



## Clinical trial results:

### Efficacy of pregabalin and duloxetine in patients with painful diabetic peripheral neuropathy (PDPN): the effect of pain on cognitive function, sleep and quality of life (BLOSSOM)

#### Summary

EudraCT number	2017-004341-24
Trial protocol	SI PL HR
Global end of trial date	21 December 2021

#### Results information

Result version number	v1 (current)
This version publication date	23 April 2023
First version publication date	23 April 2023
Summary attachment (see zip file)	BLOSSOM CSR SYNOPSIS (Blossom_CSR_SYNOPSIS_EudraCT_2023-04.docx)

#### Trial information

##### Trial identification

Sponsor protocol code	KCT11/2017-BLOSSOM
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	Krka, d.d., Novo mesto
Sponsor organisation address	Dunajska cesta 65, Ljubljana, Slovenia, 1000
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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	11 November 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2021
Global end of trial reached?	Yes
Global end of trial date	21 December 2021
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The purpose of the trial is to assess the efficacy of Pregabalin Krka (pregabalin) and Dulsevia® (duloxetine) in patients with PDPN, investigate the effect of Pregabalin Krka and Dulsevia® on pain and on quality of life (QOL), depression symptoms, cognitive functions, sleep quality and daytime sleepiness as well as to assess the safety of Pregabalin Krka and Dulsevia® in patients with PDPN.

Protection of trial subjects:

Inclusion criteria served to select the homogeneous population with a diagnosis of PDPN caused by type 2 diabetes mellitus. Exclusion criteria also facilitated a reduction of possible biases through selection of study population without concomitant therapy that could influence pain results, excluded patients with a history of inadequate pain response, considered factors, which could influence patient safety. Inclusion and exclusion criteria were, however, permissive enough to allow a selection of the patients.

The use of concomitant medication with known interactions and/or contraindications as related to the study medications was restricted in the interest of patient safety.

During 12 weeks of treatment patients had 5 study visits and two phone calls. The study was divided in screening period with screening visit and initial baseline visit, three treatment periods and the last visit for conclusion of study. Patients were randomly assigned into two treatment arms, Pregabalin Arm and Duloxetine Arm. Patients started taking the allocated study medication on day of baseline visit (Visit 2), after all procedures of the baseline visit were finished.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 November 2019
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	North Macedonia: 58
Country: Number of subjects enrolled	Serbia: 18
Country: Number of subjects enrolled	Poland: 44
Country: Number of subjects enrolled	Slovenia: 14
Country: Number of subjects enrolled	Croatia: 67
Worldwide total number of subjects	201
EEA total number of subjects	125

Notes:

<b>Subjects enrolled per age group</b>	
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)	89
From 65 to 84 years	112
85 years and over	0

## Subject disposition

### Recruitment

#### Recruitment details:

Patient recruitment in the study began in November 2019 (FPI date: 12th November 2019) and was concluded in September 2021 (LPI date: 16th September 2021). A total of 254 patients were screened and 201 patient were allocated to treatment in five participating countries - Croatia, North Macedonia, Poland, Serbia and Slovenia.

### Pre-assignment

#### Screening details:

Eligible patients were adults aged 18 to 85 years, with a history of type 2 diabetes mellitus, with a diagnosis of PDPN caused by type 2 diabetes mellitus based on DN4 questionnaire  $\geq 4$  and whose pain intensity level in the last 24 hours was more than 40 mm on VAS scale.

### Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

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

#### Arm description:

Patients were randomly assigned into two treatment arms, Pregabalin Arm and Duloxetine Arm. The randomisation list was prepared for each study site separately. There were two treatment groups group A for pregabalin and group B for duloxetine. Block size was 4, so the list length was divisible with 4. Pregabalin treatment was preferably started at a daily dose of 150 mg pregabalin. Based on investigator's opinion, the treatment could have been started at a lower dose 25 mg, 50 mg or 75 mg. Based on individual patient response, tolerability and investigator's opinion, the dose may have been increased up to 300 mg per day after Phone call 1 (1 week after baseline visit - Visit 2). The minimum dose of 150 mg per day must have been achieved at Visit 3 (2 weeks after Visit 2). After Visit 3 the daily dose of pregabalin could have been increased up to 600mg per day. If necessary, therapy with rescue medicine (Doreta®) could have been initiated from Visit 2.

Arm type	Active comparator
Investigational medicinal product name	Pregabalin Krka 25 mg
Investigational medicinal product code	
Other name	Pragiola®
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

#### Dosage and administration details:

Pregabalin Krka 25 mg hard capsules, each capsule contains 25 mg of pregabalin. One capsule was administered once or twice daily, at about the same time each day ( $\pm$  3 hours) orally, with or without food.

Investigational medicinal product name	Pregabalin Krka 75 mg
Investigational medicinal product code	
Other name	Pragiola®
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

#### Dosage and administration details:

Pregabalin Krka 75 mg hard capsules, each capsule contains 75 mg of pregabalin. One capsule was administered once or twice daily, at about the same time each day ( $\pm$  3 hours) orally, with or without food.

Investigational medicinal product name	Pregabalin Krka 150 mg
Investigational medicinal product code	
Other name	Pragiola®
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

**Dosage and administration details:**

Pregabalin Krka 150 mg hard capsules, each capsule contains 150 mg of pregabalin. One capsule was administered once or twice daily, at about the same time each day ( $\pm$  3 hours) orally, with or without food.

Investigational medicinal product name	Pregabalin Krka 300 mg
Investigational medicinal product code	
Other name	Pragiola®
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

**Dosage and administration details:**

Pregabalin Krka 300 mg hard capsules, each capsule contains 300 mg of pregabalin. One capsule was administered once or twice daily, at about the same time each day ( $\pm$  3 hours) orally, with or without food.

Investigational medicinal product name	Doreta® 37.5/325 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

**Dosage and administration details:**

Rescue medicine. Doreta® film-coated tablets 37.5 mg/325 mg, each tablet contains 37.5 mg of tramadol hydrochloride equivalent to 32.94 mg tramadol and 325 mg paracetamol. RM must have been taken according to the protocol and investigator's instructions. Maximum daily dose was 8 tablets (equivalent to 300 mg tramadol hydrochloride and 2600 mg paracetamol). The dosing interval for RM should not have been less than six hours with maximum two tablets taken per once.

<b>Arm title</b>	Duloxetine Arm
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**Arm description:**

Patients were randomly assigned into two treatment arms, Pregabalin Arm and Duloxetine Arm. The randomisation list was prepared for each study site separately. There were two treatment groups group A for pregabalin and group B for duloxetine. Block size was 4, so the list length was divisible with 4. Duloxetine treatment could be started at a dose of 30 mg or 60 mg of duloxetine per day. Based on individual patient response, tolerability and investigator's opinion the dose may have been increased up to 60 mg per day after an interval of 1 to 14 days. The minimum dose of 60 mg per day must have been achieved at Visit 3 (2 weeks after baseline visit - Visit 2). After Visit 3 the daily dose of duloxetine could have been increased up to 90 or 120 mg per day. If necessary, therapy with rescue medicine (Doreta®) could have been initiated from Visit 2.

Arm type	Active comparator
Investigational medicinal product name	Dulsevia® 30 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

**Dosage and administration details:**

Dulsevia® 30 mg hard gastro-resistant capsules, each capsule contains 30 mg of duloxetine (as hydrochloride). One capsule was administered once or twice daily, at about the same time each day ( $\pm$  3 hours) orally, with or without food.

Investigational medicinal product name	Dulsevia® 60 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

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**Dosage and administration details:**

Dulsevia® 60 mg hard gastro-resistant capsules, each capsule contains 60 mg of duloxetine (as hydrochloride). One capsule was administered once or twice daily, at about the same time each day ( $\pm$  3 hours) orally, with or without food.

Investigational medicinal product name	Doreta® 37.5/325 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

**Dosage and administration details:**

Rescue medicine. Doreta® film-coated tablets 37.5 mg/325 mg, each tablet contains 37.5 mg of tramadol hydrochloride equivalent to 32.94 mg tramadol and 325 mg paracetamol. RM must have been taken according to the protocol and investigator`s instructions. Maximum daily dose was 8 tablets (equivalent to 300 mg tramadol hydrochloride and 2600 mg paracetamol). The dosing interval for RM should not have been less than six hours with maximum two tablets taken per once.

<b>Number of subjects in period 1</b>	Pregabalin Arm	Duloxetine Arm
Started	99	102
Completed	82	76
Not completed	17	26
Adverse event, serious fatal	1	2
Consent withdrawn by subject	3	5
Other exclusion	2	1
Adverse event, non-fatal	10	13
Incorrect inclusion	-	4
Lack of efficacy	1	-
Noncompliance	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	Pregabalin Arm
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#### Reporting group description:

Patients were randomly assigned into two treatment arms, Pregabalin Arm and Duloxetine Arm. The randomisation list was prepared for each study site separately. There were two treatment groups group A for pregabalin and group B for duloxetine. Block size was 4, so the list length was divisible with 4. Pregabalin treatment was preferably started at a daily dose of 150 mg pregabalin. Based on investigator's opinion, the treatment could have been started at a lower dose 25 mg, 50 mg or 75 mg. Based on individual patient response, tolerability and investigator's opinion, the dose may have been increased up to 300 mg per day after Phone call 1 (1 week after baseline visit - Visit 2). The minimum dose of 150 mg per day must have been achieved at Visit 3 (2 weeks after Visit 2). After Visit 3 the daily dose of pregabalin could have been increased up to 600mg per day. If necessary, therapy with rescue medicine (Doreta®) could have been initiated from Visit 2.

Reporting group title	Duloxetine Arm
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#### Reporting group description:

Patients were randomly assigned into two treatment arms, Pregabalin Arm and Duloxetine Arm. The randomisation list was prepared for each study site separately. There were two treatment groups group A for pregabalin and group B for duloxetine. Block size was 4, so the list length was divisible with 4. Duloxetine treatment could be started at a dose of 30 mg or 60 mg of duloxetine per day. Based on individual patient response, tolerability and investigator's opinion the dose may have been increased up to 60 mg per day after an interval of 1 to 14 days. The minimum dose of 60 mg per day must have been achieved at Visit 3 (2 weeks after baseline visit - Visit 2). After Visit 3 the daily dose of duloxetine could have been increased up to 90 or 120 mg per day. If necessary, therapy with rescue medicine (Doreta®) could have been initiated from Visit 2.

Reporting group values	Pregabalin Arm	Duloxetine Arm	Total
Number of subjects	99	102	201
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	64.4	63.4	
standard deviation	± 9.1	± 10.1	-
Gender categorical			
Units: Subjects			
Female	56	61	117
Male	43	41	84

## End points

### End points reporting groups

Reporting group title	Pregabalin Arm
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#### Reporting group description:

Patients were randomly assigned into two treatment arms, Pregabalin Arm and Duloxetine Arm. The randomisation list was prepared for each study site separately. There were two treatment groups group A for pregabalin and group B for duloxetine. Block size was 4, so the list length was divisible with 4. Pregabalin treatment was preferably started at a daily dose of 150 mg pregabalin. Based on investigator's opinion, the treatment could have been started at a lower dose 25 mg, 50 mg or 75 mg. Based on individual patient response, tolerability and investigator's opinion, the dose may have been increased up to 300 mg per day after Phone call 1 (1 week after baseline visit - Visit 2). The minimum dose of 150 mg per day must have been achieved at Visit 3 (2 weeks after Visit 2). After Visit 3 the daily dose of pregabalin could have been increased up to 600mg per day. If necessary, therapy with rescue medicine (Doreta®) could have been initiated from Visit 2.

Reporting group title	Duloxetine Arm
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#### Reporting group description:

Patients were randomly assigned into two treatment arms, Pregabalin Arm and Duloxetine Arm. The randomisation list was prepared for each study site separately. There were two treatment groups group A for pregabalin and group B for duloxetine. Block size was 4, so the list length was divisible with 4. Duloxetine treatment could be started at a dose of 30 mg or 60 mg of duloxetine per day. Based on individual patient response, tolerability and investigator's opinion the dose may have been increased up to 60 mg per day after an interval of 1 to 14 days. The minimum dose of 60 mg per day must have been achieved at Visit 3 (2 weeks after baseline visit - Visit 2). After Visit 3 the daily dose of duloxetine could have been increased up to 90 or 120 mg per day. If necessary, therapy with rescue medicine (Doreta®) could have been initiated from Visit 2.

### Primary: Clinically meaningful improvement of 24h-API after 12 weeks

End point title	Clinically meaningful improvement of 24h-API after 12 weeks <sup>[1]</sup>
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#### End point description:

The proportion of patients with clinically meaningful improvement of pain in PDPN after a 12 week treatment with pregabalin and the proportion of patients with clinically meaningful improvement of pain in PDPN after a 12 week treatment with duloxetine. Improvement of pain in PDPN is considered as clinically meaningful if reduction of average pain intensity (API) in PDPN in last 24-h (measured by VAS) is equal or more than 30 % in comparison to the initial (baseline) level AND/OR if average pain intensity in PDPN in last 24-h (measured by VAS) does not exceed 30 mm after 12 weeks of treatment.

End point type	Primary
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#### End point timeframe:

Each patient was monitored for 12 weeks. Timeframe for AE reporting was the same throughout the whole trial.

#### Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: For the assessment of each proportion, the two-sided "equal-tails" Clopper-Pearson exact 95%-confidence interval was employed. For a randomized patient, any record from Visit 2 onwards that was necessary for the evaluation of an efficacy endpoint was treated as a missing value if it was unavailable for any reason. Missing values were imputed by means of multiple imputation (MI), and on estimates obtained by MI statistical inference methods specifically devised for MI were employed.



<b>End point values</b>	Pregabalin Arm	Duloxetine Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	102		
Units: Proportion of patients				
number (confidence interval 95%)				
% of patients with meaningful improvement of API	88.3 (81.7 to 94.8)	86.9 (76.7 to 97.1)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Each patient was monitored for 12 weeks. Timeframe for AE reporting was the same throughout the whole trial.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

### Reporting groups

Reporting group title	Pregabalin Arm
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Reporting group description:

Patients were randomly assigned into two treatment arms, Pregabalin Arm and Duloxetine Arm. The randomisation list was prepared for each study site separately. There were two treatment groups group A for pregabalin and group B for duloxetine. Block size was 4, so the list length was divisible with 4. Pregabalin treatment was preferably started at a daily dose of 150 mg pregabalin. Based on investigator's opinion, the treatment could have been started at a lower dose 25 mg, 50 mg or 75 mg. Based on individual patient response, tolerability and investigator's opinion, the dose may have been increased up to 300 mg per day after Phone call 1 (1 week after baseline visit - Visit 2). The minimum dose of 150 mg per day must have been achieved at Visit 3 (2 weeks after Visit 2). After Visit 3 the daily dose of pregabalin could have been increased up to 600mg per day. If necessary, therapy with rescue medicine (Doreta®) could have been initiated from Visit 2.

Reporting group title	Duloxetine Arm
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Reporting group description:

Patients were randomly assigned into two treatment arms, Pregabalin Arm and Duloxetine Arm. The randomisation list was prepared for each study site separately. There were two treatment groups group A for pregabalin and group B for duloxetine. Block size was 4, so the list length was divisible with 4. Duloxetine treatment could be started at a dose of 30 mg or 60 mg of duloxetine per day. Based on individual patient response, tolerability and investigator's opinion the dose may have been increased up to 60 mg per day after an interval of 1 to 14 days. The minimum dose of 60 mg per day must have been achieved at Visit 3 (2 weeks after baseline visit - Visit 2). After Visit 3 the daily dose of duloxetine could have been increased up to 90 or 120 mg per day. If necessary, therapy with rescue medicine (Doreta®) could have been initiated from Visit 2.

Serious adverse events	Pregabalin Arm	Duloxetine Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 99 (3.03%)	3 / 102 (2.94%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	1	0	
Vascular disorders			
Shock haemorrhagic			
subjects affected / exposed	0 / 99 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Cerebrovascular accident			

subjects affected / exposed	1 / 99 (1.01%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	1 / 99 (1.01%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 99 (1.01%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 99 (0.00%)	1 / 102 (0.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	1 / 99 (1.01%)	0 / 102 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 99 (0.00%)	2 / 102 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Pregabalin Arm	Duloxetine Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 99 (32.32%)	31 / 102 (30.39%)	
Nervous system disorders			

Somnolence subjects affected / exposed occurrences (all)	9 / 99 (9.09%) 11	7 / 102 (6.86%) 8	
Dizziness subjects affected / exposed occurrences (all)	7 / 99 (7.07%) 7	8 / 102 (7.84%) 9	
Headache subjects affected / exposed occurrences (all)	2 / 99 (2.02%) 2	3 / 102 (2.94%) 3	
Balance disorder subjects affected / exposed occurrences (all)	2 / 99 (2.02%) 2	1 / 102 (0.98%) 1	
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	7 / 99 (7.07%) 7	2 / 102 (1.96%) 2	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	2 / 99 (2.02%) 3	10 / 102 (9.80%) 11	
Vomiting subjects affected / exposed occurrences (all)	0 / 99 (0.00%) 0	5 / 102 (4.90%) 5	
Dry mouth subjects affected / exposed occurrences (all)	0 / 99 (0.00%) 0	4 / 102 (3.92%) 4	
Abdominal pain subjects affected / exposed occurrences (all)	0 / 99 (0.00%) 0	3 / 102 (2.94%) 3	
Diarrhoea subjects affected / exposed occurrences (all)	1 / 99 (1.01%) 1	2 / 102 (1.96%) 2	
Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 99 (0.00%) 0	4 / 102 (3.92%) 6	
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	0 / 99 (0.00%) 0	4 / 102 (3.92%) 4	
Hyperglycaemia subjects affected / exposed occurrences (all)	2 / 99 (2.02%) 2	1 / 102 (0.98%) 1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported