25 September 2014
EMA/620639/2014
Committee for Medicinal Products for Human Use (CHMP)

# Lyrica

(pregabalin)

Procedure No. EMEA/H/C/000546/P46/045

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

**Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted**

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# I. EXECUTIVE SUMMARY

No SmPC and PL changes are proposed by the MAH.

# II. RECOMMENDATION[1]

Based on the data submitted, the answers provided by the MAH, and the update on the progress of the ongoing program intending to provide additional paediatric data including timelines, it is considered necessary that corresponding changes in the label be made to reflect the availability of PK and safety information of the use of Lyrica in the paediatric population.

# III. INTRODUCTION

In April 2013, the MAH submitted a completed paediatric study for Lyrica (CSR A0081074). In August 2013 CHMP issued a RSI to be addressed at the time of submission of CSR A0081075 (the open label extension study from A0081074). The MAH has now provided answers to the questions, results from the open label extension of the study and overview of the paediatric programme including update on studies to be performed and timelines. The previous full assessment of CSR A8001074 is included below. The assessment of the responses to the RSI and the additional data start from page 17 onwards. The updated conclusion and recommendation is stated on page 16.

Currently Lyrica has no paediatric indication. The MAH stated that the submitted paediatric study does not influence the benefit risk for Lyrica, no update of the product information is required and that there is no consequential regulatory action.

# IV. SCIENTIFIC DISCUSSION

## IV.1 Information on the pharmaceutical formulation used in the study

There is no paediatric indication for Lyrica and no specific paediatric formulation is available. In the paediatric study the following formulations were administered:

- pregabalin 25 mg capsule (no. D0400923),
- pregabalin 100 mg capsule (no. D0401363),
- pregabalin 15 ml/mg oral bottle solution (200ml) (no. D0401261, D0904631)

***Rapporteur's comment:***
*The use of these different formulations throughout the study is acceptable as it is not expected that the use of these different oral formulations will influence the pharmacokinetic properties of pregabalin to a degree that it will influence the outcome of the study.*

## IV.2 Clinical aspects

### 1. Introduction

The MAH submitted a final report for study A0081074: An escalating, multiple dose study to evaluate safety, tolerability and pharmacokinetics of pregabalin in paediatric patients with partial onset seizures. The MAH is of the opinion that the results of this study require no update of the product information and that there is no consequential regulatory action required.

### 2. Clinical study

A0081074: A placebo controlled, escalating , multiple dose study to evaluate safety, tolerability and pharmacokinetics of pregabalin in paediatric patients with partial onset seizures.

#### ➢ Description

This study is a placebo-controlled, escalation multiple-dose study to characterize the safety, tolerability, and the single- and multiple-dose pharmacokinetics of pregabalin at several dose levels in paediatric patients with refractory partial onset seizures.
The data is used to identify a therapeutic dose range for the anticipated Phase III studies of short term efficacy and of short- and long-term safety in the paediatric population. These studies explore the potential benefit of a new adjunctive treatment for partial onset seizures to paediatric patients.
Subjects who complete the study and who tolerate study medication (pregabalin or placebo) were eligible to enroll in the 12-month open-label treatment study of pregabalin (Protocol A0081075), where long-term safety and tolerability were to be evaluated.

#### ➢ Methods

- Objective(s)

To evaluate the escalating single- and multiple-dose safety and tolerability of pregabalin, in comparison to placebo, in paediatric patients 1 month through 16 years of age with partial onset seizures. And to evaluate the single-dose and steady-state pharmacokinetics of pregabalin in paediatric patients 1 month through 16 years of age with partial onset seizures.

- Study design

This was a parallel-group, multiple-dose, dose-escalation study involving paediatric subjects, ages 1 month through 16 years, with refractory partial onset seizures. Up to 64 subjects were planned to be enrolled, with subjects stratified among 4 age cohorts with 4 incremental dose levels.

Table: Study design dose level/ age cohort

| Dose Level / Age Cohort | 2.5 mg/kg | 5 mg/kg | 10 mg/kg | 15 mg/kg | 0 mg/kg (Placebo) | Total Subjects |
|---|---|---|---|---|---|---|
| 1 to 23 months | 3 (3) | 3 (3) | 3 (3) | 3 (3) | 4 (4) | 16 (16) |
| 2 to 6 years | 3 (4) | 3 (3) | 3 (3) | 3 (3) | 4 (5) | 16 (18) |
| 7 to 11 years | 3 (3) | 3 (3) | 3 (2) | 3 (3) | 4 (5) | 16 (16) |
| 12 to 16 years | 3 (3) | 3 (3) | 3 (4) | 3 (2) | 4 (3) | 16 (15) |

Actual numbers of randomized subjects are in parentheses.

Within an age group, data of each dose level was unblinded to the investigators for safety, tolerability and pharmacokinetic review before initiation of the higher dose level. Dosing in the younger age cohorts 1 to 23 months and 2 to 6 years was only initiated after review of the data in the older age groups 7 to 11 years and 12 to 16 years ensured that dose level was safe and well tolerated.
Pregabalin 2.5, 5, 10, and 15 mg/kg/day or matching placebo was to be administered orally, divided in two doses (b.i.d., i.e. every 12 hours), for 7 days. On day 8, all subjects received a single dose of pregabalin after a fasting period (2 hours for the youngest age cohort, 4 hours for the other 3 cohorts).
Multiple-dose subjects received pregabalin BID on Days 1 to 7 and on the morning of Day 8.
Single-dose subjects received placebo BID on Days 1 to 7 followed by a single pregabalin dose on the morning of Day 8.
Each dose level/ age group was randomized in a 3:1 ratio to pregabalin and placebo. Due to errors in the randomization system there was an imbalance for this ratio in the 2 older age cohorts for the 10 mg/kg/day dose level.
Plasma and urine samples were analysed for pregabalin. Plasma samples were collected pre-dosing on day 8 and at 0.5, 1, 2, 4, 8, 12, and 24 hours following administration and collected in heparin containing tubes (2 mL for subjects aged 7 years and up and 0.5 mL for subjects 1 month to 6 years).
For urine analysis of pregabalin, subjects emptied their bladder pre-dosing and urine was collected at the intervals 0-12 and 12-24 hours after dosing on day 8.

***Rapporteur's comment:***
*This design is acceptable for the objective and scope of this investigation. A higher frequency sampling scheme would have allowed more precise estimation of pharmacokinetic parameters, however due to the young age of the subjects the used sampling scheme is deemed adequate. The stepwise approach with exposure of the youngest age groups after data from the older age groups was available is agreed and supported.*

- Study population /Sample size

A total of 65 subjects were randomized to treatment and received at least 1 dose of study medication. Subjects were both male (33) and female (32) epilepsy patients aged 1 month to 16 years, with a minimum body weight of 3.5 kg. Subjects had diagnosed seizures classified as simple partial, complex partial, or partial becoming secondarily generalized, according to the International League Against Epilepsy (ILAE) classification of seizures, at least 1 seizure per 28-day period prior to the study. Subjects were receiving a stable dosage of 1 to 3 AEDs (stable within 7 days before screening), with blood levels within typically accepted therapeutic range.
A total of 58 subjects completed the study, thus there were a total of 7 discontinuations from the study: 4 pregabalin treated subjects and 3 placebo treated subjects. In the age cohort 1 to 23 months, 1 subject was discontinued due to an adverse event (sedation) for the 15 mg/kg/day dose level. In the age group 2 to 6 years there was 1 discontinuation (adverse event, lethargy) for the 2.5 mg/kg/day dose level and 1 in the placebo group (adverse event, dermatitis contact). In the age group 7 to 11 years there was 1 discontinuation (adverse event, ataxia, dizziness and somnolence) for the 15 mg/kg/day dose level and 1 in the placebo group (adverse event, convulsions). In the age group 12 to 16 years there was 1 discontinuation (adverse event, nausea, vomiting, dizziness) for the 15 mg/kg/day dose level and 1 in the placebo group (lost to follow-up).

***Rapporteur's comment:***
*In order to increase the power of the study a higher number of subjects per dose level and age cohort would have been advisable, however is expected not practically feasible. Due to the low sampling frequency a population PK approach would have been helpful as well for analysing the data. The applicant is requested to perform a POP-PK analysis of the data for additional*

*confirmation. It is not expected that the drop-out of subjects affect PK results and final conclusions, however, from a safety point of view is can be noted that a common reason for drop out was somnolence, lethargy, sedation, indicating the need for dose finding in the paediatric population.*

- Treatments

Based on the negligible metabolism and renal excretion of pregabalin, it is anticipated that its pharmacokinetic parameters in children will be well-predicted from renal clearance. The starting dose of 2.5 mg/kg/day was thus predicted to result in exposures similar to the adult dose of 150 mg/day, which is the recommended starting dose of pregabalin in adults. The proposed study doses of 5 mg/kg/day and 10 mg/kg/day were expected to result in exposures similar to the approved adult doses of 300 mg/day and 600 mg/day. The highest proposed dose in this study, 15 mg/kg/day, was expected to result in exposures similar to the adult dose of 900 mg/day, which is above the recommended dose range for adults and is associated with a higher incidence of adverse events.
Pregabalin 2.5, 5, 10, and 15 mg/kg/day or matching placebo was to be administered orally, every 12 hours, for 7 days. On day 8, all subjects received a single dose of pregabalin after a fasting period (2 hours for the youngest age cohort, 4 hours for the other 3 cohorts).

***Rapporteur's comment:***
*In principle the choice of dosing frequency is acceptable. But, it is insufficiently justified whether the applied doses are representative for the corresponding adult doses. Dose reduction was based on body weight, which could be acceptable since pregabalin is predominantly eliminated by renal clearance. However, the applicant should provide a discussion on the choice of the body weight for this dose reduction.*

- Analytical methods

Plasma pregabalin samples were assayed using a validated, sensitive and specific high-performance liquid chromatography tandem mass spectrometric method (HPLC/MS/MS) method. Plasma samples were stored at approximately -20°C until analysis and assayed within the 371 days of established stability data generated during validation. Calibration standard responses were linear over the range of 0.02500 µg/ml to 10.00 µg/ml.
Urine pregabalin samples were assayed using a validated, sensitive and specific HPLC/MS/MS method. Urine specimens were stored at approximately -20°C until analysis and assayed within the 1537 days of established stability data generated during validation. Calibration standard responses were linear over the range of 0.0600 µg/ml to 60.00 µg/ml. An Incurred Sample reanalysis was performed for both analytical methods (both sites for plasma analysis), demonstrating acceptable results for these methods.

***Rapporteur's comment:***
*These analytical methods are acceptable and sufficiently validated.*

- Outcomes/endpoints – pharmacokinetic parameters

Pregabalin pharmacokinetics parameters were calculated for each subject using a non-compartmental analysis method of plasma and urine concentration-time data. The following pharmacokinetic parameters were estimated:

*single dose:*
$AUC_{24}$, $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $T_{max}$, $t_{1/2}$, Cl/F, Vz/F, dose normalized $C_{max}$, dose normalized $AUC_{inf(dn)}$, $Ae_{24}$, $Ae_{24\%}$, $CL_{\tau}$

*multiple dose:*
$AUC_{\tau}$, $C_{max}$, $T_{max}$, $t_{1/2}$, CL/F, Vz/F, dose normalized $C_{max(dn)}$, dose normalized $AUC_{\tau(dn)}$, $Ae_{\tau}$, $Ae_{\tau\%}$, $Cl_{\tau}$

***Rapporteur's comment:***
*The choice of pharmacokinetic parameters is acceptable.*

- Statistical Methods

No statistical hypotheses was tested in this trial and only descriptive statistics were applied to the subject demographics, pharmacokinetic parameters and safety results.

***Rapporteur's comment:***
*With regard to the objective of the study, this is in general acceptable. However, due to the low sampling frequency a population PK approach is a logical choice for analysing the data. The applicant is requested to present POP-PK data for additional confirmation.*

## ➢ Results

- Pharmacokinetic results

**Table 17. Plasma Pregabalin Pharmacokinetic Parameters –Multiple-Dose Subjects**

| Age Group | Parameter, Units | Parameter Summary Statistics[a,b] by Treatment Group | | | |
|---|---|---|---|---|---|
| | | 2.5 mg/kg/day | 5 mg/kg/day | 10 mg/kg/day | 15 mg/kg/day |
| 1 to 23 Months | N | 3 | 3 | 3 | 2 |
| | $AUC_\tau$, µg.hr/mL | 9.518 (22) | 18.92 (25) | 38.28 (6) | 48.8, 96.6 |
| | $C_{max}$, µg/mL | 1.835 (24) | 3.943 (10) | 7.523 (16) | 9.36, 13.5 |
| | $T_{max}$, hr | 0.617 (0.500-1.00) | 1.05 (1.00-2.08) | 1.12 (1.02-2.00) | 0.967, 4.02 |
| | $t_{½}$, hr | 4.433±0.176 | 3.397±0.586 | 3.263±0.499 | 3.24, 4.81 |
| | CL/F, mL/min | 19.00 (10) | 17.70 (47) | 18.54 (49) | 14.2, 20.5 |
| | $V_z$/F, L | 7.286 (11) | 5.152 (34) | 5.197 (58) | 5.74, 5.93 |
| 2 to 6 Years | N | 3 | 2 | 2 | 3 |
| | AUCτ, µg.hr/mL | 10.04 (30) | 17.7, 18.2 | 25.9, 33.5 | 62.31 (25) |
| | $C_{max}$, µg/mL | 2.021 (6) | 2.72, 2.74 | 4.08, 5.03 | 14.13 (9) |
| | $T_{max}$, hr | 0.500 (0.500-2.00) | 1.17, 2.17 | 1.17,4.07 | 1.00 (0.967, 1.17) |
| | $t_{½}$, hr | 3.90[c] | 3.53, 4.35 | 3.523 ± 0.251[d] | 3.520 ± 0.918 |
| | CL/F, mL/min | 34.18 (61) | 37.7, 38.9 | 47.0, 101 | 30.49 (9) |
| | $V_z$/F, L | 17.7[c] | 11.9, 14.2 | 15.1, 28.4 | 9.057 (23) |
| 7-11 Years | N | 3 | 3 | 1 | 2 |
| | $AUC_\tau$, µg.hr/mL | 14.34 (26) | 24.31 (11) | 39.3 | 55.6, 82.9 |
| | $C_{max}$, µg/mL | 2.894 (26) | 4.214 (14) | 4.89 | 14.0, 16.4 |
| | $T_{max}$, hr | 0.583 (0.583-1.00) | 1.00 (1.00-1.00) | 4.00 | 0.500, 1.08 |
| | $t_{½}$, hr | 4.287±0.277 | 4.113±0.259 | 3.62, 4.83[e] | 4.26, 8.62 |
| | CL/F, mL/min | 58.23 (42) | 49.49 (19) | 63.7 | 55.3, 60.0 |
| | $V_z$/F, L | 21.57 (37) | 17.59 (22) | 26.6 | 20.4, 44.7 |
| 12-16 Years | N | 3 | 3 | 4 | 1 |
| | $AUC_\tau$, µg.hr/mL | 12.36 (19) | 27.75 (8) | 48.01 (43) | 103 |
| | $C_{max}$, µg/mL | 2.140 (26) | 5.385 (14) | 6.748 (59) | 13.8 |
| | $T_{max}$, hr | 0.500 (0.500- 4.00) | 0.583 (0.483- 1.00) | 2.09 (1.50-8.08) | 2.15 |
| | $t_{½}$, hr | 4.960 ±1.386 | 3.953 ± 0.805 | 5.643±0.889 | 6.61 |
| | CL/F, mL/min | 90.56 (26) | 78.38 (12) | 85.87 (17) | 73.1 |
| | $V_z$/F, L | 37.97 (26) | 26.45 (28) | 41.56 (25) | 41.8 |

Source: Table 14.4.3.3
Parameters are defined in Table 5.
Abbreviations: N = number of subjects; hr = hour(s); SD = standard deviation; CV = coefficient of variation
[a] Summary statistics for N ≥3: geometric mean (geometric %CV) for all except median (range) for $T_{max}$, arithmetic mean ±SD for $t_{½}$.
[b] Individual subject values for N=1.
[c] N=1
[d] N=3
[e] N=2

**Table 20. Plasma Pregabalin Pharmacokinetic Parameters for Single-Dose Subjects**

| | | Individual Subject Parameter Values by Treatment Group[a] | | | |
|---|---|---|---|---|---|
| **Age Group** | **Parameter, Units** | **2.5 mg/kg/day** | **5 mg/kg/day** | **10 mg/kg/day** | **15 mg/kg/day** |
| 1 to 23 Months | Subject ID: | 10331002 | 10411002 | 10451002 | 10121015 |
| | $AUC_{24}$, µg.hr/mL | 8.17 | 20.1 | 33.7 | 53.2 |
| | $AUC_{last}$, µg.hr/mL | 7.54 | 20.1 | 33.8 | 53.2 |
| | $AUC_{inf}$, µg.hr/mL | 7.93 | 20.2 | 34.2 | 53.6 |
| | $C_{max}$, µg/mL | 1.78 | 4.53 | 5.73 | 11.6 |
| | $T_{max}$, hr | 1.00 | 0.967 | 1.13 | 1.00 |
| | $t^{1}/_{2}$, hr | 2.64 | 3.78 | 3.76 | 3.22 |
| | CL/F, mL/min | 31.5 | 24.7 | 20.1 | 28.0 |
| | $V_z$/F, L | 7.21 | 8.07 | 6.55 | 7.80 |
| 2 to 6 Years | Subject ID: | 10011019 | 10021005 | 10231002 | 10121013 |
| | $AUC_{24}$, µg.hr/mL | 9.53 | 17.1 | 44.5 | 71.0 |
| | $AUC_{last}$, µg.hr/mL | 9.53 | 15.8 | 44.3 | 71.0 |
| | $AUC_{inf}$, µg.hr/mL | 9.66 | 16.6 | 45.1 | 71.4 |
| | $C_{max}$, µg/mL | 2.25 | 3.90 | 8.73 | 12.0 |
| | $T_{max}$, hr | 0.450 | 1.00 | 1.00 | 1.98 |
| | $t^{1}/_{2}$, hr | 3.88 | 2.70 | 3.83 | 3.08 |
| | CL/F, mL/min | 32.3 | 60.1 | 38.8 | 45.5 |
| | $V_z$/F, L | 10.9 | 14.0 | 12.9 | 12.1 |
| 7 to 11 Years | Subject ID: | 10011004 | 10011020 | 10121008 | 10371001 |
| | $AUC_{24}$, µg.hr/mL | 12.5 | 24.2 | 37.2 | 112 |
| | $AUC_{last}$, µg.hr/mL | 12.5 | 24.2 | 37.2 | 112 |
| | $AUC_{inf}$, µg.hr/mL | 12.9 | 24.6 | 37.4 | 123 |
| | $C_{max}$, µg/mL | 1.69 | 5.57 | 5.79 | 9.84 |
| | $T_{max}$, hr | 1.00 | 0.583 | 2.00 | 4.00 |
| | $t^{1}/_{2}$, hr | 4.77 | 4.02 | 3.13 | 6.54 |
| | CL/F, mL/min | 58.2 | 45.8 | 64.8 | 54.3 |
| | $V_z$/F, L | 24.0 | 15.9 | 17.6 | 30.7 |
| 12 to 16 Years | Subject ID: | 10011006 | 10121006 | NA | NA |
| | $AUC_{24}$, µg.hr/mL | 11.7 | 25.5 | | |
| | $AUC_{last}$, µg.hr/mL | 11.7 | 25.5 | | |
| | $AUC_{inf}$, µg.hr/mL | 12.6 | 25.8 | | |
| | $C_{max}$, µg/mL | 1.65 | 4.37 | | |
| | $T_{max}$, hr | 4.05 | 1.00 | | |
| | $t^{1}/_{2}$, hr | 5.80 | 3.85 | | |
| | CL/F, mL/min | 99.6 | 90.0 | | |
| | $V_z$/F, L | 50.0 | 30.0 | | |

Source: Table 16.2.5.4.1

Parameters are defined in Table 6.

Abbreviations: NA = not applicable (no subjects with PK parameters in this age/treatment group); ID = dentification number

[a] Subjects received placebo on Days 1-7 followed by a single pregabalin dose equal to ½ of the daily dose for the treatment group (eg, 2.5 mg/kg/day = 1.25 mg/kg single dose) on the morning of Day 8.

**Table 18. Plasma Pregabalin Dose-Normalized Pharmacokinetic Parameters for Multiple-Dose Subjects**

| Parameter, Units | Age Group | Parameter Summary Statistics[a,b] by Treatment Group | | | |
|---|---|---|---|---|---|
| | | 2.5 mg/kg/day | 5 mg/kg/day | 10 mg/kg/day | 15 mg/kg/day |
| $AUC_{\tau}$(dn), µg/hr/mL/mg/kg | 1-23 Months | 7.614 (19) | 7.563 (26) | 7.595 (6) | 6.26, 12.0 |
| | 2-6 Years | 7.962 (29) | 6.81, 7.21 | 5.38, 6.59 | 8.203 (31) |
| | 7-11 Years | 11.64 (29) | 9.571 (9) | 7.59 | 7.14, 10.3 |
| | 12-16 Years | 10.20 (13) | 13.07 (34) | 9.642 (44) | 14.4 |
| $C_{max}$(dn), µg/mL/mg/kg | 1-23 Months | 1.468 (23) | 1.577 (11) | 1.496 (14) | 1.20, 1.68 |
| | 2-6 Years | 1.601 (13) | 1.06, 1.08 | 0.803, 1.05 | 1.856 (15) |
| | 7-11 Years | 2.350 (29) | 1.660 (13) | 0.945 | 1.80, 2.03 |
| | 12-16 Years | 1.762 (22) | 2.538 (44) | 1.355 (59) | 1.94 |

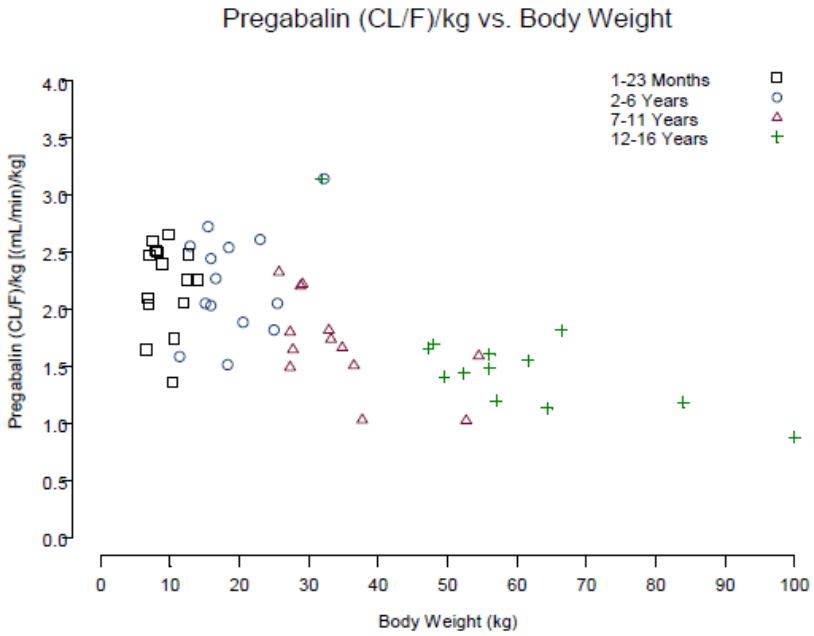
Source: Table 14.4.3.3
Parameters are defined in Table 5. Parameter values are normalized to the subject's individual Day 8 morning dose in mg/kg.
Abbreviations: N= number of subjects; CV = coefficient of variation; SD = standard deviation
[a] Summary statistics for N ≥3: geometric mean (geometric %CV) for all except median (range) for $T_{max}$, arithmetic mean ±SD for $t_{½}$.
[b] Individual subject values for N<3.

**Table 21. Plasma Pregabalin Dose-Normalized Pharmacokinetic Parameters for Single-Dose Subjects**

| Parameter, Units | Age Group | Parameter Values by Treatment Group | | | |
|---|---|---|---|---|---|
| | | 2.5 mg/kg/day | 5 mg/kg/day | 10 mg/kg/day | 15 mg/kg/day |
| $AUC_{inf}$(dn), µg/hr/mL/mg/kg | 1-23 Months | 6.70 | 8.10 | 7.05 | 7.02 |
| | 2-6 Years | 8.30 | 6.38 | 8.76 | 9.16 |
| | 7-11 Years | 10.0 | 10.1 | 8.00 | 15.9 |
| | 12-16 Years | 13.8 | 10.6 | NA | NA |
| $C_{max}$(dn), µg/mL/mg/kg | 1-23 Months | 1.51 | 1.81 | 1.18 | 1.52 |
| | 2-6 Years | 1.93 | 1.50 | 1.70 | 1.54 |
| | 7-11 Years | 1.31 | 2.29 | 1.24 | 1.28 |
| | 12-16 Years | 1.81 | 1.79 | NA | NA |

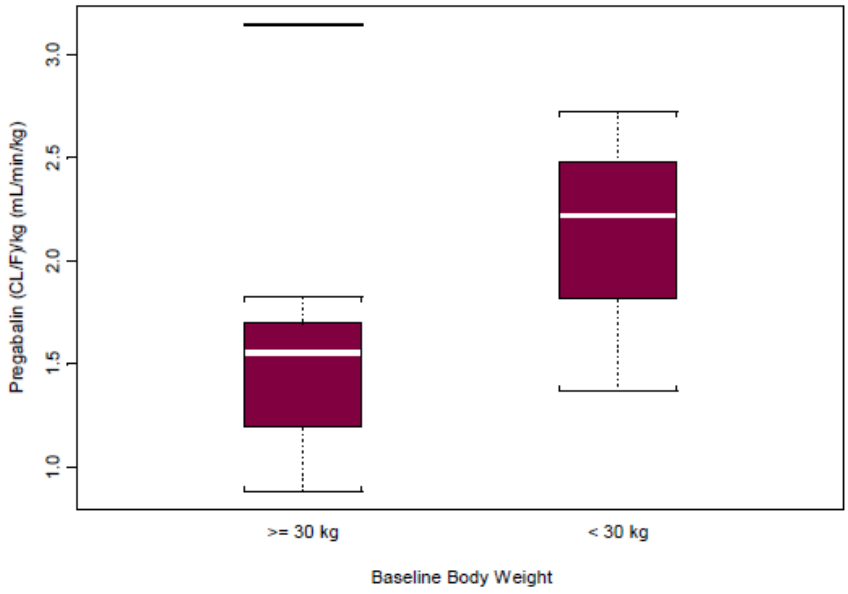
Source: Table 16.2.5.4.1
Parameters are defined in Table 6.
Parameter values are normalized to the subject's individual Day 8 morning dose in mg/kg.
Abbreviation: NA = not applicable (no subjects with PK parameters in this age/treatment group)

**Figure 17. Individual Pregabalin Oral Clearance Normalized for Body Weight and Baseline Body Weight; All Subjects**




Source: Section 16.2.9, Figure 17
Abbreviations: CL/F = oral clearance; vs = versus

**Figure 18. Box plot of Pregabalin Oral Clearance Normalized per Body Weight vs Body Weight Cutoff at 30 kg; All Subjects**




Source: Section 16.2.9, Figure 18
Abbreviation: CL/F = oral clearance; vs = versus

It is concluded in the study report that after oral administration of pregabalin in paediatric subjects in the fasted state, time to reach peak plasma concentration was similar across the entire age group and occurred 0.5 hours to 2 hours post-dose. Pregabalin exposure ($C_{max}$ and AUC) generally appeared to increase linearly with dose within each age group. Across age groups, pregabalin AUC was approximately 30% lower in paediatric subjects less than 30 kg of body weight than in those with a body weight of 30 kg and higher. Accordingly, pregabalin oral clearance normalized per body weight was approximately 43% higher in the children with body weight less than 30 kg than in children whose body weight was 30 kg and higher. Apparent oral clearance of pregabalin was directly related to renal clearance. Pregabalin apparent oral volume of distribution was linearly related to body weight and the values normalized per body weight were constant across the age range. Pregabalin terminal $t_{½}$ averaged about 3 to 4 hours in paediatric subjects from 1 month to 6 years of age, and 4 hours to 6 hours in those 7 years of age and older.
The study report mentions a population pharmacokinetic analysis performed of which details can be found in PMAR-00287. From this population PK it is concluded that renal clearance was a significant covariate on pregabalin oral clearance, body weight was a significant covariate on pregabalin apparent oral volume of distribution and these relationships were similar in paediatric and adult subjects.

***Rapporteur's comment:***
*Conclusions have been drawn regarding the pharmacokinetic comparability of paediatric data and adult data. It is concluded that $t_{max}$ is not altered when pregabalin is administered in a paediatric population. However, it is unclear on which data these conclusions have been drawn as there was no exposure data comparison reported. Furthermore, $C_{max}$ and AUC parameters are concluded to be linear within each age group. The AUC was lower in paediatric subjects below a weight of 30 kg due to an observed increased clearance for these subjects. The cut-off value of 30 kg has not been substantiated and should be substantiated by a more thorough analysis of the data. Although the applicant has performed a POP-PK analysis, details are not provided. The applicant should provide the full report of the POP-PK analysis in order to confirm the drawn conclusions.*

- Safety results

In all age cohorts, the most frequently experienced AEs were nervous system disorders; the majority of these AEs were considered by the investigators as treatment-related.
During double-blind treatment, 5 subjects were discontinued due to AEs: 4 subjects were discontinued during pregabalin treatment and 1 subject was discontinued during placebo treatment (Table S10).

Subjects aged 1 to 23 months: There were no serious AEs (SAEs) reported for subjects aged 1 to 23 months. One subject in the pregabalin 15 mg/kg/day cohort was discontinued from the study due to severe sedation (Table S10). The most frequently reported AE in this age cohort among subjects treated with pregabalin was somnolence (4 subjects). An additional 4 AEs were reported during open-label (single dose) treatment: 1 AE of somnolence in 1 subject in the pregabalin 15 mg/kg/day dose group and 3 AEs (somnolence, irritability, and erythema) were reported for 1 subject in the placebo group.

Subjects aged 2 to 6 years: There were no SAEs or severe AEs reported for subjects aged 2 to 6 years. Two subjects discontinued due to AEs - 1 in the pregabalin 2.5 mg/kg/day group (Table S10) during double-blind dosing, and 1 in the placebo group (open-label treatment). The most frequently reported AE in this age cohort was pyrexia (2 pregabalin subjects and 2 placebo subjects), which was considered to be not related to treatment. An additional 3 AEs were reported during open-label treatment: 1 AE of moderate decreased

platelet count in 1 subject in the pregabalin 15 mg/kg/day dose group and 2 AEs (lethargy and edema) were reported for 1 subject each in the placebo group.

Subjects aged 7 to 11 years: Two subjects had severe AEs that were serious and resulted in discontinuation (1 pregabalin 15 mg/kg/day during double-blind dosing and 1 in placebo during open-label treatment; Table S11 and Table S10). The most frequently experienced AE in this age group was somnolence (5 pregabalin subjects [considered related to treatment for 4 subjects]); no other AEs were reported by more than 2 subjects overall. An additional 3 AEs were reported during open-label treatment: 1 AE of mild psychomotor hyperactivity in 1 subject in the pregabalin 10 mg/kg/day dose group and 2 AEs (moderate lethargy and severe convulsion) were reported for 1 subject each in the placebo group. The severe convulsion was an SAE.

Subjects aged 12 to 16 years: There were no SAEs reported for subjects aged 12 to 16 years. One subject had a severe AE (pregabalin 5 mg/kg/day cohort) and 1 subject discontinued due to an AE (Table S10; pregabalin 15 mg/kg/day cohort). The most frequently reported AE for this age group was dizziness (3 pregabalin subjects, all considered related to treatment). An additional 2 AEs were reported during open-label treatment: moderate irritability and severe sedation in 1 subject in the pregabalin 5 mg/kg/day dose group.

**Table S10. Discontinuations Due to Adverse Events**

| Sex/ Age [Years]/ Weight [kg] | Preferred Term[a] | Treatment at Onset | Adverse Event | | | Severity/ Outcome | Causality |
|---|---|---|---|---|---|---|---|
| | | | Study Start Day[b]/ Study Stop Day[b] | Time Postdose (Hours) | Duration (Hours) | | |
| ***Age cohort: 1 to 23 months*** | | | | | | | |
| M/ 0.6/7 9 | Sedation | Pregabalin 15 mg/kg/day | 1/ 2 | 0.72 | 36.5 | Severe/ resolved | Study drug |
| ***Age cohort: 2 to 6 years*** | | | | | | | |
| F/ 4/ 14.7 | Lethargy | Pregabalin 2.5 mg/kg/day | 9/ 21 | 3.33 | 288.00 | Moderate/ resolved | Study drug |
| M/ 4/ 15.9 | Dermatitis contact | Placebo | 2/ 11 | 1.25 | 207.00 | Moderate/ resolved | Other (reaction to adhesive from ECG leads) |
| ***Age cohort: 7 to 11 years*** | | | | | | | |
| M/ 10/ 36.6 | Ataxia[c] | Pregabalin 15 mg/kg/day | 1/ 3 | 2.33 | 35.50 | Severe/ resolved | Study drug |
| | Dizziness | Pregabalin 15 mg/kg/day | 1/ 3 | 2.33 | 35.50 | Severe/ resolved | Study drug |
| | Somnolence[c] | Pregabalin 15 mg/kg/day | 1/ 2 | 0.83 | 7.37 | Severe/ resolved | Study drug |
| F/ 11/ 56.9 | Convulsions[c] | Pregabalin 10 mg/kg/day | 8/ 9 | 2.07 | 22.35 | Severe/ resolved | Study drug |
| ***Age cohort: 12 to 16 years*** | | | | | | | |
| M/ 16/ 53.6) | Nausea | Pregabalin 15 mg/kg/day | 1/ 2 | 2.5 | [35.00][d] | Moderate/ resolved | Study drug |
| | Vomiting | Pregabalin 15 mg/kg/day | 1/ 2 | 3.25 | [34.25][d] | Moderate/ resolved | Study drug |
| | Dizziness | Pregabalin 15 mg/kg/day | 1/ 2 | 2 | [35.50][d] | Moderate/ resolved | Study drug |

Abbreviations: ECG = electrocardiogram, F = female, M = male, MedDRA = Medical Dictionary for Regulatory Activities

[a] MedDRA (Version 15.1) coding dictionary applied.
[b] Day relative to start of study treatment; first day of study treatment = Day 1.
[c] Serious adverse event according to investigator's assessment.
[d] Values in brackets were imputed from incomplete dates and times.

Two subjects experienced a total of 3 SAEs (Table S11).

**Table S11. Serious Adverse Events**

| Sex/ Age [Years]/ Weight [kg] | Suspect Drug/ Dose[a] | Therapy Stop Date[b] | Onset Day[c] | Stop Day[d] | MedDRA Preferred Term[e] | Investigator Causality/ Sponsor Causality | Clinical Outcome |
|---|---|---|---|---|---|---|---|
| F/ 12[f]/ 57 | Pregabalin/ 275 mg[g] | 8 | 8 | 9 | Convulsion | Related/ unrelated | Recovered |
| M/ 10/ 37 | Pregabalin/ 15 mg/kg/day | 1 | 1 | 2 | Somnolence | Related/ related | Recovered |
| | | 1 | 1 | 3 | Ataxia | Related/ related | Recovered |

Both subjects were permanently withdrawn from the study.
Abbreviations: F = female, M = male, MedDRA = Medical Dictionary for Regulatory Activities, No. = number, SAE = serious adverse event

[a] Dose for treatment at the earliest onset date of the event.
[b] Therapy stop date was calculated as last active therapy date minus first active therapy date plus 1.
[c] Onset day was calculated as onset date minus first active therapy date plus 1.
[d] Event stop day was calculated as SAE stop date minus first active therapy date plus 1.
[e] MedDRA Version 15.1 coding dictionary applied.
[f] This subject was 11 years old at screening and 12 years old at the time of the SAE.
[g] This subject had been on placebo Days 1 through 7; received a single dose of pregabalin 275 mg on Day 8 (ie, 10 mg/kg/day).

No clinically important dose- or treatment-related trends were observed with regards to laboratory analyses, ECGs, neurological examinations, or vital signs measurements.

**Conclusions of the MAH:**

After oral administration of pregabalin in pediatric subjects in the fasted state, in general, time to reach peak plasma concentration was similar across the entire age group and occurred 0.5 hours to 2 hours postdose.

Furthermore, $C_{max}$ and AUC parameters increase in a linear manner with increasing dose within each age group. The AUC was lower in paediatric subjects below a weight of 30 kg due to an increased clearance for these subjects.
Population PK analysis concluded that creatinine clearance was a significant covariate of pregabalin oral clearance, body weight was a significant covariate of pregabalin apparent oral volume of distribution and these relationships were similar in peadiatric and adult subjects.

Pregabalin appeared to be safe and well tolerated in the subjects aged from 1 month to 16 years.

All pregabalin dose levels were well tolerated by subjects aged 1 month to 6 years, including pregabalin 15 mg/kg/day, with observed exposures in these subjects at this dose similar to the 10 mg/kg/day dose level exposures observed in older age cohorts.

The AE profile observed in pediatric subjects aged 1 month to 16 years in this study is similar in nature to that seen in adult subjects, with somnolence and dizziness being the most commonly reported AEs.

Dose levels expected to result in exposures similar to that observed at 15 mg/kg/day in subjects aged 7 to 16 years were not sufficiently well tolerated for further study in fixed dose Phase 3 efficacy studies for subjects of any age.

### 3. Discussion on clinical aspects

The MAH has presented data from the dose finding study in paediatric subjects with analysis of PK and safety data. The safety database although very limited allow the conclusion that the 10mg/kg/day dose seems to be well tolerated in all age groups, whereas the 15 mg/kg/day dose resulted more often in serious and severe AEs leading also to treatment discontinuation. Most often AEs were dizziness, somnolence, lethargy which can be expected from the mechanism of action of pregabalin. Also cases of psychomotor hyperactivity and moderate irritability were registered, as well as cases of convulsions and one case of moderate decrease of platelet count.

All in all the data from this study lead to the conclusion that dose titration would be required in the phase 3 study and caution should be made in particular with using the 15 mg/kg/day.

## V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The conclusion drawn by the applicant regarding the pharmacokinetic parameters can be accepted. Clinical safety data from this study lead to the conclusion that dose titration would be required and caution should be made in particular with using the 15 mg/kg/day. The MAH has provided additional information as requested (see answers to List of Questions below).

Subjects who completed the study and who tolerated study medication (pregabalin or placebo) were eligible to enroll in a 12-month open-label treatment study of pregabalin (Protocol A0081075), where long-term safety and tolerability was evaluated. As requested, the MAH has provided the clinical study report. Furthermore, the MAH was requested to provide an update on of the progress of the other ongoing programs intending to provide additional paediatric data including timelines. This overview is attached to the assessment report. The paediatric programme is expected to be finalized in 2017.

In answer to Q3 the MAH has not provided a proposal for update of the product information but proposed to await completion of the paediatric programme. This is not agreed. The current text in section 4.2. the SPC under paediatric population reads: "No data are available". This is not correct since some data in paediatric subjects has been generated. Additionally, it is known from PSURs that children are being treated with pregabalin. Therefore it is requested to amend the statement in section 4.2 and to include information in sections, 4.8 and 5.1/5.2 of the SPC.

- **Recommendation**

Although noted that the submitted studies are part of a paediatric development programme which is expected to be completed in 2017 the results from the presented studies should be reflected in the label.

The MAH should therefore:

- delete the current text in section 4.2. (i.e. 'No data are available') and replace it by a more appropriate text from the QRD template
- include information in section 4.8. and 5.1/5.2.

to inform prescribers about available PK and safety data of the use of Lyrica in paediatric subjects. See also under Q3 below.

# VI. REQUEST FOR SUPPLEMENTARY INFORMATION:

**In July 2014 the MAH has responded to the outstanding list of questions and provided the clinical study report for A0081075 (due Q1/Q2 2014):**

Briefly the study results are described below:

**Clinical study**

Study A0081075: A 12-Month Open-Label Extension Study Evaluating the Safety and Tolerability of Flexible Doses of Pregabalin in Pediatric Patients with Partial Onset Seizures

- **Description**

- Objective(s)

To evaluate the long-term safety and tolerability of pregabalin in pediatric subjects 1 month through 16 years of age with partial onset seizures.

- Study design

This was an open-label, flexible dose extension study, open to pediatric subjects aged 1 month through 16 years, with refractory partial-onset seizures, who had completed study A0081074. For subjects who were enrolled into study A0081074 but had not completed the study, eligibility for study A0081075 was considered on a case by case basis. The doses administered in this study (2.5, 5.0, 7.5, 10.0, and 15.0 mg/kg/day) were found to be safe and well-tolerated in study A0081074. Subjects were treated for up to 12 months.

- Study population /Sample size

N of Patients (planned):
It was estimated that 75 subjects would complete studyA0081074, and that 60 of these subjects would consent to participate in this study. Of these 60 subjects, it was estimated that 28 subjects would complete 12 months of participation in this study.

N of patients (analysed):
Of 58 subjects who completed study A0081074, 53 subjects were enrolled in study A0081075, and of 7 subjects who discontinued study A0081074, 1 subject was enrolled in study A0081075. A total of 54 subjects were treated in study A0081075, of which 29 subjects completed the study.

The table below shows the subject evaluation groups by age group analyzed for safety.

| Pregabalin 1-23 months | Pregabalin 2-6 years | Pregabalin 7-11 years | Pregabalin 12-16 years | Total |
|---|---|---|---|---|
| 16 | 15 | 12 | 11 | 54 |

- Treatments

Subjects were enrolled into study A0081075 at Visit 1, which occurred the morning after Day 8 of study A0081074, and received their first dose of medication for study A0081075 at this time. Subjects who completed study A0081074 entered study A0081075 at the same open label dose of pregabalin they received on
Day 8 of study A0081074, unless that dose was not well-tolerated or was determined to be unsafe in study A0081074. The doses available for this study included 2.5, 5, 7.5, 10, and 15 mg/kg/day. If the dose was not well tolerated, the dose level could be reduced at any time. However, each subject was restricted to the dose levels that they had previously tolerated, or that had shown acceptable safety and tolerability in study A0081074 for the subject's age group. The study medication was administered orally as liquid or capsule formulation, twice a day (BID).

- Analytical methods

The safety data (including AEs, clinical laboratory assessments, and ECGs) were summarized by each age group through standard data tabulations and descriptive statistics. Summaries included data for all subjects who took at least one dose of study medication in this study. Baseline values were the last observation made prior to initiating double-blind dosing in study A0081074.

- Outcomes/endpoints

The following Safety Endpoints were registered in the study:
• Adverse events (AEs).
• Clinical laboratory assessments (hematology, blood chemistry, urinalysis).
• Vital signs (blood pressure, pulse, weight).
• Physical and neurological examination, ECG.

- **Results**

A total of 47/54 subjects experienced at least 1 treatment-emergent AE (TEAE), 22/54 subjects experienced at least 1 treatment-related TEAE, and 12/54 subjects had at least 1 TEAE of severe intensity. A total of 12/54 subjects reported at least 1 serious AE (SAE), none of which were considered treatment-related, and 9/54 subjects discontinued the study due to TEAEs. There were no deaths reported during the study. The majority of TEAEs were mild or moderate in intensity. The most frequently reported TEAEs were pyrexia (15/54 subjects), upper respiratory tract infection (11/54 subjects), and convulsion (9/54 subjects). The most frequently reported treatment-related TEAEs were constipation (4/54 subjects), lethargy (3/54 subjects), somnolence (3/54 subjects), and proteinuria (3/54 subjects).
There were no relevant differences between the age groups regarding the number of subjects experiencing TEAEs. However, more TEAEs were noted in the 2 younger age groups (1-23 months, 2-6 years), and all but one subject with severe and serious TEAEs was in the younger age groups. While more AEs and SAEs were noted in the younger age groups (1 month to 6 years), the nature of the events that occurred such as, pyrexia and upper respiratory tract infection, was typical for this age.
The AE profile observed in this pediatric study population differed somewhat from commonly reported AEs seen in adults across all previous controlled Lyrica® (pregabalin) clinical studies. Adverse events commonly reported in adult studies such as dizziness and somnolence were reported less frequently in this study.

There were no clinically relevant changes in laboratory parameters, physical and neurological examination findings, vital signs, and ECG parameters.

The MAH concluded that:
Long-term safety and tolerability evaluations indicate that pregabalin at doses up to and including 15 mg/kg/day appeared to be safe and well-tolerated in paediatric subjects 1 month through 16 years of age with partial onset seizures. A total of 29 subjects (53.7%) completed the study.

***Rapporteur's comment:***
*The MAH has provided the results from study A0081075 as requested. The study was an open label extension of study A0081074 and monitored safety parameters only. The safety profile differs slightly from that known from the use of pregabalin in adults and the main differences are observed in the youngest age groups. In the latter pyrexia and upper respiratory infections were observed more frequently, which may be expected in this age group. This safety information is relevant for prescribers (see also under Q3 below).*

**Q. 1. It is insufficiently justified whether the applied doses are representative for the corresponding adult doses. Dose reduction was based on body weight, which could be acceptable. However, the applicant should provide a discussion on the choice of body weight parameter for this dose reduction.**

MAH response (edited)
Study A0081074 was the first study in pediatric subjects to evaluate PK, safety and tolerability of pregabalin. In this study, pregabalin was dosed in pediatric subjects 1 month to 16 years on a mg/kg basis in the range of 2.5 to 15.0 mg/kg/day, with maximum daily doses of 150, 300, 600, and 900 mg/day, respectively. These doses were expected to result in exposures similar to the adult doses of 150, 300, 600 and 900 mg/day, respectively.

*Note: the table and figure numbers in the original reports are used for easy reference.*

As shown in the study, the observed mean pregabalin clearance (CL/F) in pediatric subjects 12-16 years of age was 73.1 to 90.6 mL/min, similar to the mean CL/F values in adults (62.5-88.4 mL/min). In younger paediatric subjects, pregabalin CL/F (in mL/min) decreased with age and weight (Figure 8) as a result of lower creatinine clearance (CrCL) (Figure 7). The relationship between pregabalin CL/F vs. CrCL in paediatric subjects (solid triangle) is consistent with that in the adult population (open circle) as shown in Figure 1. When pregabalin CL/F was normalized by body weight in pediatric subjects, the CL/F/kg values (mL/min/kg) were approximately 40% higher in subjects <30 kg than those with body weight ≥ 30 kg, based on both non-compartmental analysis (Figures 18), which is consistent with the allometric scaling of total body clearance by body weight and population PK analysis (PMAR-00287).

Figure 8. Individual Pregabalin Oral Clearance Normalized for Body Weight vs Age (Upper Panel) and vs Body Weight (Lower Panel), Multiple-Dose Subjects

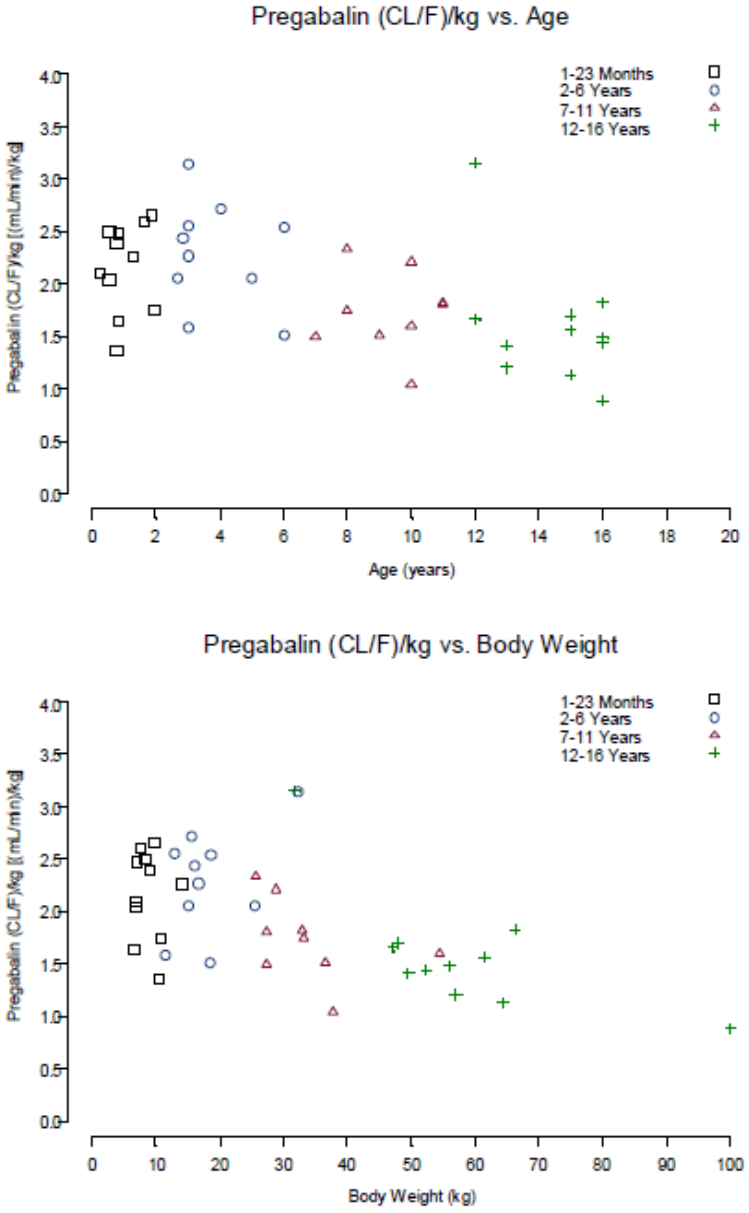


Figure 7. Individual Pregabalin Oral Clearance vs Baseline Creatinine Clearance

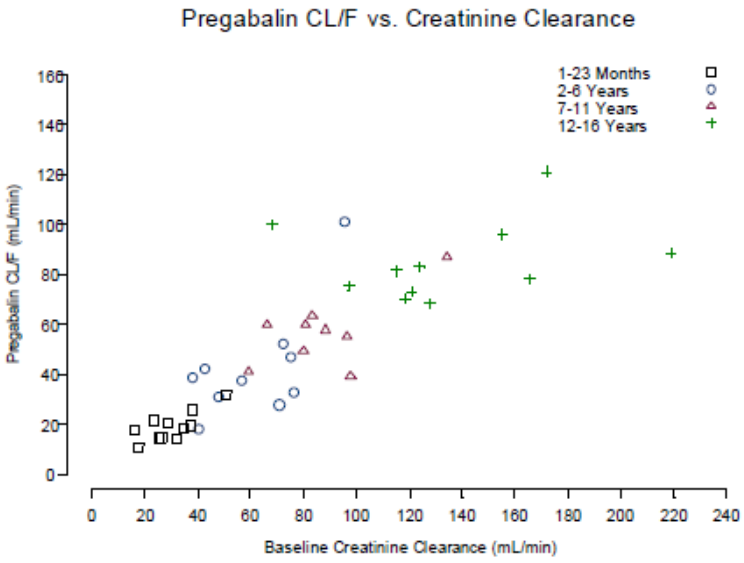



Figure 1. Relationship between pregabalin CL/F and creatinine clearance in pediatric subjects with partial epilepsy and adult subjects

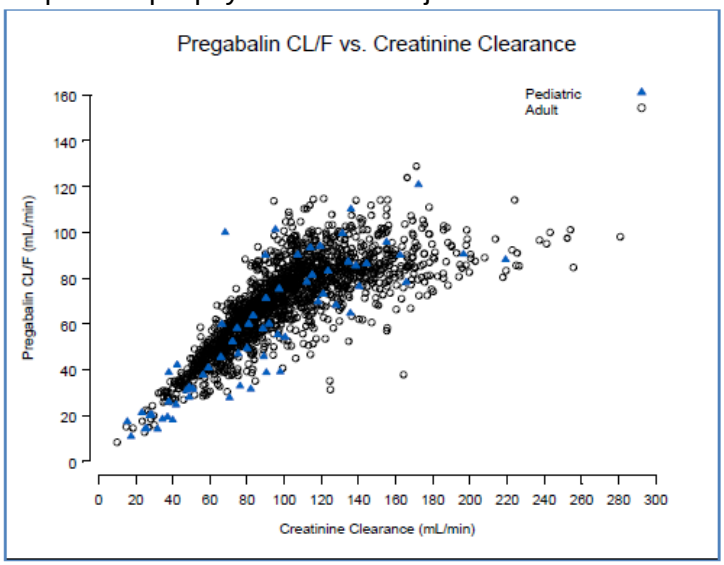
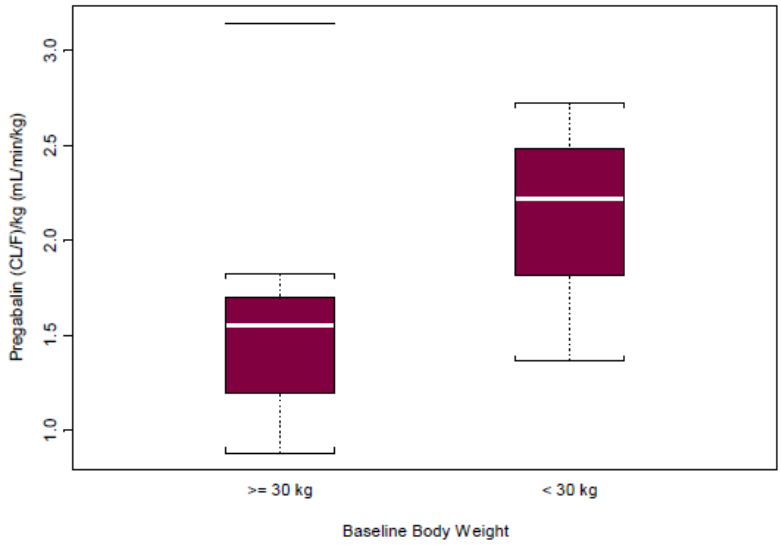


Figure 18. Box plot of Pregabalin Oral Clearance Normalized per Body Weight vs Body Weight Cut-off at 30 kg; All Subjects




The results suggest that paediatric subjects <30 kg require 40% higher daily dose than the subjects with body weight ≥ 30 kg in order to achieve comparable exposure when pregabalin is dosed on the mg/kg basis. These results were used to guide the dose selection in pregabalin efficacy and safety studies (A0081041, A0081042, A0081105 and A0081106). For example, to achieve similar exposure to the adult dose of 600 mg/day, the daily doses in pediatric subjects are 10 mg/kg/day for those ≥ 30 kg, and 14 mg/kg/day for those < 30 kg, respectively. The predicted steady-state AUC, Cmax and Cmin are considered for comparison, and are shown in Tables 2-4 below. In addition, since there was no subject below the age of 3 months old in study A0081074, to take into consideration of potential less maturation of renal function in infants 1 to 3 months old in Study A0081042, pregabalin dose is adjusted to 12 mg/kg/day in subjects 1 to 3 months old (inclusive) to achieve comparable exposure to 600 mg/day in adults. Simulated exposures in infants and adults are presented in Table 5.

**Table 2. Predicted AUCss(tau) (µg•h/mL) for adult and pediatric subjects with twice daily (BID) dosing**

| Description | 5th | 25th | Med | 75th | 95th |
|---|---|---|---|---|---|
| Adult 600 mg/day BID | 42.5 | 58.1 | 71.4 | 85.4 | 115.9 |
| Weight [40,) kg 10 mg/kg/day BID | 31.2 | 41 | 51.1 | 61.3 | 80.8 |
| Weight [30,40) kg 10 mg/kg/day BID | 31.5 | 39.4 | 47.7 | 57.1 | 71.4 |
| Weight [20,30) kg 10 mg/kg/day BID | 24.2 | 34.4 | 42.2 | 51.3 | 65.7 |
| Weight [10,20) kg 10 mg/kg/day BID | 20.9 | 29.7 | 36 | 44.2 | 59.4 |
| Weight [0,10) kg 10 mg/kg/day BID | 20.2 | 28.6 | 36.6 | 46.9 | 64.6 |
| Weight [40,)kg 14 mg/kg/day BID | 30.8 | 42.4 | 52.6 | 65.2 | 85.2 |
| Weight [30,40) kg 14 mg/kg/day BID | 43.7 | 56.4 | 68.2 | 81.5 | 104 |
| Weight [20,30) kg 14 mg/kg/day BID | 31.6 | 46.3 | 57.7 | 70.6 | 91.2 |
| Weight [10,20) kg 14 mg/kg/day BID | 30.7 | 41.2 | 51.5 | 63.7 | 87.3 |
| Weight [0,10) kg 14 mg/kg/day BID | 28.8 | 39.1 | 50.3 | 65.4 | 92.7 |

Definition. [30,40) implies the weight cohort includes 30 kg to < 40 kg.
Source: Table 15 in PMAR-00287

**Table 3. Predicted Cmaxss (µg/mL) for adult and pediatric subjects with BID dosing**

| Description | 5th | 25th | Med | 75th | 95th |
|---|---|---|---|---|---|
| Adult 600 mg/day BID | 6.2 | 7.9 | 9.2 | 10.9 | 14 |
| Weight [40,) kg 10 mg/kg/day BID | 5.2 | 7 | 8 | 9.1 | 11 |
| Weight [30,40) kg 10 mg/kg/day BID | 5.3 | 6.6 | 7.6 | 8.6 | 10 |
| Weight [20,30) kg 10 mg/kg/day BID | 4.9 | 6.3 | 7.3 | 8.3 | 9.6 |
| Weight [10,20) kg 10 mg/kg/day BID | 4.1 | 5.4 | 6.4 | 7.3 | 8.7 |
| Weight [0,10) kg 10 mg/kg/day BID | 3.8 | 4.9 | 5.8 | 6.7 | 8.2 |
| Weight [40,)kg 14 mg/kg/day BID | 5.1 | 7.1 | 8.6 | 10.1 | 12.2 |
| Weight [30,40) kg 14 mg/kg/day BID | 7.4 | 9.4 | 10.7 | 12.2 | 14.4 |
| Weight [20,30) kg 14 mg/kg/day BID | 6.5 | 8.7 | 10 | 11.5 | 13.9 |
| Weight [10,20) kg 14 mg/kg/day BID | 5.8 | 7.7 | 9 | 10.5 | 12.6 |
| Weight [0,10) kg 14 mg/kg/day BID | 5.3 | 7 | 8.2 | 9.5 | 11.8 |

Definition. [30,40) implies the weight cohort includes 30 kg to < 40 kg.
Source: Table 16 in PMAR-00287

**Table 4. Predicted Cminss (µg/mL) for adult and pediatric subjects with BID dosing**

| Description | 5th | 25th | Med | 75th | 95th |
|---|---|---|---|---|---|
| Adult 600 mg/day BID | 1.3 | 2.3 | 3.1 | 4.1 | 6 |
| Weight [40,)kg 10/mg/kg/day BID | 0.5 | 1 | 1.6 | 2.3 | 3.6 |
| Weight [30,40) kg 10 mg/kg/day BID | 0.5 | 1 | 1.5 | 2.1 | 3.2 |
| Weight [20,30) kg 10 mg/kg/day BID | 0.2 | 0.7 | 1.1 | 1.7 | 2.7 |
| Weight [10,20) kg 10 mg/kg/day BID | 0.2 | 0.5 | 0.9 | 1.4 | 2.3 |
| Weight [0,10) kg 10 mg/kg/day BID | 0.2 | 0.7 | 1.2 | 1.9 | 3.1 |
| Weight [40,)kg 14 mg/kg/day BID | 0.4 | 1 | 1.6 | 2.4 | 3.7 |
| Weight [30,40) kg 14 mg/kg/day BID | 0.8 | 1.4 | 2.1 | 3 | 4.5 |
| Weight [20,30) kg 14 mg/kg/day BID | 0.2 | 0.8 | 1.4 | 2.3 | 3.9 |
| Weight [10,20) kg 14 mg/kg/day BID | 0.2 | 0.7 | 1.3 | 2.1 | 3.5 |
| Weight [0,10) kg 14 mg/kg/day BID | 0.3 | 0.8 | 1.5 | 2.5 | 4.3 |

Definition. [30,40) implies the weight cohort includes 30 kg to < 40 kg.
Source: Table 17 in PMAR-00287

**Table 5. Predicted pregabalin exposure in adult and pediatric subjects 1 to 3 months old**

| | AUCss (0-12h) for BID AUCss(0-8h) for TID (µg.h/mL) | | Cmax,ss (µg/mL) | | Cmin,ss (µg/mL) | |
|---|---|---|---|---|---|---|
| | Median | $5^{th}$-$95^{th}$ percentiles | Median | $5^{th}$-$95^{th}$ percentiles | Median | $5^{th}$-$95^{th}$ percentiles |
| Adult 600 mg/day, BID (PMAR-00287, Tables 21, 22, 23) | 71.4 | 42.5-115.9 | 9.2 | 6.2-14.0 | 3.1 | 1.3-6.0 |
| Adult 600 mg/day, TID (PMAR-00287, Tables 27,28,29) | 46.2 | 30.2-74.1 | 7.8 | 5.2-11.7 | 3.8 | 2.0-6.9 |
| Approach 1 – Extrapolation of creatinine clearance by age [a] | | | | | | |
| Age [1,2) months, 10 mg/kg/day TID | 35.8 | 22.4-53.6 | 5.6 | 3.9-8.2 | 3.3 | 1.7-5.5 |
| Age [2,3) months, 10 mg/kg/day TID | 36.1 | 23.1-59.2 | 5.8 | 4.0-8.7 | 3.3 | 1.8-6.2 |
| Age [3,4) months, 10 mg/kg/day TID | 31.6 | 20.8-48.7 | 5.3 | 3.7-7.7 | 2.7 | 1.5-4.6 |
| Age [1,2) months, 12 mg/kg/day TID | 44.4 | 29.0-67.2 | 6.9 | 4.7-10.3 | 4.1 | 2.3-6.9 |
| Age [2,3) months, 12 mg/kg/day TID | 41.2 | 27.3-64.4 | 6.8 | 4.6-9.7 | 3.6 | 2.0-6.5 |
| Age [3,4) months, 12 mg/kg/day TID | 38.6 | 25.1-59.7 | 6.4 | 4.5-9.2 | 3.2 | 1.7-5.7 |
| Age [1,2) months, 14 mg/kg/day TID | 49.7 | 31.8-76.5 | 7.8 | 5.4-11.5 | 4.6 | 2.5-7.9 |
| Age [2,3) months, 14 mg/kg/day TID | 46.7 | 31.3-72.4 | 7.7 | 5.4-11.1 | 4.0 | 2.2-7.0 |
| Age [3,4) months, 14 mg/kg/day TID | 43.8 | 27.7-72.3 | 7.3 | 5.1-11.2 | 3.7 | 1.8-7.3 |

Note: [1,2) implies the age cohort includes subjects 1 month old, but not including the exact 2 months old.
[a] PMAR-00287 Tables 27, 28, 29

In summary, pregabalin exposure decreases as pediatric body weight decreases when subjects are dosed on a mg/kg/day basis. A 40% increase in pregabalin daily dose (in mg/kg/day) in pediatric subjects weighing <30 kg but 20% increase in subject 1 to 3 months old (inclusive) will achieve exposure across the range of pediatric subjects similar to the exposure achieved in adults.

***Rapporteurs's comment to response to Q 1:***
*Study A0081074 was a dose-escalation study using a stepwise approach: younger age groups were dosed after data from the older age groups was available. The PK of pregabalin was expected to be predictable based on the negligible metabolism and renal excretion of*

*pregabalin. Subjects were initially exposed to a dose of 2.5 mg/kg/day. PK data collected at each dose was used to predict exposures at the higher doses prior to each escalation of dose.*

*The data demonstrated that when dosed based on weight, pregabalin clearance increased with age and weight. The increased pregabalin clearance is due to increased CLCR (Figures 7 and 1). A similar relationship has been observed in adults (Figure 1).*

*However, pregabalin clearance (CL/F) normalized for body weight (mL/min/kg) was about 40% higher in subjects less than 30 kg bw than subjects with ≥ 30 kg bw (Fig 18). Based on the PopPK modelling, a similar exposure is expected with 10 mg/kg/day dosing in subjects weighing ≥ 30 kg and 14 mg/kg/day in subjects weighing < 30 kg. However, based on the predicted pregabalin steady state exposures (Tables 2 - 4), the two dosing schemes will result in lower exposures of about 20-30% in comparison with adults. It has to be addressed that the 15 mg/kg/day dose level was not sufficiently tolerated in some paediatric subjects. However, final proof of efficacy and safety will have to be demonstrated in the on-going Phase 3 paediatric clinical studies.*

*No data are available in children younger than 3 months. The assumption of a reduced clearance in children 1 to 3 months old when compared with older children is agreed as renal function is not yet mature at this age. A 14% dose reduction from 14 mg/kg was assumed but this number has not been justified. Based on the PopPK-analysis and simulation, a dose increase of not only 20% but also of 40 % can be used (Table 5). It is assumed that a dose of 12 mg/kg was chosen due to the vulnerability of these very young children. As in the case of older children, the efficacy and safety of the proposed dose remains to be demonstrated in the on-going Phase 3 paediatric clinical studies.*

*In conclusion, in the pediatric population > 3 months, the recommended doses of 10 mg/kg/day in subjects weighing ≥ 30 kg and 14 mg/kg/day in subjects weighing < 30 kg were based on the observed increased clearance normalized for body weight in subjects less than 30 kg bw. In the infants 1 to 3 months old (inclusive), a dose of 12 mg/kg was recommended due to potential renal immaturity in this age group. In the PoP-PK analysis using these doses, lower exposures (about 20-30% ) are predicted when compared with those in adults. As these doses were selected due to safety reasons and confirmation of the efficacy and safety of these dosing regimes has to be demonstrated from the on-going Phase 3 paediatric clinical studies, this will not be currently raised as an issue.*

***Issue considered resolved.***

**Q 2. The MAH is requested to provide a detailed report of the POP-PK analysis of the pharmacokinetic data for confirmation of the drawn conclusions**

MAH response

The population PK reports (PMAR-00287 and PMAR-00287 Supplement) are provided with this response.

Summary of the reports by Rapporteur

The Pop-PK analysis included data from single or multiple dose administration of pregabalin to pediatric patients with epilepsy in Study A0081074. The data from this study (57 subjects out of a total of 60 subjects were included in the analysis dataset) was combined with data from five clinical pharmacology studies involving adult subjects which were reported in another Pop-PK analysis (PMAR-00250) because of their similar study design involving serial PK sampling.

The pediatric study (Study A0081074) included 419 plasma pregabalin concentrations and the adult clinical pharmacology studies contributed 2868 plasma pregabalin concentrations from 123 adult subjects from studies (Studies 1008-001, 1008-002, 1008-003, 1008-023 and 1008-049). In the <2 yr age cohort/15 mg/kg/day dose group (not included in PMAR-00287 and included in PMAR-00287 Supplemet ) only 23 plasma pregabalin concentrations from 3 pediatric subjects were available as only 3 subjects in this group completed the PK portion of the study.

The analysis was performed using non-linear mixed effects modeling methodology. Model selection criteria included: 1) successful minimization and completion of covariance steps in NONMEM, 2) assessment of standard goodness of fit plots, 3) reductions in NONMEM objective function value (OFV) for hierarchical models, 4) model parameter estimates not approaching a boundary condition and 5) reductions in inter-individual and residual variability. In addition, the stability of the models throughout the model development process was given close attention. To avoid ill-conditioning, inspection of the covariance matrix of estimates at every stage of model development was performed to verify that extreme pair-wise correlations ($\rho > 0.95$) of the parameters were not encountered. The condition number of the correlation matrix of the parameter estimates (ie, the ratio of the largest to smallest eigenvalues) were also assessed to ensure values less than 1000. Values greater than 1000 are indicative of an ill-conditioned model (Montgomery DC and Peck EA, 1982). If during the course of model development convergence or covariance estimation problems occurred, ad hoc NONMEM runs were performed to evaluate the nature of the ill-conditioning.

A set of diagnostic plots for the base, full, and final models were generated. The empirical Bayes' predictions of the inter-individual random effects ($\eta$) were plotted versus the covariates for the base, full and final model to evaluate trends, and whether inclusion of the covariate effects resolved these trends. The full model underwent a stepwise backward elimination procedure in order to identify a parsimonious final model.

**Table 14. Parameter Estimates for Base, Full and Final Models**

| | Model Estimate (SE) | | | 95%CI | |
|---|---|---|---|---|---|
| Parameter | Base | Full | Final | Final | Units |
| MOF | -2847.001 | -2918.152 | -2907.853 | | - |
| Clearance | | | | | |
| CL/F | 4.27 (0.0743) | 4.36 (0.604) | 4.28 (0.0737) | (4.14 – 4.42) | L/hr |
| BWT | - | 0.0298 (0.144) | - | | - |
| AGE | - | 0.00542 (0.0837) | - | | - |
| SEX | - | -0.068 (0.0403) | - | | - |
| RACE(BLACKS) | - | 0.0762 (0.089) | - | | - |
| RACE(OTHERS) | - | 0.0404 (0.0372) | - | | - |
| Volume | | | | | |
| V/F | 37.2 (0.570) | 48.2 (4.59) | 47.3 (3.00) | (41.4 – 53.2) | L |
| BWT | 0.807 (0.0229) | 0.970 (0.0991) | 0.955 (0.0678) | (0.822 – 1.09) | - |
| SEX | - | -0.157 (0.0273) | -0.137 (0.0246) | (-0.185 - -0.089) | - |
| AGE | - | -0.100 (0.0562) | -0.102 (0.0374) | (-0.175 - -0.029) | - |
| RACE(BLACKS) | - | -0.0238 (0.0455) | - | | |
| RACE(OTHERS) | - | -0.0325 (0.0225) | - | | |
| Absorption | | | | | |
| $k_a$ | 2.80 (0.260) | 2.57 (0.392) | 2.79 (0.256) | (2.29 – 3.29) | $hr^{-1}$ |
| KTR FED | 1.25 (0.195) | 1.23 (0.191) | 1.23 (0.192) | (0.854 – 1.61) | $hr^{-1}$ |
| NTR FED | 2.07 (0.179) | 2.06 (0.177) | 2.06 (0.177) | (1.71 – 2.41) | - |
| WEIBULL SCALE FACTOR | 0.446 (0.0367) | 0.410 (0.032) | 0.411 (0.032) | (0.348 – 0.474) | - |
| Residual Error | 34.2 (3.25) | 34.3 (3.22) | 34.2 (3.22) | (27.9 – 40.5) | % |
| IIV | | | | | |
| $k_{20}$ | 0.0448 (0.00774) | 0.0396 (0.00747) | 0.0417 (0.00792) | (0.0262 – 0.0572) | - |
| V/F | 0.0216 (0.00364) | 0.0101 (0.00274) | 0.0105 (0.00278) | (0.0051 – 0.0159) | - |
| $k_a$ | 0.992 (0.176) | 0.966 (0.166) | 0.989 (0.172) | (0.652 – 1.33) | - |

Source: Tables 8, 10 &12 of report

Table 14 above shows that the full model had 9 more covariates than the base model while the final model had only 2 more covariates than the base model. The final model had a 60.9 lower OFV than the base model and only a 10.3 higher OFV than the full model suggesting that the final model is parsimonious. The condition number of the final model (ratio of the largest to smallest eigenvalues) was 393 and the model was considered stable since the condition number was below the threshold value of 1000. The parameter estimates in the final model for pediatric and adult subjects yielded the following information.

Clearance. Across the entire age range (>3 months and up) of pediatric and the adult subjects, pregabalin oral clearance (CL/F) increased proportionally to creatinine clearance (BCCL).

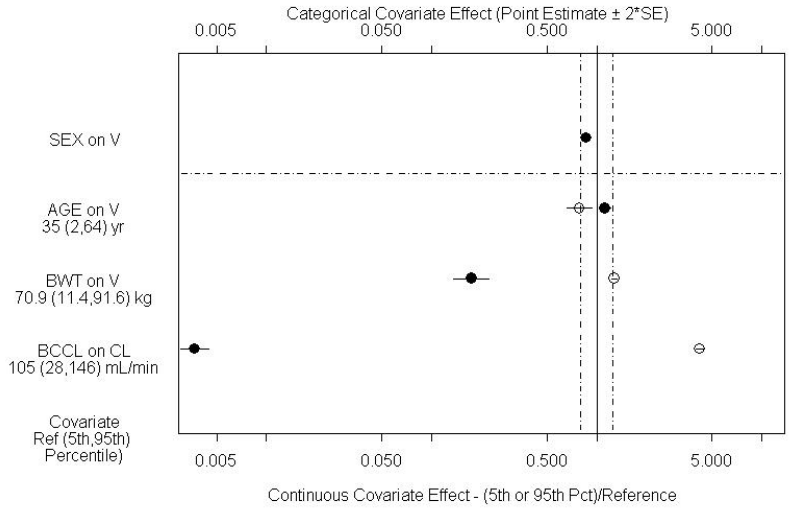
The population estimate (95% CI) of pregabalin CL/F for a subject with normal renal function (BCCL=104.8 mL/min) is 4.28 (4.14-4.42) L/hr (~71 mL/min). The slope estimate for the relationship between CL/F and BCCL would be 0.0408 L·min/(hr·mL). This slope estimate is similar to what was observed in the adult population pharmacokinetic analysis (PMAR -00250).

Distribution Volume. The population estimate (95% CI) of V/F is 47.3 (41.4-53.2) L for a typical subject with a body weight of 70.9 kg. Females had, in general, a 13.7% lower V/F than males which is consistent with a lower percent total body water per kg of total body weight. The parameter V/F decreased with increasing subject age with a power estimate of -0.102. The age effect reduces V/F by approximately 25% over the age range of 3 months to

4 years and ~27% from age 4 to 80 years. The population estimate of V/F is similar to what was observed in the adult population pharmacokinetic analysis (PMAR -00250) and included the same covariate effects of body weight, sex and age on V/F.

Graphical presentation of the effect of categorical and continuous covariates on the typical value of the structural model parameters are presented in Figure 9 below. The estimated covariate effects are represented as the ratio of typical parameters to reference values of the covariates. For the continuous covariates, the open and solid circles show the estimated covariate effects at 5th (solid circle) and 95th percentiles (open circles) of the covariate values. The 95% confidence intervals of these estimated effects are represented by the error bars.

Figure 9. Effect of Continuous and Categorical Covariates on Population Pharmacokinetic Parameters in the Final Model




Creatinine clearance on CL/F, and body weight on V/F covariate effects had the effect magnitude fall outside ±20% reference value indicating these covariates are important for the population pharmacokinetic model involving pediatric and adult subjects. The effect magnitude for age and sex covariates on V/F did not fall outside the ±20% reference value. The age and sex covariates on V/F were statistically significant in the final model but may not be clinically relevant.

A posterior predictive check (PPC, Figures 11 and 15) was performed using the final population PK model. Specifically, the final model was used to simulate geometric means of concentration-time profiles and to compare the predictive concentration-time profiles to the observed data.

Figure 11. PPC Results by Age Group– Observed Plasma Concentrations (geometric mean) and 90% Prediction Intervals of Simulated Concentration for Pregabalin Following Multiple Dose Administration

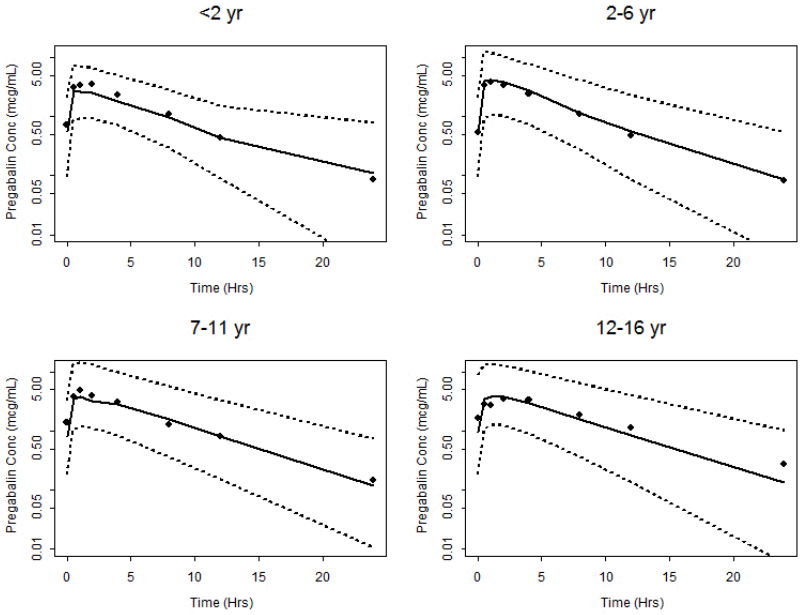
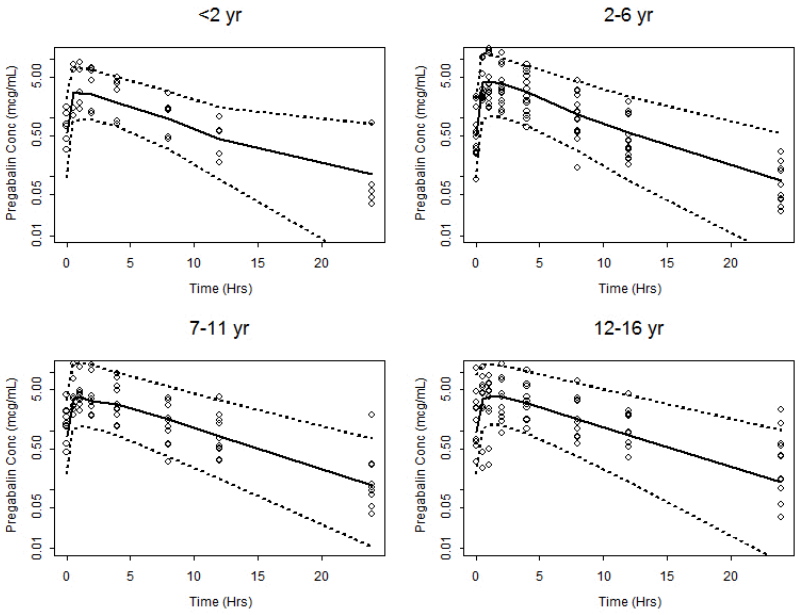
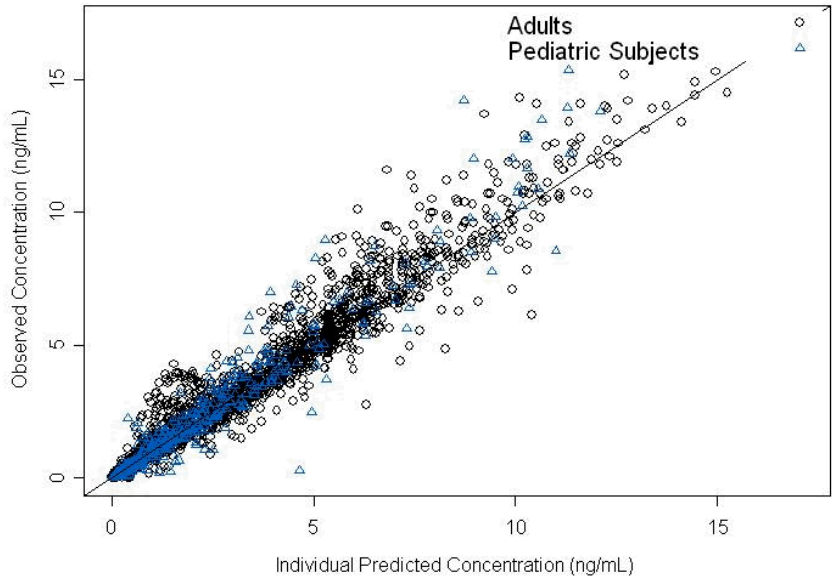



Figure 15. PPC Results by Age Group - Observed Plasma Pregabalin Concentrations (Raw) and 90% Prediction Intervals of Simulated Concentrations for Pregabalin Following Multiple Dose Administration




Diagnostic plots for the final model are shown below (figures 22 and 23). Diagnostic plots for the final model are shown below (Figures 23).

Figure 23. Observed versus Individual Predicted Concentrations




In the report PMAR-00287 Supplement, the final model from PMAR-00287 was used to predict the exposure for pediatric subjects in the <2 yr age cohort/15 mg/kg/day dose group. In addition, the final model was re-run with all the adult and pediatric subjects (including the <2 yr age cohort at 15 mg/kg/day) to confirm that the addition of the <2 yr age cohort/15 mg/kg/day dose group had minimal impact on the final parameter estimates.

The final population pharmacokinetic model in PMAR-00287 adequately described the observed exposure for the 3 pediatric subjects in the <2 yr age cohort/15 mg/kg/day. The inclusion of these three subjects had minimal impact on the final parameter estimates. As reported in PMAR-00287, pregabalin CL/F was directly related to BCCL. Pregabalin V/F was directly related to body weight. Sex and age covariates were also included on V/F but were not considered clinically relevant.

In summary, the final population pharmacokinetic model for all population pharmacokinetic analyses (PMAR-00287 and PMAR-00287 Supplement) was a one-compartment model with first-order elimination and first order absorption with a lag time. Important covariates in the model included creatinine clearance on drug clearance, sex and body weight on volume of distribution, and fed/fasted state on pregabalin absorption.

***Rapporteur's comment to response to Q2:***
*Report PMAR-00287 included data from 57 out of 60 subjects of the paediatric study A0081074 (data from 3 subjects of the <2 yr age cohort/15 mg/kg/day dose group were not included) and adults from five clinical pharmacology studies (previously reported in Pop-PK analysis report PMAR-00250). In the final model developed in PMAR-00287 the data of the 3 subjects of the <2 yr age cohort/15 mg/kg/day dose group were included and the results were reported (in Report PMAR-00287 Supplement). The addition of these data did not change the results shown in the PMAR-00287 report. The final model for both reports was a one-compartment model with first-order elimination and first order absorption with a lag time. The model included, among others,*

*the covariates, creatinine clearance on drug clearance, and sex and body weight on volume of distribution on pregabalin absorption..*

*Creatinine clearance on pregabalin clearance (CL/F) and body weight on volume distribution (V/F) were shown to be important covariates (Figure 9).The Pop-PK analysis further showed that CL/F was directly related to creatinine clearance and V/F was directly related to body weight. There is a good agreement between the predicted and observed plasma concentrations as depicted in the posterior predictive check (Fig. 15) and diagnostic plots (Figs. 22 and 23). The developed final model is appropriate as the predicted concentrations were confirmed by the observed plasma concentrations..*

*In summary, the conclusions drawn on the pharmacokinetic comparability of paediatric data and adult data appear to be justified. However, as mentioned under Q1 above, final confirmation of these conclusions will come from the results of the on-going Phase 3 paediatric clinical studies.*

***Issue resolved.***

**Question 3:**
**Pfizer should provide a proposal for inclusion of the data in the product information based on the data of study A0081074 and A0081075.**

MAH Response:
Pfizer proposes not to include information in the SmPC based on A0081074 (Clinical Study Report (CSR) submitted on 10th April 2013) and A0081075 (CSR submitted in this submission) at this time. The reasoning behind this is that as these two studies are part of a broader program, Pfizer plans to wait and propose paediatric labelling for the SmPC when the paediatric epilepsy clinical program has completed.

***Rapporteurs' comment to response to Q 3:***

*The MAH refused to propose inclusion of any text in the labelling reflecting the data generated from study A0081074 and A0081075 with the argument that the paediatric programme is broader and still to be completed. The currently discussed studies were intended to explore tolerability and define the appropriate dose for use in the paediatric population. The latter is to be used in the planned phase III studies in paediatric subjects. In this respect the studies have achieved their goal.*

*Although on one hand it is agreed that the analysis of the complete paediatric programme would provide more complete information about efficacy and safety of the use of pregabalin in the paediatric population, on the other hand, obtaining these results requires more time (timelines of the rest of the studies have been provided by the MAH as requested and the paediatric programme is expected to be completed in 2017.*
*However, the currently mentioned statement in section 4.2 of the SPC regarding the paediatric population (i.e. 'No data are available') is not correct since some data in paediatric subjects has been generated. Additionally it is known from PSURs that children are being treated with pregabalin. Therefore it is requested to include information in the SPC:*

*Section 4.2. under Paediatric population*
*The current statement should be replaced by: 'The safety and efficacy of Lyrica in children below the age of 12 years and in adolescents (12-17 years of age) have not been established. Some data has been generated (please refer to 4.8. and 5.1/5.2.)*

*Section 4.8, and 5.1/5.2*
*Relevant information should be included and the applicant should provide a text proposal.*

***Issue not resolved.***