 and Final Visit (if applicable).
- To assess the clinical tolerability of the drug:
    - Adverse events (AEs).
    - Vital signs.

- Study design
    - multicentre, single stage, non-comparative, open-phase study to start on the day of the last visit (M6) of the 2-54-52014-143 study.
    - children were to be injected every 3 months over 48 months
    - the study was to last until the end of the therapeutic period (i.e. at a chronological age of 11 in girls and 13 in boys). When this chronological age was reached, the patient was considered to have completed the study (without necessarily having received all the injections).

- Study population /Sample size
    - N= 35
    - Inclusion criteria:
        - Patient having completed the phase III 2-54-52014-143 study.
        - Patient with an effective response to two injections of triptorelin pamoate 11.25 mg according to investigator's evaluation with no significant treatment related side effects during the phase III 2-54-52014-143 study.
    - Exclusion criteria:
        - Patient with a known hypersensitivity to any of the test materials or related compounds.
        - Patient unable or unwilling to comply fully with the protocol

- Treatments
    - **Triptorelin pamoate 11.25 mg prolonged release** formulation was administered by intramuscular injection once every three months until the end of the treatment.

- Outcomes/endpoints
    - Primary efficacy parameter - proportion of children with a stabilisation or regression of Tanner breast (girls) or genital (boys) pubertal stage at the end of the study (early withdrawal or final visit), as compared to the stage at baseline and at pre-treatment.

    - The primary efficacy endpoints were:
        - The proportion of children with stabilisation or regression of Tanner breast (girls) or genital (boys) pubertal stage at the end of the study compared to the stage at study entry (and at Pretreatment).
        - The pubertal stage variation at Baseline, M12, M24, M36, M48 and Final Visit (if applicable).

- Secondary Efficacy Variable The secondary efficacy endpoints were the following (at Pretreatment, Baseline, M12, M24, M36, M48 and Final Visit (if applicable):
  - Hormonal data
    - LH response to GnRH tests.
    - Levels of oestradiol in girls or testosterone in boys (Radio Immune Assay: RIA).
    - FSH response to GnRH tests.
  - Non hormonal data
    - Pubertal stage (pubic hair).
    - Body Mass index and standard deviation (BMI and SD) score for chronological age variation.
    - Auxological parameters variations (height, growth velocity, weight).
    - Bone age variation (Greulich and Pyle method, hand and wrist x-rays).
    - Predicted adult height variation.
    - Proportion of girls with a uterine length < 36 mm.
    - Uterine length variation (pelvic ultrasound measurement).
  - Safety:
    - Adverse events (AEs) reported spontaneously.
    - Vital signs (supine blood pressure and heart rate)

- Statistical Methods
  - The primary efficacy parameter was the proportion of children with a stabilisation or regression of Tanner breast (girls) or genital (boys) pubertal stage at the end of the study (Early Withdrawal or Final Visit), as compared to the stage at study entry (Baseline) and at Pretreatment. The primary efficacy analysis was planned to be performed on the ITT, mITT and PP populations. No patient was excluded from any of the study populations. Hence, the ITT, mITT, PP and Safety populations were identical (each consisting of the 35 patients who received IMP). Therefore, only the results for the ITT population are presented in this report. All secondary efficacy analyses were performed on the ITT population.
  - Post-Hoc Analysis were performed to add « Last Visit on Treatment » as a derived variable which is « the last visit » if it occurred less than 3 months after the last injection or in other cases, the last visit made under treatment (M12, M24, M36 or M48). This was derived by the fact that most final visits from the original plan were made way after the 3months after last IMP administration were the therapeutic effect of triptorelin has disappeared and the expected resumption of pubertal development has already started compromising efficacy results.

- **Results**

- Recruitment/ Number analysed
  - Planned: All children who completed the previous phase III study (2-54-52014-143) and who signed the informed consent form.
  - Analysed: 35 patients were screened.
  - No patient was excluded from any of the study populations (ITT, mITT, PP and Safety populations were identical

  - There were four early withdrawals from the study; two patients were lost to follow up, one patient discontinued due to an AE and one patient withdrew consent due to “injection’s difficulties”.

- Baseline data

- Efficacy results
  - Since there was only one boy included in the study, the results are not presented for this patient.
  - Around half of the girl patients (18 patients: 52.9%) under treatment with triptorelin 11.25 mg maintained stabilisation or regression of Tanner breast pubertal stage at the end of the study compared to at entry in this study (95% CI [35.1 to 70.2]). It should be noted that these girls had already been treated for six months with triptorelin 11.25 mg during the 2-54-52014-143 study.
  - The proportion of girl patients maintaining stabilisation or regression of Tanner breast pubertal stage was higher (61.8%: 21 patients; 95% CI [43.6 to 77.8]) at the end of the study when compared to pre-treatment, i.e. before enrolment in the previous study.
    - Before any treatment, i.e. pre-treatment, all girls were at either Tanner breast pubertal stage 2 (13 patients, 32.8%) or 3 (21 patients: 61.8%), whereas at inclusion in the study (baseline), all development stages were represented but stages 2 and 3 remained the most frequent (11 patients: 32.4% and 14 patients: 41.2%, respectively). Stages 1 and 4 were reported for seven patients (20.6%) and two patients (5.9%) respectively.
    - At the final visit, compared to baseline, the proportion of girls with Tanner breast pubertal stage 1, 2 or 3 decreased (Stages 1 and 4 patients: 13.3%; Stages 2 and 3 each with 8 patients: 26.7%), whereas the proportion at Stage 4 increased (10 patients: 33.3%). Both girls who discontinued the study prematurely were at Tanner breast pubertal stage 3 at withdrawal.
  - In the post-hoc analysis, the time point used for efficacy analysis was defined as the final visit which occurred within 3 months after an injection *(this assessment was made upon request of the investigator team following acquaintance of a higher than 3 months period of realization of the final visit compared to last IM administration, that is, quite after the therapeutic effect of the last IMP; the goal of this assessment was to have data still under therapeutic effect of the IMP to avoid results compromised by the expected pubertal resumption after treatment discontinuation). As such* ***results of this post-hoc analysis are indeed the efficacy results of this prolonged treatment period with triptorelin***.
    - At the final visit, a great majority of girls with CPP treated with triptorelin pamoate 11.25 mg 3-month formulation had maintained stabilization or regression of Tanner breast pubertal stage (91.2%: 95% CI [76.3 to 98.1]) whatever the comparison: compared to before any treatment with triptorelin pamoate 11.25 mg, i.e. since entering the previous study (2-54-52014-143) or compared to the baseline of this study.
    - From the Pre-treatment visit to the Last Visit on Treatment (e.g. from the 1st injection to at the latest 3 months after the last injection of Triptorelin), 15/35 patients had a Pubic Hair Stage progression, as it was expected due to progression of adrenal androgen secretion.
      After 12 and 24 months of follow-up, respectively more than 80% and 67 % of patients are still without progression. After 31 months, the calculated rates of subjects without progression of their Tanner Pubic Hair Stage are not relevant because less than 10 patients were still followed.
    - The comparison between these results and those presented in the original CSR (% vs baseline and % vs M0) further demonstrate the resumption of pubertal development after the cessation of triptorelin pamoate 11.25 mg.

- Hormonal Data - **Almost no hormonal data was collected after Baseline.**
  - Oestradiol and Testosterone - Overall mean±SD oestradiol level in girls decreased from 18.6±9.8 pg/mL before any treatment with IMP to 8.7±4.5 pg/mL at Baseline and testosterone level decreased from 6.80 ng/mL to 0.56 ng/mL for the single boy included in the study.
  - LH response to GnRH test - Overall mean±SD LH level decreased from 18.5±15.2 IU/L before any treatment with IMP to 1.9±2.0 IU/L at inclusion in the present study; an overall mean±SD change from Pretreatment at Baseline of -16.6±14.4 IU/L. At Pretreatment, no patient had a suppressed LH response to the GnRH test compared to 91.4% of patients (32 patients) at Baseline; an overall mean±SD percentage change from Pretreatment at Baseline of LH response of -87.2±8.0 %.
  - FSH response to GnRH test - Overall mean±SD FSH level decreased from 11.9±3.3 IU/L before any treatment with IMP to 2.3±1.7 IU/L at inclusion in the present study; an overall mean±SD change from Pretreatment at Baseline of -9.5±3.6 IU/L. At Pretreatment, no patient had a suppressed FSH response to the GnRH test compared to 82.9% of patients (29 patients) at Baseline; an overall mean±SD percentage change from Pretreatment at Baseline of FSH response of -79.4±13.1 %.
- Non Hormonal Data
  - Tanner pubic hair - The proportions of patients at each Tanner pubic hair stage were similar at Pretreatment and at Baseline (stage 1: 31.4% and 34.3%, stage 2: 45.7% and 42.9%, respectively, stage 3: each 22.9% and none were at stage 4). There was a slight shift to a higher pubic hair stage at the end of the study (stage 1: 9.7%, stages 2 or 3: 29.0%, and stage 4: 32.3%). Overall, around a third of patients had stabilisation or regression of Tanner pubic hair pubertal stage at the end of the study and the proportion was slightly higher with longer treatment (31.4% from Baseline: 95% CI [16.9 to 49.3]) and 37.1% from Pretreatment: 95% [21.5 to 55.1]).
  - Bone age maturation - Overall mean±SD difference between bone age and chronological age was 2.1±0.9 years at Pretreatment and 2.0±0.9 years at Baseline; a change of difference from Pretreatment at Baseline of -0.2±0.5 years.
  - Auxological parameters - Height (cm and SDS), growth velocity (cm/year and SDS) and weight were evaluated. Overall mean±SD changes from Pretreatment in height at Baseline, M12 and end of the study were 3.4±0.9 cm, 8.3±1.4 cm and 6.2±15.0 cm, respectively, and changes in height SDS were -0.1±0.1, -0.05±0.3 and -0.4±0.5, respectively. Overall mean±SD changes from Baseline in height at M12 and end of the study were 4.9±1.1 cm and 12.0±6.1 cm, respectively, and changes in height SDS were -0.1±0.2 and -0.4±0.5, respectively. Overall mean±SD changes from Pretreatment of growth velocity at Baseline, M12 and the end of the study were -1.9±2.9 cm/year, -3.0±2.8 cm/year and -3.2±3.1 cm/year, respectively, and changes in growth velocity SDS were -1.9±2.1, -2.4±2.1 and -2.7±2.5, respectively. Overall mean±SD change from Baseline in growth velocity was constant during the study; -1.7±2.0 cm/year at M12 and -1.8±2.0 cm/year at the end of the study. Overall mean±SD weight changes from Pretreatment compared to Baseline, M12 and end of study were 2.5±1.5 kg, 7.6±3.5 kg and 13.2±6.2 kg, respectively, and mean±SD changes from Baseline were 5.1±2.8 cm at M12 and 10.7±6.0 cm at the end of the study. **These changes in auxological parameters indicate a progressive slowing down of growth towards normal prepubertal rates**, as expected during treatment with triptorelin. Predicted adult height

variation Overall mean±SD changes from Pretreatment at Baseline in predicted adult height and height SDS were 2.0±1.1 cm and 0.3±0.2, respectively.

- Uterine length - Mean±SD uterine length decreased by 1.6±9.4 mm between Pretreatment and Baseline, and increased by 2.3±36.7% at M12. Less than half of girls had uterine length < 36 mm at Pretreatment and at Baseline (42.4% and 41.2%, respectively).
- Body Mass Index (BMI) - Overall mean±SD BMI changes between Pretreatment and Baseline, M12 and end of study were 0.4±0.7 kg/m², 1.6±1.3 kg/m² and 2.4±1.6 kg/m², respectively, and mean±SD changes from Pretreatment of BMI SDS at Baseline, M12 and end of study were 0.06±0.3, 0.8±0.8 and 0.1±0.5, respectively. Changes from Baseline were 1.1±1.0 kg/m² at M12 and 1.9±1.5 kg/m² at the end of the study.

- Safety results
  - More than half of patients (20 patients: 57.1%) reported at least one AE during the study, 64 events in total, all of which were treatment emergent.
  - Two patients had a **TEAE** considered by the investigator as severe (5.7%, 4 events, unrelated to study treatment).
  - Seven patients (20.9%, 9 events) reported a **TEAE** related to treatment during the study. The related TEAEs were
    - injection site pain and hot flush (each 2 patients),
    - vaginal haemorrhage (1 patient)
    - pelvic pain (1 patient)
    - abdominal pain (1 patient).

    None of the TEAEs related to the treatment were severe.

    Nineteen patients (54.3%, 55 events) experienced a TEAE unrelated to treatment during the study.

    The most frequent TEAEs, by descending order of frequency, were abdominal pain (17.1%), injection site pain (11.4%) then headache and hot flush (each 8.6%).
  - Only one patient withdrew from the study due to a TEAE (vaginal haemorrhage, moderate intensity, serious and related to study treatment).
  - There was no death during the study.
  - Three patients experienced four **SAEs** during the study (8.6%): gait disturbance and myalgia (same patient), foot fracture and vaginal haemorrhage.

    Only one of these SAEs was considered by the investigator as related to the study treatment (vaginal haemorrhage leading to study **withdrawal**). However, this SAE was judged as unrelated to study drug by the Sponsor since the event occurred two weeks after the injection.
  - Overall, vital signs (blood pressure and heart rate) were constant during the study.
  - Study drug exposure was on average eight injections over a period of 30 months (ranging from 2 to 26 injections over 12 to 84 months).
  - There were no particular safety concerns during the study and the injections with triptorelin pamoate 11.25 mg were well tolerated.

STUDY D-CN-52014-243 - An open-label, multicentre, single-arm study to assess the efficacy and safety of triptorelin 3-month formulation in Chinese children with central precocious puberty

- **Description** – The study was a prospective, open-label, multicentre, single-arm, interventional study intended to evaluate the efficacy and safety of triptorelin 3-month formulation in Chinese children with CPP.
  - The study was conducted in two 6-month parts (i.e. main study phase and extension phase). Note, only the main study phase data at the time of data cut-off is presented in this document.

- **Methods**
  - Objective(s)
    - Primary - to assess the efficacy of the triptorelin 3-month prolonged release (PR) formulation in suppressing luteinising hormone (LH) levels to prepubertal levels (defined as a peak LH ≤3 IU/L) after intravenous (i.v.) gonadotropin-releasing hormone (GnRH) stimulation at Month 3 in Chinese children with central precocious puberty (CPP).
    - Secondary
      - To assess the efficacy in suppressed LH response to GnRH test at Month 6
      - To assess follicle-stimulating hormone (FSH) response to GnRH test at Month 3 and Month 6
      - To assess LH and FSH levels at Month 3 and Month 6
      - To assess sex hormone serum concentrations (oestradiol for girls and testosterone for boys) at Month 3 and Month 6
      - To assess sexual maturation (pubertal stage as per Tanner method) at Month 6
      - To assess auxological parameters including height, growth velocity, weight and body mass index (BMI) at Month 3 and Month 6
      - To assess bone age (BA), the difference between BA and chronological age (CA) at Month 6
      - To assess gonadal development as determined by uterine length in girls and testicular volume in boys at Month 6
      - To assess the safety profile.
    - Exploratory Objective: to assess plasma triptorelin levels at Day 1, Month 3 and Month 6.

  - Study design
    - *Main Study Phase*

      A total of 32 subjects, including at least three boys, were enrolled in the study and treated with an intramuscular (i.m.) injection of triptorelin 3-month PR formulation on Day 1 of the study and at Month 3 (3 months after the first injection). Triptorelin injections did not have to be adapted based on body weight but the subject should have a minimum weight of 20 kg.

      The study consisted of screening visit, Day 1 visit and drug administration, Month 3 visit and drug administration and Month 6 visit (end of study [EOS]/early withdrawal) for efficacy and safety assessments. Subjects received a total of two injections during the study period before they attended the EOS visit at Month 6.

  - Study population / Sample size
    - N= 32 subjects, including three boys
    - Inclusion criteria:
      - (1) Provision of written informed consent prior to any study-related procedures. Consent was provided by the parent(s)/legal guardian. If

determined by local requirements, a signed assent must be obtained from the paediatric subject.

- (2) Evidence of CPP documented by:
  - Onset of development of secondary sex characteristics (breast development in girls or testicular enlargement in boys according to the Tanner method: Stage II) before the age of 8 years in girls and 9 years in boys
  - Pubertal response of LH to GnRH stimulation test (stimulated peak LH ≥5 IU/L) in both sexes
  - Difference between BA and CA >1 year
  - Girls with Tanner staging ≥2 for breast development and who had enlarged uterine length and several follicles with diameter >4 mm in the ovary observed by pelvic type B ultrasound at the Screening visit; boys who had testicular volume ≥4 mL observed by testicular type B ultrasound at the Screening visit
- (3) Age less than 9 years old for girls and less than 10 years old for boys at initiation of triptorelin treatment
- (4) Weight at least 20 kg
- (5) Girls who had already had menophania/menarche must have a negative pregnancy test prior to the start of study treatment and should not be at risk of pregnancy throughout the study period.

➢ Exclusion criteria:

- Participants will be ineligible for study participation if they meet any of the following criteria:
  - (1) Gonadotropin-independent (peripheral) precocious puberty: extrapituitary secretion of gonadotropins or gonadotropin-independent gonadal or adrenal sex steroid secretion
  - (2) Non-progressing isolated premature thelarche
  - (3) Presence of an unstable intracranial tumour or an intracranial tumour requiring neurosurgery or cerebral irradiation. Participants with hamartomas not requiring surgery are eligible
  - (4) Evidence of renal (creatinine >1.5 x upper limit of normal (ULN)) or hepatic impairment (bilirubin >1.5 x ULN or alanine aminotransferase (ALT)/aspartate transaminase (AST) >3 x ULN)
  - (5) Any other condition or chronic illness or treatment possibly interfering with growth or other study endpoints (e.g. chronic steroid use except topical steroids, renal failure, diabetes, moderate to severe scoliosis)
  - (6) Prior or current therapy with a GnRH agonist (GnRHa), medroxyprogesterone acetate, growth hormone or insulin-like growth factor-1 (IGF-1)
  - (7) Diagnosis of short stature, i.e. >2.25 standard deviation (SD) below the mean height
    for age
  - (8) Major medical or psychiatric illness that could interfere with study visits
  - (9) Known hypersensitivity to any of the test materials or related compounds
  - (10) Use of anticoagulants (heparin and coumarin derivatives) within the 2 weeks prior to the Screening visit.

- Treatments
  - The test product was **triptorelin pamoate 15 mg for injection** (manufactured by Ipsen Pharma Biotech), which was created to guarantee the release of 11.25 mg of triptorelin

- Outcomes/endpoints
  - *Primary Efficacy Endpoint and Evaluation*
    The primary endpoint in this study was the proportion of children with LH suppression defined as stimulated peak LH ≤3 IU/L after GnRH stimulation at Month 3.

  - *Secondary Efficacy Endpoints and Evaluations* (baseline values corresponded to those obtained with measurements performed at the Screening visit)

Table 1 Secondary Efficacy Endpoints and Evaluations in Protocol table 5

Measure	Timepoint	Variable	Endpoint
Basal LH and FSH serum levels	Baseline, Month 3 and Month 6 (EOS)	LH and FSH concentration	Change in basal serum LH and FSH levels at Month 3 and Month 6 compared to baseline.
Peak LH after GnRH stimulation test	Baseline, Month 3 and Month 6 (EOS)	Peak LH levels after GnRH stimulation (30, 60 and 90 minutes)	Change in peak LH levels after GnRH stimulation test at Month 3 and Month 6 compared to baseline; Proportion of children with LH suppression defined as stimulated peak LH ≤3 IU/L after GnRH stimulation at Month 6.
Peak FSH levels after GnRH stimulation test	Baseline, Month 3 and Month 6 (EOS)	Peak FSH levels after GnRH stimulation (30, 60 and 90 minutes)	Change in peak FSH levels after GnRH stimulation test at Month 3 and Month 6 compared to baseline.
E_2 and testosterone serum concentrations	Baseline, Month 3 and Month 6 (EOS)	Sex steroids levels	Proportion of children with sex steroids suppressed within prepubertal ranges (E_2 ≤20 pg/mL in girls and testosterone ≤0.3 ng/mL in boys); Change in sex steroids levels compared to baseline.
Pubertal stage (Tanner Method)	Baseline, Month 6 (EOS)	Pubertal stage	Change in pubertal stage (genital stage in boys, breast stage in girls and pubic hair stage in both sexes) compared to baseline; Proportion of children with stabilised pubertal stage compared to baseline.
Auxological parameters (height, growth velocity, weight, BMI)	Baseline, Month 3 and Month 6 (EOS)	-	Change in auxological parameters compared to baseline.
BA	Baseline, Month 6 (EOS)	-	Change in BA, difference between BA and CA compared to baseline.
Uterine/ovary or testis volume	Baseline, Month 6 (EOS)	Gonad development	Change in uterine length in girls and testicular volume in boys compared to baseline.

BA = Bone age; BMI = Body mass index; CA = Chronological age; E_2 = Oestradiol; EOS = End of Study; FSH = Follicle-stimulating hormone; GnRH = Gonadotropin-releasing hormone; LH = Luteinising hormone.

  - *Secondary Safety Endpoints*
    - Incidence of treatment-emergent adverse events (TEAEs) throughout the study, including local tolerability
    - Change in clinical safety laboratory (blood biochemistry, haematology and urinalysis) parameters at Month 3 and 6

- Change in physical examination and vital signs (blood pressure and heart rate) measurements at each visit.

➢ *Pharmacokinetics Exploratory Endpoint*

- To assess sparse plasma triptorelin concentrations at Day 1, Month 3 and Month 6.

- Statistical Methods
  - ➢ The primary efficacy analysis was performed in the Modified Intention-To-Treat (mITT) population. Supportive analysis of the primary efficacy endpoints were based on the ITT and the Per protocol (PP) populations.
  - ➢ The secondary efficacy analyses were based on the mITT population. Supportive analysis of the secondary analyses were performed in the PP population.
  - ➢ The analyses of safety data were performed based on the safety population.
  - ➢ The analyses of PK data were performed based on the PK Set population.
  - ➢ All safety summaries and analyses were based upon the safety population. All safety data were included in subject data listings. There was no statistical comparison between the gender groups for safety data, unless otherwise specified within the relevant section.
  - ➢ All AEs were recorded and graded according to the current version of National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

➢ **Results**

- Recruitment/ Number analysed
  - ➢ A total of 32 subjects were enrolled in the study, including 29 females and 3 males.
  - ➢ 2 patients withdrawn during the trial with the primary reason being *withdrawal by parent/guardian*

- Baseline data

- Efficacy results
  - The proportion of subjects with a suppressed response (GnRH-stimulated LH peak ≤3 IU/L) at 3 months was 100% (90% CI: 90.8% to 100.0%), 93.5% subjects kept their LH suppressed at Month 6.
  - The mean basal levels of LH and FSH were substantially suppressed after 3 and 6 months by triptorelin 3-month PR formulation treatment.
  - The assessment of GnRH-stimulated peak LH levels showed substantial reductions after triptorelin 3-month PR formulation treatment, all subjects peak LH levels were ≤3 IU/L after GnRH stimulation test at Month 3 and Month 6.
  - Peak FSH was similarly suppressed at Month 3 and Month 6, mean peak FSH change from 12.6784 IU/L at baseline to 1.4027 IU/L at Month 3 and 1.6802 IU/L at Month 6.
  - Sex steroids were suppressed at Month 3 and Month 6. For females, mean serum oestradiol decreased from 25.9407 pg/mL at baseline to 17.936 pg/mL at Month 3 and Month 6; for males, mean serum testosterone decreased from 1.4850 ng/mL at baseline to 0.120 ng/mL at Month 3 and Month 6. Eleven subjects with sex steroids above prepubertal levels at baseline declined to prepubertal levels at both Month 3 and Month 6.
  - Most of subjects had stable pubertal stage at Month 6, there was a slowing of pubertal development over time.

- Mean growth velocity decreased at each time point also suggesting a slowing of height increase as pubertal development is slowed.
- The difference between BA and CA slightly decreased, mean difference from 2.85 years at baseline to 2.40 years at Month 6.
- The mean uterine length and testicular volume was stable or reduced.

- Safety results
  - Twenty-four (75.0%) subjects experienced any adverse events, of which 22 (68.8%) reported 48 TEAEs.
  - The most frequently reported TEAEs (reported in ≥5% of patients) by PT were upper respiratory tract infection (31.3%), weight increased (9.4%), urticaria (6.3%), cough (6.3%), rhinorrhea (6.3%) and overweight (6.3%).
  - Seven patients (21.9%) experienced drug-related TEAEs, included upper respiratory tract infection (6.3%), gastroenteritis (3.1%), gingivitis (3.1%), tonsillitis (3.1%), impaired fasting glucose (3.1%), overweight (3.1%), vaginal haemorrhage (3.1%), nasal obstruction (3.1%), rhinorrhea (3.1%).
  - All TEAEs but one were grade 1 or 2 in intensity, with only 1 subject experiencing 1 case of grade 3 (PT is dermatitis allergic, not related).
  - No subject died and no SAE nor AE leading to discontinuation of study treatment occurred.
  - The laboratory test results of all subjects remained stable, changes from baseline at Month 3 and Month 6 were similar, and no laboratory parameters with CTCAE ≥3 appeared.
  - No potentially clinically significant abnormalities changes from baseline were observed in laboratory tests and vital signs.
  - All subjects had no abnormal physical examination finding after administration in overall assessments.
  - The injections were well tolerated, no subject reported any local tolerability reaction.

3. Discussion on clinical aspects

- **Study 2-54-52014-159**

The results of this study in children with CPP indicate that treatment by injection of triptorelin pamoate 11.25 mg was associated with stabilisation or regression of Tanner breast pubertal stage in around half of patients associated with a slowing down of growth velocity towards pre-pubertal rate, as expected. When final visit occurred within 3 months after triptorelin pamoate 11.25 mg injection, more than 90% of the girls had maintained stabilization or regression of Tanner breast pubertal stage.
Overall non hormonal data pointed to the benefit of continuing suppression treatment until the end of the therapeutic period (at a chronological age of 11 in girls and 13 in boys). The current study didn't provide any significant hormonal data as only residual data was collected beyong baseline.

Triptorelin pamoate 11.25 mg improves quality of life since the children are subjected to fewer, less frequent injections with this long-release formulation. In addition, there were no safety concerns during the study and the treatment was well tolerated.

- **Study D-CN-52014-243**

The proportion of subjects with a suppressed response (GnRH-stimulated LH peak ≤3 IU/L) at Month 3 was 100%, 93.5% subjects kept their LH suppressed at Month 6. Not only GnRH stimulated peak LH and FSH were suppressed at Month 3 and Month 6, but basal levels of each

hormone were also decreased. Other secondary efficacy analyses offered further support for the primary efficacy criterion demonstration of treatment efficacy. These results are similar to those seen in the overseas studies.
Safety findings of triptorelin 3-month PR formulation in this study were identified with the known safety profile of triptorelin 3-month PR formulation in this indication, the most reported drug-related TEAEs was upper respiratory tract infection. There is no new safety profile found in this study comparing to the oversea studies. Overall, the safety of triptorelin 3-month PR formulation is acceptable.
Triptorelin 3-month PR formulation as monotherapy in CPP demonstrated sufficient clinical activity to support the registration in this indication in Chinese children.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The results from studies **2-54-52014-159** and **D-CN-52014-243** do not change the conclusion of previous studies.
Study **2-54-52014-159** provides important information on long-term efficacy and safety and an update to SmPC section 5.1 (efficacy data) and sections 4.3-4.9 (safety data) of the prescribing information with this information would be considered of interest. The PL should be updated accordingly.

- **Recommendation**

Based on the data submitted, the MAH should provide supplementary information as part of this worksharing procedure (see section VII "Request for Supplementary Information").

VI. COMMENTS FROM CMS AT DAY 85

The rapporteur's conclusions and recommendations were validated by Member State.

VII. REQUEST FOR SUPPLEMENTARY INFORMATION

List of questions

- The MAH is requested to update SmPC section 5.1 (efficacy data) and sections 4.3-4.9 (safety data) of the prescribing information with the long-term data generated in study 2-54-52014-159. The PL should be updated accordingly.
- A proposal for text to update the above-mentioned sections should be made by the MAH.

VIII. ASSESSMENT OF RESPONSE TO QUESTIONS

The MAH has provided the following response to the Request for Supplementary Information:

Question 1: The MAH is requested to update SmPC section 5.1 (efficacy data) and sections 4.3-4.9 (safety data) of the prescribing information with the long-term data generated in study 2-54-52014-159. The PL should be updated accordingly.

MAH Response:
The MAH acknowledges the rapporteur's request and provides the below proposed text to be implemented within the SmPC & PL.

Question 2: A proposal for text to update the above-mentioned sections should be made by the MAH.

MAH Response:
Above the proposed changes

Proposed by MAH:	**Proposed by Rapporteur**
SmPC proposed changes by the MAH • Section 4.8 (safety data) □ Long term tolerance in children population: The long-term clinical trial 2-54-52014-159 (NCT00909844) included 35 patients, age ranging from 4 to 10.4 years, who had received treatment (up to 4 years) with triptorelin 11.25 mg. More than half of patients (20 patients: 57.1%) reported at least one adverse event during the study, of which the most frequent were abdominal pain (17.1%), injection site pain (11.4%) headache and hot flush (each 8.6%). Overall, the safety profile was similar as seen in the other CPP studies. • Section 5.1 (efficacy data) In the long-term clinical trial 2-54-52014-159 (NCT00909844), thirty-five children with central precocious puberty (CPP) have been treated with triptorelin pamoate 11.25 mg every 3 months for a period of 4 years. A stabilization or regression of Tanner breast pubertal stage in around half of patients associated with a slowing down of growth velocity towards pre-pubertal rate was recorded, as expected. At their final visit, within3 months after triptorelin pamoate 11.25 mg injection, more than 90% of the girls had maintained stabilization or regression of Tanner breast pubertal stage. Overall, nonhormonal data pointed to the benefit of continuing suppression treatment until the end of the therapeutic period (at a chronological age	**SmPC proposed changes** **Section 4.8 Undesirable effects** <u>Safety data</u> □ Long term tolerance in children population: • The long-term clinical trial 2-54-52014-159 (NCT00909844) included 35 patients, age ranging from 4 to 10.4 years, who had received treatment (up to 4 years) with triptorelin 11.25 mg. More than half of patients (20 patients: 57.1%) reported at least one adverse event during the study, of which the most frequent were abdominal pain (17.1%), injection site pain (11.4%) headache and hot flush (each 8.6%). Overall, the safety profile was similar as seen in the other CPP studies. **Section 5.1 Pharmacodynamic properties** <u>Efficacy data</u> • In the long-term clinical trial 2-54-52014-159 (NCT00909844), thirty-five children with central precocious puberty (CPP) have been treated with triptorelin pamoate 11.25 mg every 3 months for a period of 4 years. A stabilization or regression of Tanner breast pubertal stage in around half of patients associated with a slowing down of growth velocity towards pre-pubertal rate was recorded, as expected. At their final visit, within 3 months after triptorelin pamoate 11.25 mg injection, more than 90% of the girls had maintained stabilization or regression of Tanner breast pubertal stage. Overall, nonhormonal data pointed to the benefit of

of 11 in girls and 13 in boys). Triptorelin pamoate 11.25 mg improves quality of life since the children are subjected to fewer, less frequent injections with this long-release formulation. **PL proposed changes by the MAH** • Section 4 – *In children* Long term trial (up to 4 years) did not bring any new and significant safety concerns.	continuing suppression treatment until the end of the therapeutic period (at a chronological age of 11 in girls and 13 in boys). Triptorelin pamoate 11.25 mg improves quality of life since the children are subjected to fewer, less frequent injections with this long-release formulation. **PL proposed changes** **Section 4 Possible side effects** *Paediatric population* Long term trial (up to 4 years) did not bring any new and significant safety concerns.

Assessor's comment:
The MAH has submitted as requested a proposal of text to update SmPC and PL, this proposal is considered acceptable with minor editorial adjustments.

IX. FINAL RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The MAH has provided a text for the SmPC and PL with the safety and efficacy information from the long-term study 2-54-52014-159 (NCT00909844). This is acknowledged and acceptable.

SmPC proposed changes

Section 4.8 Undesirable effects
Safety data
 Long term tolerance in children population:
• The long-term clinical trial 2-54-52014-159 (NCT00909844) included 35 patients, age ranging from 4 to 10.4 years, who had received treatment (up to 4 years) with triptorelin 11.25 mg. More than half of patients (20 patients: 57.1%) reported at least one adverse event during the study, of which the most frequent were abdominal pain (17.1%), injection site pain (11.4%) headache and hot flush (each 8.6%). Overall, the safety profile was similar as seen in the other CPP studies.

Section 5.1 Pharmacodynamic properties
Efficacy data
• In the long-term clinical trial 2-54-52014-159 (NCT00909844), thirty-five children with central precocious puberty (CPP) have been treated with triptorelin pamoate 11.25 mg every 3 months for a period of 4 years. A stabilization or regression of Tanner breast pubertal stage in around half of patients associated with a slowing down of growth velocity towards pre-pubertal rate was recorded, as expected. At their final visit, within 3 months after triptorelin pamoate 11.25 mg

injection, more than 90% of the girls had maintained stabilization or regression of Tanner breast pubertal stage. Overall, nonhormonal data pointed to the benefit of continuing suppression treatment until the end of the therapeutic period (at a chronological age of 11 in girls and 13 in boys). Triptorelin pamoate 11.25 mg improves quality of life since the children are subjected to fewer, less frequent injections with this long-release formulation.

PL proposed changes

Section 4 Possible side effects
Paediatric population
Long term trial (up to 4 years) did not bring any new and significant safety concerns.

- **Recommendation**

A type IB variation shall be submitted within 30 days by the MAH after de end of this procedure in order to update the product information in accordance.

X. COMMENTS FROM CMS AT DAY 115

Comments were received from Member States.

Comments from Member State 2

After further internal discussion, the proposed text in SmPC section 5.1

Efficacy data

In the long-term clinical trial 2-54-52014-159 (NCT00909844), thirty-five children with central precocious puberty (CPP) have been treated with triptorelin pamoate 11.25 mg every 3 months for a period of 4 years. A stabilization or regression of Tanner breast pubertal stage in around half of patients associated with a slowing down of growth velocity towards pre-pubertal rate was recorded, as expected. At their final visit, within 3 months after triptorelin pamoate 11.25 mg injection, more than 90% of the girls had maintained stabilization or regression of Tanner breast pubertal stage. Overall, nonhormonal data pointed to the benefit of continuing suppression treatment until the end of the therapeutic period (at a chronological age of 11 in girls and 13 in boys). Triptorelin pamoate 11.25 mg improves quality of life since the children are subjected to fewer, less frequent injections with this long-release formulation.

is considered not acceptable and needs to be revised thoroughly. The following is proposed:

Efficacy data

In the long-term clinical trial 2-54-52014-159 (NCT00909844), 34 girls and 1 boy with central precocious puberty (CPP) have been treated with triptorelin pamoate 11.25 mg every 3 months for a period of up to 4 years. Treatment ended when the investigator decided the patient had

completed his/her treatment, that is to say at about 11 years in girls and 13 in boys, usually after 1-3 years of treatment. At that timepoint, 31/34 (91%) of girls had maintained stabilization or regression of Tanner breast pubertal stage.

Rationale:

The proposed text is easily read as suggesting that n=35 participants were treated for 4 years. The proposed text is also considered too vague ("around half of patients", "more than 90% of the girls", "nonhormonal data").

Although *post-hoc* analyses are unusual in section 5.1, the second post-hoc analysis (CSR addendum) can be accepted as the "on treatment" analysis is most informative in this case.

As in Member State 2 (by MAH IPSEN Farmaceutica B.V.) the CPP indication is only approved for Pamorelin **22.5 mg** (triptorelin pamoate), the proposed text should only be implemented in the product information of this medicinal product and not the other strengths authorized in Member State 2 from MAH IPSEN Farmaceutica B.V. (3.75 mg and 11.25 mg).

This is according to the SmPC guideline, where is stated (https://health.ec.europa.eu/system/files/2016-11/smpc_guideline_rev2_en_0.pdf):
Sections 5.1 – 5.3 should normally mention information, which is relevant to the prescriber and to other health-care professionals, ***taking into account the approved therapeutic indication(s)*** *and the potential adverse drug reactions. Statements should be brief and precise.*

In The Member State 2, another MAH does have the CPP indication registered for the lower strength 3.75 mg. That MAH should submit the proposed text for the lower strength product.
This is according to the BPG Article 45 and 46 – Paediatric Regulation - EU Worksharing Procedure, section 3.5.3. (https://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/Paediatric_Regulation/Guidance_Documents/CMDh_394_2019_Rev.2_07_2022_clean_-_BPG__Article_45_and_46.pdf).

When the approved text is implemented via the mentioned type IB variation, the MAH should look sharply to which triptorelin-containing products the agreed wording is applicable to (based on the approved indications).

Comments from Member State 1

The suggested new information in PL section 4 is redundant and could be removed in line with QRD product-information annotated template which states:

"Additional side effects in children [If appropriate (and in line with information stated in section 4.8 of the SmPC), a subsection should highlight any clinically relevant differences in terms of side effects in any relevant subset of the paediatric population compared to another or to the adult population."

Assessor's comment:
Member State 2 proposed a new text for efficacy under section 5.1 of the SmPC. A rationale is presented and is endorsed. The comments on the need to only amend the SmPC of the formulations that have an approved indication for CPP are also endorsed.

Regarding the comment made by Member State 1 it is our understanding that keeping with the information might be valuable as it is the first data available on the long-term use of this drug in the paediatric setting. A sentence stating the lack of any new and significant safety concerns on long-term exposure, even though it is not novelty considering adult data, is still relevant and different from not having information at all.

XI. FINAL RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The MAH should amend the SmPC and PL with the safety and efficacy information from the long-term study 2-54-52014-159 (NCT00909844) for all triptorelin formulations that have an indication for CPP.

SmPC proposed changes

Section 4.8 Undesirable effects
Safety data
 Long term tolerance in children population:
• The long-term clinical trial 2-54-52014-159 (NCT00909844) included 35 patients, age ranging from 4 to 10.4 years, who had received treatment (up to 4 years) with triptorelin 11.25 mg. More than half of patients (20 patients: 57.1%) reported at least one adverse event during the study, of which the most frequent were abdominal pain (17.1%), injection site pain (11.4%) headache and hot flush (each 8.6%). Overall, the safety profile was similar as seen in the other CPP studies.

Section 5.1 Pharmacodynamic properties
Efficacy data

In the long-term clinical trial 2-54-52014-159 (NCT00909844), 34 girls and 1 boy with central precocious puberty (CPP) have been treated with triptorelin pamoate 11.25 mg every 3 months for a period of up to 4 years. Treatment ended when the investigator decided the patient had completed his/her treatment, that is to say at about 11 years in girls and 13 in boys, usually after 1-3 years of treatment. At that timepoint, 31/34 (91%) of girls had maintained stabilization or regression of Tanner breast pubertal stage.

PL proposed changes

Section 4 Possible side effects
Paediatric population
Long term trial (up to 4 years) did not bring any new and significant safety concerns.

- **Recommendation**

A type IB variation shall be submitted within 30 days by the MAH after de end of this procedure in order to update the product information in accordance of all relevant formulations with an indication for CPP.