



Clinical trial results:

A Phase I/IIA Dose Escalation Safety Study of Subretinally Injected SAR421869, Administered to Patients with Retinitis Pigmentosa Associated with Usher Syndrome Type 1B

Summary

EudraCT number	2012-002574-31
Trial protocol	FR
Global end of trial date	16 August 2019

Results information

Result version number	v1 (current)
This version publication date	30 April 2020
First version publication date	30 April 2020

Trial information

Trial identification

Sponsor protocol code	TDU13600
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01505062
WHO universal trial number (UTN)	-
Other trial identifiers	Oxford Biomedica: US1/001/10

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)	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	13 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 evaluate the safety and tolerability of ascending doses of subretinal injections of SAR421869 in subjects with Usher Syndrome Type 1B.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of adult Usher syndrome type 1B. 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 was 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	26 March 2012
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: 4
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	9
EEA total number of subjects	4

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)	9
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In 2017, Sanofi suspended trials of SAR421869, while assessing its future. Until final decision was made, trial TDU13600 was not complete and in fact, further recruitment was planned. In 2019, Sanofi decided to terminate trial due to final decision on SAR421869, and shared decision with health authorities. Results have been reported expeditiously.

Pre-assignment

Screening details:

A total of 11 subjects were screened. Nine subjects of them were enrolled in the study with 3 subjects in each of Cohorts 1 to 3. Due to early termination no subject was recruited in Cohorts 4 and 5.

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 received subretinally a single injection of SAR421869 at target dose of 1.4×10^5 transducing units (TU) per eye.

Arm type	Experimental
Investigational medicinal product name	SAR421869
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 1.4×10^5 TU into one eye (study eye).

Arm title	Cohort 2
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Arm description:

Subjects received subretinally a single injection of SAR421869 at target dose of 4.7×10^5 TU per eye.

Arm type	Experimental
Investigational medicinal product name	SAR421869
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 4.7×10^5 TU into one eye (study eye).

Arm title	Cohort 3
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Arm description:

Subjects received subretinally a single injection of SAR421869 at target dose of 1.4×10^6 TU per eye.

Arm type	Experimental
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Investigational medicinal product name	SAR421869
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 1.4×10^6 TU into one eye (study eye).

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

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1
Reporting group description: Subjects received subretinally a single injection of SAR421869 at target dose of 1.4×10^5 transducing units (TU) per eye.	
Reporting group title	Cohort 2
Reporting group description: Subjects received subretinally a single injection of SAR421869 at target dose of 4.7×10^5 TU per eye.	
Reporting group title	Cohort 3
Reporting group description: Subjects received subretinally a single injection of SAR421869 at target dose of 1.4×10^6 TU per eye.	

Reporting group values	Cohort 1	Cohort 2	Cohort 3
Number of subjects	3	3	3
Age categorical Units: Subjects			

Age continuous Units: years median full range (min-max)	25 22 to 28	42 32 to 57	50 32 to 56
Gender categorical Units: Subjects			
Female	2	2	2
Male	1	1	1
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	3	3	3
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	9		
Age categorical Units: Subjects			

Age continuous Units: years median full range (min-max)	-		
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Gender categorical			
Units: Subjects			
Female	6		
Male	3		
Race			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	0		
White	9		
More than one race	0		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	Cohort 1
Reporting group description: Subjects received subretinally a single injection of SAR421869 at target dose of 1.4×10^5 transducing units (TU) per eye.	
Reporting group title	Cohort 2
Reporting group description: Subjects received subretinally a single injection of SAR421869 at target dose of 4.7×10^5 TU per eye.	
Reporting group title	Cohort 3
Reporting group description: Subjects received subretinally a single injection of SAR421869 at target dose of 1.4×10^6 TU per 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 medicinal product (IMP). 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 diagnosed with Retinitis Pigmentosa associated Usher syndrome type 1B 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	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	3	
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 IMP. The TEAEs were defined as any event that started or increased in severity after the subject	

received IMP, including abnormal laboratory results, electrocardiogram, etc. 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 diagnosed with Retinitis Pigmentosa associated Usher syndrome type 1B who were included in the study.

End point type	Primary
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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	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	3	
Units: Percentage of subjects				
number (not applicable)				
Mild	100	100	100	
Moderate	0	33	67	
Severe	0	0	67	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from time of first dose of study drug up to 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 diagnosed with Retinitis Pigmentosa associated Usher syndrome type 1B who were included in the study.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Cohort 1
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Reporting group description:

Subjects received subretinally a single injection of SAR421869 at target dose of 1.4×10^5 TU per eye.

Reporting group title	Cohort 2
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Reporting group description:

Subjects received subretinally a single injection of SAR421869 at target dose of 4.7×10^5 TU per eye.

Reporting group title	Cohort 3
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Reporting group description:

Subjects received subretinally a single injection of SAR421869 at target dose of 1.4×10^6 TU per eye.

Serious adverse events	Cohort 1	Cohort 2	Cohort 3
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 3 (66.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Eye disorders			
Uveitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual Acuity Reduced			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	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	3 / 3 (100.00%)	3 / 3 (100.00%)	3 / 3 (100.00%)
Investigations			
Blood Creatine Phosphokinase Increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Intraocular Pressure Decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Intraocular Pressure Increased			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	2 / 3 (66.67%)
occurrences (all)	0	2	2
Urine Analysis Abnormal			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
White Blood Cell Count Increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	3	0
Migraine			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Occipital Neuralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Syncope			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Injection Site Extravasation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Eye disorders			
Anterior Chamber Cell			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Cataract			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Conjunctival Haemorrhage			
subjects affected / exposed	3 / 3 (100.00%)	2 / 3 (66.67%)	0 / 3 (0.00%)
occurrences (all)	3	2	0
Dyschromatopsia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Eye Pain			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	2	1	1
Eye Pruritus			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	2	1	0
Macular Fibrosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Photophobia			

subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Photopsia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	2	1
Retinal Detachment			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Retinal Haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	2
Subretinal Fluid			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences (all)	2	0	0
Vision Blurred			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Visual Acuity Reduced			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Vitreous Floaters			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 3 (33.33%)
occurrences (all)	0	1	2
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1
Dental Caries			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (0.00%)
occurrences (all)	0	1	0
Dry Mouth			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	1	0	1
Gastrooesophageal Reflux Disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 3 (33.33%)
occurrences (all)	0	0	1

Nausea subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Vomiting subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0
Psychiatric disorders Nervousness subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0
Renal and urinary disorders Glycosuria subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0
Pollakiuria subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Urge Incontinence subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1
Increased Appetite subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	1 / 3 (33.33%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 October 2011	Amendment 1: 1) Modification of Part B of the study to include subjects' greater than or equal to (\geq) 18years old (Cohort 4) with less severe disease, treated at the maximum tolerated dose from Part A. 2) Addition of Part C of the study to include subjects ≥ 6 years of age (Cohort 5), administered the maximum tolerated dose determined from Part A following review of the safety and efficacy data (where available) by the data safety monitoring board, regulatory authorities and institutional review board/ethics committee. 3) Modifications were made to ophthalmology assessment timepoints.
31 August 2012	Amendment 2: 1) Addition of an inclusion criterion required French subjects to be affiliated with the French social security system which was followed by the addition of sites in France.
31 January 2013	Amendment 3: 1) To ensure consistency across sites: a centralised independent assessor evaluated subject's Day -28 visual field data to confirm eligibility, references to the subject's legal blindness as defined by the United States of America federal statute were removed from the eligibility criteria, and details of the parameters that were used to identify the "worst seeing eye" were added. 2) Addition of 'AEs of Special Interest' to the protocol. 3) Update to AE severity terms to reflect the impact on the subjects wellbeing. 4) Addition of information regarding post-mortem requirements.
22 January 2014	Amendment 4: 1) To add that subjects in France were asked to consent to a post-mortem as part of informed consent. 2) Update to inclusion criteria to include both rod and cone derived amplitudes on the full field electroretinogram. 3) Addition of exclusion criterion to exclude breast-feeding women from the study. 4) Removal of an exclusion criteria that could have been classed as discriminatory to mentally or physically disabled subjects. 5) Amendment ensured blood volume drawn from paediatric subjects was appropriate for their body weight.
14 April 2014	Amendment 5: 1) Study sponsorship was transferred from Oxford BioMedica Ltd. to Sanofi; administrative updates and alignment with Sanofi protocol standards regarding the AE of special interest (AESI) and serious AE process were made.
22 April 2015	Amendment 6: 1) Correction of errors to versioning of previous protocol amendments. 2) Revision of the inclusion criteria for Cohorts 3, 4, and 5 to clarify target populations to include subjects with no detectable rod-derived amplitudes on the full field electroretinogram. 3) Inclusion of collection of the results of the MYO7A gene mutation documenting subject eligibility. 4) Removal of 'Appendix C – Clinical Laboratory Tests' as multiple local labs were used with the addition of new sites. 5) Removal of text that states that if no clinical efficacy was observed in subjects after 1 year then the subject was offered alternative therapies. 6) Addition of text to allow video of the surgery and/or intraoperative Optical Coherence Tomography were collected/obtained consent from subjects already enrolled if a video was collected at surgery.

23 September 2015	Amendment 7: 1) Removal of inclusion criteria added in protocol amendment 2. 2) Addition of text defining a common perioperative medication regimen.
07 August 2018	Amendment 8: 1) Additional 6 subjects added to Part A (dose finding) to test additional dose levels. 2) Added mention of a diluent for IMP. 3) Inclusion criteria modified to better define target population. 4) Prophylactic glucocorticoid schedule added as mandatory after surgery and IMP injection. 5) Additional list of ophthalmic AESIs were added for better safety. 6) Simplified retinotomy description to allow better adaptation of retinotomy and IMP injection to individual subjects, with respect to lesion size and target retinal areas. 7) Correction of baseline definition was provided to use the data most close to the treatment for more precise evaluation of treatment-emergent safety events and efficacy signals. This amended protocol was approved by Health Authorities, but not by institutional review boards (IRBs)/Ethics committee (EC) and not implemented at study 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 only on the available safety and tolerability data collected before the Sponsor's decision to stop SAR421869 development prematurely.

Notes: