London, 20 August 2015
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Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Lyrica

PREGABALIN

Procedure no: EMEA/H/C/000546/P46/048

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Lyrica

International non-proprietary name: Pregabalin

Procedure no.: EMEA/H/C/000546/P46/048

Marketing authorisation holder (MAH): Pfizer

Rapporteur:	NL
Start of the procedure:	
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Introduction

In the European Union (EU), Lyrica is approved for the treatment of peripheral and central neuropathic pain in adults, as adjunctive therapy in adults with partial seizures with or without secondary generalization, and for the treatment of Generalised Anxiety Disorder in adults. Pregabalin is not approved for the treatment in paediatrics and for the treatment of fibromyalgia in the EU for any age category. In the United States (US), Lyrica is approved for fibromyalgia, neuropathic pain associated with diabetic peripheral neuropathy and spinal cord injury, post herpetic neuralgia, and adjunctive therapy for adult patients with partial onset seizures. In Japan, Lyrica is approved for neuropathic pain and fibromyalgia.

The application for the indication fibromyalgia in adults was refused by the CHMP in 2009 due to the following reasons:

- the short-term efficacy of Lyrica in the claimed indication, treatment of fibromyalgia in adults experiencing moderate to severe pain, has not been sufficiently demonstrated since no consistent and clinically relevant benefit for patients has been shown in pain and functional improvement;

- the maintenance of effect has not been convincingly demonstrated;

- the efficacy and safety of Lyrica in a representative EU-population with fibromyalgia have not been demonstrated. The US population cannot be extrapolated to the EU population taking into account the differences in practices, consistency in phenotypes and results;

- the known adverse events and doubtful clinical relevance of the effect size observed renders the overall benefit/risk negative;

On the 17th of June 2015, the MAH submitted a completed paediatric study for Lyrica in adolescents, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. A short critical expert overview has also been provided. Study A0081180 is titled "A 15 week, randomized, double blind, parallel-group, placebo controlled, flexible-dose, safety and efficacy study of pregabalin in adolescents (12-17 years old) with fibromyalgia" was provided. This study was conducted to fulfil the US Food and Drug Administration (FDA) requirements for a safety and efficacy study in adolescent fibromyalgia patients (12-17 years old; NDA 21- 446/S-010) given at the time of approval of the management of fibromyalgia indication on 21 June 2007.

1. Scientific discussion

1.1. Information on the development program

The MAH stated that study A0081180 titled "A 15 week, randomized, double blind, parallel-group, placebo controlled, flexible-dose, safety and efficacy study of pregabalin in adolescents (12-17 years old) with fibromyalgia" is part of the clinical post-marketing development program. The study was conducted to fulfil the US Food and Drug Administration (FDA) requirements for a safety and efficacy

study in adolescent fibromyalgia patients. The plasma concentration data obtained in study A0081180 were used for population PK modelling (report PMAR-EQDD-A008h-DP4-415).

The MAH does not propose any changes to the product information based on this study. The study is briefly described in the sections below, with limited commentary from the Rapporteur.

1.2. Information on the pharmaceutical formulation used in the study

Lyrica capsules were used, which is a suitable formulation for adolescents.

1.3. Clinical aspects

1.3.1. Introduction

Pregabalin (Lyrica) is an α2-δ ligand that binds with high affinity to the auxiliary subunit of voltage-gated calcium channel in central nervous system tissues. Pregabalin has been developed clinically for neuropathic pain, fibromyalgia, anxiety, and epilepsy.

Pregabalin PK has been studied before in healthy adults and in adult subjects with partial seizures, neuropathic pain, fibromyalgia, generalized anxiety disorder and impaired renal function. In addition, the PK of pregabalin was evaluated in paediatric subjects 1 month to 16 years of age. The information below is included in section 5.2 of the SmPC.

Absorption

Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1 hour following both single and multiple dose administration (t_{max} ranges between 0.5 to 1.5 hours). Pregabalin oral bioavailability is estimated to be 90% and is independent of dose. Administration of pregabalin with food has no clinically significant effect on the extent of pregabalin absorption. Following repeated administration, steady state is achieved within 24 to 48 hours and multiple-dose PK can be predicted from single-dose data. Pregabalin pharmacokinetics are linear over the recommended daily dose range (75 to 900 mg/day). Inter-subject pharmacokinetic variability for pregabalin is low (<20%). Gender does not have a clinically significant influence on the plasma concentrations of pregabalin.

Distribution

The apparent volume of distribution of pregabalin following oral administration is approximately 0.56 L/kg. Pre-clinical studies indicate that pregabalin is able to pass the blood brain barrier. Pregabalin is not bound to plasma proteins.

Biotransformation

Pregabalin undergoes negligible metabolism in humans. In pre-clinical studies, there was no indication of racemisation of pregabalin S-enantiomer to the R-enantiomer.

Elimination

Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Pregabalin mean elimination half-life is 6.3 hours in subjects with normal renal function. Pregabalin elimination is essentially proportional to creatinine clearance (CLcr).

Paediatric population

The PK, safety, and tolerability of pregabalin were evaluated in paediatric subjects 1 month to 16 years of age with partial onset seizures in the double-blind, placebo-controlled Phase 1 study A0081074. Dose levels of 2.5, 5.0, 10.0, and 15.0 mg/kg/day (given in equally divided doses twice daily) were administered for 8 days. Single and multiple dose PK were evaluated. Pregabalin peak concentration and AUC increased linearly with increasing dose (2.5, 5.0, 10.0 and 15.0 mg/kg/day) for each age group (1 month to 23 months, 2 to 6 years, 7 to 11 years, and 12 to 16 years). The PK data in children aged 12 to 16 years from study A0081074 versus adults (study 1008-002) are summarised in Table 1.

Table 1. PK data in children aged 12 to 16 years (study A0081074) versus adults (study 1008-002)

Dose	**age (N)**	**AUC_{0-12h} (µg h/mL)**	**C_{max} (µg/mL)**	**t_{max} (h)**	**$t_{½}$ (h)**	**study**
2.5 mg/kg/day	12-16 (N=3)	12.4 ± 2.4	2.14	0.5	5.0	A0081074
5.0 mg/kg/day	12-16 (N=3)	27.8 ± 2.2	5.39	0.6	4.0	A0081074
10.0 mg/kg/day	12-16 (N=4)	48.0 ± 20.6	6.75	2.1	5.6	A0081074
15.0 mg/kg/day	12-16 (N=1)	103.0	13.8	2.2	6.6	A0081074
600 mg/day (~10 mg/kg/day)	adults (N=8)	59.0 ± 3.5	9.07	1.4	6.7	1008-002

1.3.2. Clinical study A0081180

Description

Clinical study A0081180 is a 15-week, multi-centre, randomized, double-blind, parallel group, placebo-controlled study consisted of 4 phases: screening/baseline (1 week), dose optimization (3 weeks), fixed dose (12 weeks) and follow-up/taper (1 week).

Methods

Objective(s)

The primary objective of study A0081180 was to evaluate the safety and efficacy of pregabalin (75-450 mg/day) compared with placebo in an adolescent fibromyalgia population. The secondary objective was to evaluate the pharmacokinetics of pregabalin in an adolescent fibromyalgia population. The pharmacokinetics obtained in study A0081180 were used for population pharmacokinetics of pregabalin in adolescent patients with fibromyalgia an provided in report PMAR-EQDD-A008h-DP4-415.

Other objectives were to collect data that will help characterize the adolescent fibromyalgia population and facilitate future clinical studies.

Pregabalin 300 to 450 mg/day (~5 to 7.5 mg/kg bw/day based on a body weight of 60 kg) is the recommended daily dose range for fibromyalgia in adults. These daily doses were planned as the maximum doses for this adolescent study population. In addition, doses of 75 mg/day and 150 mg/day were also included to allow for smaller, low-weight adolescents, who may have enrolled in the study.

GCP

During study conduct, Pfizer or its representative conducted periodic monitoring visits to ensure that the protocol and GCPs were followed. The monitors reviewed source documents to confirm that the data recorded on the CRFs were accurate. The investigator and institution allowed Pfizer monitors or its representative and appropriate regulatory authorities direct access to source documents in order to perform these verifications.

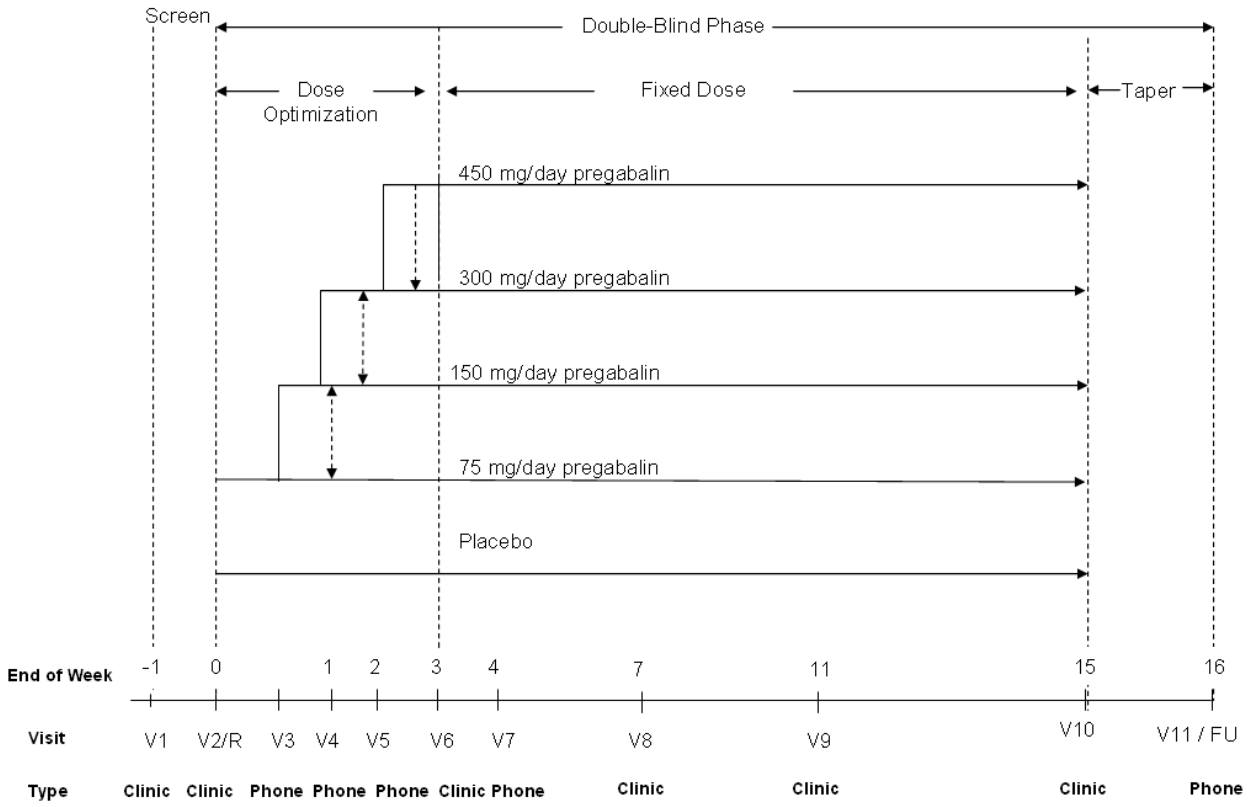
No centre inspections were conducted by the FDA or any IRB\IEC. Centre audits were performed by Pfizer at Centres 1002, 1003, 1007, 1017, 1022, 1033, 1037, 1047, 1058 and 1064. There were no audit certificates issued. Two centre terminations (USA centre 1016 and Indian centre 1037) occurred due to noncompliance issues and per recommendation of the Independent Data Monitoring Committee (IDMC).

Study population

The study population consisted of male and female subjects of any race and 12-17 years of age, inclusive. Subjects must have met the Yunus and Masi criteria for fibromyalgia: generalized musculoskeletal aching at ≥3 sites for ≥3 months, ≥5 tender points, and ≥3 of the following 10 minor criteria had to be present: chronic anxiety or tension, fatigue, non-restorative sleep, chronic headaches, irritable bowel syndrome, subjective soft tissue swelling, numbness, pain modulation by physical activities, pain modulation by weather factors, and pain modulation by anxiety or stress.

Study design

Study consisted of 4 phases: screening/baseline (1 week), dose optimization (3 weeks), fixed dose (12 weeks) and follow-up/taper (1 week) (see Figure below). The first subject was enrolled on 07 May 2010, and the last subject's last visit was on 08 December 2014.



At Visit 1, subjects were to sign informed consent and be screened for eligibility. In addition, subjects were to be given a pain and quality of sleep diary which they were instructed to complete on a daily basis in the afternoon or evening. At Visit 2, at least 4 pain diaries were to be completed satisfactorily within the last 7 days and the average pain score had to be ≥4. In addition, laboratory and ECG results from Visit 1 were to be assessed for eligibility. Subjects were to initiate dosing at 75 mg/day and have their dose optimized (75-450 mg) over a 3 week period. The doses were administered as follows:

- Pregabalin 75 mg/day (25 mg morning and 50 mg evening) or placebo
- Pregabalin 150 mg/day (75 mg BID) or placebo
- Pregabalin 300 mg/day (150 mg BID) or placebo
- Pregabalin 450 mg/day (225 mg BID) or placebo

After this 3 week optimization period, subjects were to remain at the optimized dose for 12 weeks with no further dose adjustment allowed. At the end of the 12 week period, subjects were to taper their study medication over a 1-week period and given the option to enter into an open-label extension study.

Concomitant pain medications that might have affected the pain or sleep disturbance associated with fibromyalgia were to be discontinued within 1 to 30 days (or possibly longer if needed for tapering) prior to Visit 1

Pharmacokinetic design

Two PK samples were to be collected at Visit 6 (Week 3). The first sample was to be collected as soon as possible upon arrival at the clinic, and the second sample was to be collected just prior to leaving the clinic. Subjects with a clinic visit scheduled in the morning should not have taken their morning dose until immediately after the first PK sample was drawn. Subjects with a clinic visit scheduled in the afternoon should have taken their morning dose at the usual time, collect the PK samples upon arrival and departure, and no dose was to be administered during the clinic visit. Subjects with a clinic visit scheduled in the evening should not have taken their evening dose until immediately after the first PK sample was drawn.

Information concerning the times when the two blood samples were drawn, the times when the last two doses were administered (the two doses prior to the 2nd PK blood sample), and the time of last meal prior to the PK samples was to be recorded. Blood samples were collected into tubes containing sodium heparin. To obtain plasma, samples were centrifuged at 1700 g for about 10 minutes at 4°C. The plasma samples were stored at -20°C within 1 hour of collection.

Analytical method

Analysis of pregabalin was performed using the anlytical method 08BASM037V3. The analytical method was developed and validated at the concerned laboratory. A copy of the validation report is presented in Validation Report 08BAS0048. Pregabalin and internal standard (PD-403609) were measured by LC-MS/MS.

Plasma samples were stored at approximately -20 ±5 °C until analysis. The LLOQ was 0.0250 µg/mL and the ULOQ was 10.00 µg/mL. Samples with concentrations above ULOQ were adequately diluted into calibration range. The inter-day precision and accuracy ranged from to ≤4% and from 101.6 to 109.5%, respectively. The storage stability was stated as 371 days at -20°C and -70°C. A total of 32 samples of the total of 97 plasma samples were assayed for pregabalin later than the established stability of 371 days. No information on the storage stability under other conditions (e.g. autosampler), dilution integrity and intra-day accuracy and precision were provided.

A total of 21 samples (21.6% of the total 97 study samples analysed) were selected, re-assayed and evaluated for the Incurred Samples Reproducibility. The percentage of the incurred samples meeting the acceptance criteria was 100%.

Chromatograms of 28 out of 48 subjects (58%) used in PK analysis, including plasma blank, QC samples and calibration standards were submitted with the report.

PK analysis

The PK analysis data set consisted of all subjects who took at least 1 dose of pregabalin and who had at least 1 post-dose PK measurement. A previously developed population PK model was used to evaluate pregabalin PK in adolescent subjects with fibromyalgia.

The population PK model was developed using serial sampling data from 60 paediatric subjects (3 months to 16 years) and 103 healthy and 20 renally impaired adults. Pregabalin pharmacokinetics were adequately characterized using a one compartment open model with first order elimination, first order absorption rate constant describing pregabalin absorption when given in the fasted state and a Weibull input function describing pregabalin absorption when given in the fed state. Pregabalin oral clearance was directly related to creatinine clearance and was unaffected by race, age, gender or body weight. Pregabalin apparent distribution volume was directly related to body weight to power of 0.955.

A typical female has approximately 14% lower V/F relative to males. However, this gender difference was considered not to be of clinical importance. The inverse relationship between weight normalized V/F and patient age reduced V/F by ~13% over the age range of 3 months to 1 years and another 25% over the age range of 4 to 80 years. This decrease in V/F with increasing age is consistent with age-related decrease in total body water across both paediatrics and adults. In infants and paediatric subjects, total body water per kg of body weight decreases with age and in adults, the ratio of total body water to body weight declines with age as a result of increasing body fat with increasing age. The covariate, race, did not have a significant impact on pregabalin V/F parameter.

This population PK model was adapted to be used to predict plasma pregabalin concentrations for adolescent subjects with fibromyalgia in study A0081180. For simplicity, the Weibull function was replaced with first order (k_a) to describe pregabalin absorption in the fed state. Additionally, a creatinine clearance breakpoint was evaluated given the artificially inflated calculated creatinine clearance observed in overweight patients.

Statistical Methods

NONMEM version 7.2 (ICON Development Solutions, Ellicott City, MD) analysis was used for generating the PK/PD data files. Prediction-corrected visual predictive checks (pcVPC) were conducted by PsN version 3.5.4. Pre-processing of input data was conducted with Splus 8.0 (see Table below). Post-processing of output tables was conducted using R version 2.12.2 with the package Xpose4. The analysis data files contain sparse concentration data, dosing and demographic information. The variables age, sex, race, body weight, height, and serum creatinine (used to calculate creatinine clearance) were recorded based on the value at the time of the first visit. The datasets include information on whether the dose was given fed or after fasting. Only the time of last meal prior to the first PK sample was collected. This information was used to populate fed/fasted status for the two most recent doses. All other doses within the dataset were assigned as food unknown.

Data File name/Location	ePharmacology Artifact ID Number
A0081180_POPPK_15JUN2015.csv	10124118
A0081180_POPPK_Programming_Plan	10124119
Analyst manipulated file	
A0081180_15JUN_manipulated_Weibull.csv	10143465
A0081180_15JUN_manipulated_Ka.csv	10143462

Clinical outcomes/endpoints

The primary endpoint of the study was the change from baseline to week 15 in mean pain score derived from daily pain numeric rating scale (24-hour recall) ranging from 0 (no pain) to 10 (worst possible pain).

The secondary endpoints were:

- Weekly mean pain score at each week - derived from daily pain NRS (24-hour recall).
- 30% and 50% pain responders.
- Weekly pain NRS at Week 15 (1-week recall).
- Weekly mean sleep quality score at endpoint, from the daily sleep diary. Endpoint is defined as the mean of the last 7 diary entries prior to Week 15 while the subject is on study drug.
- Weekly mean sleep quality score at each week, from the daily sleep diary.

- Patient Global Impression of Change (PGIC) at Week 15.

Exploratory endpoints were Parent Global Impression of Change (Parent-GIC) at Week 15 and Fibromyalgia Impact Questionnaire for children (FIQ-C) at Week 15.

Safety endpoints were incidence and severity of AEs, physical and neurological examinations, vital signs, electrocardiogram (ECG), laboratory assessment, Tanner staging and suicidality assessment.

Rapporteur's comment:

The endpoints PGIC and FIQ-C are considered the most important secondary endpoints as these reflect the functional improvement of the patient.

As fibromyalgia is a condition with many dimensions, it is considered important that endpoints other than pain (sleep, function) show consistent effects with the primary endpoint change in mean pain score.

Statistical Methods

The Full Analysis Set (FAS) population consisted of all randomized subjects who received at least one dose of study drug (either pregabalin or placebo). The FAS population was the primary population for efficacy analyses. The primary analysis of the primary endpoint (change from baseline to endpoint in weekly mean pain scores) was carried out based on the FAS population with multiple imputation applied to the weekly data and using analysis of covariance (ANCOVA) techniques, with terms for baseline mean pain score, center and treatment in the model. The multiple imputation method assigned to missing pain scores a value similar to those of the baseline distribution of pain scores if the subject discontinued for adverse events or lack of efficacy. All other missing scores were assigned according the distribution of those for completer subjects. For sensitivity analyses of the primary endpoint, a mixed model repeated measures (MMRM) analysis was used. Additional sensitivity analyses were based on imputation rules described below:

- Baseline observation carried forward (BOCF) for subjects with missing Week 15 mean pain score.
- Last observation carried forward (LOCF) for subjects with missing Week 15 mean pain score.
- Modified baseline observation carried forward (mBOCF) for subjects with missing Week 15 mean pain score, which will apply the BOCF rule for subjects discontinued due to AEs and the LOCF rule for subjects discontinued due to any other reason.

Secondary endpoints based on the daily diary were analyzed in the FAS population using a MMRM model with terms of treatment, center, baseline value, visit week, and treatment-by-visit interaction. This model was used to estimate treatment difference and the associated 95% 2-sided confidence intervals (CIs). Unadjusted and adjusted weekly means and 95% CIs were presented for each treatment group at each week.

Statistical significance was defined at the level of $p<0.05$ (2-sided test).

Results

A total of 147 subjects were screened and 107 subjects at 23 study centres (US 17 centres with in total 67 subjects; India 4 centres with in total 35 subjects, Czech Republic 1 centre with 4 subjects, and Taiwan 1 centre with 1 subject) were randomized to treatment. Of the 107 randomized subjects, 107 (100%) took at least one dose of study drug. A total of 44 (81.5%) subjects in the pregabalin group and 36 (67.9%) subjects in the placebo group completed the study, and 10 (18.5%) subjects in the pregabalin group and 17 (32.1%) subjects in the placebo group discontinued the study.

The majority of subjects (92 of 107) were female. All but 2 of the female subjects (2.2%) were in menarche. Mean (range) age of all subjects was 14.7 (12-17) years. The majority of subjects were White (57.0%) or Asian (33.6%). Demographic characteristics were similar between the treatment groups (Table 2).

Table 2. Demographic characteristics – safety population

Demographic Characteristics	Pregabalin (N=54)	Placebo (N=53)	Total (N=107)
Age (years)			
Mean	14.6	14.7	14.7
SD	1.2	1.2	1.2
Range	12-17	12-16	12-17
Race - Number (%) of Subjects			
White	29 (53.7)	32 (60.4)	61 (57.0)
Black	2 (3.7)	3 (5.7)	5 (4.7)
Asian	21 (38.9)	15 (28.3)	36 (33.6)
Other	2 (3.7)	3 (5.7)	5 (4.7)
Weight (kg)			
Mean	60.4	59.7	60.1
SD	21.4	17.7	19.6
Range	28.5-154.7	39.0-127.6	28.5-154.7
Height (cm)			
Mean	160.1	162.3	161.2
SD	7.6	8.2	7.9
Range	141.0-177.8	147.0-183.0	141.0-183.0

Abbreviations: SD=standard deviation.

The 107 randomized subjects had been experiencing FM symptoms for a mean of 1.9 years (range: 0.3-11.7 years) and were diagnosed with fibromyalgia for a mean of 5.7 months (range: 0-45.1 months) prior to study start. Of the 107 randomized subjects, 95 (88.8%) subjects met the ACR fibromyalgia diagnostic criteria in addition to the Yunus and Masi criteria, which were a study eligibility requirement.

Rapporteur's comment:

As expected based on the prevalence of fibromyalgia, the majority of patients were female. Only four patients from the EU were included. Due to the geographical differences in the way in which fibromyalgia is perceived, diagnosed and managed, the results of this study can not be readily extrapolated to the EU population. As mentioned in the introduction of this report, the outcomes were inconclusive for European subgroup in the adult fibromyalgia studies.

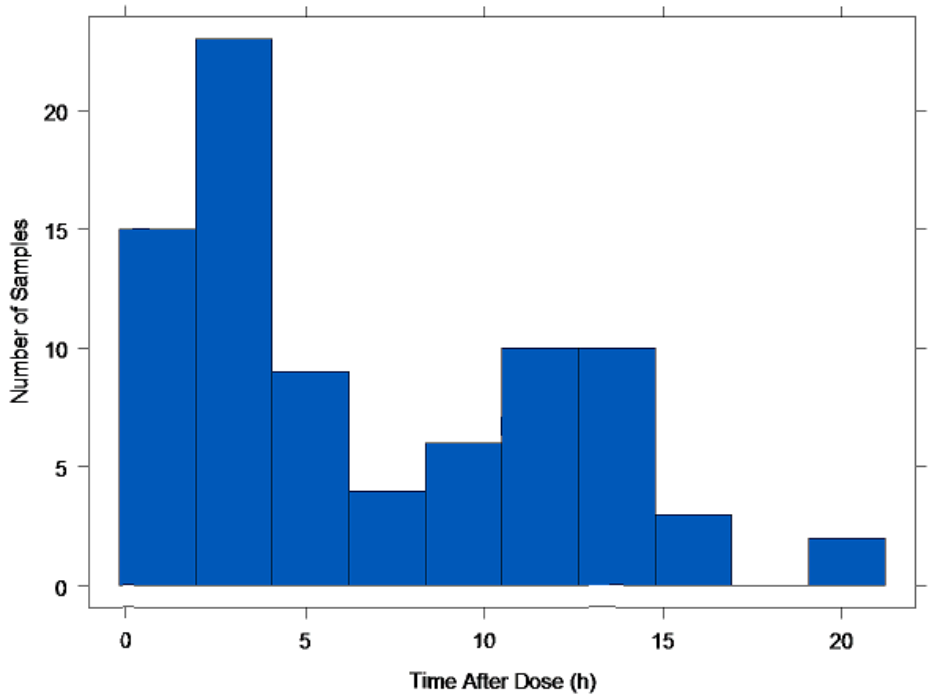
Analytical results

There were no subjects with missing covariate data. Some plasma samples were excluded, because of plasma samples with missing values, plasma samples having incomplete or a high likelihood of inaccurate sample collection, plasma samples obtained ≥ 36 hours after the last recorded dose (concentration most likely below LLOQ) and plasma samples collected <36 hours after last dose but with a value below the LLOQ. In the Table below the excluded data are summarised.

ID	NSID	Study Day	TAD (h)	Dose (mg)	Conc (µg/mL)	Comments
Plasma Samples with Missing Values						
31		22	7.83	25	Missing	One sample removed due to missing concentration
Plasma Samples with Incomplete or Inaccurate Information						
3		20	1	225	1.4	Samples were evaluated for possible data reporting discrepancies by first flagging samples in which 1) a dose was reported as being taken at the site but the second PK concentration was at least 10% lower than the pre-dose PK sample or 2) no dose was reported as being taken at the site but the second PK concentration was at least 10% higher than the first. Visual inspection of flagged data (i.e., time after dose for both PK sample 1 and 2 and whether or not reported last dose was administered fasted) was then used to select samples for exclusion.
13		19	9.43	225	5.72	
28		28	2.05	150	0.895	
37		22	14.25	50	1.15	
45		23	8.17	75	1.46	
Plasma Samples ≥ 36 hours TAD						
39		29	84.17	50	0.935	Two samples ≥ 36 hours after the reported last dose were collected from a single subject on the same occasion
39		29	85.92	50	0.165	
Plasma Samples < 36 hours and BLQ						
31		22	6.5	25	0	Seven samples were excluded from analyses due to BLQ. Two of these samples were collected from ID 34 on Day 41, unplanned per protocol. Subjects 47, 48, 49, and 50 had detectable pregabalin concentrations for their second PK sample collected following observed study medication administration at site; this data was retained. Subject 31 had one sample BLQ and one sample with missing pregabalin concentration as noted above.
34		41	3	25	0	
34		41	4	25	0	
47		21	11.25	225	0	
48		18	12.17	225	0	
49		20	11.88	225	0	
50		20	10.92	75	0	

BLQ=below limit of quantification of 0.025 µg/mL; Conc=pregabalin concentration; Dose=last reported dose prior to PK sample; ID=NONMEM ID; NSID=study assigned subject ID; TAD=time after the last reported dose [ePharm Step ID: 574567]

In total 82 plasma concentration-time data from 48 subjects were included in analyses. The sampling time after dosing is shown in the Figure below.



The samples obtained per total daily dose is shown in the Table below.

Total daily dose (mg/day)	N	# of PK samples	# samples analysed >371 days
75	12	21	4
150	9	16	5
300	9	17	4
450	18	28	15

PK results

The prediction-corrected observed and predicted values using the population PK model with and without a creatinine clearance breakpoint are shown in **Figure 1**. The model adequately predicted pregabalin concentrations in adolescent patients with fibromyalgia. Addition of a creatinine clearance breakpoint, in order to account for artificially inflated creatinine clearance in overweight patients, improved the model fit. This model had similar predictive value for PK samples assayed within and outside established long term stability indicating that storage for >371 days did not have any impact on results of the PK analyses. There was no obvious difference in model performance based on subject's age, creatinine clearance (**Figure 2**), or baseline body weight.

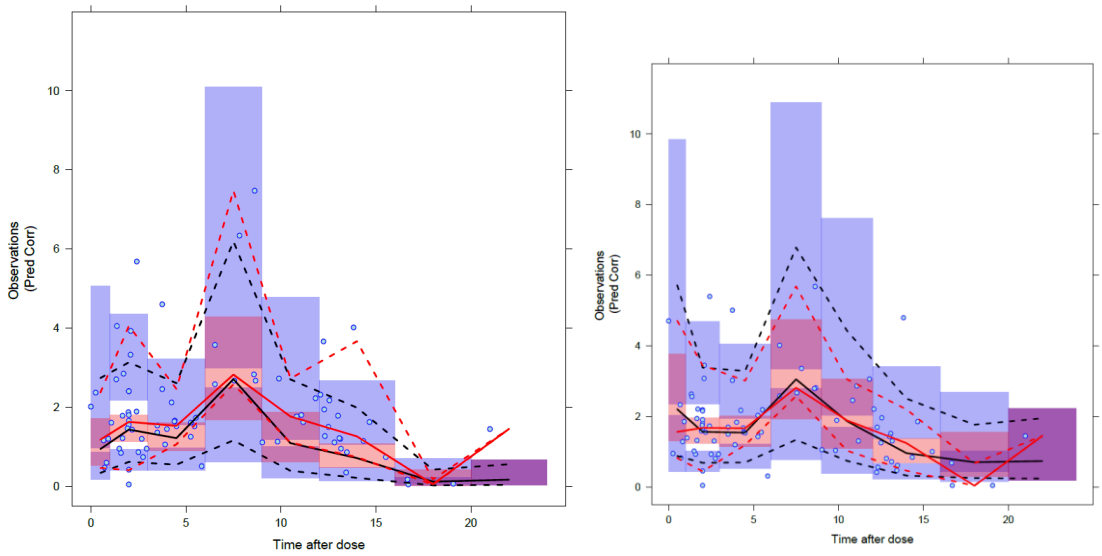


Figure 1. *Prediction-Corrected Observed and Simulated Pregabalin Concentrations [Linear and Breakpoint]. Open circles are prediction-corrected observed data. Black solid and dotted lines and red solid and dotted lines represent the median, 5th and 95th percentile of the prediction-corrected simulated and observed pregabalin concentrations, respectively. The bands around the simulated percentiles represented the 95% confidence intervals of the simulated concentrations. Bins: 1, 3, 6, 9, 12, 16, 20, 24. Left: Linear relationship between pregabalin clearance and Cockcroft-Gault calculated creatinine clearance. Right: Linear relationship between pregabalin clearance and Cockcroft-Gault calculated creatinine clearance with breakpoint of 107 mL/min.*

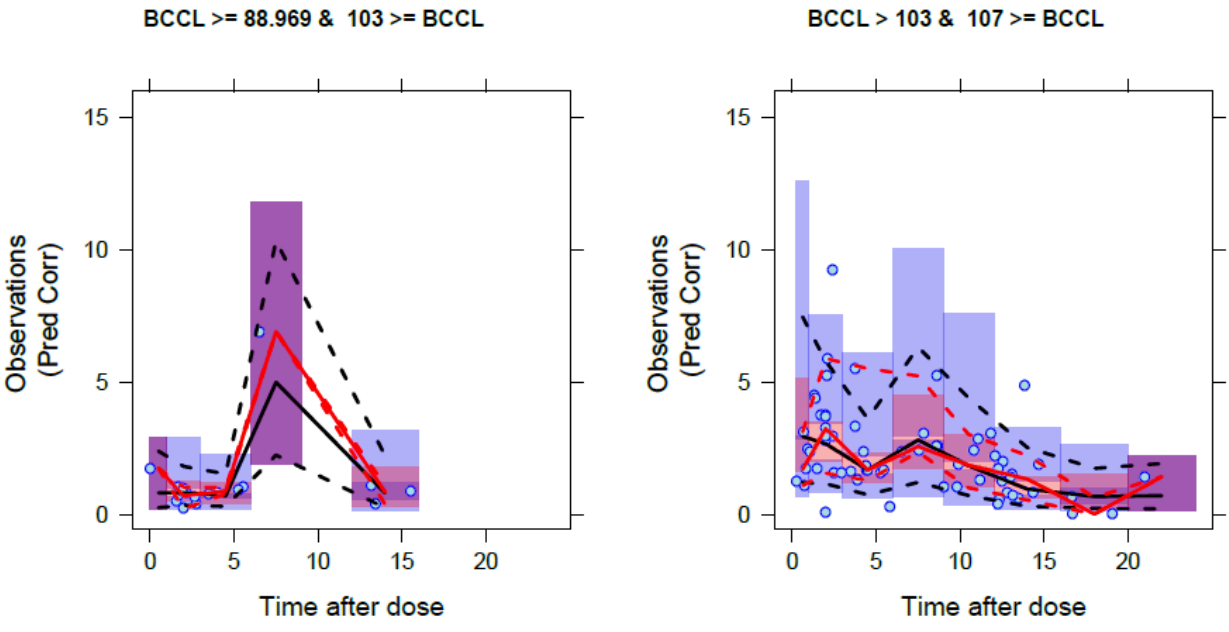


Figure 2. *Prediction-Corrected Observed and Simulated Pregabalin Concentrations: Stratification by Creatinine Clearance [Breakpoint]. Open circles are prediction-corrected observed data. Black solid and dotted lines and red solid and dotted lines represent the median, 5th and 95th percentile of the prediction-corrected simulated and observed pregabalin concentrations, respectively. The bands*

around the simulated percentiles represented the 95% confidence intervals of the simulated concentrations. Bins: 1, 3, 6, 9, 12, 16, 20, 24.

In conclusion, the pregabalin concentration values observed for adolescent subjects with fibromyalgia were adequately described by the population PK one compartment model with first order absorption, first order elimination, and a direct relationship between individual's creatinine clearance and pregabalin clearance.

Assessor's comments

Since pregabalin is rapidly absorbed (F = ~90%), undergoes negligible metabolism, is primarily renally eliminated and dose is based on body weight, no differences in kinetics are expected between adolescents with fibromyalgia and adolescents and adults without fibromyalgia. The similar pharmacokinetics are confirmed by the limited PK data provided by the Applicant from study A0081180.

Efficacy results

The mean and median doses during the fixed dose period (maintenance dose) in the pregabalin group were 244.5 mg/day and 262.3 mg/day, respectively. Mean and median doses were higher for male subjects and for subjects weighing at least 50 kg. The highest number of subjects (40.4%) was treated with 450 mg/day; another 15.4% of subjects were treated with 300 mg/day, 19.2% with 150 mg/day, and 25.0% with 75 mg/day.

Primary endpoint

The results of the primary endpoint analysis a presented in table 3. A placebo-adjusted treatment difference of -0.66 favouring pregabalin was observed, which was not a statistically significant difference (p=0.121). Pregabalin-treated subjects experienced an improvement of 1.60 points from baseline on the 0-10 scale, while placebo-treated subjects experienced a 0.94 point improvement from baseline (LS mean changes).

Table 3. Change from Baseline to Week 15 in Weekly Mean Pain Score - Daily Pain NRS (24-Hour Recall) – FAS Population (MI)

									Pregabalin vs Placebo		
	N	n	Raw mean	LS mean	95% CI	Raw change	LS mean change	SE change	LS mean differ-ence	95% CI	p-value
Pregabalin	54	54	5.19	5.35	(4.71, 5.98)	-1.75	-1.60	0.32	-0.66	(-1.51, 0.18)	0.121
Placebo	53	51	5.81	6.01	(5.40, 6.62)	-1.14	-0.94	0.31			

Abbreviations and Notes:
Missing data for Week 15 mean pain score were imputed based on distribution of baseline pain scores if subjects discontinued due to adverse events or abnormal laboratory test results or lack of efficacy; otherwise if subjects discontinued due to other reasons, it was imputed based on distribution of post baseline weekly mean pain scores using a Markov Chain Monte Carlo Method. Weekly mean pain NRS scores were derived from the daily pain NRS and calculated as the mean of the available scores in that week. At least 4 entries within the week were required to calculate a mean.
N is the number of subjects in the FAS Population; n is the number of subjects that can be summarized for the endpoint at the given timepoint. Based on LS Means using ANCOVA model (including treatment, center, baseline value as covariate). NRS=Numeric Rating Scale; ANCOVA=Analysis of Covariance; SE=Standard Error; CI=Confidence Interval; LS=Least Square; MI=Multiple Imputation; FAS=Full Analysis Set.

Sensitivity analyses (BOCF, mBOCF, LOCF, MMRM at Week 15) were in the same direction as the primary efficacy result and showed greater numerical improvements for pregabalin-treated subjects compared to placebo but these were not statistically significant.

Rapporteur's comment:

The mean difference of -0.66 in pain score between pregabalin and placebo is considered very modest magnitude of effect and its clinical relevance is doubtful.

Secondary endpoints

Weekly mean pain scores derived from the daily pain diary were determined using the MMRM analysis with no imputation. Weekly mean pain scores demonstrated statistically significant improvements with pregabalin compared to placebo starting at Week 3 (-0.83, p=0.019), and for most of the fixed dose period (11 of 13 weeks), with treatment differences between -0.68 and -1.06.

More pregabalin-treated than placebo-treated subjects were 30% or 50% pain responders, regardless of imputation. The observed 30% responder rate was 51.4% for pregabalin and 50.0% for placebo. The observed 50% responder rate was 25.7% from pregabalin and 12.5% for placebo. These treatment differences were not statistically significant.

Statistically significant improvements at Week 15 with pregabalin (compared to placebo) were observed for some secondary and exploratory endpoints, including the pain NRS with 1-week recall administered at clinic visits (treatment difference -0.87; p=0.037), PGIC (53.1% vs 29.5% very much or much improved; p=0.013 across all 7 categories), and the Parent-GIC (51.0% vs 25.0% very much or much improved; p=0.011 across all 7 categories). Improvements were not statistically significant for pregabalin vs placebo on the FIQ-C total score and subscales and sleep quality as assessed by daily sleep diaries.

Rapporteur's comment:

The secondary endpoints show inconsistent results. Although the weekly mean pain scores demonstrated statistically significant improvements with pregabalin compared to placebo starting at Week 3, the magnitude of effect is again modest. Further the differences in 30% and 50% responder rates are not statistically significant.

Although the PGIG and Parent-GIC indicate improvements in patients' overall status with pregabalin, these improvements are not reflected in functionality (FIQ-C) or effects on sleep.

Safety results

A total of 54 subjects in the pregabalin group and 53 subjects in the placebo group were included in the analysis of adverse events (AEs).

The most common AEs were dizziness, nausea, headache, weight gain, and fatigue (Table 4). No deaths occurred in this study. One pregabalin-treated subject experienced 2 serious AEs (cholelithiasis, major depression). Similar numbers of severe AEs (n=3 per group) and discontinuations due to AEs (n=4 per group) occurred in each treatment group. No suicidal behaviour was reported. Three subjects (5.6%) treated with pregabalin and 2 subjects (3.8%) treated with placebo reported suicidal ideation. More subjects experienced weight gain in the pregabalin group, with 11 subjects reporting weight gain of at least 7% and none in the placebo group. There were no clinically relevant findings in Tanner stage development (breast and pubic hair) during the study; the majority of subjects were at stage 4 or 5 at screening and at the end of the study. There were no other clinically significant findings for other safety assessments including physical examinations, neurological examinations, laboratory test results, and ECG

Table 4. Analysis of Treatment-Emergent Adverse Events by Preferred Term (All Causality): Events in ≥4 Subjects in Either Treatment Group.

Event	Pregabalin	Placebo
	n/N (%)	n/N (%)
Dizziness	16/54 (29.6)	7/53 (13.2)
Nausea	12/54 (22.2)	5/53 (9.4)
Headache	10/54 (18.5)	10/53 (18.9)
Weight increased	9/54 (16.7)	0/53 (0.0)
Fatigue	8/54 (14.8)	4/53 (7.5)
Somnolence	5/54 (9.3)	2/53 (3.8)
Oropharyngeal pain	4/54 (7.4)	2/53 (3.8)
Pain in extremity	4/54 (7.4)	0/53 (0.0)
Pyrexia	4/54 (7.4)	3/53 (5.7)
Back pain	3/54 (5.6)	5/53 (9.4)
Upper respiratory tract infection	3/54 (5.6)	4/53 (7.5)
Vomiting	3/54 (5.6)	4/53 (7.5)
Arthralgia	1/54 (1.9)	4/53 (7.5)
Cough	1/54 (1.9)	4/53 (7.5)
Pharyngitis streptococcal	0/54 (0.0)	4/53 (7.5)

N is the total number of subjects for the given treatment group; n is the number of subjects with adverse events for the given treatment group. % is [n/N]*100. Ordered by incidence in pregabalin group.

Rapporteur's comment:
The most common adverse events dizziness, nausea, headache and increased weight are typical for pregabalin. In overall the safety profile is consistent to what is known based on the prior adult and paediatric studies.

1.3.3. Discussion on clinical aspects

The MAH has presented data from a clinical study performed in adolescent patients with fibromyalgia. Study A0081180 was conducted to fulfil the US Food and Drug Administration (FDA) requirements. Lyrica is not registered in the EU for the treatment of fibromyalgia.
Thus far, beyond this fibromyalgia study in adolescents. paediatric data were available from a PK and tolerability study in epileptic children. No posology recommendations for paediatric patients are given in the approved indications neuropathic pain, partial seizures with or without secondary generalisation and generalized anxiety disorder, paediatric data are however presented in SmPC sections 4.8, 5.1 and 5.2.

The pharmacokinetics in adolescent with fibromyalgia are similar to previously obtained PK parameters in adolescents without fibromyalgia. Pregabalin is rapidly absorbed (F = ~90%), undergoes negligible metabolism, is primarily renally eliminated and the dose is based on body weight, therefore, no differences in kinetics are expected between adolescents with fibromyalgia and adolescents and adults without fibromyalgia.

The submitted study shows a very modest decrease in mean pain score from baseline to 15 weeks with pregabalin in adolescent patients with fibromyalgia, the treatment difference relative to placebo was not statistically significant. The results on secondary and exploratory endpoints showed inconsistent results. The modest changes in pain are not reflected in other relevant endpoints such as functionality or sleep.
The observed safety profile was comparable to the safety profile of adult fibromyalgia patients, apart from mild nausea which was reported more frequently in adolescent patients. The safety profile is comparable to previous safety data on children obtained from prior paediatric studies.

The MAH does not propose any changes to the product information, as Lyrica is not approved for the treatment of fibromyalgia in the EU. The MAH further states that the safety results in adolescent studies do not warrant changes or limitations to the ongoing paediatric fibromyalgia and epilepsy studies. The information provided in this submission does not change the favourable benefit-risk profile of pregabalin.

2. Rapporteur's overall conclusion and recommendation

The conclusion drawn by the MAH is accepted. Fibromyalgia is not an approved indication for adults in the EU. The provided clinical study in adolescents did not demonstrate a clinically meaningful effect of pregabalin in fibromyalgia symptoms. Therefore no amendments in indications are warranted.

The plasma concentrations in adolescents with fibromyalgia were comparable to concentrations observed in adolescents and adults without fibromyalgia. Therefore no amendments to the pharmacokinetic data already presented in the SmPC are warranted.

The observed safety profile in the provided study was comparable to the one observed in previous paediatric studies. Therefore no amendments to product information or protocols for the planned or ongoing paediatric studies are warranted.

√ Fulfilled

☐ Not fulfilled