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REFUSAL ASSESSMENT REPORT
FOR
Lyrica

International non-proprietary name/Common name:
(pregabalin)

Procedure No. EMEA/H/C/000546/II/0024

Variation Assessment Report as adopted by the CHMP with
All information of a commercially confidential nature deleted

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LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
BL	Baseline
BID	Twice Daily
CFA	Confirmatory Factor Analysis
CGIC	Clinical Global Impression of Change
CHMP	Committee for Medical Products for Human Use
CI	Confidence Interval
CID	Clinically Important Difference
CMH	Cochran-Mantel-Haenszel
DPN	Diabetic Peripheral Neuropathy
EU	European Union
EULAR	European League Against Rheumatism
FAS	Full Analysis Set
FIQ	Fibromyalgia Impact Questionnaire
FM	Fibromyalgia
GAD	Generalised Anxiety Disorder
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale - Anxiety
HADS-D	Hospital Anxiety and Depression Scale – Depression
ITT	Intent-to-Treat
K-M	Kaplan-Meier
LOCF	Last Observation Carried Forward
LS	Least Squares
LTR	Loss of Therapeutic Response
MAA	Marketing Authorization Application
MAH	Marketing Authorization Holder
MOS	Medical Outcomes Study
MOS - SS	Medical Outcomes Study – Sleep Scale
NA	Not Applicable
OL	Open Label
OMERACT	Outcomes Measures in Rheumatoid Arthritis Clinical Trials
PGB	Pregabalin
PGIC	Patient Global Impression of Change
PHN	Post-Herpetic Neuralgia
PP	Protocol Population
QOL	Quality of Life
ROW	Rest of World
SAE	Serious Adverse Event
SCE	Summary of Clinical Efficacy
SD	Standard Deviation
SE	Standard Error
SF-36	Short-Form 36 Health Survey
SF-MPQ	Short-Form – McGill Pain Questionnaire
TID	Three Times Daily
USPI	United States Package Insert
VAS	Visual Analog Scale

I. SCIENTIFIC DISCUSSION

1.1. About the product and Problem statement

The active substance of Lyrica, pregabalin, is a gamma-aminobutyric acid analogue ((S)-3-(aminomethyl)-5-methylhexanoic acid). Pregabalin binds to an auxiliary subunit (α_2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [^{3}H]-gabapentin.

With this type II variation, the MAH applied for a new indication in the treatment of fibromyalgia in adults. Subsequently, the MAH changed the claimed indication to treatment of fibromyalgia in adults experiencing moderate to severe pain.

The clinical pharmacology of oral pregabalin was investigated in 21 phase I studies included in the original application for pregabalin capsules. No new clinical pharmacology studies were carried out to support this application for treatment of fibromyalgia.

Pregabalin is currently registered for the treatment of 1) peripheral and central neuropathic pain in adults; 2) as adjunctive therapy in adults with partial seizures with or without secondary generalisation and 3) treatment of generalised anxiety disorder in adults.

1.2 Development programme and scientific advice

Fibromyalgia is a complex disorder that is characterized by pain, fatigue, sleep disturbance, and impaired cognitive and physical function. The CHMP gave scientific advice for Lyrica in the proposed indication of fibromyalgia in 2005. The CHMP agreed to the diagnostic criteria of fibromyalgia according to the criteria of the American College of Rheumatology. However, the CHMP considered fibromyalgia an ill defined and extremely heterogeneous condition without universal consensus on its characteristic and diagnostic features and no objective investigations to aid diagnosis. It was noted that there are geographical differences in the way in which fibromyalgia is perceived, diagnosed and managed, making studies in the EU population recommendable in view of an approval for the European market. The endpoints for this complex disorder were also discussed and the CHMP concluded at the time that pain alone was insufficient and should be complemented by an effect on aspects of fibromyalgia beyond pain.

The CHMP adopted a negative opinion on the sought indication on 23 April 2009. The MAH requested a re-examination of the CHMP opinion on 6 May 2009 and submitted the grounds for re-examination on 22 June 2009.

During the re-examination procedure, the CHMP sought experts' opinion via the Scientific Advisory Group (SAG) for Clinical Neuroscience (CNS) to consolidate its evaluation.

The clinical development programme for the applied indication consisted of 5 double-blind, placebo-controlled studies (1008-105, A0081056, A0081077, A0081100 and A0081059) and 4 open-label extension studies (A0081057, A0081078, A0081101 and 1008-033/1008-197). In total 2068 patients with fibromyalgia were randomised and treated in these trials (see tables 1 and 2). The number of patients was sufficient to assess the efficacy and safety of pregabalin in patients with fibromyalgia.

Table 1: Overview of clinical efficacy trials performed in patients with fibromyalgia

Study ID	Study Design	Treatment Groups, N (ITT)	Efficacy Measures
8-14 week Controlled Studies, N=2757			
105 USA	Randomised, double-blind: 8 weeks (7 weeks at fixed dose) N=529	PGB 150 mg/day, 132 PGB 300 mg/day, 134 PGB 450 mg/day, 132 Placebo, 131	Endpoint Mean Pain Score * Patient Global Impression of Change Sleep Disturbance - MOS Sleep Scale
1056 USA	Randomised, double-blind: 13 weeks (12 weeks at fixed dose) N=748	PGB 300 mg/day, 185 PGB 450 mg/day, 183 PGB 600 mg/day, 190 Placebo, 190	Endpoint Mean Pain Score* Patient Global Impression of Change Fibromyalgia Impact Questionnaire Sleep Disturbance - MOS Sleep Scale
1077 USA	Randomised, double-blind: 14 weeks (12 weeks at fixed dose) N=745 Patients with ≥30% decrease on VAS pain during run-in period were excluded	PGB 300 mg/day, 183 PGB 450 mg/day, 190 PGB 600 mg/day, 188 Placebo, 184	Endpoint Mean Pain Score* Patient Global Impression of Change Fibromyalgia Impact Questionnaire Sleep Disturbance - MOS Sleep Scale
1100 International	Randomised, double-blind: 14 weeks (12 weeks at fixed dose) N=735 Patients with ≥30% decrease on VAS pain during run-in period were excluded	PGB 300 mg/day, 183 PGB 450 mg/day, 182 PGB 600 mg/day, 186 Placebo, 184	Endpoint Mean Pain Score* Patient Global Impression of Change Fibromyalgia Impact Questionnaire Sleep Disturbance - MOS Sleep Scale
6-Month Controlled Study, N=1051			
1059 USA	Open-label: 6 weeks N=1051 followed by randomised, double-blind: 6-month N=566	Open-label phase PGB: (300, 450 or 600 mg/day), 1051 Double-blind phase PGB 300 mg/day, 63 PGB 450 mg/day, 73 PGB 600 mg/day, 143 Placebo, 287	Time to Loss of Therapeutic Response* Time to Worsening of Patient Global Impression of Change Time to Worsening of Fibromyalgia Impact Questionnaire Time to Worsening of Sleep Disturbance – MOS Sleep Scale
* = Primary Endpoint; PGB = Pregabalin; MOS = Medical Outcomes Survey; FIQ = Fibromyalgia Impact Questionnaire			

Table 2: Pregabalin open-label safety studies

Study ID	Study Design	Total Pregabalin-Treated, N
1057	Open-label extension of Study A0081056	429
033/197[a]	Open-label extension of Study 1008-105	413/25
1078	Open-label extension of Study A0081077	420
1101	Open-label extension of Study A0081100	Not applicable – ongoing

[a] Studies 033 and 197 are 2 separate open-label studies; Study 197 was an extension of Study 033. Both studies enrolled patients from various double-blind studies of chronic pain including diabetic peripheral neuropathy, post herpetic neuralgia, and fibromyalgia.

The MAH confirmed that all studies were conducted in accordance with applicable regulatory and International Conference on Harmonisation (ICH)-Good Clinical Practice (GCP) requirements, the ethical principles that have their origin in the principles of the Declaration of Helsinki, and the local laws of the countries involved, as well as the ICH Tripartite Guidelines, Guideline for GCP, January 1997.

1.3. Clinical aspects

1.3.1 Pharmacokinetics

No changes to the pharmacokinetic or interaction data within the product information were proposed with this submission. It is expected that the pharmacokinetics are similar for fibromyalgia patients as for patients with neuropathic pain, epilepsy or generalised anxiety disorder. Therefore, no additional pharmacokinetic studies were considered necessary.

1.3.2 Clinical efficacy

Study design

Studies 105, 1056, 1077 and 1100 were double blind studies that consisted of a baseline phase, a dose escalation phase, and a fixed dose phase (Table 3). During the baseline phase subjects were screened for eligibility to enter the double-blind phase of the study.

Table 3: Overall study design of controlled 8-14-week fibromyalgia studies 105, 1056, 1077, and 1100

Study	Baseline Phase	Dose Escalation Phase	Fixed-Dose Phase	Total Double-Blind Duration	Post-Study/ Follow Up
105	1 week	1 week	7 weeks	8 weeks	Optional open-label or withdrawal
1056		1 week	12 weeks	13 weeks	
1077, 1100		2 weeks	12 weeks	14 weeks	

The run in phase was single blind. The subsequent double-blind treatment phase included an initial 1- or 2-week dose escalation period followed by a 7-week (Study 105) or 12-week (Studies 1056, 1077, 1100) fixed-dose period. Patients who completed the double-blind phase could elect to continue in open-label extension studies or discontinue treatment; those who did not continue in open-label were seen for a follow-up visit 1 week later. In trial 1077 and 1100 patients who demonstrated a high response (≥30% decrease on the pain visual analogue scale (VAS)) to placebo during the baseline phase were not randomised at the end of that phase. Exclusion of these patients in principle results in a selected study population. As the patient population of study 1077/100 differs from the other studies, the pooling of the results over all studies is questionable.

Study 1059 was designed as a maintenance of treatment effect study, in which responders to open-label treatment at 6 weeks were randomized in a double-blind fashion to continue pregabalin or to receive placebo treatment for 6 months. This study is further discussed later in this report.

Patient population

The main inclusion criteria were:
- At screening (Visit 1), subjects met the American College of Rheumatology (ACR) criteria for fibromyalgia (i.e., widespread pain present for at least 3 months and pain in at least 11 of 18 specific tender point sites).
- At screening (Visit 1) and randomization (Visit 2), subjects had a score of ≥40 mm on the Pain VAS.
- At randomization (Visit 2), subjects had at least 4 pain diaries completed satisfactorily within the previous 7 days with an average pain score ≥4.

The main exclusion criteria were:
- Subjects with ≥30% decrease on the VAS at randomization (Visit 2) as compared with screening (Visit 1). (For study 1077 and 1100 only).
- Subjects with severe pain due to other conditions [e.g., diabetic peripheral neuropathy (DPN) or post herpetic neuralgia (PHN)] that may have confounded assessment or self-evaluation of the pain associated with fibromyalgia.
- Subjects with any widespread inflammatory musculoskeletal disorders, widespread rheumatic diseases other than fibromyalgia, active infections, or untreated endocrine disorders.
- Subjects with severe depression that in the judgment of the investigator made the subject inappropriate for entry into this trial.

- Subjects using prohibited pain/sleep medications (including antidepressants, sedatives, hypnotics, NSAIDs, opiates, muscle relaxants) in the absence of appropriate washout periods

Rescue medication

Aspirin and Acetaminophen were allowed as rescue medication.
Aspirin: up to 1 aspirin tablet (≤ 325 mg) daily for myocardial infarction and stroke prophylaxis
Acetaminophen (i.e paracetamol): up to 4 g/day as needed for pain relief

Baseline characteristics

The patient population of the efficacy trials is summarised in table 4. As expected, many more females were included in the studies compared to male patients.The age group of 65 years and older was small (<10%). Baseline characteristics were equally distributed over the different study arms in each study. Of note, only 280 patients from the European Union (all in study 1100) were randomised and took study medication.

Table 4: Summary of patient characteristics: studies 105, 1056, 1077 and 1100.

Characteristic		**Study 105 N = 529 (%)**	**Study 1056 N = 748 (%)**	**Study 1077 N = 745 (%)**	**Study 1100 N= 735 (%)**
Sex, n (%)	Male	45 (8.5)	42 (5.6)	41 (5.5)	63 (8.6)
	Female	484 (91.5)	706 (94.4)	704 (94.5)	672 (91.4)
Race, n (%)	White	493 (93.2)	675 (90.2)	678 (91.0)	558 (75.9)
	Black	12 (2.3)	35 (4.7)	33 (4.4)	1 (0.1)
	Hispanic	18 (3.4)	33 (4.4)	NA	92 (12.5)
	Asian or Pacific Islander	3 (0.6)	2 (0.3)	NA	NA
	American Indian or Alaskan Native	NA	1 (0.1)	NA	NA
	Other	3 (0.6)	2 (0.3)	34 (4.6)	84 (11.4)
Age	Mean (SD)	48.6 (10.6)	48.8 (10.9)	50.1 (11.4)	48.5 (11.2)
	18-64 years , n (%)	489 (92.4)	702 (93.9)	690 (92.6)	679 (92.4)
	≥65 years , n (%)	40 (7.6)	46 (6.1)	55 (7.4)	56 (7.6)
Estimated creatinine clearance (mL/min)	Mean (SD)	94.46 (27.06)	100.3 (31.4)	93.4 (27.2)	87.4 (23.6)
	Median	89.20	93.6	88.2	84.0
	Range	41.2 - 208.6	48.5 - 291.9	43.7 - 255	40 - 216.3
Weight (kg)	Mean (SD)	79.55 (19.33)	82.0 (20.2)	83.1 (20.1)	72.5 (16)
	Range	45.4 - 151.8	43.1 - 172.3	43.6 - 156	40 - 149.7
Duration of fibromyalgia (months)	Mean (SD)	107.7 (100.5)	111.7 (95.0)	120.2 (96.2)	98.8 (93.9)
	Median	77	85.0	97.0	71.0
	Range	0.0 - 654.0	3 - 656	1.0 - 614	3.0 - 554.0
Number of tender points	Mean (SD)	17.1 (1.5)	17.1 (1.6)	16.9 (1.8)	17.1 (1.6)
	Median	18	18.0	18.0	18.0
	Range	10.0 - 18.0	6 - 18	7.0 - 18.0	8 - 18
Mean Pain Score	Mean (SD)	7.0 (1.3)	7.1 (1.3)	6.7 (1.3)	6.65 (1.36)
FIQ Total Score	Mean (SD)	NA	64.3 (13.6)	59.7 (15.7)	61.07 (14.52)
MOS-SS Sleep Disturbance Score	Mean (SD)	62.5 (24.5)	67.8 (23.4)	60.0 (24.9)	60.45 (25.73)
HADS-A Score	Mean (SD)	10.1 (4.3)	9.5 (4.6)	8.73 (4.17)	8.86 (4.49)
HADS-D Score	Mean (SD)	8.6 (4.0)	8.3 (4.2)	7.05 (4.08)	7.51 (4.20)

Endpoints

The primary efficacy endpoint in each of the 8-14 week studies was the change from baseline in mean pain score The Patient Global Impression of Change and change from baseline in the total score on the Fibromyalgia Impact Questionnaire (FIQ) were co-primary endpoints in studies 1056 and 1077. The Patient Global Impression of Change (PGIC) was co-primary endpoint in study 1100.

The two key secondary endpoints included change from baseline in the total score on the Fibromyalgia Impact Questionnaire (FIQ) and improvement in sleep as assessed with the Medical Outcomes Study (MOS) Sleep Scale Sleep Disturbance subscale. Other secondary endpoints included assessments of sleep, fatigue, mood disturbance, additional assessments of pain, health status, and functioning.

- *Pain*

Pain was assessed with a daily pain diary which uses an 11 point numeric rating scale from 0 (no pain) to 10 (worst possible pain). In Study 1059, pain was assessed at each visit with the self-administered Pain Visual Analogue Scale (VAS).

- *Patient Global Impression of Change (PGIC)*

Global assessment was conducted with the Patient Global Impression of Change (PGIC), a patient-rated instrument that measures change in patient's overall status on a scale ranging from 1 (very much improved) to 7 (very much worse). The PGIC is a measure of the overall perception of the advantages and disadvantages of the treatment. The PGIC was scored by patients at study termination.

- *Function – Fibromyalgia Impact Questionnaire (FIQ)*

The Fibromyalgia Impact Questionnaire (FIQ) is a 20 item patient-reported outcome instrument designed to assess health status, progress, and outcomes. It contains 10 subscales, which are combined to yield a total score.

- *Sleep*

The MOS-SS is a self reporting survey which yields a subscale score for sleep disturbance as well as 6 other parameters and a 9-item overall Sleep Problems Index. Because sleep disturbance is considered a key aspect of the constellation of fibromyalgia symptoms, the MOS-SS Sleep Disturbance subscale is the sleep parameter of prominence in this application.

Statistics

All primary and secondary analyses were performed using data from the full analysis set (FAS) population, defined as all randomized patients who took at least 1 dose of study medication. The intention to treat (ITT) and FAS were considered equivalent by the MAH. This was agreed by the CHMP given the limited loss of patients in the randomized population and the FAS population.

All statistical testing was 2-sided and compared each treatment arm of pregabalin to placebo. The primary analysis compared the endpoint mean pain score between the treatment groups using an analysis of covariance (ANCOVA) with treatment and centre in the model and the baseline mean pain score as covariate in the FAS population. For the comparison of the dose arms Hochberg's approach was used to protect the Type I error rate at the 0.05 level. Because the second objective required 2 measures to be significant, the PGIC was tested at the $\alpha = 0.05$ for each dose, without adjustment for multiple comparisons to placebo. Interpretation focused on those doses that demonstrated a significant efficacy in endpoint mean pain. Secondary measures were assessed in the following order: firstly, the Sleep Disturbance domain from the MOS-Sleep Scale, then the FIQ total score, and then all other secondary endpoints. All supplemental analyses based on the pain diary, and all secondary analyses, were tested at the $\alpha = 0.05$ for each dose, without adjustment for multiple comparisons to placebo.

Endpoint analysis, including the primary analysis, used the last observation carried forward (LOCF) imputation. Additional analyses, including mixed-model repeated measures (MMRM) and analysis of duration adjusted average change (DAAC) were conducted to assess the robustness of the primary analysis and potential impact of missing data.

Results for individual short-term efficacy studies

- *Primary endpoint - Pain score:*

The primary efficacy endpoint was the mean pain scores for pregabalin treatment compared with those for placebo treatment in the FAS population. Mean Pain Scores were calculated from the last 7 available scores while on study medication, up to and including day after last dose. Results are summarised in table 5.

Table 5: Mean Pain Scores (FAS set) per study (* Statistically significant at 0.05 based on adjusted p-values according to Hochberg's procedure). Mean baseline scores (SD) filled in by assessor; values for study 105 calculated by assessor.

		Least Squares			**Treatment Comparison (Pregabalin – Placebo)**			
Study/Treatment Group	**N**	**Mean**	**Mean Change**	**SE** ***SD***	**Difference**	**95% CI**	**p-Value**	**Adjusted p-Value**
Study 105	520	7.03		*0.19*				
Placebo	129	5.88	-1.15	0.18				
Pregabalin 150 mg	131	5.74	-1.28	0.18	-0.13	[-0.63, 0.37]	0.6044	0.6044
Pregabalin 300 mg	132	5.47	-1.56	0.18	-0.41	[-0.90, 0.09]	0.1114	0.2228
Pregabalin 450 mg	128	4.94	-2.08	0.18	-0.93	[-1.43, -0.43]	0.0003*	0.0009*
Study 1056	748	7.1		*1.3*				
Placebo	190	5.70	-1.40	0.16				
Pregabalin 300 mg	185	5.26	-1.84	0.16	-0.43	[-0.86, -0.01]	0.0449 *	0.0449*
Pregabalin 450 mg	183	5.23	-1.87	0.16	-0.47	[-0.89, -0.04]	0.0310 *	0.0449*
Pregabalin 600 mg	190	5.04	-2.06	0.16	-0.66	[-1.08, -0.23]	0.0023 *	0.0070*
Study 1077	745	6.7		*1.3*				
Placebo	184	5.64	-1.04	0.15				
Pregabalin 300 mg	183	4.93	-1.75	0.16	-0.71	[-1.13, -0.29]	0.0009*	0.0009*
Pregabalin 450 mg	190	4.66	-2.03	0.15	-0.98	[-1.40, -0.57]	<.0001*	<.0001*
Pregabalin 600 mg	188	4.64	-2.05	0.15	-1.00	[-1.41, -0.59]	<.0001*	<.0001*
Study 1100	734	6.65		*1.36*				
Placebo	184	5.93	-0.72	0.14				
Pregabalin 300 mg	183	5.60	-1.05	0.14	-0.34	[-0.72, 0.05]	0.0841	0.1683
Pregabalin 450 mg	181	5.39	-1.26	0.14	-0.54	[-0.92, -0.16]	0.0055*	0.0164*
Pregabalin 600 mg	186	5.70	-0.95	0.14	-0.23	[-0.61, -0.15]	0.2339	0.2339
European Union (part of study 1100)								
Placebo	98	5.95	-0.70	0.19				
Pregabalin 300 mg	93	5.71	-0.94	0.20	-0.24	[-0.78, 0.30]		
Pregabalin 450 mg	91	5.46	-1.19	0.20	-0.49	[-1.03, 0.05]		
Pregabalin 600 mg	96	5.62	-1.02	0.19	-0.33	[-0.86, 0.21]		
Rest of the world (study 1100 minus EU population)								
Placebo	86	5.78	-0.87	0.20				
Pregabalin 300 mg	90	5.34	-1.31	0.20	-0.45	[-1.01, 0.11]		
Pregabalin 450 mg	90	5.13	-1.52	0.20	-0.66	[-1.22, -0.10]		
Pregabalin 600 mg	90	5.60	-1.05	0.20	-0.18	[-0.74, 0.38]		

In study 1100, the mean baseline pain score was 6.65 (SD 1.36) and the mean difference in pain scores with placebo for the 450mg pregabalin dose is -0.54. This is the only dose statistically significant different from placebo in this study. For US studies 1056 and 1077, the results showed a statistically significant improvement of pain scores and are consistent within the three doses. However, the mean difference in pain scores with placebo was 1 point or less on an 11-point pain-scale, which is considered a small magnitude of effect.

When the >50% responder rate is considered for each individual studies, it was higher for pregabalin 300 and 450 mg/day than for placebo treatment. Although this difference was statistically significant in 2 studies out of 3, the responder rates differ only of about 8-12% (study 1100 and 1077), as shown in table 6.

Table 6: Results of Analyses of 30% and 50% Responder Status at Endpoint at Pregabalin Doses of 300, 450, and 600 mg/day: Studies 1056, 1077, 1100 (*p<0.05, significantly greater response than in the placebo-treatment group; n=Number of responders; N=Number assessed, %=(n/N)*100)

30% Responder Analysis

	Placebo			**300 mg/day**			**450 mg/day**			**600 mg/day**		
	n	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**
Study 1056	66	190	34.7	79	185	42.7	79	183	43.2	83	190	43.7
Study 1077	56	184	30.4	76	183	41.5*	94	190	49.5*	90	188	47.9*
Study 1100	34	184	18.5	59	183	32.2*	60	181	33.1*	49	186	26.3

For all pregabalin-treated in combined 13-14-week studies (1056, 1077, 1100), (n/N) =(669/1669)=40.1%

50% Responder Analysis

	Placebo			**300 mg/day**			**450 mg/day**			**600 mg/day**		
	n	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**	**n**	**N**	**%**
Study 1056	37	190	19.5	46	185	24.9	46	183	25.1	51	190	26.8
Study 1077	28	184	15.2	44	183	24.0*	52	190	27.4*	57	188	30.3*
Study 1100	17	184	9.2	32	183	17.5*	33	181	18.2*	28	186	15.1

For all pregabalin-treated in combined 13-14-week studies (1056, 1077, 1100), (n/N) =(389/1669)=23.3%

- *Patient Global Impression of Change (PGIC)*

Table 7 displays the results of the PGIC, and a breakdown by degree of improvement is presented in table 8.

Table 7: Summary of Patient Global Impression of Change (PGIC) at Endpoint: Studies 105, 1056, 1077, and 1100 (* Statistically significant at 0.05 level).

Study/Treatment Group	N [a]	% Patients With Any Improvement [b]	% Patients With No Change	% Patients With Any Worsening [c]	p-Value [d]
Study 105					
Placebo	122	52.5	24.6	23.0	-
Pregabalin 150 mg/day	125	60.0	20.0	20.0	0.301
Pregabalin 300 mg/day	125	66.4	17.6	16.0	0.004*
Pregabalin 450 mg/day	126	74.6	8.7	16.7	0.003*
Study 1056					
Placebo	178	56.2	20.8	23.0	-
Pregabalin 300 mg/day	175	70.9	12.0	17.1	0.0183*
Pregabalin 450 mg/day	173	72.3	9.8	17.9	0.0467*
Pregabalin 600 mg/day	175	68.6	20.0	11.4	0.0127*
Study 1077					
Placebo	166	47.6	30.7	21.7	
Pregabalin 300 mg/day	160	68.1	14.4	17.5	0.0034*
Pregabalin 450 mg/day	171	77.8	10.5	11.7	<0.0001*
Pregabalin 600 mg/day	177	66.1	16.4	17.5	0.0005*
Study 1100					
Placebo	169	56.2	25.4	18.3	
Pregabalin 300 mg/day	162	66.7	16.7	16.7	0.0539
Pregabalin 450 mg/day	165	73.3	16.4	10.3	0.0017*
Pregabalin 600 mg/day	155	69.0	16.1	14.8	0.0227*

CMH=Cochran-Mantel-Haenszel
[a] Number of patients with data available for this analysis
[b] Includes PGIC categories of Very Much Improved, Much Improved, and Minimally Improved
[c] Includes PGIC categories of Very Much Worse, Much Worse, Minimally Worse
[d] Based on CMH test, adjusted for centre; examined shift across all 7 response categories.

Table 8: Frequency of Patients Reporting Much Improved or Very Much Improved in Patient Global

	Placebo			300 mg/day			450 mg/day			600 mg/day		
Study/Category	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**	**N**	**n**	**%**
Study 1056												
Much Improved	178	41	23.	175	48	27.	173	45	26.0	175	54	30.
Very Much Improved	178	21	11.	175	28	16.	173	26	15.0	175	27	15.
Study 1077												
Much Improved	166	27	16.	160	33	20.	171	55	32.2	177	59	33.
Very Much Improved	166	12	7.2	160	18	11.	171	25	14.6	177	19	10.
Study 1100												
Much Improved	169	43	25.	162	45	27.	165	50	30.3	155	46	29.
Very Much Improved	169	7	4.1	162	13	8.0	165	16	9.7	155	20	12.

PGIC results were consistent. However, the placebo effect is important in all studies and the difference in responder rates between placebo and pregabalin treatment effect are small, which questions the clinical relevance of the effect: in study 1056 a total of 56.2 % of the patients in the placebo group improved whereas 68.6 % to 72.3% of the patients in the pregabalin treated group improved. In study 1077 a total of 47.6 % of the patients in the placebo group improved whereas 66.1 % to 77.8% of the

patients in the pregabalin treated group improved. In study 1100 a total of 56.2 % of the patients in the placebo group improved whereas 66.7 % to 73.3% of the patients in the pregabalin treated group improved. Taking into account only the patients who improved "much" or "very much", the treatment effect remains small.

- *Fibromyalgia Impact Questionnaire (FIQ)*

The FIQ has 10 subscales: Physical impairment, Feel Good, Work Missed, Do Work, Pain, Fatigue, Rested, stiffness, Anxiety and Depression. Results are presented in table 9 (FIQ assessment was not conducted in Study 105).

Table 9: Fibromyalgia Impact Questionnaire (FIQ) Total Scores at Endpoint: Results of Analysis of Covariance (* Statistically significant at 0.05 level)

Study / Treatment Group	**N**	**Least Squares**			**Treatment Comparison (Pregabalin – Placebo)**		
		Mean	**Mean Change**	**SE**	**Difference**	**95% CI**	**p-Value[a]**
1056							
Placebo	190	50.66	-13.66	1.44			
Pregabalin 300 mg/day	185	48.18	-16.15	1.46	-2.48	[-6.38, 1.41]	0.2113
Pregabalin 450 mg/day	183	48.62	-15.71	1.47	-2.05	[-5.96, 1.86]	0.3040
Pregabalin 600 mg/day	190	49.45	-14.88	1.45	-1.21	[-5.10, 2.67]	0.5390
1077							
Placebo	183	51.99	-7.74	1.34			
Pregabalin 300 mg/day	183	49.03	-10.70	1.34	-2.96	[-6.57, 0.65]	0.1078
Pregabalin 450 mg/day	190	46.75	-12.98	1.31	-5.24	[-8.81, -1.67]	0.0041*
Pregabalin 600 mg/day	188	46.65	-13.08	1.33	-5.34	[-8.92, -1.77]	0.0034*
1100							
Placebo	184	54.13	-6.94	1.30			
Pregabalin 300 mg/day	183	52.79	-8.28	1.29	-1.34	[-4.86,2.17]	0.4540
Pregabalin 450 mg/day	179	48.26	-12.80	1.32	-5.87	[-9.40, -2.34]	0.0012*
Pregabalin 600 mg/day	186	52.67	-8.40	1.28	-1.46	[-4.96, 2.04]	0.4120

Range 0-100; Decrease in score represents improvement

[a] Based on LS Means using ANCOVA model (including effects for treatment, centre, and the baseline value as covariate).

Results were inconsistent across trials and doses, and were not statistically significant in study 1056. Inconsistency across doses suggests a lack of a dose-response relationship which is not supportive of a treatment effect. Again, the magnitude of the placebo effect in all studies and the difference in responder rates between placebo and treatment groups make the numerical results of questionable clinical relevance.

- *MOS-SS Sleep disturbance*

Table 10 summarises the results of the different trials on the MOS-SS Sleep disturbance. Results were consistent across studies and a dose effect was observed in studies 105 and 1077.

Table 10: Summary of MOS-SS Sleep Disturbance at Endpoint (Studies 105, 1056, 1077, and 1100).
* Statistically significant at 0.05 level.

Study/Treatment Group	N [a]	Least Squares Mean	Difference	Treatment Comparisons (Pregabalin-Placebo) 95% CI	p-Value
Study 105					
Placebo	121	52.47	-	-	-
Pregabalin 150 mg/day	123	41.41	-11.06	(-17.03, -5.09)	0.0003*
Pregabalin 300 mg/day	124	39.54	-12.93	(-18.88, -6.97)	0.0001*
Pregabalin 450 mg/day	123	32.81	-19.66	(-25.62, -13.70)	0.0001*
Study 1056					
Placebo	188	49.26	-		-
Pregabalin 300 mg/day	185	41.65	-7.61	(-12.77, -2.46)	0.0039*
Pregabalin 450 mg/day	183	38.99	-10.27	(-15.43, -5.11)	0.0001*
Pregabalin 600 mg/day	188	39.41	-9.85	(-14.99, -4.71)	0.0002*
Study 1077					
Placebo	182	51.88	-	-	-
Pregabalin 300 mg/day	183	42.97	-8.91	(-13.98, -3.8)	0.0006*
Pregabalin 450 mg/day	187	41.25	-10.63	(-15.98, -5.5)	<0.0001*
Pregabalin 600 mg/day	188	36.95	-14.93	(-19.96, -9.9)	<0.0001*
Study 1100					
Placebo	183	54.47	-	-	-
Pregabalin 300 mg/day	182	47.14	-7.32	(-12.20, -2.45)	0.0033*
Pregabalin 450 mg/day	177	41.18	-13.29	(-18.19, -8.39)	<0.0001*
Pregabalin 600 mg/day	185	41.74	-12.73	(-17.58, -7.87)	<0.0001*

[a] Number of patients with data available for this analysis

Combined results for short-term efficacy studies (pooling data from studies 1056, 1077 and 1100)

- *Results on pain*

The proportion of 50% pain responders when pooling data is shown in table 11. A statistically significant difference in the proportion of 50% responders was demonstrated in each treatment group. When pooling data, results for pain show that the 50% responder rates difference between pregabalin all dose treatment groups and placebo is of 8.6%. Whether this difference is clinically significant is questionable.

Table 11. 50% Responder Analysis

	Placebo			300 mg/day			450 mg/day			600 mg/day		
	n	N	%	n	N	%	n	N	%	n	N	%
Studies1056/1077/110	82	558	14.7	122	551	22.19	131	554	23.75	136	564	24.1
Diff, CI95%				7.4%	2.9% ; 12%		7.6%	3.1% ; 12.1%		9.4%	4.8% ; 14.0%	

* Statistically significant at <0.05 level; p-value is based on the results of the CMH procedure, adjusting for protocol

- *Results on FIQ*

Results on the FIQ in individual short-term studies were inconsistent and of little magnitude compared to placebo. In the pooled analysis, at least for the 450 mg/day dose, the results in the overall FIQ score and even the results for the different subscales were more or less consistent (table 12).

Using the minimal clinical important criteria difference (MCID) definition of 8.05 points, each of the pregabalin treatment groups achieved the minimal clinically important difference, with mean changes from baseline of -11.95, -14.18, and -12.46 for the 300, 450, and 600 mg/day pregabalin groups,

respectively. However, the difference in the placebo group (-9.93) is also well above the MCID. Hence as the differences versus placebo are 2.02, 4.25, and 2.53 points for PGB300, PG450 and PG600 respectively, the clinical significance of the results on FIQ is questionable.

Table 12 – FIQ subscales and total scores at endpoint

			Least Squares			Treatment Comparison (Pregab –Placebo)		
FIQ Subscale	Treatment Group (N)	n	Mean	Mean Change	SE	Difference	95% CI	p-Value[a]
Physical Impairment	Placebo	556	3.61	-0.43	0.08			
	Pregabalin 300 mg/day	551	3.41	-0.64	0.08	-0.21	[-0.43, 0.01]	0.0664
	Pregabalin 450 mg/day	550	3.40	-0.65	0.08	-0.22	[-0.44, 0.00]	0.0522
	Pregabalin 600 mg/day	564	3.42	-0.62	0.08	-0.19	[-0.41, 0.03]	0.0886
Feel Good	Placebo	555	6.10	-1.52	0.13			
	Pregabalin 300 mg/day	551	5.99	-1.63	0.13	-0.11	[-0.46, 0.24]	0.5414
	Pregabalin 450 mg/day	548	5.65	-1.98	0.13	-0.46	[-0.81, -0.10]	0.0109*
	Pregabalin 600 mg/day	559	5.83	-1.79	0.13	-0.27	[-0.62, 0.08]	0.1296
Work Missed	Placebo	555	2.63	-0.51	0.11			
	Pregabalin 300 mg/day	546	2.41	-0.74	0.11	-0.23	[-0.52, 0.07]	0.1332
	Pregabalin 450 mg/day	548	2.31	-0.83	0.11	-0.32	[-0.61, -0.02]	0.0335*
	Pregabalin 600 mg/day	559	2.40	-0.74	0.11	-0.23	[-0.52, 0.06]	0.1250
Do Work	Placebo	552	5.57	-1.12	0.10			
	Pregabalin 300 mg/day	549	5.33	-1.37	0.10	-0.25	[-0.54, 0.04]	0.0973
	Pregabalin 450 mg/day	549	5.06	-1.63	0.10	-0.51	[-0.80, -0.22]	0.0006*
	Pregabalin 600 mg/day	562	5.25	-1.44	0.10	-0.32	[-0.61, -0.03]	0.0301*
Pain	Placebo	554	6.00	-1.32	0.10			
	Pregabalin 300 mg/day	550	5.73	-1.58	0.10	-0.26	[-0.55, 0.02]	0.0703
	Pregabalin 450 mg/day	550	5.39	-1.93	0.10	-0.61	[-0.90, -0.32]	<.0001*
	Pregabalin 600 mg/day	562	5.62	-1.70	0.10	-0.38	[-0.66, -0.09]	0.0094*
Fatigue	Placebo	554	6.75	-1.11	0.11			
	Pregabalin 300 mg/day	550	6.58	-1.28	0.11	-0.17	[-0.46, 0.12]	0.2555
	Pregabalin 450 mg/day	550	6.39	-1.47	0.11	-0.36	[-0.65, -0.06]	0.0169*
	Pregabalin 600 mg/day	561	6.54	-1.32	0.10	-0.21	[-0.50, 0.08]	0.1514
Rested	Placebo	553	6.58	-1.23	0.11			
	Pregabalin 300 mg/day	550	6.19	-1.62	0.11	-0.39	[-0.70, -0.07]	0.0154*
	Pregabalin 450 mg/day	549	5.95	-1.86	0.11	-0.63	[-0.94, -0.32]	<.0001*
	Pregabalin 600 mg/day	562	5.99	-1.83	0.11	-0.59	[-0.91, -028]	0.0002*
Stiffness	Placebo	554	6.29	-1.36	0.11			
	Pregabalin 300 mg/day	550	6.20	-1.44	0.11	-0.08	[-0.38, 0.21]	0.5813
	Pregabalin 450 mg/day	550	5.95	-1.70	0.11	-0.34	[-0.63, -0.04]	0.0248*
	Pregabalin 600 mg/day	562	6.22	-1.43	0.11	-0.07	[-0.36, 0.22]	0.6400
Anxiety	Placebo	554	4.25	-0.74	0.11			
	Pregabalin 300 mg/day	550	4.05	-0.94	0.11	-0.21	[-0.50, 0.09]	0.1723
	Pregabalin 450 mg/day	550	3.80	-1.19	0.11	-0.45	[-0.75, -0.15]	0.0029*
	Pregabalin 600 mg/day	562	4.03	-0.96	0.11	-0.22	[-0.51, 0.07]	0.1436
Depression	Placebo	552	4.02	-0.57	0.11			
	Pregabalin 300 mg/day	550	3.95	-0.64	0.11	-0.07	[-0.37, 0.23]	0.6544
	Pregabalin 450 mg/day	550	3.65	-0.94	0.11	-0.37	[-0.67, -0.07]	0.0161*
	Pregabalin 600 mg/day	561	3.84	-0.75	0.11	-0.18	[-0.47, 0.12]	0.2483
Total Score	Placebo	557	51.79	-9.93	0.77			
	Pregabalin 300 mg/day	551	49.77	-11.95	0.77	-2.02	[-4.15, 0.11]	0.0635
	Pregabalin 450 mg/day	552	47.54	-14.18	0.77	-4.25	[-6.38, -2.11]	<.0001*
	Pregabalin 600 mg/day	564	49.25	-12.46	0.76	-2.53	[-4.66, -0.41]	0.0194*

- *Results on SF-36 Vitality score and sleep quality*

Assuming that the SF-36 Vitality score is indicative for fatigue and functional outcome, and assuming that a 10 point reduction is clinically important, SF-36- responder rates of 39%, 46%, 45% and 43% for placebo, PGB300, PGB450 and PGB600 respectively hardly point at relevant differences despite statistical significance.

Concerning the effect on sleep, the results were consistent. All three pregabalin treatment groups (300, 450, and 600 mg/day) showed a statistically significant improvement for each of these measures, both in the pooled data, with p-values <0.0001, and in each individual study. However, somnolence is a well-known adverse event of pregabalin and it is unclear as to how this might have impacted on the results.

- *Sub-analysis looking at the independence between pain response and response in multiple symptom domain*

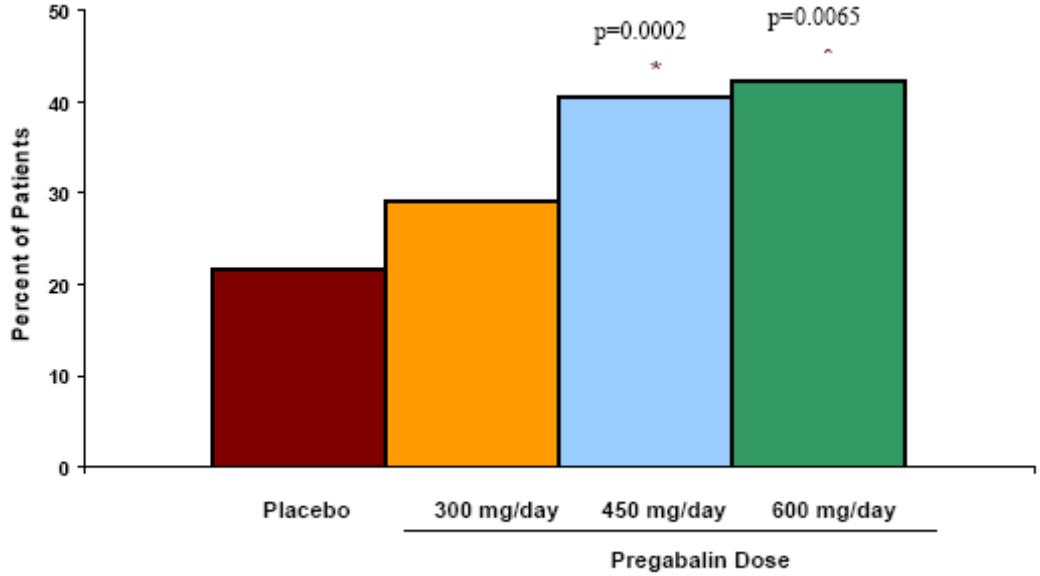
The CHMP was concerned that the effect on multiple symptoms domain could be driven by the effect on pain, especially as the functional improvement remains doubtful in clinical terms. To address this concern, the MAH presented the results obtained from an analysis with Spearman's correlation coefficients. It was shown that there is a moderate correlation (0.4≤ correlation coefficient <0.7) between PGIC and changes in mean pain score, and between PGIC and changes in FIQ total score. PGIC correlations with changes in MOS-Sleep Disturbance Subscale were weak (<0.4). In addition, a Venn diagram analysis evaluating the contributions of pain and sleep improvements to PGIC response (and performed with the SF-36 Vitality subscale being evaluated in the place of FIQ total score) was also presented. The CHMP acknowledged that altogether, the data presented suggest that patient global assessment might be impacted by more than just reduction in pain.

Results in the EU population

The number of subjects from European Union and the extrapolation of results to the European population were of concern to the CHMP, especially as the perception of fibromyalgia, diagnosis and medical management of this condition might differ across regions.

The MAH analysed the results for the European population and concluded that European patients demonstrated statistically significant and clinically meaningful responses to pregabalin treatment across multiple symptom domains of fibromyalgia, including PGIC (figure 1), composite response (table 13), function (table 14) and sleep disturbance (table 15).

Figure 1. Patient Global Impression of Change (PGIC) – European Patients: Very Much or Much Improved at Endpoint



* Statistically significant (p<0.05), based on the results of the CMH procedure
Source: Section 2.7.3, SCE Appended Table EU13.17

Table 13. Composite Responder Status: Improvement of Pain ≥30%, FIQ Total Score ≥16 Points, MOS-SS Sleep Disturbance ≥15.8 Points - European Patients

Treatment Group	Number Assessed	Responder on Any (Pain, FIQ, *or* sleep)			Responder on All (Pain, FIQ, *and* sleep)		
		N	%	Treatment Comparison (p-value)	N	%	Treatment Comparison (p-value)
Placebo	98	49	50.0		5	5.1	
Pregabalin 300 mg/day	93	54	58.1	0.2643	9	9.7	0.2327
Pregabalin 450 mg/day	89	56	62.9	0.0762	17	19.1	0.0055*
Pregabalin 600 mg/day	96	55	57.3	0.3090	10	10.4	0.1744

Source: Section 2.7.3, SCE Appended Tables EU3.8.3.1.1, EU3.8.3.2.1
* p-value <0.05

Table 14. Endpoint Mean FIQ Total Score by Dose – European Patients

Treatment Group	N	Least Squares			Treatment Comparison (Pregabalin – Placebo)		
		Means	Mean Change	SE	Difference	95% CI	p-value
Placebo	98	54.48	-7.24	1.83			
Pregabalin 300 mg/day	93	56.94	-4.77	1.88	2.46	[-2.68, 7.60]	0.3474
Pregabalin 450 mg/day	91	48.69	-13.03	1.90	-5.79	[-10.96, -0.62]	0.0282*
Pregabalin 600 mg/day	96	54.08	-7.63	1.85	-0.39	[-5.50, 4.71]	0.8794

CI = Confidence Interval; SE = Standard Error; * Statistically significant at p<0.05 level.
Scores range from 0 to 100 with higher scores indicating decreased function.
Source: Section 2.7.3, SCE Appended Table EU1.3

Table 15. Endpoint Mean MOS-SS Sleep Disturbance Score by Dose – European Patients

Region/ Treatment Group	N	Least Squares			Treatment Comparison (Pregabalin – Placebo)		
		Means	Mean Change	SE	Difference	95% CI	p-value
Placebo	98	55.81	-6.96	2.49			
Pregabalin 300 mg/day	93	48.72	-14.05	2.56	-7.09	[-14.10, -0.08]	0.0474*
Pregabalin 450 mg/day	89	41.87	-20.91	2.62	-13.95	[-21.04, -6.86]	0.0001*
Pregabalin 600 mg/day	96	38.85	-23.93	2.52	-16.97	[-23.92, -10.01]	<0.0001*

CI = Confidence Interval; SE = Standard Error; * Statistically significant at p<0.05 level
Scores range from 0 to 100 with higher scores indicating worse sleep disturbance.
Source: Section 2.7.3, SCE Appended Table EU1.4

The CHMP observed that results on pain of study 1100, with the EU subpopulation were inconsistent with those of the US studies, and especially when compared to study 1077 having a selected population as well (Table 5). In study 1100, the size effect is considered to be very small on the European population. The mean baseline pain score was 6.65 (SD 1.36) and the mean difference in pain scores with placebo for the 450 mg pregabalin dose is -0.54, and this is the only dose statistically significant different from placebo in this study. It is even lower when the EU population is analysed separately (-0.49). This represents half of the result obtained in study 1077 for the same dose (-0.98). When the 30% and 50% responder analyses are concerned (see table 6), the differences between the 2 studies are respectively of 11.4% (49.5% in study 1077 and 33.1% in study 1100, with statistical significance of the 450 mg/day vs placebo in both studies) and 9.2% (27.4% in study 1077 and 18.2% in study 1100, with statistical significance of the 450mg/day vs placebo in both studies). Of note, the 50% responder rate difference between the 450mg/day dose and placebo is 9% in study 1100 (although statistically significant). The clinical relevance of such a difference is therefore doubtful.

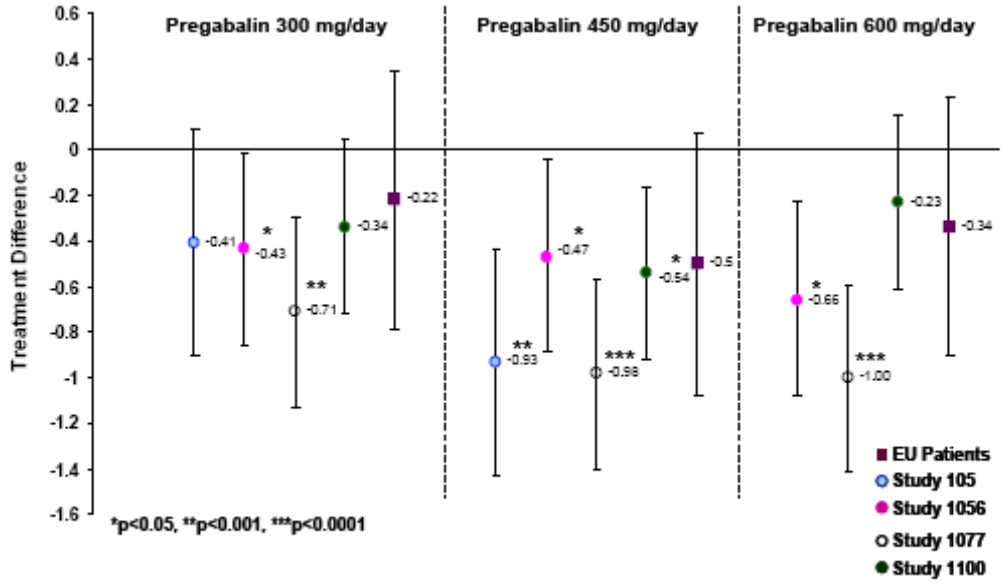
As regards PGIC, the results show better consistency between the 2 studies (see table 7). For the 450 mg dose, the difference of percentage of patients with improvement is 4.5%. However, when the differences between PGB 450 mg and placebo are concerned, the difference in study 1077 is of 30.2% and 17.7% in study 1100 (the difference is statistically significant in both studies). It is acknowledged

that the placebo effect is important in the "European study" as compared to study 1077 (56.2% vs. 47.6%).

As far as functional outcome is concerned, the same remarks as for PGIC can be drawn (see table 9).

The MAH also provided a pooled analysis of study results by region, which showed similarity of effect for multiple domains of fibromyalgia. However, the CHMP noted the substantial difference in size effect between the US and the European population. The impact of variability in the magnitude of effect was further assessed by the MAH by comparing individual study results (Figure 2). For instance, endpoint mean pain scores (placebo-corrected) appear similar for pregabalin 450 mg/day in the United States (Study 1056; -0.47) and Europe (-0.50). However, the European results were not statistically significant and of limited effect size (-0.50).

Figure 2. Improvement in Pain by Dose and Study, and in European Patients



Source: SCE Table 23; SCE Appended Table EU1.1

Overall, the CHMP concluded that for the EU population, the differences in mean pain score and FIQ, and to a lesser extent in PGIC between placebo and pregabalin are not considered consistently clinically meaningful as regards short term efficacy of Lyrica in the claimed indication in Europe.

Consulted by the CHMP, the SAG CNS agreed that the results from the US studies could not be extrapolated to the EU population taking into account the differences in results. Patients in the studies were not phenotypically well defined and therefore overlap with other syndromes and symptoms cannot be excluded. The SAG was not convinced that the MAH has set up the studies to ensure similar balance of patients in different geographic regions. The different result in the EU population cannot be overlooked and further studies might be required in a population that is ensured to be phenotypically equivalent.

Results on maintenance of treatment effect – Study 1059

Study 1059 was designed as a maintenance of treatment effect study, in which responders to open-label treatment at 6 weeks were randomized in a double-blind fashion to continue pregabalin or to receive placebo treatment for 6 months. All patients enrolled in Study 1059 were given pregabalin at their optimized dose (optimized during the first 3 weeks of open-label treatment) through the end of a 6-week open-label treatment phase. For randomization, patients were required to meet the definition of a responder (≥50% reduction in pain from baseline as assessed on VAS and a PGIC rating of "much improved" or "very much improved" during Weeks 4 or 5 and 6). Eligible patients were then

randomly assigned to continue treatment with pregabalin at their optimized dose or to receive placebo. Patients randomized to placebo treatment were tapered off pregabalin in a blinded manner over the first week of double-blind treatment. Double-blind treatment continued up to 6 months or until patients met the study exit criteria which defined the loss of therapeutic response (LTR).

The primary efficacy endpoint was the time to loss of therapeutic response, which was based on the Pain VAS or investigator judgment. The secondary objectives were: to evaluate the efficacy of pregabalin compared with placebo treatment to relieve pain and to improve global assessment, functional status, sleep, and fatigue associated with fibromyalgia. Results for the primary endpoint are illustrated in table 15 and figure 3.

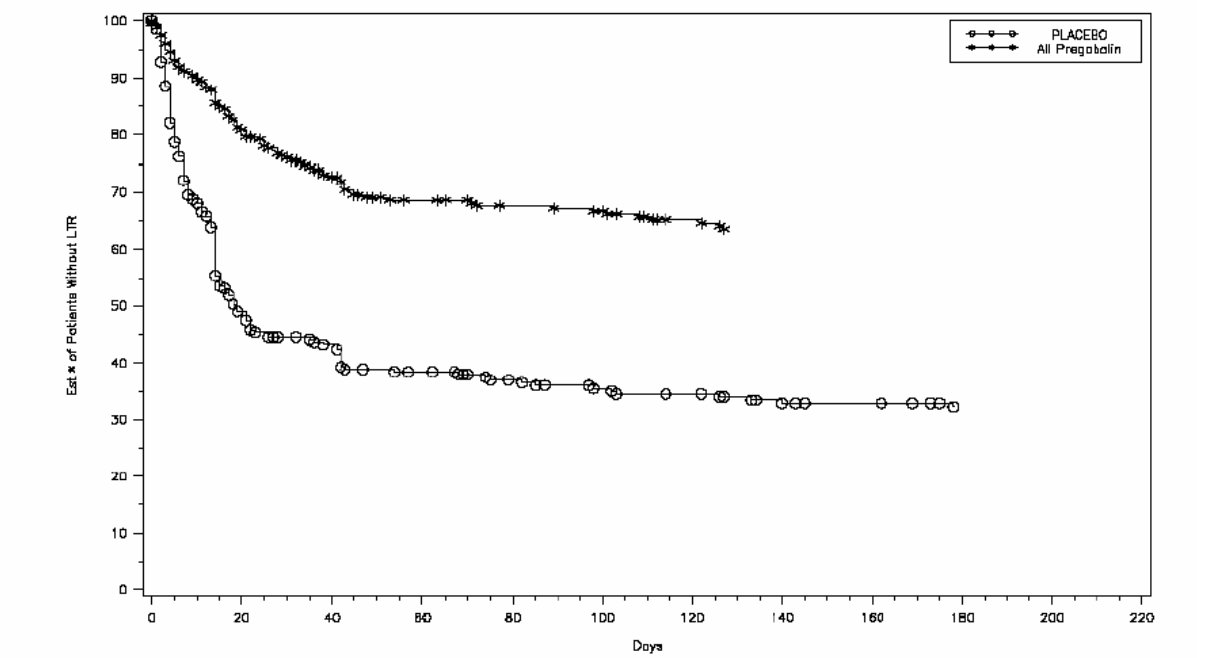
Table 16: Summary of Kaplan-Meier estimates of time to loss of therapeutic response for VAS pain.

Treatment	N	Time to LTR (days)				p-value, comparison with placebo in time to LTR (log-rank test)	Failed‡	Censored†	Percent censored
		1st Quartile*	95% CI	Median	95% CI				
Placebo	287	7	5 – 9	19	14 – 36		174	113	39.4
All pregabalin	279	34	21 – 48	NA	NA	p < 0.0001	90	189	67.7

Source: Table 13.4.9.1

* one quarter of subjects lost therapeutic response by the day listed.
‡ failed = experienced an LTR
† censored = an LTR event not reported.
CI (confidence interval); LTR (loss of therapeutic response); NA (not applicable)

Figure 3: Kaplan-Meier plot of time (days) to loss of therapeutic response.



During the 6-month double-blind maintenance phase, time to loss of therapeutic response was significantly longer for subjects treated with pregabalin compared with those treated with placebo ($p<0.0001$). Based on Kaplan-Meier estimates of time-to-event, 25% of placebo-treated subjects recorded loss of therapeutic response at day 7. On day 34, 25% of pregabalin treated subjects reported loss of efficacy. A total of 174/287 (61%) placebo-treated patients lost therapeutic response compared with 90/279 (32%) of pregabalin-treated patients over the 6 months.

The CHMP observed that the rapid fall of proportion of the subjects without LTR under pregabalin does not substantiate the maintenance of effect despite the fact that for placebo this fall was even more rapid. After this initial drop of the Kaplan-Meier curves, there is almost no additional failure either in the placebo or in the pregabalin group. This and the lack of further divergence of the Kaplan-Meier curves, i.e. worsening under placebo, are implausible. The placebo group was expected to further deteriorate. However, the placebo effect appears to be considerable in this particular population.

During the re-examination, the MAH argued that a possible factor in the initial rate of LTR following randomization is that patients were aware of the randomization to double-blind treatment at the end of the open-label phase, with 50% of patients receiving placebo from that point onward. Therefore, patients may have been more likely at that time to perceive any change in symptoms as being due to a switch to placebo treatment, potentially affecting their perception of pain symptoms. By contrast, patients who had participated in the double-blind phase for a longer period of time were aware that their treatment had not been changed recently, and therefore were less likely to perceive symptom changes as resulting from a change in treatment. The MAH also pointed out that similar Kaplan-Meier response profiles are observed across the pain randomized withdrawal design in pain (tramadol in the treatment of fibromyalgia), anxiety (GAD Lyrica), and depression (relapse prevention studies) literature.

The SAG agreed that the early loss of effect is difficult to explain and it is unclear as to how physical and psychological features might have influenced the loss of efficacy. The SAG expressed concerns over the blinding and how it could affect psychiatric comorbidities. Beside, a nocebo effect cannot be excluded if patients believed to have been put on placebo arm (again proving the high placebo effect). The SAG also noted that responders to active treatment were randomised to continue active treatment or receive placebo. This creates a rather enriched and compliant population which is not representative of the fibromyalgia population.

Finally, as study 1059 was performed in the US maintenance of the effect in the EU population has therefore not been established. This is even more unfortunate in view of the lack of demonstration of consistent and clinically relevant short term effect of Lyrica in the treatment of fibromyalgia, as shown by the rather small effect size on pain and functional improvement, especially on EU patients.

Proposed indication in treatment of fibromyalgia in adults experiencing moderate to severe pain

The original indication claimed within the present application was treatment of fibromyalgia in adults. The MAH suggested a modified indication specific to the clinical trial population studied in the pregabalin fibromyalgia clinical development program. Although the MAH support the position that pregabalin should be indicated for treatment of fibromyalgia, they believed that this modified version of the indication would be consistent with the clinical trial population in which significant relevant benefit has been demonstrated. Asked about whether pain in fibromyalgia might be from neuropathic origin, the SAG CNS concluded that there is no evidence of a primary neurological cause for fibromyalgic pain. It is not excluded that the pain might be nociceptive in origin but this is not proven. A subset of patients might have had pain of neuropathic origin in spite of the exclusion criteria of the study, but this would not be valid for the general fibromyalgia population. Based on the above and the known modulator effect of pregabalin on neuropathic pain, the CHMP disagreed with the modified indication proposed by the MAH.

1.3.3 Clinical safety

Patient exposure

In the combined controlled and uncontrolled studies in patients with fibromyalgia, 3446 patients were exposed to pregabalin of whom 2081 (60.4%) prematurely withdrew from treatment. The disposition of subjects in the controlled studies is summarized in table 17.

Table 17: Summary of Patient Disposition: Controlled Fibromyalgia Studies

Patient Status	**Placebo N=689**	**Pregabalin 150 mg/day N=132**	**Pregabalin 300 mg/day N=685**	**Pregabalin 450 mg/day N=687**	**Pregabalin 600 mg/day N=564**
	%	%	%	%	%
Completed study	71.6	78.0	70.1	69.6	61.2
Discontinued study	28.4	22.0	29.9	30.4	38.8
Insufficient response	6.7	9.1	2.9	2.5	2.0
Adverse event	10.4	8.3	16.4	20.2	28.2
Protocol violation	0.3	0.8	0.6	0.6	0.0
Lost to follow-up	3.2	0.0	3.5	2.2	2.5
Withdrew consent	1.9	0.0	2.6	1.6	3.4
Other	6.0	3.8	3.9	3.3	2.8
Duration of exposure	Days	Days	Days	Days	Days
Median	91	56	90	90	91
Range	1-122	1-71	1-132	1-127	1-119

Adverse events

The global safety profile of pregabalin in the fibromyalgia clinical program is summarised in table 18.

Table 18: Global Safety Profile of Pregabalin in fibromyalgia

	Controlled Studies		Controlled + Uncontrolled Studies
Patient Category	Placebo N=689	Pregabalin All N=2068	Pregabalin All N=3446
Any AE	74.5%	88.2%	90.0%
Any SAE	1.6%	1.6%	2.8%
Any severe AE	10.2%	15.2%	19.4%
Death	0.0%	0.0%	0.1%*
Discontinued due to AEs	10.9%	20.4%	25.1%
Dose reduction or temporarily interrupted due to AEs	2.9%	5.1%	15.4%

The overall frequency of adverse events reported in the pregabalin treatment group was higher than that in the placebo treatment group and this frequency increased with increasing dose. The most common treatment-emergent adverse events experienced by pregabalin-treated patients were dizziness, somnolence, headache and weight increased. As regards dose distribution, the respective percentages for the 300 mg/day, 450 mg/day and 600 mg/day were the following: Dizziness (32.6%, 42.5% 46.5%), somnolence (18.5%, 19.9%, 20.7 %%), weight increase (11.1%, 10.9%, 13.7%). Median time onset of AE varied from less than a week to more than 3 weeks.

Table 19 Adverse Events > 2% of : Controlled Fibromyalgia Study					
	Placebo	**Pregabalin**			
		150 mg/day	**300 mg/day**	**450 mg/day**	**600 mg/day**
n	**689**	**132**	**685**	**687**	**564**
	%	%	%	%	%
Any adverse event	74.5	78.0	**85.7**	**90.2**	**91.3**
Dizziness	10.4	**22.7**	**32.6**	**42.5**	**46.5**
Somnolence	4.6	**12.9**	**18.5**	**19.9**	**20.7**
Headache	13.1	11.4	12.4	13.7	9.6
Weight increased	2.5	**7.6**	**11.1**	**10.9**	**13.7**
Dry mouth	1.7	**6.8**	**6.7**	**9.2**	**9.4**
Fatigue	5.4	4.5	7.2	8.4	8.2
Nausea	8.7	9.1	8.2	5.7	9.0
Oedema peripheral	2.5	**5.3**	**6.7**	**6.4**	**10.8**
Vision blurred	1.0	**8.3**	**5.8**	**6.4**	**10.1**
Constipation	2.8	3.8	**5.8**	**6.8**	**9.2**
Attention disturbances	1.3	**3.8**	**4.4**	**6.4**	**6.9**
Balance disorder	0.1	**1.5**	**3.2**	**4.9**	**6.9**
Nasopharyngitis	4.6	4.5	5.1	4.2	4.1
Euphoric mood	0.9	1.5	**4.1**	**4.8**	**5.1**
Increased appetite	1.3	**3.8**	**3.4**	**4.5**	**5.5**
Influenza	4.8	4.5	3.8	0.5	4.8
Sinusitis	3.0	3.8	3.6	5.2	4.1
Diarrhoea	6.1	1.5	4.7	4.1	4.4
Arthralgia	2.5	3.8	3.6	3.2	4.6
Back pain	3.2	2.3	3.2	4.2	3.5
IRTI	4.8	1.5	2.8	3.9	4.1
Muscle spasms	1.9	2.3	3.4	3.3	3.2
Vomiting	2.5	2.3	2.8	2.8	2.5
Hypoaesthesia	0.6	**1.5**	**2.0**	**2.8**	**2.3**
Pain in extremity	1.9	0.8	2.2	0.9	2.1
Depression	1.9	1.5	2.0	2.5	2.0
Abdominal distension	1.5	2.3	2.2	1.9	2.0
Anxiety	0.9	1.5	**1.9**	**2.5**	**1.8**
Confusional state	0.1	0.0	**2.0**	**1.9**	**2.7**
Fluid retention	0.7	**1.5**	**2.2**	**2.0**	**2.0**
Pharyngolaryngeal pain	1.6	1.5	1.0	2.0	3.2
Tremor	0.6	0.0	0.6	**2.9**	**3.0**

Serious adverse events and deaths

Overall, 34 (1.6%) of the 2068 pregabalin-treated patients (controlled studies) experienced serious adverse events compared to 11 (1.6%) of the 689 placebo-treated patients. Four deaths were reported in the clinical studies but none was related to pregabalin treatment. The rate of severe adverse events is also reduced when a lower dose range of pregabalin 300-450 mg/day (as opposed to 300-600 mg/day) is considered. Across the pregabalin doses, the frequency of severe adverse events generally increased with increasing dose from 12.9% (150 mg/day) to 15.6% (300 mg/day), to 13.8% (450 mg/day), to 16.8% (600 mg/day).

Laboratory findings

The overall pattern of changes in clinical laboratory values was similar among the controlled and the combined controlled and uncontrolled studies and no new clinical laboratory findings of concern were identified with longer-term pregabalin treatment. However, there were four cases of pregabalin-treated patients participating in controlled studies who discontinued treatment due to abnormal clinical

laboratory test i.e. elevated alanine aminotransferase (ALT; 71 IU/L under pregabalin 600 mg daily, possibly related), elevated levels of aspartate aminotransferase (AST) and ALT (pregabalin 600 mg daily, possibly related), abnormally high liver function tests (AST=77 IU/L, ALT=98 IU/L, on pregabalin 600 mg daily, although possibly related) and mild neutropenia (Pregabalin 150-mg, recovered).

Safety in special populations

The safety profile of pregabalin among elderly patients with fibromyalgia participating in the controlled studies was generally comparable with that among younger patients, with some adverse events reported at higher frequencies among elderly patients (eg, dizziness, edema peripheral, fatigue, vision blurred, balance disorder, tremor) and some adverse events reported at higher frequencies among non-elderly patients (e.g. disturbance in attention, euphoric mood, memory impairment, anxiety, depression, disorientation).

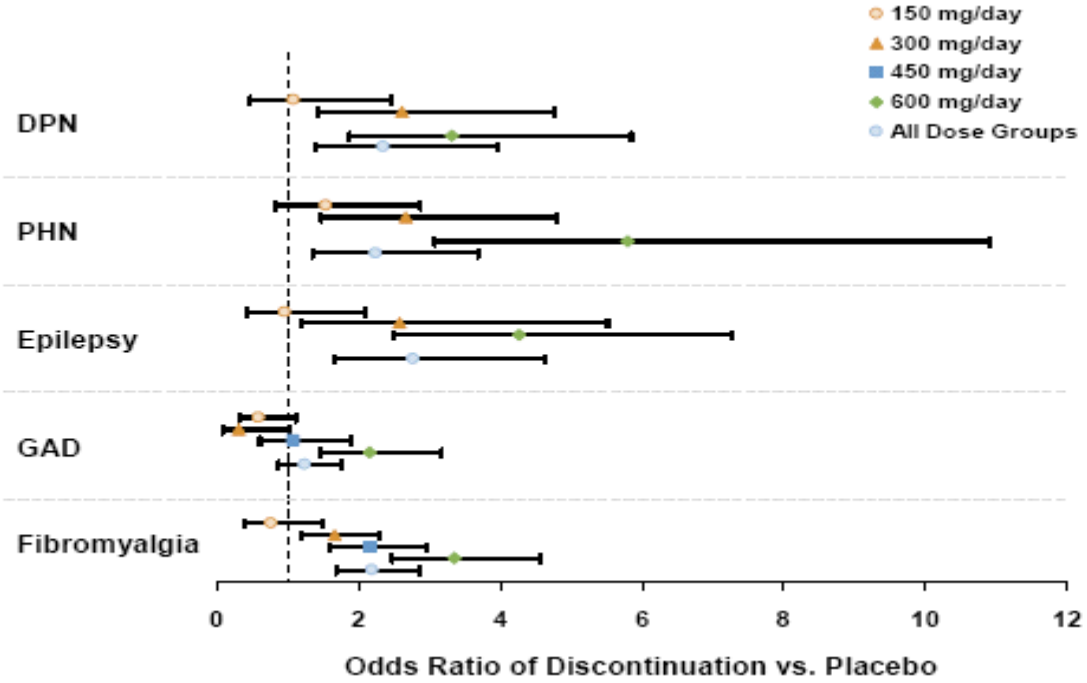
Discontinuation due to AES

Discontinuation rate due to adverse events in pregabalin-treated patients was higher in the combined controlled and uncontrolled studies (25.1%) than that in the controlled studies (20.4%). In the controlled studies, the frequency of withdrawals among pregabalin-treated patients (20.4%) was approximately double that among placebo-treated patients (10.9%). Of note, it is currently mentioned under section 4.8 of the approved SPC for Lyrica that in all controlled studies, the discontinuation rate due to adverse reactions was 13% for patients receiving pregabalin and 7% for patients receiving placebo. This rate is lower than in fibromyalgia studies. Therefore, the MAH's conclusion that fibromyalgia patients have a similar likelihood of discontinuing due to adverse events relative to placebo as compared with the other indications treated with pregabalin is questionable. However, this incidence maybe considered high due to the fact that fibromyalgic patients are more reactive to stress and have a spontaneously high rate of complaints which might impact negatively on their motivation to remain in a clinical study environment. This is also observed to a lesser extent in the placebo treated patients. As regards dose distribution, the discontinuations rates were 10.4%, 8.3%, 16.4%, 20.2% and 28.2% for placebo, pregabalin 150 mg/day, 300 mg/day, 450 mg/day and 600 mg/day respectively.

During pregabalin treatment phase in the 6-month maintenance of effect Study 1059, the frequency of patient discontinuations due to adverse events (25.0%), treatment-related adverse events (20.9%), and serious adverse events (1.0%) were almost identical to those in the combined controlled and uncontrolled studies. Events with a withdrawal rate ≥1% were Dizziness (5.9%), Somnolence (3.5%), Weight increase (1.7%), Nausea (1.5%), Fatigue (1.2%), Headache (1.2%) and disturbances in attention (1.1%).

Although similar in nature to those observed in previously approved indications, the CHMP has expressed concern over the rate of withdrawals due to adverse events in the fibromyalgia studies. The overall safety and tolerability data indicate that fibromyalgia patients are likely to discontinue due to adverse effects when treated with pregabalin at rates consistent with that for other approved indications. Fibromyalgia patients appear more prone to discontinue due to adverse events even when treated with placebo. When the discontinuation rates due to adverse events with pregabalin are examined relative to the incidence rates with placebo treatment, the relative rates are similar across indications (figure 4).

Figure 4. Discontinuation due to Adverse Events by Dose Group and Indication: Odds Ratio vs. Placebo and 95% Confidence Intervals



DPN – Diabetic Peripheral Neuropathy; PHN – Postherpetic neuralgia; GAD – Generalized Anxiety Disorder;

The overall safety profile does not appear very different for fibromyalgia patients than for patients treated with pregabalin for neuropathic pain, epilepsy and anxiety. During the re-examination, the MAH proposed a new dose range of pregabalin 300-450 mg/day, excluding the 600 mg/day dose to allow for a lower incidence of adverse events compared with pregabalin 600 mg/day. It is uncertain that all adverse events are dose dependent but it appears that with respect to the three most commonly reported ADRs (dizzines, somnolence and weight gain) the ADR rates are lower over the dose range of 300-450 mg/day vs. 600 mg/day.

Risk Management plan

The MAH submitted an updated version of the RMP (version 4.0, dated March 2008). However, as this indication was not approved, the assessment of the updated RMP is not relevant.

User testing

A user testing performed by the MAH was submitted with this extension of indication application. However, as this indication was not approved, the assessment of the user testing is not relevant.

However, the MAH indicated that the same key safety issues, same dosing scheme, route of administrations, contra-indications, warnings and side effects apply to the indication fibromyalgia as for the other approved indications, and these issues have already been tested in the leaflet with reference to the currently approved indications. Therefore, the CHMP agreed with the MAH that no new user testing round is considered necessary.

1.3.4 Conclusions and Benefit / Risk Assessment

Four pivotal short-term studies and a long-term maintenance study were provided to support this application.

In the pooled results, the 50% responder rates difference between pregabalin all dose treatment groups and placebo is of 8.6%. Whether this difference is clinically significant is questionable.

When the results on primary efficacy analyses of each individual study are concerned, the size effect is considered to be inconsistent and small. The US Studies 1056 and 1077 show a consistent dose response effect which is not observed in study 1100, the only study containing European patients .

In study 1100, the mean baseline pain score was 6.65 (SD 1.36) and the mean difference in pain scores with placebo for the 450 mg pregabalin dose is -0.54. This is the only dose statistically significant different from placebo in this study.

For 2 of the 3 US studies (studies 1056 and 1077), the results showed a statistically significant improvement of pain scores and are consistent within the 3 doses. However, the mean difference in pain scores with placebo was 1 point (only for the 600 mg dose that is no more proposed by the MAH) or less for the other doses on an 11-point pain-scale. This is considered a small magnitude of effect.

When the >50% responder rate is considered for each individual studies, it was higher for pregabalin 300 and 450 mg/day than for placebo treatment. Although this difference was statistically significant in 2 studies out of 3, the responder rates differ only about 8-12% (study 1100 and 1077).

The CHMP is of the opinion that stringent consistency of secondary measures with the primary outcome variables was not demonstrated, especially on the Fibromyalgia Impact Questionnaire (FIQ), the functional outcome of fibromyalgia. The significant differences in mean pain score, PGIC and FIQ between placebo and pregabalin are not considered clinically meaningful. Pregabalin is already recognized for having an effect on neuropathic pain. However, it was not demonstrated that there is a short-term effect (pain and functional outcome) in the specific indication of fibromyalgia.

The CHMP also considered that a clear dose response effect was not observed. On the primary efficacy analysis, pregabalin dose of 450 mg/day was statistically significant different from placebo in the three pivotal studies. A statistically significant reduction in pain scores was demonstrated with the dose of 300 mg/day in two of the four studies and with the 600 mg/day dose. For the 600 mg dose, results are inconsistent across the studies, especially in the study including EU patients. In addition, on the functional aspect of the indication, the results of the pivotal studies in the overall FIQ score are more or less consistent for the 450 mg/day dose. These results were even less consistent for pregabalin 300 and 600 mg/day. No dose response relationship could be shown. It is however acknowledged that the MAH proposed to remove the 600 mg dose as a dosing regimen option and put the maximum optimal dose at 450 mg/day.

An additional concern was the lack of a demonstrated maintenance of the effect.

As far as the EU population is concerned, the differences in mean pain score and FIQ and to a lesser extent in PGIC between placebo and pregabalin are not considered consistently clinically meaningful as regards short term efficacy of Lyrica in the claimed indication. Furthermore, maintenance of the effect in the EU population has not been established. It is therefore considered that proof of efficacy of pregabalin specifically in the European fibromyalgia population has not been demonstrated.

The known safety profile of pregabalin, the high discontinuation rate due to adverse events and the considerable placebo effect in the overall development programme for fibromyalgia appearing to be somewhat related to this specific population, are not counterbalanced by a significantly clinical meaningful effect of the product in the claimed indication.

The MAH's grounds for re-examination, provided by the MAH on 22 June 2009, were divided into 5 major parts, according to the grounds for refusal adopted on 23 April 2009. These were related to the short-term efficacy, the dose-response relationship, the maintenance of effect, the safety and efficacy in a representative EU population, the known adverse events and the clinical relevance of the effect size and overall benefit/risk.

The above-mentioned information could not change the previous view of the CHMP.

II. CONCLUSION

On 23 July 2009 the CHMP considered this Type II variation not to be acceptable on the following grounds:

- 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;

Therefore, on the basis of the current available efficacy and safety data, the CHMP considered that the benefit/risk of Lyrica in the treatment of fibromyalgia in adults experiencing moderate to severe pain is unfavourable.