Clinical trial results:
A Phase III, Multinational, Multicenter, Randomized, Double-Masked, Study Assessing the Safety and Efficacy of Intravitreal Injections of DE-109 (three doses) for the Treatment of active, Non-Infectious Uveitis of the Posterior Segment of the eye.

Summary

EudraCT number	2011-001595-19
Trial protocol	GB ES DE AT IT
Global end of trial date	14 September 2016

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)	SAKURA study 2_Result Summary (DE-109 SAKURA Study2_Result Summary.pdf) SAKURA study 1_Result Summary (DE-109 SAKURA Study1_Result Summary.pdf)

Trial information

Trial identification

Sponsor protocol code	32-007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01358266
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., +1 415 268-9161,
Scientific contact	Abu Abraham, M.D., Vireous & Retina Therapeutic Area Strategy, Santen, Inc., +1 415 268-9161,

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	27 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 April 2015
Global end of trial reached?	Yes
Global end of trial date	14 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of DE-109 by comparing the proportion of subjects with vitreous haze score of 0 at Month 5 (SUN scale).

Protection of trial subjects:

The study was conducted in accordance with Santen Protocol 32-007 and protocol amendments, Good Clinical Practice (GCP), International Conference on Harmonization (ICH) of technical requirements for registration of pharmaceuticals for human use guidelines, and Santen's standard operating procedures 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 ICH guidelines, and national regulations as appropriate. Prior to undergoing any study-related activity or administration of the study medication, the Principal Investigator or his/her designee discussed the purpose and pertinent details of the study with each potentially eligible subject. The explanation was sufficiently detailed to allow the subject to make an informed decision to participate in the study. If the subject was willing to participate in the study, he/she was requested to give written informed consent. A copy of the ICF was signed by both the subject and the Principal Investigator or his/her designee.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 May 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 10
Country: Number of subjects enrolled	Turkey: 6
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Argentina: 43
Country: Number of subjects enrolled	Chile: 9

Country: Number of subjects enrolled	Colombia: 13
Country: Number of subjects enrolled	India: 199
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Japan: 18
Country: Number of subjects enrolled	Peru: 26
Country: Number of subjects enrolled	United States: 186
Worldwide total number of subjects	592
EEA total number of subjects	71

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)	532
From 65 to 84 years	60
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects with active non-infectious uveitis of the posterior segment, with a VH score of ≥ 1.5+ and a BCVA score of ≥ 19 letters (20/400 Snellen equivalent or better) in the study eye, were eligible to participate in the SAKURA program.

Pre-assignment

Screening details:

All systemic immunosuppressive agents other than corticosteroids were to be discontinued 30 days prior to the first administration of the study medication on Day 1. Ocular topical corticosteroids were to be rapidly tapered to to discontinue on Day 1.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
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	44 µg DE-109

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	sirolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intraocular instillation solution
Routes of administration	Ocular use

Dosage and administration details:

Eligible subjects for SAKURA Study 1 were randomized in a 1:1:1 ratio to receive the 44, 440 or 880 µg dose of DE-109 during the 6-month Double-Masked Treatment Period. All doses were administered via IVT injection into the study eye.
Under Amendments #3 and #4, study subjects who completed the 6-month Double-Masked Treatment Period started to receive the open-label 880 µg dose of DE-109 at Month 6 and later visits, no more frequently than every 2 months.

Arm title	440 µg DE-109

Arm description: -

Arm type	Experimental
Investigational medicinal product name	sirolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intraocular instillation solution
Routes of administration	Ocular use

Dosage and administration details:

Eligible subjects for SAKURA Study 1 were randomized in a 1:1:1 ratio to receive the 44, 440 or 880 µg dose of DE-109 during the 6-month Double-Masked Treatment Period. All doses were administered via IVT injection into the study eye.
Under Amendments #3 and #4, study subjects who completed the 6-month Double-Masked Treatment Period started to receive the open-label 880 µg dose of DE-109 at Month 6 and later visits, no more frequently than every 2 months.

Arm title	880 µg DE-109

Arm description: -	
Arm type	Experimental
Investigational medicinal product name	sirolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intraocular instillation solution
Routes of administration	Ocular use

Dosage and administration details:

Eligible subjects for SAKURA Study 1 were randomized in a 1:1:1 ratio to receive the 44, 440 or 880 µg dose of DE-109 during the 6-month Double-Masked Treatment Period. All doses were administered via IVT injection into the study eye.
Under Amendments #3 and #4, study subjects who completed the 6-month Double-Masked Treatment Period started to receive the open-label 880 µg dose of DE-109 at Month 6 and later visits, no more frequently than every 2 months.

Number of subjects in period 1	44 µg DE-109	440 µg DE-109	880 µg DE-109
Started	208	208	176
Completed	38	28	34
Not completed	170	180	142
Completed and exited earlier than defined visit	70	74	28
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	18	27	18
Adverse event, non-fatal	20	12	14
Other	4	7	12
Non-compliance with study drug	2	2	2
Lost to follow-up	11	12	5
Failed to meet clinical benefit criteria	43	43	62
Lack of efficacy	1	3	1

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	592	592	
Age categorical Units: Subjects			
Adults (18-64 years)	532	532	
From 65-84 years	60	60	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	45.17		
standard deviation	± 14.446	-	
Gender categorical Units: Subjects			
Female	343	343	
Male	249	249	

Subject analysis sets

Subject analysis set title	overall trials
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population was comprised of all randomized subjects. The ITT population was the analysis population for the primary analysis and was analyzed with subjects as randomized.

Reporting group values	overall trials		
Number of subjects	592		
Age categorical Units: Subjects			
Adults (18-64 years)	532		
From 65-84 years	60		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	45.17		
standard deviation	± 14.446		
Gender categorical Units: Subjects			
Female	343		
Male	249		

End points

End points reporting groups

Reporting group title	44 µg DE-109
Reporting group description: -	
Reporting group title	440 µg DE-109
Reporting group description: -	
Reporting group title	880 µg DE-109
Reporting group description: -	
Subject analysis set title	overall trials
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population was comprised of all randomized subjects. The ITT population was the analysis population for the primary analysis and was analyzed with subjects as randomized.

Primary: VH 0 response

End point title	VH 0 response

End point description:

End point type	Primary

End point timeframe:

VH 0 response, was defined as having a VH score of 0 at Month 5 (1 month after receiving the third double-masked injection at Month 4) based on the modified SUN photographic scale.

End point values	44 µg DE-109	440 µg DE-109	880 µg DE-109	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	208	208	176	
Units: Responders	28	44	27	

Statistical analyses

Statistical analysis title	Primary analysis: 44 µg vs 440 µg

Statistical analysis description:

The primary analysis of the primary endpoint was performed using the Fisher's Exact test for a 2×2 contingency table conducted for the following pairs of testing hypotheses:
H0A: п44 = п440 vs. H1A: п44 ≠ п440

Comparison groups	440 µg DE-109 v 44 µg DE-109
Number of subjects included in analysis	416
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0381 [1]
Method	Fisher exact

Notes:

[1] - The difference between the 440 µg dose group and the 44 µg dose group was statistically significant, with an unadjusted p-value of 0.0126 and an adjusted p-value of 0.0252.

Statistical analysis title	Primary analysis: 44 µg vs 880 µg

Statistical analysis description:

The primary analysis of the primary endpoint was performed using the Fisher’s Exact test for a 2×2 contingency table conducted for the following pairs of testing hypotheses:
H0A: п44 = п880 vs. H1A: п44 ≠ п880

Comparison groups	44 µg DE-109 v 880 µg DE-109
Number of subjects included in analysis	384
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6004 [2]
Method	Fisher exact

Notes:

[2] - The difference between the 440 µg dose group and the 44 µg dose group was statistically significant, with an unadjusted p-value of 0.0126 and an adjusted p-value of 0.0252.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were elicited from subjects following the first DE-109 injection on Day 1 through the end of 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	173 / 590 (29.32%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Central nervous system lymphoma			
subjects affected / exposed	2 / 590 (0.34%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Breast cancer metastatic			
subjects affected / exposed	1 / 590 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 590 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Medication residue			

subjects affected / exposed	12 / 590 (2.03%)		
occurrences causally related to treatment / all	18 / 18		
deaths causally related to treatment / all	0 / 0		
Device dislocation			
subjects affected / exposed	1 / 590 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Contrast media allergy			
subjects affected / exposed	1 / 590 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	1 / 590 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Intraocular pressure increased			
subjects affected / exposed	13 / 590 (2.20%)		
occurrences causally related to treatment / all	8 / 13		
deaths causally related to treatment / all	0 / 0		
Fibrin			
subjects affected / exposed	1 / 590 (0.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Intraocular pressure decreased			
subjects affected / exposed	1 / 590 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Cataract traumatic			

subjects affected / exposed	3 / 590 (0.51%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Corneal abrasion				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Foot fracture				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hip fracture				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower limb fracture				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Coronary artery disease				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				

subjects affected / exposed	1 / 590 (0.17%)		
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 / 590 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Multiple sclerosis			
subjects affected / exposed	1 / 590 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Optic neuritis			
subjects affected / exposed	1 / 590 (0.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 590 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Uveitis			
subjects affected / exposed	35 / 590 (5.93%)		
occurrences causally related to treatment / all	11 / 44		
deaths causally related to treatment / all	0 / 0		
Choroiditis			
subjects affected / exposed	18 / 590 (3.05%)		
occurrences causally related to treatment / all	1 / 21		
deaths causally related to treatment / all	0 / 0		
Cataract			
subjects affected / exposed	16 / 590 (2.71%)		
occurrences causally related to treatment / all	3 / 19		
deaths causally related to treatment / all	0 / 0		
Cataract subcapsular			

subjects affected / exposed	4 / 590 (0.68%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Non-infectious endophthalmitis				
subjects affected / exposed	18 / 590 (3.05%)			
occurrences causally related to treatment / all	18 / 19			
deaths causally related to treatment / all	0 / 0			
Iridocyclitis				
subjects affected / exposed	6 / 590 (1.02%)			
occurrences causally related to treatment / all	4 / 6			
deaths causally related to treatment / all	0 / 0			
Visual acuity reduced				
subjects affected / exposed	4 / 590 (0.68%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Vitritis				
subjects affected / exposed	8 / 590 (1.36%)			
occurrences causally related to treatment / all	3 / 8			
deaths causally related to treatment / all	0 / 0			
Glaucoma				
subjects affected / exposed	4 / 590 (0.68%)			
occurrences causally related to treatment / all	1 / 5			
deaths causally related to treatment / all	0 / 0			
Retinal detachment				
subjects affected / exposed	6 / 590 (1.02%)			
occurrences causally related to treatment / all	2 / 9			
deaths causally related to treatment / all	0 / 0			
Intermediate uveitis				
subjects affected / exposed	3 / 590 (0.51%)			
occurrences causally related to treatment / all	1 / 4			
deaths causally related to treatment / all	0 / 0			
Cystoid macular oedema				

subjects affected / exposed	5 / 590 (0.85%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 0			
Eye inflammation				
subjects affected / exposed	3 / 590 (0.51%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Macular oedema				
subjects affected / exposed	2 / 590 (0.34%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Optic atrophy				
subjects affected / exposed	2 / 590 (0.34%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Optic neuropathy				
subjects affected / exposed	2 / 590 (0.34%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Vitreous haemorrhage				
subjects affected / exposed	2 / 590 (0.34%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Anterior chamber inflammation				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Choroidal neovascularisation				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Corneal deposits				

subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Corneal epithelium defect				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Corneal oedema				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eye haemorrhage				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Eye pain				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Iritis				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Macular fibrosis				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Macular hole				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ocular hypertension				

subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Ocular vasculitis				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Open angle glaucoma				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal haemorrhage				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal infiltrates				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal oedema				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal tear				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Uveitic glaucoma				
subjects affected / exposed	1 / 590 (0.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholecystitis acute				

subjects affected / exposed	1 / 590 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	2 / 590 (0.34%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	2 / 590 (0.34%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 590 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Endophthalmitis			
subjects affected / exposed	6 / 590 (1.02%)		
occurrences causally related to treatment / all	5 / 6		
deaths causally related to treatment / all	0 / 0		
Eye infection toxoplasmal			
subjects affected / exposed	2 / 590 (0.34%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Appendicitis			
subjects affected / exposed	2 / 590 (0.34%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 590 (0.34%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Anal abscess			
subjects affected / exposed	1 / 590 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Candidiasis			
subjects affected / exposed	1 / 590 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Keratitis herpetic			
subjects affected / exposed	1 / 590 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tooth infection			
subjects affected / exposed	1 / 590 (0.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 590 (0.17%)		
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	514 / 590 (87.12%)		
Investigations			
Intraocular pressure increased			
subjects affected / exposed	139 / 590 (23.56%)		
occurrences (all)	236		
Eye disorders			
Iridocyclitis			
subjects affected / exposed	114 / 590 (19.32%)		
occurrences (all)	214		
Uveitis			

subjects affected / exposed	84 / 590 (14.24%)		
occurrences (all)	117		
Conjunctival haemorrhage			
subjects affected / exposed	79 / 590 (13.39%)		
occurrences (all)	115		
Cataract			
subjects affected / exposed	68 / 590 (11.53%)		
occurrences (all)	75		
Cataract subcapsular			
subjects affected / exposed	46 / 590 (7.80%)		
occurrences (all)	48		
Eye pain			
subjects affected / exposed	67 / 590 (11.36%)		
occurrences (all)	88		
Intermediate uveitis			
subjects affected / exposed	60 / 590 (10.17%)		
occurrences (all)	103		
Cystoid macular oedema			
subjects affected / exposed	53 / 590 (8.98%)		
occurrences (all)	70		
Conjunctival hyperaemia			
subjects affected / exposed	35 / 590 (5.93%)		
occurrences (all)	43		
Choroiditis			
subjects affected / exposed	33 / 590 (5.59%)		
occurrences (all)	45		
Macular oedema			
subjects affected / exposed	30 / 590 (5.08%)		
occurrences (all)	39		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 March 2012	SAKURA commenced subject randomization and treatments under Protocol 32-007, Amendment #2. Protocol Amendment #3 was developed to extend the overall study duration to 24 months and to introduce open-label treatments with the 880 µg dose to ensure enough safety information would be established to support regulatory filings. The transition from Protocol Amendment #2 to Protocol Amendment #3 resulted in a total of 88 subjects whose data from Month 6 to Month 12 were collected during the Double-Masked PRN Treatment Period under Amendment #2. Under Protocol Amendment #3, subjects who completed the 6-month Double-Masked Treatment Period entered the 6-month Open-Label Treatment Period with 3 IVT injections of open-label 880 µg dose administered at Month 6, Month 8, and Month 10. At Month 12, subjects were assessed to determine if they have achieved clinical benefit. Subjects who did not achieve clinical benefit during the first 12 months of the study concluded participation at the Month 12 visit. Subjects who achieved clinical benefit were invited to continue participating in the study and were eligible to receive open-label 880 µg DE-109 PRN per retreatment criteria on or after Month 12, no more frequently than every 2 months up to Month 22, and completed the study at the Month 24 visit (Open-Label Retreatment Period). The overall study duration was 24 months under Protocol Amendment #3.
06 November 2012	Key changes in the Protocol Amendment #4 included: - Modified the definition of clinical benefit assessed at Month 12 - Clinical benefit was defined as achieving of a VH score of ≤ 0.5+ at both Month 10 and Month 12, without any use of rescue therapy between Months 6 through 12. This adjusted definition reflected what key opinion leaders in the treatment of posterior segment uveitis consider clinical benefit in practice. It also more closely aligned with the primary endpoint of the study (i.e., having a VH score of 0 at Month 5 [modified SUN scale]). If a subject continued to have a VH score of ≥ 1, the subject were discontinued from study participation and could have been treated with additional alternative treatments. - Clarified the retreatment criteria and the DE-109 dose for the 12-month Open-Label Retreatment Period - Added a secondary endpoint: "Proportion of subjects with a VH score of 0 or 0.5+ at Month 5 (modified SUN scale)", i.e., VH 0 or 0.5+ response - Clarified a secondary endpoint: "Proportion of subjects with a VH score of 0 or at least a 2-unit improvement in VH score at Month 5 (modified SUN scale)", i.e., VH 0 or 2-unit response

08 April 2014	Santen decided to proceed with commercial development of the 440 µg dose for the treatment of non-infectious uveitis of the posterior segment with a planned unmasked analysis of SAKURA Study 1 that was conducted on the 6-month data of the 347 randomized subjects. Based on this decision, the 32-007 protocol was further amended (Amendment #5) to randomize subjects to receive only the 44 µg or the 440 µg dose during the 6-month Double-Masked Treatment Period in Study 2. This amendment also resulted in phasing out the 880 µg dose in the Open-Label Treatment and Retreatment Periods of both SAKURA studies. Specifically, all ongoing SAKURA subjects who had completed the 6-month Double-Masked Treatment Period and were being treated with open-label 880 µg returned to the investigational site at the next scheduled visit and exited from the study. Key changes: For SAKURA Study 1 and Study 2: - The overall sample size of the SAKURA program (Study 1 and Study 2 combined) was adjusted from approximately 500 to approximately 600 subjects - Subjects beyond the Double-Masked Treatment Period (i.e., subjects under the treatment of open-label 880 µg dose in the Open-Label Treatment Period or the Open-Label Retreatment Period) returned to the investigational site at the next scheduled visit and exited the study For SAKURA Study 2 Alone: - Enrollment was limited to the US and India to approximate subject demographics/characteristics of the SAKURA Study 1 subject population - Eligible subjects from the US and India were randomized in a 1:1 ratio to receive either 44 or 440 µg DE-109 and continued treatment through Month 6 after Amendment #5 was in effect - There was no Open-Label Treatment or Retreatment Period - Response rates for the primary endpoint (VH 0 response) were compared between the 44 and 440 µg doses as the primary comparison - All treatment comparisons of the efficacy endpoints between the 880 µg dose and the 44 µg dose were performed for exploratory purposes only

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported