Clinical trial results:
A Phase I/IIA Dose Escalation Safety Study of Subretinally Injected SAR422459, Administered to Patients With Stargardt's Macular Degeneration

Summary

EudraCT number	2010-023111-34
Trial protocol	FR NL IT Outside EU/EEA
Global end of trial date	16 August 2019

Results information

Result version number	v1 (current)
This version publication date	29 February 2020
First version publication date	29 February 2020

Trial information

Trial identification

Sponsor protocol code	TDU13583

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01367444
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & Développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly-Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002407-PIP01-18
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 September 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 August 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and tolerability of ascending doses of SAR422459 in subjects with Stargardt Macular Degeneration (SMD).

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of adult and paediatric subjects with SMD. In case of pediatric subjects recruited: the parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimised. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. Anesthesia had been used to minimise distress and discomfort. Adult subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the sponsors personal data protection charter ensuring that the Sponsor abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 June 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	France: 14
Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	27
EEA total number of subjects	14

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)	1
Adults (18-64 years)	25
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The Study was conducted in France and the United States between 08-June-2011 and 02-July-2019. The trial ended prematurely, end of trial date declaration to health authorities was 16-August-2019.

Pre-assignment

Screening details:

A total of 35 subjects who had SMD were screened, out of which 27 subjects were enrolled in 7 cohorts (Cohorts 1 to 7).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1

Arm description:

Subjects (aged greater than or equal to [>=] 18 years) with advanced SMD, and visual acuity (VA) less than or equal to (<=) 20/200 in the worst eye and severe cone-rod dysfunction with no detectable or severely abnormal full-field electroretinography (ERG) responses, received SAR422459 at lowest target dose level 1.8*10^5 transducing units (TU)/eye.

Arm type	Experimental
Investigational medicinal product name	SAR422459
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subretinal use

Dosage and administration details:

Subjects received 300 microlitres (µL) of subretinal injection with vector total target dose of 1.8*10^5 TU per eye.

Arm title	Cohort 2

Arm description:

Subjects (aged >=18 years) with SMD, and VA <=20/200 in the worst eye with abnormal full-field ERG responses, received SAR422459 at lowest target dose level 1.8*10^5 TU/eye.

Arm type	Experimental
Investigational medicinal product name	SAR422459
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subretinal use

Dosage and administration details:

Subjects received 300 µL of subretinal injection with vector total target dose of 1.8*10^5 TU per eye.

Arm title	Cohort 3

Arm description:

Subjects (aged >=18 years) with SMD, and VA <=20/200 in the worst eye with abnormal full-field ERG responses, received SAR422459 at escalated target dose level 6*10^5 TU/eye.

Arm type	Experimental

Investigational medicinal product name	SAR422459
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subretinal use

Dosage and administration details:

Subjects received 300 µL of subretinal injection with vector total target dose of 6*10^5 TU per eye.

Arm title	Cohort 4

Arm description:

Subjects (aged >=18 years) with SMD, and VA <=20/200 in the worst eye with abnormal full-field ERG responses, received SAR422459 at target dose level 1.8*10^6 TU/eye.

Arm type	Experimental
Investigational medicinal product name	SAR422459
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subretinal use

Dosage and administration details:

Subjects received 300 µL of subretinal injection with vector total target dose of 1.8*10^6 TU per eye.

Arm title	Cohort 5

Arm description:

Subjects (aged >=18 years) with SMD, and VA <=20/100 in the worst eye with abnormal full-field ERG responses, received SAR422459 at highest target dose level 1.8*10^6 TU/eye.

Arm type	Experimental
Investigational medicinal product name	SAR422459
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subretinal use

Dosage and administration details:

Subjects received 300 µL of subretinal injection with vector total target dose of 1.8*10^6 TU per eye.

Arm title	Cohort 6

Arm description:

Subjects (aged 6 to 26 years) with symptomatic early or childhood-onset SMD, and VA >=20/200 in both eyes at the time of the screening visit and anticipated to experience rapid deterioration in visual function and/or retinal structure, received SAR422459 at highest target dose level 1.8*10^6 TU/eye.

Arm type	Experimental
Investigational medicinal product name	SAR422459
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subretinal use

Dosage and administration details:

Subjects received 300 µL of subretinal injection with vector total target dose of 1.8*10^6 TU per eye.

Arm title	Cohort 7

Arm description:

Paediatric subjects (aged 6 to 17 years) with symptomatic SMD, and VA >=20/100 in both eyes at the time of the screening visit and anticipated to experience rapid deterioration in visual function and/or retinal structure, received SAR422459 at highest target dose level 1.8*10^6 TU/eye.

Arm type	Experimental

Investigational medicinal product name	SAR422459
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subretinal use

Dosage and administration details:

Paediatric subjects received 300 µL of subretinal injection with vector total target dose of 1.8*10^6 TU per eye.

Number of subjects in period 1	Cohort 1	Cohort 2	Cohort 3
Started	4	4	4
Completed	4	4	4

Number of subjects in period 1	Cohort 4	Cohort 5	Cohort 6
Started	4	6	4
Completed	4	6	4

Number of subjects in period 1	Cohort 7
Started	1
Completed	1

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1
Reporting group description:	
Subjects (aged greater than or equal to [>=] 18 years) with advanced SMD, and visual acuity (VA) less than or equal to (<=) 20/200 in the worst eye and severe cone-rod dysfunction with no detectable or severely abnormal full-field electroretinography (ERG) responses, received SAR422459 at lowest target dose level 1.8*10^5 transducing units (TU)/eye.	
Reporting group title	Cohort 2
Reporting group description:	
Subjects (aged >=18 years) with SMD, and VA <=20/200 in the worst eye with abnormal full-field ERG responses, received SAR422459 at lowest target dose level 1.8*10^5 TU/eye.	
Reporting group title	Cohort 3
Reporting group description:	
Subjects (aged >=18 years) with SMD, and VA <=20/200 in the worst eye with abnormal full-field ERG responses, received SAR422459 at escalated target dose level 6*10^5 TU/eye.	
Reporting group title	Cohort 4
Reporting group description:	
Subjects (aged >=18 years) with SMD, and VA <=20/200 in the worst eye with abnormal full-field ERG responses, received SAR422459 at target dose level 1.8*10^6 TU/eye.	
Reporting group title	Cohort 5
Reporting group description:	
Subjects (aged >=18 years) with SMD, and VA <=20/100 in the worst eye with abnormal full-field ERG responses, received SAR422459 at highest target dose level 1.8*10^6 TU/eye.	
Reporting group title	Cohort 6
Reporting group description:	
Subjects (aged 6 to 26 years) with symptomatic early or childhood-onset SMD, and VA >=20/200 in both eyes at the time of the screening visit and anticipated to experience rapid deterioration in visual function and/or retinal structure, received SAR422459 at highest target dose level 1.8*10^6 TU/eye.	
Reporting group title	Cohort 7
Reporting group description:	
Paediatric subjects (aged 6 to 17 years) with symptomatic SMD, and VA >=20/100 in both eyes at the time of the screening visit and anticipated to experience rapid deterioration in visual function and/or retinal structure, received SAR422459 at highest target dose level 1.8*10^6 TU/eye.	

Reporting group values	Cohort 1	Cohort 2	Cohort 3
Number of subjects	4	4	4
Age categorical Units: Subjects			
Age continuous Units: years			
median	55.5	40	44.5
full range (min-max)	32 to 66	30 to 63	35 to 60
Gender categorical Units: Subjects			
Female	1	3	4
Male	3	1	0

Race Units: Subjects			
Asian	0	0	1
Black or African American	0	0	0
White	4	4	3

Reporting group values	Cohort 4	Cohort 5	Cohort 6
Number of subjects	4	6	4
Age categorical Units: Subjects			
Age continuous Units: years			
median	40	28	23
full range (min-max)	28 to 56	24 to 41	21 to 37
Gender categorical Units: Subjects			
Female	0	2	2
Male	4	4	2
Race Units: Subjects			
Asian	0	0	0
Black or African American	1	0	0
White	3	6	4

Reporting group values	Cohort 7	Total	
Number of subjects	1	27	
Age categorical Units: Subjects			
Age continuous Units: years			
median	16		
full range (min-max)	16 to 16	-	
Gender categorical Units: Subjects			
Female	1	13	
Male	0	14	
Race Units: Subjects			
Asian	0	1	
Black or African American	0	1	
White	1	25	

End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description:	
Subjects (aged greater than or equal to [>=] 18 years) with advanced SMD, and visual acuity (VA) less than or equal to (<=) 20/200 in the worst eye and severe cone-rod dysfunction with no detectable or severely abnormal full-field electroretinography (ERG) responses, received SAR422459 at lowest target dose level 1.8*10^5 transducing units (TU)/eye.	

Reporting group title	Cohort 2
Reporting group description:	
Subjects (aged >=18 years) with SMD, and VA <=20/200 in the worst eye with abnormal full-field ERG responses, received SAR422459 at lowest target dose level 1.8*10^5 TU/eye.	

Reporting group title	Cohort 3
Reporting group description:	
Subjects (aged >=18 years) with SMD, and VA <=20/200 in the worst eye with abnormal full-field ERG responses, received SAR422459 at escalated target dose level 6*10^5 TU/eye.	

Reporting group title	Cohort 4
Reporting group description:	
Subjects (aged >=18 years) with SMD, and VA <=20/200 in the worst eye with abnormal full-field ERG responses, received SAR422459 at target dose level 1.8*10^6 TU/eye.	

Reporting group title	Cohort 5
Reporting group description:	
Subjects (aged >=18 years) with SMD, and VA <=20/100 in the worst eye with abnormal full-field ERG responses, received SAR422459 at highest target dose level 1.8*10^6 TU/eye.	

Reporting group title	Cohort 6
Reporting group description:	
Subjects (aged 6 to 26 years) with symptomatic early or childhood-onset SMD, and VA >=20/200 in both eyes at the time of the screening visit and anticipated to experience rapid deterioration in visual function and/or retinal structure, received SAR422459 at highest target dose level 1.8*10^6 TU/eye.	

Reporting group title	Cohort 7
Reporting group description:	
Paediatric subjects (aged 6 to 17 years) with symptomatic SMD, and VA >=20/100 in both eyes at the time of the screening visit and anticipated to experience rapid deterioration in visual function and/or retinal structure, received SAR422459 at highest target dose level 1.8*10^6 TU/eye.	

Primary: Percentage of Subjects With Treatment-emergent Adverse Events (TEAEs)

End point title	Percentage of Subjects With Treatment-emergent Adverse Events (TEAEs)[1]
End point description:	
An adverse event (AE) was any unfavorable and unintended physical sign, symptom, or laboratory parameter that developed or worsened in severity during the course of the study, whether or not considered related to the investigational product. The TEAEs were defined as any event that started or increased in severity after the subject received IMP, including abnormal laboratory results, electrocardiogram, etc. Analysis was performed on all subjects with SMD who were included in the study.	
End point type	Primary
End point timeframe:	
From Baseline to Week 48	

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: Incidence of TEAEs were computed statistically, though they were descriptive. No p-values

of cohort comparisons were derived for the early-terminated study.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	4
Units: percentage of subjects				
number (not applicable)	100	100	100	100

End point values	Cohort 5	Cohort 6	Cohort 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	4	1	
Units: percentage of subjects				
number (not applicable)	100	100	100	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With TEAEs by Severity

End point title	Percentage of Subjects With TEAEs by Severity[2]

End point description:

An AE was any unfavorable and unintended physical sign, symptom, or laboratory parameter that developed or worsened in severity during the course of the study, whether or not considered related to the investigational product. For each AE, the severity was categorised as either mild, moderate or severe where 'mild' was defined as discomfort noticed but did not interfere with the subject's daily routines (an annoyance), 'moderate' was defined as some impairment of function, not hazardous to health (uncomfortable or embarrassing), and 'severe' was defined as significant impairment of function, hazardous to health (incapacitating). Analysis was performed on all subjects with SMD who were included in the study.

End point type	Primary

End point timeframe:

From Baseline to Week 48

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: Incidence of TEAEs were computed statistically, though they were descriptive. No p-values of cohort comparisons were derived for the early-terminated study.

End point values	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	4	4
Units: percentage of subjects				
number (not applicable)				
Mild	100	100	100	100
Moderate	0	50	25	25
Severe	0	0	0	25

End point values	Cohort 5	Cohort 6	Cohort 7	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	4	1	
Units: percentage of subjects				
number (not applicable)				
Mild	100	100	100	
Moderate	33	75	100	
Severe	17	25	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from time of first dose of study drug up to end of study (Week 48) regardless of seriousness or relationship (causality) to investigational product.

Adverse event reporting additional description:

Reported AEs were TEAEs that developed/worsened during the 'on treatment period' (from Day 0 to Week 48). Analysis was performed on all subjects with SMD who were included in the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Cohort 1

Reporting group description:

Subjects (aged >=18 years) with advanced SMD, and VA <=20/200 in the worst eye and severe cone-rod dysfunction with no detectable or severely abnormal full-field ERG responses, received SAR422459 at lowest target dose level 1.8*10^5 TU/eye.

Reporting group title	Cohort 2

Reporting group description:

Subjects (aged >=18 years) with SMD, and VA <=20/200 in the worst eye with abnormal full-field ERG responses, received SAR422459 at lowest target target dose level 1.8*10^5 TU/eye.

Reporting group title	Cohort 3

Reporting group description:

Subjects (aged >=18 years) with SMD, and VA <=20/200 in the worst eye with abnormal full-field ERG responses, received SAR422459 at escalated target dose level 6*10^5 TU/eye.

Reporting group title	Cohort 4

Reporting group description:

Subjects (aged >=18 years) with SMD, and VA <=20/200 in the worst eye with abnormal full-field ERG responses, received SAR422459 at target dose level 1.8*10^6 TU/eye.

Reporting group title	Cohort 5

Reporting group description:

Subjects (aged >=18 years) with SMD, and VA <=20/100 in the worst eye with abnormal full-field ERG responses, received SAR422459 at highest target dose level 1.8*10^6 TU/eye.

Reporting group title	Cohort 6

Reporting group description:

Subjects (aged 6 to 26 years) with symptomatic early or childhood-onset SMD, and VA >=20/200 in both eyes at the time of the screening visit and anticipated to experience rapid deterioration in visual function and/or retinal structure, received SAR422459 at highest target dose level 1.8*10^6 TU/eye.

Reporting group title	Cohort 7

Reporting group description:

Paediatric subjects (aged 6 to 17 years) with symptomatic SMD, and VA >=20/100 in both eyes at the time of the screening visit and anticipated to experience rapid deterioration in visual function and/or retinal structure, received SAR422459 at highest target dose level 1.8*10^6 TU/eye.

Serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0
Investigations			
Intraocular Pressure Increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (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
Eye disorders			
Chorioretinopathy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (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
Uveitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (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

Serious adverse events	Cohort 4	Cohort 5	Cohort 6
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Intraocular Pressure Increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (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			
Chorioretinopathy			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (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
Uveitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 7		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Intraocular Pressure Increased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Chorioretinopathy			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Uveitis			
subjects affected / exposed	0 / 1 (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: 0 %

Non-serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	4 / 4 (100.00%)	4 / 4 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Influenza Like Illness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal Pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Rhinorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Investigations			
Colour Vision Tests Abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Fundoscopy Abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Intraocular Pressure Decreased			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Intraocular Pressure Increased			
subjects affected / exposed	2 / 4 (50.00%)	3 / 4 (75.00%)	2 / 4 (50.00%)
occurrences (all)	3	3	2
Monoclonal Immunoglobulin Present			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Visual Field Tests Abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Cartilage Injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Corneal Abrasion			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Tongue Injury			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Ventricular Extrasystoles			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Tremor			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Visual Field Defect			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Eye disorders			

Anterior Chamber Cell			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Anterior Chamber Inflammation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cataract			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Chalazion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Choroidal Effusion			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Conjunctival Haemorrhage			
subjects affected / exposed	3 / 4 (75.00%)	2 / 4 (50.00%)	2 / 4 (50.00%)
occurrences (all)	3	2	2
Corneal Disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Diplopia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Dyschromatopsia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eye Discharge			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Eye Disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eye Inflammation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Eye Irritation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eye Pain			
subjects affected / exposed	2 / 4 (50.00%)	2 / 4 (50.00%)	1 / 4 (25.00%)
occurrences (all)	2	2	1
Eye Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	2 / 4 (50.00%)
occurrences (all)	0	1	2
Eyelid Irritation			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Hypotony Of Eye			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Keratic Precipitates			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Macular Fibrosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Macular Oedema			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Necrotising Retinitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Ocular Hyperaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Ocular Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Photopsia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1

Retinal Disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Retinal Haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Retinal Tear			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Serous Retinal Detachment			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Subretinal Fibrosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Subretinal Fluid			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	1	1	1
Trichiasis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Uveitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vision Blurred			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Visual Impairment			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vitreous Detachment			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Vitreous Floaters			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1

Vitreous Haemorrhage			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Xanthopsia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Dental Caries			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Irritable Bowel Syndrome			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dermal Cyst			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rash Erythematous			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Glycosuria			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Leukocyturia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Arthritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Back Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Muscle Spasms			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Neck Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Osteoarthritis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Pain In Extremity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Synovial Cyst			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	1	1	0
Conjunctivitis Viral			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Diarrhoea Infectious			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Ear Infection			

subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	2 / 4 (50.00%)	2 / 4 (50.00%)	1 / 4 (25.00%)
occurrences (all)	2	2	1
Sinusitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 4	Cohort 5	Cohort 6
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	6 / 6 (100.00%)	4 / 4 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Influenza Like Illness			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal Pain			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Investigations			
Colour Vision Tests Abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Fundoscopy Abnormal			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Intraocular Pressure Decreased			
subjects affected / exposed	1 / 4 (25.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Intraocular Pressure Increased			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Monoclonal Immunoglobulin Present			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Visual Field Tests Abnormal			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Cartilage Injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Corneal Abrasion			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Tongue Injury			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Ventricular Extrasystoles			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	2 / 4 (50.00%)
occurrences (all)	1	1	2
Tremor			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Visual Field Defect			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Anterior Chamber Cell			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Anterior Chamber Inflammation			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Cataract			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Chalazion			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Choroidal Effusion			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Conjunctival Haemorrhage			
subjects affected / exposed	1 / 4 (25.00%)	3 / 6 (50.00%)	0 / 4 (0.00%)
occurrences (all)	1	3	0
Corneal Disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Diplopia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Dyschromatopsia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Eye Discharge			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Eye Disorder			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Eye Inflammation			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Eye Irritation			
subjects affected / exposed	1 / 4 (25.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Eye Pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Eye Pruritus			
subjects affected / exposed	0 / 4 (0.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Eyelid Irritation			

subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hypotony Of Eye			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	2
Keratic Precipitates			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Macular Fibrosis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Macular Oedema			
subjects affected / exposed	0 / 4 (0.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Necrotising Retinitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Ocular Hyperaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Ocular Hypertension			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Photopsia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Retinal Disorder			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Retinal Haemorrhage			
subjects affected / exposed	1 / 4 (25.00%)	1 / 6 (16.67%)	2 / 4 (50.00%)
occurrences (all)	1	1	3
Retinal Tear			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Serous Retinal Detachment			

subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Subretinal Fibrosis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Subretinal Fluid			
subjects affected / exposed	0 / 4 (0.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Trichiasis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Uveitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Vision Blurred			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Visual Impairment			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Vitreous Detachment			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Vitreous Floaters			
subjects affected / exposed	0 / 4 (0.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Vitreous Haemorrhage			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Xanthopsia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Dental Caries			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Irritable Bowel Syndrome			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Vomiting			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Dermal Cyst			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Rash Erythematous			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Glycosuria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Leukocyturia			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Arthritis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Back Pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Muscle Spasms			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Neck Pain			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Osteoarthritis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pain In Extremity			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Synovial Cyst			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis Viral			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Diarrhoea Infectious			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Ear Infection			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			

Decreased Appetite			
subjects affected / exposed	0 / 4 (0.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 7		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Influenza Like Illness			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Oropharyngeal Pain			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	2		
Rhinorrhoea			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Insomnia			

subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Investigations			
Colour Vision Tests Abnormal			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Fundoscopy Abnormal			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Intraocular Pressure Decreased			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Intraocular Pressure Increased			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Monoclonal Immunoglobulin Present			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Visual Field Tests Abnormal			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Cartilage Injury			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Corneal Abrasion			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Tongue Injury			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Ventricular Extrasystoles			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Nervous system disorders			

Dizziness			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	2		
Visual Field Defect			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Lymphopenia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Eye disorders			
Anterior Chamber Cell			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Anterior Chamber Inflammation			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Cataract			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Chalazion			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Choroidal Effusion			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Conjunctival Haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Corneal Disorder			

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Diplopia				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Dyschromatopsia				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Eye Discharge				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Eye Disorder				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Eye Inflammation				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Eye Irritation				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Eye Pain				
subjects affected / exposed	1 / 1 (100.00%)			
occurrences (all)	1			
Eye Pruritus				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Eyelid Irritation				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Hypotony Of Eye				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Keratic Precipitates				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Macular Fibrosis				

subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Macular Oedema				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Necrotising Retinitis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Ocular Hyperaemia				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Ocular Hypertension				
subjects affected / exposed	1 / 1 (100.00%)			
occurrences (all)	1			
Photopsia				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Retinal Disorder				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Retinal Haemorrhage				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Retinal Tear				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Serous Retinal Detachment				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Subretinal Fibrosis				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Subretinal Fluid				
subjects affected / exposed	0 / 1 (0.00%)			
occurrences (all)	0			
Trichiasis				

subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Uveitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Vision Blurred			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Visual Impairment			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	2		
Vitreous Detachment			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Vitreous Floaters			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Vitreous Haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Xanthopsia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Dental Caries			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Irritable Bowel Syndrome			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		

Skin and subcutaneous tissue disorders			
Dermal Cyst			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Rash Erythematous			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Glycosuria			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Leukocyturia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Arthritis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Back Pain			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Muscle Spasms			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Neck Pain			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Osteoarthritis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		

Pain In Extremity			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	2		
Synovial Cyst			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Conjunctivitis Viral			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Diarrhoea Infectious			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Ear Infection			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	0 / 1 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2010	1) Amendment of exclusion criteria to include any known allergy to topical, injected or systemic corticosteroids. 2) Addition of guidance on the management of ocular inflammation.
31 March 2011	1) Inclusion of rationale for clinical dose. 2) Addition of blood samples for immunology and polymerase chain reaction and urine samples for biodistribution assessment at multiple time points. 3) Addition of study stopping criteria relating to inflammation after study drug injection. 4) Inclusion of further details regarding the intraocular injection. 5) Inclusion of text to state the site of subretinal injection would be selected in all subjects based on baseline clinical evaluation and ophthalmology assessments.
16 June 2011	1) Clarification of the defined subject cohorts. 2) Addition of text to describe the long-term follow-up safety study submitted as a separate protocol.
24 January 2012	1) Modifications were made to ophthalmology assessments and time points. 2) Addition of Section 'Adverse Events of Special Interest' (AESI) and Section 'Reporting a Serious Adverse Event' to the protocol.
14 April 2014	1) Study sponsorship was transferred from Oxford BioMedica Ltd. to Sanofi; administrative updates and alignment with Sanofi protocol standards regarding the AESI and SAE process were made.
12 November 2014	1) Extension of the safety evaluation to an additional group of subjects (Cohort 6) with a much less advanced stage of the disease that could be observed in adults and children (6 years and older). 2) To decrease the Cohort 5 sample size from up to 12 to up to 6. 3) To allow review of safety and biological data from Cohorts 1 to 5 by the Data Safety Monitoring Board and for an interim report to be submitted to regulatory authorities and institutional review board/ethics committee. 4) Addition of video-recording of surgery and/or intra-operative optical coherence tomography, where available. 5) Addition of new centres in the United States and European Union. 6) Addition of a centralised review committee for Cohort 6 to preoperatively review baseline study assessments. 7) Removal or addition of assessment time points. 8) Addition of secondary endpoints to evaluate safety and biological activity at bleb level. 9) Definition of the study eye.
10 March 2015	1) To provide clarification regarding the criteria used by Investigators to identify subjects anticipated to experience rapid deterioration.
16 December 2015	1) Replacement of each occurrence of StarGen™ to SAR422459.
25 February 2016	1) Changes to inclusion criteria for Cohort 6 to make enrollment for paediatric subjects more homogenous. 2) Addition of 28-day observation period imposed between first and second paediatric subjects enrolled in Cohort 6. 3) Addition of requirement to administer high dose, tapering course of oral systemic steroids early to subjects in particular clinical circumstances following vitreoretinal procedure.

28 July 2016	1) Inclusion of treatment with systemic corticosteroids following subretinal injection to protocol-defined anti-inflammatory regimen. 2) Addition of inclusion criteria relating to donation of blood, organs, tissues, or cells.
26 September 2017	1) Addition of Cohort 7. 2) Amendment to definition of baseline for treatment-emergent safety and efficacy signal assessments. 3) Update of inclusion criteria relating to rapid deterioration to better define period of reference assessments.
29 November 2018	1) Addition of Cohorts 8 and 9 to be treated with a 3-fold lower measured dose. 2) Addition of Diluent to be used with the IMP. 3) Added information of the administered dose by measured strength. 4) Reduction of subject number in Cohorts 6 and 7. 5) Prophylactic intravenous methylprednisolone injection would be administered 2 hours before surgery instead of after surgery. 6) Subretinal recommendation shortening to allow better adaptation of retinotomy and IMP injection to individual subject and surgery practices. 7) Correction of inconsistencies. This amended protocol was approved by Health Authorities, but not by institutional review boards (IRBs)/Ethics committee (EC) and not implemented at site level.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The planned analysis was adjusted and carried out on the available safety data collected before the Sponsor’s decision to stop SAR422459 development prematurely.

Notes: