

**Clinical trial results:****Prospective Randomised 12-Week Controlled Study of Visual Field Change in Subjects With Partial Seizures Receiving Pregabalin or Placebo****Summary**

EudraCT number	2009-014269-25
Trial protocol	HU CZ PL BG
Global end of trial date	04 February 2020

**Results information**

Result version number	v1 (current)
This version publication date	17 February 2021
First version publication date	17 February 2021

**Trial information****Trial identification**

Sponsor protocol code	A0081096
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00351611
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

**Paediatric regulatory details**

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 October 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	04 February 2020
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate visual fields in subjects with partial epilepsy receiving 12 weeks treatment of pregabalin compared to placebo.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 July 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 10
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	India: 30
Country: Number of subjects enrolled	Korea, Republic of: 33
Country: Number of subjects enrolled	Mexico: 3
Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Thailand: 11
Country: Number of subjects enrolled	United States: 86
Worldwide total number of subjects	187
EEA total number of subjects	24

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	186
From 65 to 84 years	1
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

This study was conducted in multiple sites from 26-Jul-2006 to 04-Feb-2020. This study used an Internal Review Committee (IRC).

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Subject

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Pregabalin

Arm description:

Subjects were randomised to receive pregabalin. In Week 1 (titration), subjects received pregabalin 150 milligram (mg) per day (mg/day) as 75 mg oral capsules twice daily. From Week 2 to 12, subjects received pregabalin 300 mg/day as 150 mg oral capsules twice daily. In Week 13 (tapering), subjects received 150 mg/day as 75 mg oral capsules twice daily. Subjects were followed up from Week 14 to 15. If subjects not tolerated 300 mg/day dose, they were discontinued from the study.

Arm type	Experimental
Investigational medicinal product name	Pregabalin
Investigational medicinal product code	PD-0144723
Other name	CI-1008
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

In Week 1, subjects received pregabalin 150 mg/day as 75 mg oral capsules twice daily. From Week 2 to 12, subjects received pregabalin 300 mg/day as 150 mg oral capsules twice daily. In Week 13, subjects received 150 mg/day as 75 mg oral capsules twice daily.

<b>Arm title</b>	Placebo
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Arm description:

Subjects with were randomised to receive placebo matched to pregabalin for Week 1 to 13 and were followed up from Week 14 to 15.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo matched to pregabalin from Week 1 to 13.

<b>Number of subjects in period 1</b>	Pregabalin	Placebo
Started	89	98
Completed	75	88
Not completed	14	10
Adverse event, serious fatal	1	-
Adverse event, non-fatal	11	3
No Longer Willing to Participate in Study	-	5
Unspecified	1	-
Lost to follow-up	1	-
Protocol deviation	-	2

## Baseline characteristics

### Reporting groups

Reporting group title	Pregabalin
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Reporting group description:

Subjects were randomised to receive pregabalin. In Week 1 (titration), subjects received pregabalin 150 milligram (mg) per day (mg/day) as 75 mg oral capsules twice daily. From Week 2 to 12, subjects received pregabalin 300 mg/day as 150 mg oral capsules twice daily. In Week 13 (tapering), subjects received 150 mg/day as 75 mg oral capsules twice daily. Subjects were followed up from Week 14 to 15. If subjects not tolerated 300 mg/day dose, they were discontinued from the study.

Reporting group title	Placebo
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Reporting group description:

Subjects with were randomised to receive placebo matched to pregabalin for Week 1 to 13 and were followed up from Week 14 to 15.

Reporting group values	Pregabalin	Placebo	Total
Number of subjects	89	98	187
Age categorial Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	88	98	186
From 65-84 years	1	0	1
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	38.1	39.1	
standard deviation	± 12.1	± 11.6	-
Sex: Female, Male Units: Subjects			
Female	44	46	90
Male	45	52	97
Race/Ethnicity, Customised Units: Subjects			
White	47	51	98
Black	4	5	9
Asian	34	40	74
Others	4	2	6

## End points

### End points reporting groups

Reporting group title	Pregabalin
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Reporting group description:

Subjects were randomised to receive pregabalin. In Week 1 (titration), subjects received pregabalin 150 milligram (mg) per day (mg/day) as 75 mg oral capsules twice daily. From Week 2 to 12, subjects received pregabalin 300 mg/day as 150 mg oral capsules twice daily. In Week 13 (tapering), subjects received 150 mg/day as 75 mg oral capsules twice daily. Subjects were followed up from Week 14 to 15. If subjects not tolerated 300 mg/day dose, they were discontinued from the study.

Reporting group title	Placebo
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Reporting group description:

Subjects with were randomised to receive placebo matched to pregabalin for Week 1 to 13 and were followed up from Week 14 to 15.

### Primary: Percentage of Subjects With a Decrease ( $p < 0.05$ ) From Baseline in Threshold Value in any 5 or More Points in Humphrey 24-2 Swedish Interactive Threshold Algorithm (SITA) Standard Testing at Week 12 or Early Termination

End point title	Percentage of Subjects With a Decrease ( $p < 0.05$ ) From Baseline in Threshold Value in any 5 or More Points in Humphrey 24-2 Swedish Interactive Threshold Algorithm (SITA) Standard Testing at Week 12 or Early Termination
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End point description:

Percentage of subjects is reported, with a decrease in threshold value from baseline to Week 12 or termination in any 5 or more points (in either eye) at the  $p < 0.05$  level repeated in same 5 points on subsequent computerized automated perimetry testing. It was derived from Humphrey 24-2 SITA standard visual field analyzer. For each eye there were 52 test points. For each test point, Humphrey analyzer determined threshold value for sensitivity to light by subject. In addition, for each points, test provided probabilities ( $p < 0.05$ ,  $p < 0.02$ , etc) that a subject with normal vision of same age would have same result, i.e., that measured value at that point was at or below respective percentile of age-specific empiric distribution at that position of field for normal subjects. Per protocol population: all subjects randomized to treatment who received at least 1 dose of study medication and excluded subjects with decrease in at least 5 points at termination but did not return for repeat test.

End point type	Primary
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End point timeframe:

Baseline, Week 12 or Early Termination (any time up to Week 12)

End point values	Pregabalin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78	90		
Units: Percentage of subjects				
number (not applicable)	3.8	5.6		

### Statistical analyses

Statistical analysis title	Pregabalin versus Placebo
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Statistical analysis description:

A 2-sided 95 percent (%) confidence interval (CI) on the difference in percentage of subjects, between

pregabalin and placebo was constructed using unconditional exact methods.

Comparison groups	Pregabalin v Placebo
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[1]</sup>
Parameter estimate	Difference in percentage of subjects
Point estimate	-1.7094
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.1751
upper limit	5.9784

Notes:

[1] - Non-inferiority was demonstrated if the upper CI bound was less than 0.10 (10%).

### Secondary: Change From Baseline in Mean Deviation Score From Humphrey Threshold Test at Week 12 or Early Termination

End point title	Change From Baseline in Mean Deviation Score From Humphrey Threshold Test at Week 12 or Early Termination
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End point description:

Mean Deviation (MD) is a global index of visual field depression. The MD ranges from 0 decibels (dB) (no defect) to about -32 dB (end-stage damage), higher scores indicate worse condition. It is derived from Humphrey 24-2 SITA Standard visual field analyzer. Change in mean deviation from baseline to Week 12 or termination was computed for each subject. As planned, for each subject, the worst eye (eye with the greatest decrease in mean deviation) was used in the analysis and data is reported for same. ITT population included all subjects randomised to treatment, who received at least 1 dose of study medication. Here, "Number of Subjects Analysed" refers to those subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 12 or Early Termination (any time up to Week 12)

End point values	Pregabalin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	96		
Units: Decibels				
least squares mean (standard error)	-0.339 (± 0.1467)	-0.214 (± 0.1321)		

### Statistical analyses

Statistical analysis title	Pregabalin versus Placebo
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Statistical analysis description:

Analysis of covariance (ANCOVA) with treatment and center in the model and the baseline mean deviation as the covariate was used to construct a 2-sided 95% CI on the difference in least squares (LS) means between pregabalin and placebo.

Comparison groups	Pregabalin v Placebo
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Number of subjects included in analysis	179
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[2]</sup>
P-value	= 0.4414
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-0.125
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.443
upper limit	0.194

Notes:

[2] - Non-inferiority with respect to mean deviation was demonstrated if the lower bound of the CI is greater than -2.0 decibels.

### Secondary: Change From Baseline in Visual Acuity at Week 12 or Early Termination

End point title	Change From Baseline in Visual Acuity at Week 12 or Early Termination
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End point description:

Visual acuity best-corrected (with glasses or best possible glasses prescription) was measured using early treatment diabetic retinopathy study (ETDRS) charts. There were 2 ETDRS charts. The letters on chart A were read using the right eye and on chart B using the left eye. The subjects started from the top of the chart to down. The subjects read down the chart until they reached a row where a minimum of 3 letters on a line could not be read. The subjects were scored by number of letters identified correctly. Range was from 0 to 70, with higher scores indicate better visual acuity. As planned, for each subject, the worst eye (eye with the greatest decrease in visual acuity) was used in the analysis and data is reported for same. ITT population included all subjects randomised to treatment, who received at least 1 dose of study medication. Here, "Number of Subjects Analysed" refers to those subjects who were evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Week 12 or Early Termination (any time up to Week 12)

End point values	Pregabalin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	94		
Units: Letters identified correctly				
least squares mean (standard error)	-1.890 (± 0.5515)	-0.990 (± 0.5057)		

### Statistical analyses

Statistical analysis title	Pregabalin versus Placebo
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Statistical analysis description:

ANCOVA with treatment and center in the model and the baseline visual acuity as the covariate was used to construct a 2-sided 95% confidence interval on the difference in LS means between pregabalin and placebo.

Comparison groups	Pregabalin v Placebo
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Number of subjects included in analysis	177
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1346
Method	ANCOVA
Parameter estimate	Difference in LS mean
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.083
upper limit	0.283

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 15

Adverse event reporting additional description:

Same event may appear as both an adverse event and serious adverse event. However, what is presented are distinct events. An event may be categorised as serious in 1 subject and as non-serious in another, or a subject may have experienced both a serious and non-serious event. Safety was evaluated on safety analysis set.

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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### Reporting groups

Reporting group title	Pregabalin
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Reporting group description:

Subjects were randomised to receive pregabalin. In Week 1 (titration), subjects received pregabalin 150 mg/day as 75 mg oral capsules twice daily. From Week 2 to 12, subjects received target dose of pregabalin, 300 mg/day as 150 mg oral capsules twice. In Week 13 (tapering), subjects again received 150 mg/day as 75 mg oral capsules twice daily. If subjects could not tolerate 300 mg/day dose, they were discontinued from the study. Subjects were followed up from Week 14 to 15.

Reporting group title	Placebo
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Reporting group description:

Subjects were randomised to receive placebo matched to pregabalin for Week 1 to 13 and were followed up from Week 14 to 15.

<b>Serious adverse events</b>	Pregabalin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 89 (4.49%)	1 / 98 (1.02%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Nervous system disorders			
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 89 (1.12%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postictal state			
subjects affected / exposed	1 / 89 (1.12%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			

subjects affected / exposed	1 / 89 (1.12%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Pregnancy, puerperium and perinatal conditions</b>			
Ectopic pregnancy			
subjects affected / exposed	0 / 89 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Respiratory, thoracic and mediastinal disorders</b>			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 89 (1.12%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
<b>Psychiatric disorders</b>			
Major depression			
subjects affected / exposed	1 / 89 (1.12%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 89 (1.12%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
Pneumonia			
subjects affected / exposed	1 / 89 (1.12%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 4 %

<b>Non-serious adverse events</b>	Pregabalin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 89 (37.08%)	13 / 98 (13.27%)	

Investigations Weight increased subjects affected / exposed occurrences (all)	5 / 89 (5.62%) 5	2 / 98 (2.04%) 2	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	20 / 89 (22.47%) 25	3 / 98 (3.06%) 3	
Headache subjects affected / exposed occurrences (all)	3 / 89 (3.37%) 4	5 / 98 (5.10%) 6	
Somnolence subjects affected / exposed occurrences (all)	7 / 89 (7.87%) 7	3 / 98 (3.06%) 3	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	6 / 89 (6.74%) 6	3 / 98 (3.06%) 3	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 October 2006	Increase in the number of centers participating from 10 to 15. Eliminate weight restriction enrollment criteria. Increase the screening period from 1 week to 21 days.
12 August 2009	Protocol template language updated to current SOP protocol template. Increase in the number of centers participating from 15 to 60. Removal of exclusion of subjects with prior treatment with pregabalin. Exclusion of subjects with history of pregabalin intolerance and subjects with a history of intolerability to pregabalin, or with a history of insufficient response in the treatment of epilepsy. Change of concomitant medication exclusion from exclusion of CNS active medications to exclusion of psychotropic compounds. Addition of safety assessments using the Sheehan-Suicidality Tracking Scale and the Patient Health Questionnaire-8.
12 December 2011	To add new safety wording. To allow for rescreening of subjects. To add clarification around the timing of the visual field testing (VFT) and handling of the primary endpoint as an AE. Also clarification of prohibited and allowed concomitant medications; and documentation of adverse events related to changes from entry in vital signs, weight and on the physical exam. PASS language added, Subject Selection, Compliance, DMC text added.

15 December 2015	<p>Single Reference Safety Document (SRSD) for this study was changed from the Core Data Sheet (CDS) to the Investigators Brochure (IB). The following changes were made to comply with FDA and Neuropsychiatric and Abuse Potential Advisory Council (NAPAC) Guidance:</p> <ul style="list-style-type: none"> <li>• Suicidality assessment: the Columbia-Suicide Severity Rating Scale (C-SSRS) will be performed instead of the Sheehan-Suicidality Tracking Scale (S-STTS) for subjects screened following approval/initiation of Amendment 4. Subjects who are randomized under Amendment 3 will not switch to the C-SSRS.</li> <li>• Suicidal Behaviors Questionnaire-Revised (SBQ-R) will be performed at screening.</li> <li>• Scoring instructions for the PHQ8 have been inserted as well as a reference to the Instruction Manual.</li> </ul> <p>The following protocol exclusion has been inserted to increase subject safety:</p> <ul style="list-style-type: none"> <li>• Any subject at risk of suicide or self-harm based on investigator judgment and/or details of a mental health risk assessment (MHRA) by a qualified mental health professional.</li> <li>• The number of sites to participate in the study has been deleted.</li> </ul> <p>The following changes were made to comply with the current protocol template and required language/wording:</p> <ul style="list-style-type: none"> <li>• Abbreviation list moved to an Appendix.</li> <li>• Updated terms study drug and study medication to investigational product for consistency.</li> <li>• Inserted Lifestyle Guidelines which includes template contraception language.</li> <li>• Inserted Sponsors Medically Qualified Personnel.</li> <li>• Updated Trial Treatments including insertion of new sections for Investigational Product Storage, Investigational Product Accountability and Destruction of <ul style="list-style-type: none"> <li>• Investigational Product Supplies.</li> <li>• Updated Drug Supplies.</li> <li>• Updated Investigational Product Storage.</li> <li>• Updated Quality Control and Quality Assurance.</li> <li>• Inserted Medication Errors.</li> <li>• Updated Exposure During Pregnancy.</li> <li>• Inserted Occupational Exposure.</li> <li>• Updated Publication of Results.</li> </ul> </li> </ul>
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Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported