Clinical trial results:
A Phase IIIb, Multinational, Multicenter, Open-Label Extension Study Assessing the Long-Term Safety of PRN Intravitreal Injections of DE-109 in Subjects with Non-Infectious Uveitis of the Posterior Segment of the Eye Who Have Participated in the SAKURA Development Program

Summary

EudraCT number	2014-004042-96
Trial protocol	DE AT IT
Global end of trial date	01 November 2017

Results information

Result version number	v1 (current)
This version publication date	21 June 2019
First version publication date	21 June 2019
Summary attachment (see zip file)	SPRING_Result Summary (DE-109 SPRING_Result Summary.pdf)

Trial information

Trial identification

Sponsor protocol code	32-009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02251938
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Santen Inc.
Sponsor organisation address	6401 Hollis Street, Suite 125, Emeryville, CA, United States, 94608
Public contact	Abu Abraham, M.D., Vireous & Retina Therapeutic Area Strategy, Santen Inc., 001 4152689161,
Scientific contact	Abu Abraham, M.D., Vireous & Retina Therapeutic Area Strategy, Santen Inc., 001 4152689161,

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	16 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 November 2017
Global end of trial reached?	Yes
Global end of trial date	01 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this extension study is to evaluate the long-term safety of treatment with DE-109 (440 µg) in subjects with non-infectious uveitis of the posterior segment of the eye who have participated in the SAKURA development program.

Protection of trial subjects:

The study was conducted in accordance with the study protocols, Good Clinical Practice (GCP) as required by US Food and Drug Administration regulations, International Council on Harmonization (ICH) guidelines, and Santen's standard operating procedures (SOPs) for clinical investigation. Compliance with these requirements is consistent with the ethical principles that have their origins in the Declaration of Helsinki.
The ICF was written in compliance with US Title 21 CFR Part 50, ICH guidelines, and other national regulations as appropriate.The Principal Investigator (PI) or his/her designee discussed the purpose and pertinent details of the study with each subject. The ICF was approved by the governing IRB. Prior to undergoing any study related activity or administration of the study medication, a subject understood, signed, and dated the IRB-approved ICF. The subject's signature was witnessed by the individual administering informed consent. If the PI administered the informed consent, then the subject's signature was witnessed by another individual (e.g., member of study site staff). The PI signed and dated the ICF where designated.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 May 2015
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	United States: 33
Country: Number of subjects enrolled	India: 17
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Italy: 2
Worldwide total number of subjects	60
EEA total number of subjects	5

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)	56
From 65 to 84 years	3
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

As this was an extension study, the study population was the subjects with non-infectious uveitis of the posterior segment who received clinical benefit from treatment with DE-109 as determined by the investigator.

Pre-assignment

Screening details:

Subjects who were randomized and received at least two injections of DE-109 during the first 5 months of the SAKURA study and obtained clinical benefit from the study medication, as determined by the Investigator, were eligible for entry in this 12-month extension study.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	440 µg DE-109

Arm description:

There was only 1 treatment group in this extension study: 440 µg DE-109.

Arm type	Experimental
Investigational medicinal product name	Sirolimus
Investigational medicinal product code	
Other name	DE-109
Pharmaceutical forms	Intraocular instillation solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Study drug was administered as an intravitreal injection in the clinic.
The Investigator was not required to administer DE-109 at any visit. DE-109 treatments were given as needed, at the discretion of the Investigator and to be administered only by the Investigator; however, DE-109 treatments were not given more frequently than every 60 days.
A subject could have received treatment with DE-109 (440 µg) on Day 1 and/or any of the Post-Baseline PRN Treatment Visits based on the Investigator's standard clinical procedures.
DE-109 was not administered at an unscheduled visit.

Number of subjects in period 1	440 µg DE-109
Started	60
Completed	43
Not completed	17
Consent withdrawn by subject	3
Adverse event, non-fatal	2
Non-compliance with study drug	2
Site Terminated by Sponsor	3
Lost to follow-up	6
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	60	60	
Age categorical Units: Subjects			
Adults (18-64 years)	56	56	
65 years and over	4	4	
Age continuous Units: years			
arithmetic mean	43.31		
standard deviation	± 15.092	-	
Gender categorical Units: Subjects			
Female	31	31	
Male	29	29	

End points

End points reporting groups

Reporting group title	440 µg DE-109
Reporting group description:	
There was only 1 treatment group in this extension study: 440 µg DE-109.	

Primary: Best Corrected Visual Acuity

End point title	Best Corrected Visual Acuity[1]
End point description:	
Change from Baseline at Month 12 in the Study Eye	
End point type	Primary
End point timeframe:	
Study assessments were conducted for all subjects at Day 1 (Baseline), Month 2, Month 4, Month 6, Month 8, Month 10, and Month 12.	
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: No statistical hypothesis testing was conducted on any parameter.	

End point values	440 µg DE-109			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: Letters				
arithmetic mean (standard deviation)				
Change from Baseline at Month 12	2.1 (± 11.35)			

Statistical analyses

No statistical analyses for this end point

Primary: Intraocular Pressure

End point title	Intraocular Pressure[2]
End point description:	
Change from Baseline at Month 12 in the Study Eye	
End point type	Primary
End point timeframe:	
Study assessments were conducted for all subjects at Day 1 (Baseline), Month 2, Month 4, Month 6, Month 8, Month 10, and Month 12.	
Notes:	
[2] - 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: No statistical hypothesis testing was conducted on any parameter.	

End point values	440 µg DE-109			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: mmHg				
arithmetic mean (standard deviation)				
Change from Baseline at Month 12 in the Study Eye	0.3 (± 4.16)			

Statistical analyses

No statistical analyses for this end point

Primary: Indirect Ophthalmoscopy: Choroid

End point title	Indirect Ophthalmoscopy: Choroid[3]

End point description:

Shift from Baseline in Status at Month 12 in the Study Eye

End point type	Primary

End point timeframe:

Study assessments were conducted for all subjects at Day 1 (Baseline), Month 2, Month 4, Month 6, Month 8, Month 10, and Month 12.

Notes:

[3] - 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: No statistical hypothesis testing was conducted on any parameter.

End point values	440 µg DE-109			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: subjects				
Normal>Normal	36			
Normal>Abnormal	0			
Abnormal>Normal	4			
Abnormal>Abnormal	3			

Statistical analyses

No statistical analyses for this end point

Primary: Vitreous Haze

End point title	Vitreous Haze[4]

End point description:

Changes from baseline in VH scores at Month 12

End point type	Primary

End point timeframe:

Study assessments were conducted for all subjects at Day 1 (Baseline), Month 2, Month 4, Month 6, Month 8, Month 10, and Month 12.

Notes:

[4] - 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: No statistical hypothesis testing was conducted on any parameter.

End point values	440 µg DE-109			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: VH scores				
arithmetic mean (standard deviation)				
Change from Baseline at Month 12 in the Study Eye	-0.09 (± 0.847)			

Statistical analyses

No statistical analyses for this end point

Primary: Rescue Therapy

End point title	Rescue Therapy[5]

End point description:

End point type	Primary

End point timeframe:

Study assessments were conducted for all subjects at Day 1 (Baseline), Month 2, Month 4, Month 6, Month 8, Month 10, and Month 12.

Notes:

[5] - 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: No statistical hypothesis testing was conducted on any parameter.

End point values	440 µg DE-109			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: subjects				
Rescued	9			

Statistical analyses

No statistical analyses for this end point

Primary: Indirect Ophthalmoscopy: Macula

End point title	Indirect Ophthalmoscopy: Macula[6]

End point description:

Shift from Baseline in Status at Month 12 in the Study Eye

End point type	Primary

End point timeframe:

Study assessments were conducted for all subjects at Day 1 (Baseline), Month 2, Month 4, Month 6, Month 8, Month 10, and Month 12.

Notes:

[6] - 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: No statistical hypothesis testing was conducted on any parameter.

End point values	440 µg DE-109			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: subjects				
Normal>Normal	20			
Normal>Abnormal	2			
Abnormal>Normal	6			
Abnormal>Abnormal	15			

Statistical analyses

No statistical analyses for this end point

Primary: Indirect Ophthalmoscopy: Optic Nerve

End point title	Indirect Ophthalmoscopy: Optic Nerve[7]

End point description:

Shift from Baseline in Status at Month 12 in the Study Eye

End point type	Primary

End point timeframe:

Study assessments were conducted for all subjects at Day 1 (Baseline), Month 2, Month 4, Month 6, Month 8, Month 10, and Month 12.

Notes:

[7] - 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: No statistical hypothesis testing was conducted on any parameter.

End point values	440 µg DE-109			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: subjects				
Normal>Normal	39			
Normal>Abnormal	2			
Abnormal>Normal	0			
Abnormal>Abnormal	2			

Statistical analyses

No statistical analyses for this end point

Primary: Indirect Ophthalmoscopy: Retina

End point title	Indirect Ophthalmoscopy: Retina[8]

End point description:

Shift from Baseline in Status at Month 12 in the Study Eye

End point type	Primary

End point timeframe:

Study assessments were conducted for all subjects at Day 1 (Baseline), Month 2, Month 4, Month 6, Month 8, Month 10, and Month 12.

Notes:

[8] - 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: No statistical hypothesis testing was conducted on any parameter.

End point values	440 µg DE-109			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: subjects				
Normal>Normal	34			
Normal>Abnormal	2			
Abnormal>Normal	1			
Abnormal>Abnormal	6			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During the study

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	overall trial

Reporting group description: -

Serious adverse events	overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 60 (13.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Intraocular pressure increased			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung Adenocarcinoma Metastatic			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Procedural complication			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Arterial occlusive disease			

subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Trigeminal neuralgia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Visual acuity reduced			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vitreous haemorrhage			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pathological fracture			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis gangrenous			

subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 60 (48.33%)		
Investigations			
Sinusitis			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Intraocular pressure increased			
subjects affected / exposed	8 / 60 (13.33%)		
occurrences (all)	11		
Intraocular pressure decreased			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	5		
Eye disorders			
Cystoid macular oedema			
subjects affected / exposed	6 / 60 (10.00%)		
occurrences (all)	9		
Uveitis			
subjects affected / exposed	8 / 60 (13.33%)		
occurrences (all)	16		
Intermediate Uveitis			
subjects affected / exposed	6 / 60 (10.00%)		
occurrences (all)	12		
Cataract			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	4		
Iridocyclitis			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences (all)	3		
Macular fibrosis			

subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported