Clinical trial results:
A phase II, multicenter, randomized, double-masked, 4 parallel arms, controlled 6-month trial designed to evaluate the safety and efficacy of PAD ciclosporin (CsA 0.06% and 0.03%) ophthalmic dispersion administered once daily in combination with lubricant therapy and a 3-month post-treatment safety follow-up in moderate to severe dry eye patients

Summary

EudraCT number	2015-000937-54
Trial protocol	GB DK NO AT ES PT FR SK CZ
Global end of trial date	30 August 2018

Results information

Result version number	v1 (current)
This version publication date	11 March 2020
First version publication date	11 March 2020

Trial information

Trial identification

Sponsor protocol code	MC2-03-C1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	MC2 Therapeutics Ltd
Sponsor organisation address	C/O Agern Alle 24-26, Hørsholm, Denmark, 2970
Public contact	Clinical Operations, MC2 Therapeutics Ltd, 45 25338893, mpr@mc2therapeutics.com
Scientific contact	Clinical Operations, MC2 Therapeutics Ltd, 45 25338893, mpr@mc2therapeutics.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	30 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 August 2018
Global end of trial reached?	Yes
Global end of trial date	30 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study are to:
1. Evaluate the ocular tolerance and overall ocular safety of PADciclo (0.06% and 0.03%) in dry eye patients.
2. Evaluate the efficacy of PADciclo (0.06% and/or 0.03%) compared to current BSC administered once daily for 6 months in improving CFS in dry eye patients using a responder approach analysis.

Protection of trial subjects:

The occurrence of AE is monitored throughout the study at all visits. During and following a patient's participation in the trial, the investigator is ensuring adequate medical care to patients for any adverse events, including clinically significant laboratory values, related to the trial.
Supportive lubricant therapy was offered to all subjects throughout the trial.

Background therapy:

The subjects are provided with Lubricant Therapy Supporting Medication (HydromoorTM, 0,3% hypromellose) for self-administration from the 2-week run-in period.

Evidence for comparator: -

Actual start date of recruitment	01 June 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Portugal: 17
Country: Number of subjects enrolled	Slovakia: 51
Country: Number of subjects enrolled	Spain: 99
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Austria: 20
Country: Number of subjects enrolled	Czech Republic: 23
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	France: 29
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Norway: 4
Worldwide total number of subjects	263
EEA total number of subjects	259

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)	145
From 65 to 84 years	112
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Subject recruitment activities were based on database searches in local databases at the clinics and local advertisements.

Pre-assignment

Screening details:

After screening, the subjects entered the run-in period(s) of up to maximal 2 x 14 days before the treatment period. The purpose of this/these run-in period(s) was to determine the dose of supporting lubricant needed. The second run-in period was only relevant if it was not possible to decide on that optimal dose during the first run-in period.

Pre-assignment period milestones

Number of subjects started	263
Number of subjects completed	263

Period 1

Period 1 title	Treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Assessor, Subject

Blinding implementation details:

All IMPs were supplied in identical appearing single-dose containers protected by paper/aluminium/polyethylene pouch packages. Each container, each pouch and each sealed cardboard box was carrying an investigational label, indicating that the content was intended for investigational use only. The labeling was complying with local regulatory requirements.

Arms

Are arms mutually exclusive?	Yes
Arm title	Safety PADciclo™ 0.06%

Arm description:

The PADciclo™ ciclosporin 0.06% is a sterile ophthalmic dispersion filled in polyethylene, low density, single-dose container.

Arm type	Experimental
Investigational medicinal product name	PADciclo™ 0.06% single-dose
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, emulsion
Routes of administration	Ophthalmic use

Dosage and administration details:

During the 6-month treatment period patients will be instructed to instill one drop of study treatment once daily in each eye, at bedtime, at least one hour after the last daily instillation of the Supporting Medication.
The first dose of IMP will be instilled after randomization, at bedtime of Day 0 (Baseline visit) at least one hour after the last daily instillation of the Supporting Medication. The treatment will continue up to 6 months.
The last dose will be instilled at bedtime, at least one hour after the last daily instillation of the Supporting Medication, the day before Month 6 (End-of-Treatment Visit).

Arm title	Safety PADciclo™ 0.03%

Arm description:

The PADciclo™ ciclosporin 0.03% is a sterile ophthalmic dispersion filled in polyethylene, low density, single-dose container.

Arm type	Experimental
Investigational medicinal product name	PADciclo™ 0.03% single-dose
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, emulsion
Routes of administration	Ophthalmic use

Dosage and administration details:

During the 6-month treatment period patients will be instructed to instill one drop of study treatment once daily in each eye, at bedtime, at least one hour after the last daily instillation of the Supporting Medication.
The first dose of IMP will be instilled after randomization, at bedtime of Day 0 (Baseline visit) at least one hour after the last daily instillation of the Supporting Medication. The treatment will continue up to 6 months.
The last dose will be instilled at bedtime, at least one hour after the last daily instillation of the Supporting Medication, the day before Month 6 (End-of-Treatment Visit).

Arm title	Safety PADciclo™ vehicle

Arm description:

The PADciclo™ vehicle, where CsA is replaced by water, is a sterile ophthalmic dispersion filled in polyethylene, low density, single-dose container.

Arm type	Placebo
Investigational medicinal product name	PADciclo™ vehicle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, emulsion
Routes of administration	Ophthalmic use

Dosage and administration details:

During the 6-month treatment period patients will be instructed to instill one drop of study treatment once daily in each eye, at bedtime, at least one hour after the last daily instillation of the Supporting Medication.
The first dose of IMP will be instilled after randomization, at bedtime of Day 0 (Baseline visit) at least one hour after the last daily instillation of the Supporting Medication. The treatment will continue up to 6 months.
The last dose will be instilled at bedtime, at least one hour after the last daily instillation of the Supporting Medication, the day before Month 6 (End-of-Treatment Visit).

Arm title	Safety Best Standard Care (Lubricant therapy)

Arm description:

The BSC (Lubricant therapy) is 0.3% hypromellose in polyethylene, low density, single-dose container.

Arm type	Active comparator
Investigational medicinal product name	Best Standard Care (Lubricant therapy)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

During the 6-month treatment period patients will be instructed to instill one drop of study treatment once daily in each eye, at bedtime, at least one hour after the last daily instillation of the Supporting Medication.
The first dose of IMP will be instilled after randomization, at bedtime of Day 0 (Baseline visit) at least one hour after the last daily instillation of the Supporting Medication. The treatment will continue up to 6 months.
The last dose will be instilled at bedtime, at least one hour after the last daily instillation of the Supporting Medication, the day before Month 6 (End-of-Treatment Visit).

Number of subjects in period 1	Safety PADciclo™ 0.06%	Safety PADciclo™ 0.03%	Safety PADciclo™ vehicle
Started	70	67	63
Treatment period	57	61	54
Completed	57	61	54
Not completed	13	6	9
Physician decision	1	-	-
Consent withdrawn by subject	2	1	5
Protocol specified withdrawal criterion met	1	-	1
Adverse event, non-fatal	9	5	2
Lost to follow-up	-	-	-
Lack of efficacy	-	-	1

Number of subjects in period 1	Safety Best Standard Care (Lubricant therapy)
Started	63
Treatment period	56
Completed	56
Not completed	7
Physician decision	-
Consent withdrawn by subject	1
Protocol specified withdrawal criterion met	-
Adverse event, non-fatal	4
Lost to follow-up	1
Lack of efficacy	1

Period 2	
Period 2 title	Follow-up Safety Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms	
Are arms mutually exclusive?	Yes
Arm title	PADciclo™ 0.06%

Arm description:

During the 3 months follow-up Safety Period, only Supporting Medication lubricant therapy (Hydromoor™) were taken.

Arm type	Experimental

Investigational medicinal product name	PADciclo™ 0.06% single-dose
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, emulsion
Routes of administration	Ophthalmic use

Dosage and administration details:

During the 3 months follow-up Safety Period, only Supporting Medication lubricant therapy (Hydromoor™) were taken.

Arm title	PADciclo™ 0.03%

Arm description:

During the 3 months follow-up Safety Period, only Supporting Medication lubricant therapy (Hydromoor™) were taken.

Arm type	Experimental
Investigational medicinal product name	PADciclo™ 0.03% single-dose
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, emulsion
Routes of administration	Ophthalmic use

Dosage and administration details:

During the 3 months follow-up Safety Period, only Supporting Medication lubricant therapy (Hydromoor™) were taken.

Arm title	PADciclo™ vehicle

Arm description:

During the 3 months follow-up Safety Period, only Supporting Medication lubricant therapy (Hydromoor™) were taken.

Arm type	Experimental
Investigational medicinal product name	PADciclo™ vehicle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, emulsion
Routes of administration	Ophthalmic use

Dosage and administration details:

During the 3 months follow-up Safety Period, only Supporting Medication lubricant therapy (Hydromoor™) were taken.

Arm title	Best Standard Care (Lubricant therapy)

Arm description:

During the 3 months follow-up Safety Period, only Supporting Medication lubricant therapy (Hydromoor™) were taken.

Arm type	Experimental
Investigational medicinal product name	Best Standard Care (Lubricant therapy)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

During the 3 months follow-up Safety Period, only Supporting Medication lubricant therapy (Hydromoor™) were taken.

Number of subjects in period 2	PADciclo™ 0.06%	PADciclo™ 0.03%	PADciclo™ vehicle
Started	57	61	54
Completed	55	60	52
Not completed	2	1	2
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	1	1	1
Unknown	1	-	-
Lost to follow-up	-	-	1

Number of subjects in period 2	Best Standard Care (Lubricant therapy)
Started	56
Completed	54
Not completed	2
Consent withdrawn by subject	1
Adverse event, non-fatal	-
Unknown	-
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Safety PADciclo™ 0.06%
Reporting group description:	
The PADciclo™ ciclosporin 0.06% is a sterile ophthalmic dispersion filled in polyethylene, low density, single-dose container.	
Reporting group title	Safety PADciclo™ 0.03%
Reporting group description:	
The PADciclo™ ciclosporin 0.03% is a sterile ophthalmic dispersion filled in polyethylene, low density, single-dose container.	
Reporting group title	Safety PADciclo™ vehicle
Reporting group description:	
The PADciclo™ vehicle, where CsA is replaced by water, is a sterile ophthalmic dispersion filled in polyethylene, low density, single-dose container.	
Reporting group title	Safety Best Standard Care (Lubricant therapy)
Reporting group description:	
The BSC (Lubricant therapy) is 0.3% hypromellose in polyethylene, low density, single-dose container.	

Reporting group values	Safety PADciclo™ 0.06%	Safety PADciclo™ 0.03%	Safety PADciclo™ vehicle
Number of subjects	70	67	63
Age categorical Units: Subjects			
Adult			
Age continuous Units: years			
arithmetic mean	59.99	62.54	61.89
standard deviation	± 14.89	± 11.84	± 13.78
Gender categorical Units: Subjects			
Female	63	64	55
Male	7	3	8

Reporting group values	Safety Best Standard Care (Lubricant therapy)	Total	
Number of subjects	63	263	
Age categorical Units: Subjects			
Adult		0	
Age continuous Units: years			
arithmetic mean	61.29		
standard deviation	± 14.09	-	
Gender categorical Units: Subjects			
Female	58	240	
Male	5	23	

End points

End points reporting groups

Reporting group title	Safety PADciclo™ 0.06%
Reporting group description:	
The PADciclo™ ciclosporin 0.06% is a sterile ophthalmic dispersion filled in polyethylene, low density, single-dose container.	
Reporting group title	Safety PADciclo™ 0.03%
Reporting group description:	
The PADciclo™ ciclosporin 0.03% is a sterile ophthalmic dispersion filled in polyethylene, low density, single-dose container.	
Reporting group title	Safety PADciclo™ vehicle
Reporting group description:	
The PADciclo™ vehicle, where CsA is replaced by water, is a sterile ophthalmic dispersion filled in polyethylene, low density, single-dose container.	
Reporting group title	Safety Best Standard Care (Lubricant therapy)
Reporting group description:	
The BSC (Lubricant therapy) is 0.3% hypromellose in polyethylene, low density, single-dose container.	
Reporting group title	PADciclo™ 0.06%
Reporting group description:	
During the 3 months follow-up Safety Period, only Supporting Medication lubricant therapy (Hydromoor™) were taken.	
Reporting group title	PADciclo™ 0.03%
Reporting group description:	
During the 3 months follow-up Safety Period, only Supporting Medication lubricant therapy (Hydromoor™) were taken.	

Reporting group title	PADciclo™ vehicle
Reporting group description:	
During the 3 months follow-up Safety Period, only Supporting Medication lubricant therapy (Hydromoor™) were taken.	

Reporting group title	Best Standard Care (Lubricant therapy)
Reporting group description:	
During the 3 months follow-up Safety Period, only Supporting Medication lubricant therapy (Hydromoor™) were taken.	

Subject analysis set title	FAS PADciclo™ 0.06%
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS is defined as subjects having received at least one instillation and had at least one efficacy endpoint assessment done.	
Subject analysis set title	FAS PADciclo™ 0.03%
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS is defined as subjects having received at least one instillation and had at least one efficacy endpoint assessment done.	
Subject analysis set title	FAS PADciclo™ vehicle
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS is defined as subjects having received at least one instillation and had at least one efficacy endpoint assessment done.	
Subject analysis set title	FAS Best Standard Care (Lubricant therapy)
Subject analysis set type	Full analysis

Subject analysis set description:

FAS is defined as subjects having received at least one instillation and had at least one efficacy endpoint assessment done.

Primary: CFS response in the worse eye.

End point title	CFS response in the worse eye.

End point description:

The primary endpoint was the efficacy of PADciclo™ 0.06% and 0.03% compared to current Best Standard Care and PADciclo™ vehicle, administered once daily for 6 months in improving CFS by at least 2 grades in dry eye patients using a responder approach analysis.

End point type	Primary

End point timeframe:

After 6 months treatment

End point values	FAS PADciclo™ 0.06%	FAS PADciclo™ 0.03%	FAS PADciclo™ vehicle	FAS Best Standard Care (Lubricant therapy)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	68	66	58	63
Units: Percentage	41	46	33	33

Statistical analyses

Statistical analysis title	Corneal Fluorescein Staining response

Statistical analysis description:

CFS (Corneal Fluorescein staining) response = improvement from Baseline to Month 6 in CFS of at least 2 grades, by using a Modified Oxford Scale (7-point ordinal scale, score 0, 0.5, 1, 2, 3, 4 and 5).

Comparison groups	FAS PADciclo™ 0.03% v FAS PADciclo™ vehicle v FAS Best Standard Care (Lubricant therapy) v FAS PADciclo™ 0.06%
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Confidence interval	
level	95 %
sides	2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Event Reporting for each subject begin when a subject has signed the informed consent form and until the final Follow-Up Safety visit.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	PADciclo™ 0.06%

Reporting group description:

The PADciclo™ is a sterile ophthalmic dispersion of CsA filled in polyethylene, low density, single-dose container. It possesses an intrinsic viscosity with a characteristic long residence time on the surface of the eye. During the 6-month treatment period patients was instructed to instill one drop of study treatment once daily in each eye, at bedtime.

Reporting group title	PADciclo™ 0.03%

Reporting group description:

The PADciclo™ is a sterile ophthalmic dispersion of CsA filled in polyethylene, low density, single-dose container. It possesses an intrinsic viscosity with a characteristic long residence time on the surface of the eye. During the 6-month treatment period patients was instructed to instill one drop of study treatment once daily in each eye, at bedtime.

Reporting group title	PADciclo™ vehicle

Reporting group description:

The PADciclo™ vehicle is identical to PADciclo™ 0.06% where CsA is replaced by water for injection and filled in polyethylene, low density, single-dose container. During the 6-month treatment period patients was instructed to instill one drop of study treatment once daily in each eye, at bedtime.

Reporting group title	Best Standard Care (Lubricant therapy)

Reporting group description:

The BSC (Lubricant therapy) is 0.3% hypromellose in polyethylene, low density, single-dose container. During the 6-month treatment period patients was instructed to instill one drop of study treatment once daily in each eye, at bedtime.

Serious adverse events	PADciclo™ 0.06%	PADciclo™ 0.03%	PADciclo™ vehicle
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 70 (4.29%)	2 / 67 (2.99%)	4 / 63 (6.35%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 70 (0.00%)	0 / 67 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myeloproliferative neoplasm			

subjects affected / exposed	0 / 70 (0.00%)	0 / 67 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic neoplasm			
subjects affected / exposed	0 / 70 (0.00%)	1 / 67 (1.49%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Injury, poisoning and procedural complications			
Mutiple injuries			
subjects affected / exposed	0 / 70 (0.00%)	0 / 67 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiopulmonary failure			
subjects affected / exposed	1 / 70 (1.43%)	0 / 67 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Sciatica	Additional description: Right-side L4		
subjects affected / exposed	0 / 70 (0.00%)	0 / 67 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment	Additional description: Left eye.		
subjects affected / exposed	0 / 70 (0.00%)	0 / 67 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastro Intestinal pain			
subjects affected / exposed	1 / 70 (1.43%)	0 / 67 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			

subjects affected / exposed	1 / 70 (1.43%)	0 / 67 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Rib fracture			
subjects affected / exposed	1 / 70 (1.43%)	0 / 67 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 67 (1.49%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 67 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium colitis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 67 (0.00%)	0 / 63 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 70 (0.00%)	0 / 67 (0.00%)	1 / 63 (1.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Best Standard Care (Lubricant therapy)		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 63 (3.17%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			

subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myeloproliferative neoplasm			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastatic neoplasm			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Mutiple injuries			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiopulmonary failure			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Sciatica	Additional description: Right-side L4		
subjects affected / exposed	1 / 63 (1.59%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal detachment	Additional description: Left eye.		
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastro Intestinal pain			

subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Rib fracture			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Clostridium colitis			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	PADciclo™ 0.06%	PADciclo™ 0.03%	PADciclo™ vehicle
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 70 (57.14%)	40 / 67 (59.70%)	37 / 63 (58.73%)
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 70 (1.43%)	4 / 67 (5.97%)	2 / 63 (3.17%)
occurrences (all)	1	4	2
General disorders and administration site conditions			
Instillation site pain			
subjects affected / exposed	11 / 70 (15.71%)	12 / 67 (17.91%)	2 / 63 (3.17%)
occurrences (all)	11	12	2
Eye disorders			
Blepharitis			
subjects affected / exposed	5 / 70 (7.14%)	5 / 67 (7.46%)	3 / 63 (4.76%)
occurrences (all)	5	5	3
Eye irritation			
subjects affected / exposed	4 / 70 (5.71%)	4 / 67 (5.97%)	2 / 63 (3.17%)
occurrences (all)	4	4	2
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 70 (2.86%)	1 / 67 (1.49%)	4 / 63 (6.35%)
occurrences (all)	2	1	4
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 70 (1.43%)	3 / 67 (4.48%)	5 / 63 (7.94%)
occurrences (all)	1	3	5

Non-serious adverse events	Best Standard Care (Lubricant therapy)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 63 (57.14%)		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 63 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Instillation site pain			

subjects affected / exposed occurrences (all)	1 / 63 (1.59%) 1		
Eye disorders Blepharitis subjects affected / exposed occurrences (all) Eye irritation subjects affected / exposed occurrences (all)	 3 / 63 (4.76%) 3 2 / 63 (3.17%) 2		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 0 / 63 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 6 / 63 (9.52%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 August 2015	Protocol version 3: Substantial amendment and corrections.
08 February 2016	Protocol version 6: Updates, protocol for France
14 June 2016	Protocol version 7: Substantial Amendment and Corrections.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported