AMENDED CLINICAL PROTOCOL NO 12

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A Phase I/IIa Dose Escalation Safety Study of Subretinally Injected SAR422459, Administered to Patients with Stargardt's Macular Degeneration

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NCT01367444

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended clinical trial protocol 12	All	[29 November 2018], version 1 (electronic 10.0)
Amended clinical trial protocol 11	All	[26 September 2017], version 1 (electronic 9.0)
Amended clinical trial protocol 10	All	[28 July 2016], version 1 (electronic 8.0)
Amended clinical trial protocol 09	All	[25 February 2016], version 1 (electronic 7.0)
Amended clinical trial protocol 08	All	[16 December 2015], version 1 (electronic 6.0)
Amended clinical trial protocol 07	All	[10 March 2015], version 1 (electronic 4.0)
Amended clinical trial protocol 06	All	[12 November 2014], version 1 (electronic 3.0)
Amended clinical trial protocol 05	All	[14 April 2014], version 1 (electronic 1.0)
Amended clinical trial protocol 04	All	[24 January 2012], version 1
Amended clinical trial protocol 03	All	[16 June 2011], version 1
Amended clinical trial protocol 02	All	[31 March 2011], version 1
Amended clinical trial protocol 01	All	[14 December 2010], version 1
Original clinical trial Protocol	All	[27 October 2010], version 1

Amended protocol 12 (29 November 2018)

This amended protocol is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The protocol is being amended to reduce the dose of administered study drug and to review number of patients in cohorts yet to recruit, as well as other changed deemed necessary by the Sponsor.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Multiple sections	Addition of Cohorts 8 and 9 to be treated with a 3-fold lower administered dose.	Due to variability observed in previous batch strength patients in Cohort s 6 and 7 have received different doses when calculated by measured strength. While strength remained within specification, the patients in Cohorts 6 and 7 (treated with a new batch) received $4.5x10^6$ TU/eye dose. Review of safety data in Cohorts 6 and 7 by Sponsor and DSMB concluded that due to an increased number of IMP related adverse events, treatment dose needs to be down-escalated 3 times to ensure more safety while preserving transduction potential.
Multiple sections	[redacted] to be used with the IMP.	[redacted] of product prior to administration is added in relevant sections.
Synopsis, multiple sections	Adding information of the administered dose by measured strength.	Due to established need to better control administered dose of the IMP, measure of dose is changed from referring to dose by target strength to measured QC strength.
Summary, Study Flow Diagram (3), Sections 4.11 and 7	Reduction of patient number in Cohorts 6 and 7.	Due to above observation it is not planned to continue recruitment in Cohorts 6 and 7 with previous maximal dose.
9.2.2	Prophylactic IV methylprednisolone injection will be administered 2 hours before surgery instead of after surgery.	In the view of possible early reactions of immune system to subretinal injection an anticipated dose of IV glucocorticoid is planned to suppress start of any inflammatory reaction.
9.2.2	Subretinal recommendation shortening.	This will allow better adaptation of retinotomy and IMP injection to individual patient and surgery practices.
Section 7	Inconsistency due to edition error in Section 7 corrected (Cohort 5 data review by DSMB) – to match to Summary and other parts of the Protocol.	Error of edition was done in modifying this part of the text, referring to already performed activities in Cohort 5 data review.

NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	MEDICAL MONITOR [redacted]
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OTHER EMERGENCY TELEPHONE NUMBERS		

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1 LIST OF ABBREVIATIONS

A2E:	diretinoid pyridinium-ethanolamine
AAV:	adeno-associated virus
ABC:	adenosine triphosphate (ATP)-binding cassette
ABCA4:	ATP-binding cassette, sub-family A, member 4
ABCR:	retina specific ABC transporter
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
AMD:	age-related macular degeneration
ARVO:	Association for Research in Vision and Ophthalmology
ATP:	adenosine triphosphate
BCVA:	best-corrected visual acuity
cDNA:	complementary deoxyribonucleic acid
CFR:	code of federal regulations
CMV:	cytomegalovirus
CRF:	case report form
CRO:	Contract Research Organization
CS:	clinically significant
CVAQC-25:	25-item Cardiff visual ability questionnaire for children
DSMB:	data safety monitoring board
EC:	Ethics Committee
ECG:	electrocardiogram
eCRF:	electronic case report form
EIAV:	equine infectious anemia virus
ERG:	electroretinogram
ETDRS:	early treatment diabetic retinopathy study
EU:	European Union
EVA:	electronic visual acuity
FAF:	fundus autofluorescence
FDA:	U.S. Food and Drug Administration
FIM:	first in man
GATE:	German Adaptive Threshold Estimation (Strategy)
GCP:	Good Clinical Practice
GLP:	good laboratory practice
IB:	investigator brochure
ICH:	International Conference on Harmonization
IMP:	investigational medical product
IOP:	intraocular pressure
IRB:	institutional review board
ISCEV:	International Society for Clinical Electrophysiology of Vision
kb:	kiloBase

kDa:	kiloDalton
KO:	knockout
LCA:	Leber's Congenital Amaurosis
MOP:	technical manual of procedures
MTD:	maximum tolerated dose
NCS:	not clinically significant
NEI:	national eye institute
NHP:	non-human primates
OCT:	optical coherence tomography
OXB:	Oxford BioMedica
PCR:	polymerase chain reaction
PI:	principal investigator
PR:	photoreceptors
PRO:	patient reported outcomes
RPE:	retinal pigmented epithelium
SAE:	serious adverse event
SD-OCT:	spectral domain optical coherence tomography
SKP:	semi-automated kinetic perimetry
SMD:	Stargardt's macular degeneration
SOC:	standard of care
SUSAR:	suspected inexpected serious adverse reaction
[redacted]	[redacted]l
TU:	transducing units
ULN:	upper limit of normal
US:	United States
VA:	visual acuity
VFQ-25:	visual function questionnaire-25
VSV-G:	vesicular stomatitis virus G

INVESTIGATOR STATEMENT

I am aware of my responsibilities as an investigator under the guidelines of ICH-Good Clinical Practice, The Declaration of Helsinki, the Code of Federal Regulations, Title 21, the applicable regulations of the study site and the study protocol and I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control who will be involved in the study, ensuring they have access to the study protocol and any amendments and are aware of their obligations.

I, the undersigned, have read and agree with protocol number TDU13583.

Signed _____

Name _____

Date _____

2 SYNOPSIS

Official Title	A Phase I/IIa Dose Escalation Safety Study of Subretinally Injected SAR422459, Administered to Patients with Stargardt's Macular Degeneration
Clinical Phase	Phase I/IIa
Study Objectives:	
Primary Objectives	To assess the safety and tolerability of ascending doses of SAR422459 in patients with Stargardt's macular degeneration (SMD)
Secondary Objective	To evaluate for possible biological activity of SAR422459
Study Endpoints:	
Primary Endpoint	• The incidence and severity of treatment emergent adverse events. • Clinically important changes from baseline in the following safety assessments: - Best-corrected visual acuity (BCVA) - Slit-lamp examination - Fundoscopy/Indirect ophthalmoscopy - Fundus photography (color and infrared reflectance) - Intraocular pressure (IOP) - Microperimetry - Full-field static perimetry - Full-field kinetic perimetry - Optical Coherence Tomography (OCT) - Electroretinogram (ERG) - Laboratory parameters - Vital signs - Concomitant medications
Secondary Endpoints	To determine a delay in retinal degeneration following subretinal injection of SAR422459, through changes from baseline in visual function and retinal structure relative to the untreated contralateral eye utilizing the following retinal analytical techniques: • For visual function: - BCVA - Microperimetry - Full-field static perimetry - Full-field kinetic perimetry • For retinal structure: - OCT - Fundus Autofluorescence (FAF)
Other safety measures	SAR422459 distribution in the blood and urine assessed by polymerase chain reaction (PCR) Humoral response to SAR422459 administration Vital signs, physical examination, hematology, biochemistry, urinalysis and other laboratory data will be measured at various time points throughout the study

Exploratory efficacy endpoints	• Contrast sensitivity • Reading speed (Cohort 1-5; Cohorts 6-7, when possible) • Visual function/Quality of life questionnaires (Cohorts 1-5; Cohorts 6-7, when possible) • Multifocal ERG (Cohorts 1-5 only) • Adaptive optics (Cohorts 1-5 only)

Study Design

This is a phase I/IIa open label dose escalation study of subretinally injected SAR422459 in patients with SMD. In this study 3 doses of SAR422459 will be evaluated over 9 patient cohorts with 5 groups of patients. The first 4 cohorts will evaluate the dose escalation phase of the study and will each consist of 4 patients. Cohort 5, consisting of 6 patients, Cohort 6 of 4 patients, Cohort 7 having 1 patient receive the highest dose tested from the dose escalation phase. Cohorts 8 and 9, consisting of up to 6 and up to 8 patients respectively will receive the intermediate dose de-escalated after previous cohorts.

One study eye will be selected. If both eyes are eligible for the study, the worse eye, as per investigator judgment, will be selected. A centralized review will advise on the choice of the study eye if both eyes are clinically similar.

For Cohorts 6-9, the centralized review will also advise on the area to inject the treatment.

Five groups of patients (groups A, B, C, D, and E), will be recruited to this study. The advancement of disease for groups A, B, and C will be defined according to BCVA and electroretinogram (ERG) recordings, whereas group D will have less advanced disease as determined by clinical parameters.

- Group A: Patients (18 years or older) with advanced SMD, visual acuity (VA) ≤20/200 in the worst eye and severe cone-rod dysfunction with no detectable or severely abnormal full-field ERG responses.
- Group B: Patients (18 years or older) with SMD, VA ≤20/200 in the worst eye with abnormal full-field ERG responses.
- Group C: Patients (18 years or older) with SMD, VA ≤20/100 in the worst eye with abnormal full-field ERG responses.
- Group D: Patients (from 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 anticipated to experience rapid deterioration in visual function and/or retinal structure (1).
- Group E: Patients (from 6 to 17 years) with symptomatic SMD and, VA ≥20/100 in both eyes at the time of the screening visit anticipated to experience rapid deterioration in visual function and/or retinal structure.

Four Group A patients will receive SAR422459 at the lowest dose level ($1.8x10^5$ TU/eye dose Cohort 1). An interval of 21 days between dosing 2 consecutive patients in the cohort will be observed in order to assess the safety and tolerability of SAR422459 in these patients.

If after a minimum interval of 28 days following the dosing of the 4th patient in the cohort the safety and tolerability of Group A at the lowest dose is considered satisfactory by the Data Safety Monitoring Board (DSMB) then 4 Group B patients will also be enrolled into Cohort 2. These patients will also receive the $1.8x10^5$ TU/eye dose (the same dose of SAR422459 as dose Cohort 1), an interval of 21 days between dosing 2 consecutive patients will be observed.

If after a minimum interval of 28 days the safety and tolerability of group B in Cohort 2 is considered satisfactory by the DSMB the dose of SAR422459 will be escalated and 4 group B patients will be enrolled into Cohort 3 and receive a dose of $6x10^5$ TU/eye dose of SAR422459. An interval of 21 days between dosing 2 consecutive patients will be observed.

If after a minimum interval of 28 days from dosing the 4th patient of Group B in Cohort 3, the safety and tolerability of SAR422459 is considered satisfactory by the DSMB then the dose of SAR422459 will be escalated to the maximal dose ($1.8x10^6$ TU/eye), and 4 Group B patients will be enrolled into the next cohort (Cohort 4). An interval of 21 days between dosing 2 consecutive patients will be observed.

If after a minimum interval of 28 days from dosing the 4th patient of Group B in Cohort 4, the safety and tolerability is considered satisfactory by the DSMB then 6 patients in Group C will be enrolled and receive SAR422459 at the maximum tolerated dose (MTD) or the highest dose tested (Cohort 5).

For Cohort 5, an interval of 21 days between dosing the first patient and 2nd patient will be observed; subsequent patients may be enrolled in parallel.

If after a minimum interval of 28 days from dosing the last patient of Cohort 5, the safety and tolerability is considered satisfactory by the DSMB then eligible patients will be enrolled in Cohort 6 (group D) and will receive SAR422459 at the highest dose tested.

Prior to the inclusion of pediatric patients, the DSMB will review all safety data including the available data from all cohorts after the last patient of Cohort 5 has completed 12 weeks of follow-up after having been dosed. An interim report including all available safety data, preliminary efficacy data and the recommendations from the DSMB will be submitted to the regulatory authorities and

institutional review boards/ethics committees for approval before enrolling pediatric patients (<18 years). Additional patient data will be submitted to DSMB, if requested so.

Group D (Cohort 6) plans to enroll and treat patients (from 6 years to 26) with early or childhood onset symptomatic SMD and VA ≥20/200 in both eyes at the time of the screening visit anticipated to experience rapid deterioration in visual function and/or retinal structure.

An interval of 28 days between dosing of the first and second pediatric patients will be observed. Thereafter, subsequent pediatric patients may be enrolled consecutively.

Group E (Cohort 7) plans to enroll and treat patients (from 6 years to 17 years old) with symptomatic SMD and VA ≥20/100 in both eyes at the time of screening visit, anticipated to experience rapid deterioration in visual function and/or retinal structure. If patient is eligible in both - Cohorts 6 and 7 - she/he will be included in Cohort 7.

Cohort 8 will be treated with the 1.5 x10^6 TU measured strength dose and will enroll patients corresponding to Group D criteria: (from 6 years to 26 years old; early or childhood onset symptomatic SMD and VA ≥20/200 in both eyes at screening; rapid deterioration).

Cohort 9 will be treated with 1.5 x10^6 TU measured strength dose and will enroll patients corresponding to Group E criteria (from 6 years to 17 years old; symptomatic SMD and VA ≥20/100 in both eyes at screening; rapid deterioration. If patient is eligible in both - Cohorts 8 and 9 - she/he will be included in Cohort 9.

DSMB review of available data will be performed before starting treating patients younger than 16 years.

For Cohorts 6-9, to ensure consistency across sites, a centralized review will be conducted prior to Day 0 visit to make recommendations on the subretinal injection location and the targeted area of the bleb.

Cohort	Group	No of patients	Subretinal Injection			
			Dilution factor	Dose by target strength (TU/eye)*	Dose by measured strength (TU/eye)**	Volume
1	A	4	1:10	1.8x10^5 TU	0.48x10^5 TU	300 µL
2	B	4	1:10	1.8x10^5 TU	0.48x10^5 TU	300 µL
3	B	4	1:3	6x10^5 TU	3.6x10^5 TU	300 µL
4	B	4	undiluted	1.8x10^6 TU	0.99x10^6 TU	300 µL
5	C	6	undiluted	1.8x10^6 TU (highest dose targeted)	0.99x10^6 TU	300 µL
6	D	4	undiluted	1.8x10^6 TU (highest dose targeted)	4.5 x10^6 TU	300 µL
7	E	1	undiluted	1.8x10^6 TU (highest dose targeted)	4.5 x10^6 TU	300 µL
8	D	Up to 6	1:3	-	1.5 x10^6 TU	300 µL
9	E	Up to 8	1:3	-	1.5 x10^6 TU	300 µL

Note: *- calculated from target product strength; **- calculated from dilution (as applicable) of measured strength.

The patients will be followed for up to 48 weeks. After this period they will enter an open-label long term safety study (LTS13588) and undergo follow-up visits including ophthalmological examinations and recording of adverse events (AEs).

Main Inclusion Criteria

Patients must meet ALL of the following criteria to be considered for enrolment into this study:

- Signed and dated written informed consent obtained from the patient and/or the patient's legally acceptable representative, if applicable, in accordance with the local regulations.
- Diagnosis of SMD, with at least 1 pathogenic mutant ABCA4 allele on each chromosome, confirmed by direct sequencing. Gene mutation analysis results conducted prior to signing the informed consent may be used provided that the analysis was conducted by a CLIA (Clinical Laboratory Improvement Amendments) certified laboratory, written results are provided to the site, and participants (patients and/or the patient's parent[s]/legal guardian[s]) give consent to utilize the results. For patients genotyped during the screening period, results demonstrating a pathogenic mutant ABCA4 allele on each chromosome must be documented prior to the administration of SAR422459.
- Women of childbearing potential must have a negative pregnancy test at Day -1 and agree to use an effective form of contraception for at least 3 months such as the contraceptive pill or intrauterine device, or be surgically sterile or postmenopausal, with the last menstrual period being over 2 years prior to enrolment (partners of study patients must agree to use barrier contraception for at least 3 months after SAR422459 administration).
- Males must agree with their partner to use 2 forms of contraception, including one barrier method for at least 3 months following SAR422459 administration if their partner is of childbearing potential, or must be surgically sterile.
- Patients must agree to not donate blood, organs, tissues or cells for at least 3 months following SAR422459 administration.
- Patients enrolled in France must be affiliated to or benefit from a social security regimen.

Specific Inclusion Criteria Patient Group A

- Patients (18 years or older) with advanced SMD.
- VA ≤20/200 in the worst eye.
- Severe cone-rod dysfunction with no detectable or severely abnormal full-field ERG responses.

Specific Inclusion Criteria Patient Group B

- Patients (18 years or older) with SMD.
- VA ≤20/200 in the worst eye.
- Abnormal full-field ERG responses.

Specific Inclusion Criteria Patient Group C

- Patients (18 years or older) with SMD.
- VA ≤20/100 in the worst eye.
- Abnormal full-field ERG responses.

Specific Inclusion Criteria Patient Group D

- Symptomatic patients (from 6 years to 26 years old) with early or childhood-onset SMD (age at disease onset <18 years) with at least one pathogenic mutant ABCA4 allele on each chromosome confirmed by direct sequencing and co-segregation analysis within the patient's family.
- Visual acuity of ≥20/200 in both eyes at the time of the screening visit.
- Patients are anticipated to experience rapid deterioration in visual function and/or retinal structure as determined by an annual progression rate in at least 1 of the following parameters occurring in at least one eye (assessments recorded up to 2 years prior to the screening visit date may be considered to document evidence of rapid deterioration):
  - Loss of ≥1 line of Snellen visual acuity (equivalent to 5 ETDRS letters),
  - Reduction in macular mean sensitivity of ≥1.2 dB as assessed by microperimetry,
  - Reduction in macular mean sensitivity of ≥5 dB or reduction in hill of vision by >14 dB-sr as assessed by static perimetry,
  - Enlargement in the area of macular RPE atrophy by fundus autofluorescence at a rate of ≥0.5 mm^2,
  - Enlargement in the area of central macular retinal thinning/photoreceptor loss by ocular coherence tomography at a rate of ≥0.5 mm^2.
- All eligible patients must demonstrate an ability to understand, willingness to cooperate and ability to reliably perform required study procedures as judged and confirmed by the study investigator.

Specific Inclusion Criteria Patient Group E

- Symptomatic patients (from 6 years to 17 years old) with SMD with at least 1 pathogenic mutant ABCA4 allele on each chromosome confirmed by direct sequencing and co-segregation analysis within the patient's family.
- Visual acuity of ≥20/100 in both eyes at the time of screening visit.
- Patients are anticipated to experience rapid deterioration in visual function and/or retinal structure as determined by an annual progression rate in at least one of the following parameters occurring in at least one eye (assessments recorded up to 2 years prior to the screening visit date may be considered to document evidence of rapid deterioration):
  - Loss of ≥1 line of Snellen visual acuity (equivalent to 5 ETDRS letters),
  - Reduction in macular mean sensitivity of ≥1.2 dB as assessed by microperimetry,
  - Reduction in macular mean sensitivity of ≥5 dB or reduction in hill of vision by >14 dB-sr as assessed by static perimetry,
  - Enlargement in the area of macular RPE atrophy by fundus autofluorescence at a rate of ≥0.5 mm^2,
  - Enlargement in the area of central macular retinal thinning/photoreceptor loss by ocular coherence tomography at a rate of ≥0.5 mm^2 .
- All eligible patients must demonstrate an ability to understand, willingness to cooperate and ability to reliably perform required study procedures as judged and confirmed by the study investigator.

Exclusion Criteria

Presence of ANY 1 of the following criteria will exclude patients from being enrolled into the study:

- Pre-existing eye conditions that would preclude the planned surgery or interfere with the interpretation of study endpoints: glaucoma or other primary optic neuropathy that has resulted in significant visual field loss, corneal or significant lens opacities, active uveitis, retinopathy and maculopathy (other than that from Stargardt disease) that in the opinion of the investigator is causing significant visual loss, myopia greater than 8 diopters spherical equivalent.
- Cataract surgery with intraocular lens implantation within 6 months of enrolment.
- Aphakia or prior vitrectomy in the study eye.
- Concomitant systemic diseases including those in which the disease itself, or the treatment for the disease, can alter ocular function. For instance malignancies whose treatment could affect central nervous system function, diabetes, juvenile rheumatoid arthritis or sickle cell disease.
- Any intraocular surgery (other than study procedure) or laser in either eye planned within 6 months of Day 0.
- Any contraindication to pupil dilation in either eye.
- Any known allergy to any component of the delivery vehicle or diagnostic agents used during the study (eg, fluorescein, dilation drops), or medications planned for use in the peri-operative period particularly topical, injected or systemic corticosteroids.
- Any injectable intravitreal treatment to the treated eye or intravitreal device in the treated eye within 6 months prior to screening.
- Any periocular injections of corticosteroids to the treated eye within 4 months prior to screening.
- Laboratory test abnormalities or abnormalities in electrocardiogram, chest X-rays that, in the opinion of the principal investigator (PI), would make the patient unsuitable for participation in the study.
- Significant intercurrent illness or infection during the 28 days prior to enrolment.
- Pre-menopausal or non-surgically sterile women who are unwilling to use an effective form of contraception such as the contraceptive pill or intrauterine device.
- Men or women who do not agree to use barrier contraception as specified in the inclusion criteria.
- Alcohol or other substance abuse.
- Contraindications to use of anesthesia (local or general, as appropriate).
- Concurrent anti-retroviral therapy that would inactivate the investigational agent.
- History of any investigational agent within 28 days prior to SAR422459 administration.
- Participation in a prior ocular gene transfer therapy study, other than the TDU13583 study.

- Enrolment in any other clinical treatment study, for any condition, including those relating to SMD, throughout the duration of the SAR422459 TDU13583 study participation.
- Current or anticipated treatment with anticoagulant therapy or the use of anticoagulation therapy within the 4 weeks prior to surgery.
- Past medical history of HIV or hepatitis A, B or C infection.
- Inability to comply with the demands of the study.
- Women who are pregnant or are breastfeeding.
- History of or signs consistent with unilateral amblyopia (strabismic, anisometropic or stimulus deprivation).

Statistical Analysis

Sample size determination

This is an exploratory study, the primary objective of which is to evaluate safety and, as a secondary objective, to estimate the biological activity. No formal sample size calculation has been performed.

Analysis population

All patients with SMD included in the study will be taken into account for the analysis.

Primary analysis

The primary analysis will be based on the treatment emergent adverse events (TEAE).

The number and percentage of patients with treatment emergent adverse events will be summarized.

An overall summary will include the number and percentage of patients with:

- A fatal AE (death).
- At least one serious AE.
- At least one severe AE.
- At least one related AE.
- Without any AEs.

An additional table will show the number and percentage of patients with treatment emergent adverse events broken down by System Organ Class, High Level Term and Preferred Term. Related AEs will be summarized separately.

A specific look will also be done on the ophthalmologic safety endpoints.

Analysis of secondary endpoints

Secondary endpoints will be summarized at each visit. Where appropriate, individual profile plots and mean plot of changes in the variable against time will be presented. Key parameters for the estimation of biological activity will be assessments of visual function (BCVA, microperimetry, static and kinetic perimetry) and retinal structure (OCT and FAF).

3 STUDY SCHEDULE

3.1 COHORT 1 TO 5

	Pre SAR422459										
	Days				Weeks						
	-28 (screening visit)	-1 (baseline visit)	0 Surgery	1	1	2	4	12	24	36	48 [l]
Visit windows	**±10 days**	**-7 days**	**N/A**	**N/A**	**±3 days**	**±3 days**	**±3 days**	**±14 days**	**±14 days**	**±14 days**	**±14 days**
SAR422459 administration			X[o]								
Entry criteria	X										
Informed consent	X										
Demographic data	X										
When available, co-segregation analysis within the patient's family	X										
Medical history [p]	X										
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Anesthesia assessment	X										
Height	X										
Weight	X										
Vital signs [d]	X	X	X	X	X	X	X	X	X	X	X
Reproductive status	X										
Clinical symptoms of SMD	X										
Treatment history	X										
Electrocardiogram (ECG)	X										

	Pre SAR422459										
	Days				Weeks						
	-28 (screening visit)	-1 (baseline visit)	0 Surgery	1	1	2	4	12	24	36	48 [l]
Chest X-ray	X										
Physical examination	X										X
Ophthalmological examination											
BCVA [a]	X	X		X	X	X	X	X	X	X	X
Slit lamp examination	X	X		X	X	X	X	X	X	X	X
Intraocular pressure	X	X		X	X	X	X	X	X	X	X
Fundoscopy / indirect ophthalmoscopy	X	X		X	X	X	X	X	X	X	X
FAF	X	X					X	X	X		X
OCT [m]	X	X		X	X	X	X	X	X	X	X
Microperimetry, Full-Field Kinetic and Static Perimetry	X	X				X	X	X	X	X	X
Fundus photography [c]	X	X	X	X		X	X		X	X	X
Multifocal and Full-Field ERG	X	X					X	X	X		X
Adaptive optics	X	X						X	X	X	X
Where available: surgery video-recording and/or intra-operative OCT			X								
Reading speed		X									X
VFQ-25		X									X
Hematology [e]	X	X		X			X		X		X
Chemistry panel [f]	X	X		X			X		X		X
Kidney function [g]	X	X					X		X		X
Liver function [h]	X	X		X			X		X		X

	Pre SAR422459										
	Days				Weeks						
	-28 (screening visit)	-1 (baseline visit)	0 Surgery	1	1	2	4	12	24	36	48 [l]
Coagulation [i]	X	X									
Urinalysis [j]	X	X		X			X		X		X
Blood for PCR	X		X [b]	X	X	X	X	X	X	X	X
Urine pregnancy test [k]	X	X									
Blood for Immunology		X					X	X	X	X [n]	X [n]
Urine for PCR	X		X [b]	X	X	X					
Adverse events	X	X	X	X	X	X	X	X	X	X	X

Notes:

If necessary, the screening and baseline assessments can be splitting on different days.

a BCVA and perimetry (full-field kinetic and static perimetry) will be performed once at the screening visit (Day -28) and on 2 occasions at baseline (Day -1). Microperimetry will be performed once at visits requiring full-field kinetic and static perimetry

b Blood and where possible Urine sample 60 minutes after surgery

c A pan-retinal photomontage will be taken at the screening visit only

d Vital signs: blood pressure (BP, sitting), heart rate (HR) and temperature taken and recorded before SAR422459 administration. Following surgery vital signs will be measured every 30 minutes for one hour. Vital signs will be obtained on all subsequent follow-up visits

e Hematology: white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), red cell distribution width (RDW), platelets, neutrophils, lymphocytes, monocytes, eosinophils and, basophils

f Chemistry panel: serum electrolytes (phosphorus, calcium, sodium, chloride, bicarbonate and potassium), blood glucose (only at screening), creatine phosphokinase (CPK), lactate dehydrogenase (LDH)

g Kidney function: Creatinine, blood urea nitrogen (BUN) and uric acid

h Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), alkaline phosphatase (AP), total protein (TP), albumin, gamma glutamic transpeptidase (γGT, GGT), cholesterol (CHOL) (only at screening)

i Coagulation: prothrombin time (PT) and partial thromboplastin time (PTT) at screening and baseline only

j Urinalysis: Microscopic or multistick strip urinalysis for protein, blood and ketones

k Urine pregnancy test if applicable for women of childbearing potential must be negative at Day -1

l Week 48 or early termination procedures

m Infra-red fundus montage to be performed at each visit

n Only in patients with positive antibody response at Week 24

o Patients will not take anything by mouth for a minimum of 8 hours prior to surgery.

p Past medical history of HIV, hepatitis A, B or C infection will be evaluated.

3.2 COHORTS 6-9

	Pre SAR422459									
	Days				Weeks					
	-28 (screening visit)	-1 (baseline visit)	0 Surgery	1	1	2	4	12	24	48[a]
Visit windows	**±10 days**	**-7 days**	**N/A**	**N/A**	**±3 days**	**±3 days**	**±3 days**	**±14 days**	**±14 days**	**±14 days**
SAR422459 administration			X[b]							
Entry criteria	X[c]	X[c]								
Informed consent	X									
Demographic data	X									
Genotyping [d]	X									
Medical history [e]	X									
Reproductive status	X	X								
Clinical symptoms of SMD	X									
Treatment history	X									
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Pre-Operative Assessments										
Anesthesia assessment	X[c]	X[c]								
Height	X[c]									
Weight	X[c]	X[c]								
Vital signs [f]	X	X	X	X	X	X	X	X	X	X
Electrocardiogram (ECG)	X[c]	X[c]								
Chest X-ray	X[c]	X[c]								

	Pre SAR422459									
	Days				Weeks					
	-28 (screening visit)	-1 (baseline visit)	0 Surgery	1	1	2	4	12	24	48[a]
Physical examination	X[c]	X[c]								X
Ophthalmological examination										
BCVA [g, s]	X	X		X	X	X	X	X	X	X
Contrast sensitivity [h, s]	X	X						X	X	X
Reading Speed (when possible) [s]		X								X
Static Perimetry [g, s]	X	X						X	X	X
Full-Field Kinetic Perimetry [g, s]	X	X						X	X	X
Slit lamp examination	X	X		X	X	X	X	X	X	X
Microperimetry [g,t]	X[u]	X					X	X	X	X
OCT [t]	X[v,u]	X		X	X	X	X	X	X	X
Fundoscopy / indirect ophthalmoscopy [t]	X	X		X	X	X	X	X	X	X
Fundus photography [i, t]	X[w]	X	X	X		X	X		X	X
FAF [t]	X[w]	X					X	X	X	X
Infrared Reflectance Imaging [t]	X [u]	X						X	X	X
Intraocular pressure [t]	X	X		X	X	X	X	X	X	X
Full-Field ERG [t]	X	X								X
Intraoperative video-recording (intra-operative OCT, where available)			X							
VFQ-25/CVAQC (when possible) [j]		X								X
Hematology [k]	X	X [x]					X		X	X

	Pre SAR422459									
	Days				Weeks					
	-28 (screening visit)	-1 (baseline visit)	0 Surgery	1	1	2	4	12	24	48[a]
Chemistry panel [l]	X	X [x]					X		X	X
Kidney function [m]	X	X [x]					X		X	X
Liver function [n]	X	X [x]					X		X	X
Coagulation	X	X [x]								
Blood for PCR [o]	X		X[o]	X	X		X	X	X	X
Blood for Immunology		X					X	X	X	X[p]
Urinalysis [q]	X	X		X			X		X	X
Urine pregnancy test [r]	X	X								
Urine for PCR	X		X[o]	X	X					
Adverse events	X	X	X	X	X	X	X	X	X	X

Notes:

If necessary, the screening and baseline assessments can be carried out over several days.

a Week 48 or early termination procedures

b Patients will not take anything by mouth for a minimum of 8 hours prior to surgery.

c Need to be done prior to surgery between -28 days or Day -1 or by request of anesthesiologist at rescreening.

d Gene mutation analysis results conducted prior to signing the informed consent may be used provided that the analysis was conducted by a CLIA (Clinical Laboratory Improvement Amendments) certified laboratory, written results are provided to the site, and participants (patients and/or the patient's parent[s]/legal guardian[s]) give consent to utilize the results. For patients genotyped during the screening period results must be documented prior to the administration of SAR422459.

e Past medical history of HIV, hepatitis A, B or C infection will be evaluated.

f Vital signs: blood pressure (BP, sitting), heart rate (HR) and temperature taken and recorded before SAR422459 administration. Vital signs will be measured at 30 and 60 minutes after the surgical procedure. Vital signs will be obtained on all subsequent follow-up visits

g BCVA, Static perimetry, Full-field Kinetic perimetry and Microperimetry will be performed during the screening period. As these measures could be subject to broad intra-individual variability, they must be repeated at least twice during the screening period to determine the patient's reliability in the performance of these psychophysical assessments. All of the above screening measures must be completed and final screening assessments submitted to the reading center as required in the MOP within 14 days of the planned surgery date.

h Contrast sensitivity on the Sloan Low contrast Letter Acuity Chart will be performed on Day -28, Day-1, and Weeks 12, 24, and 48.

i For all indicated visits subsequent to the screening visit, a single 50 degree photograph centered on the macula, and including the optic nerve, will be obtained of each eye.

j VFQ-25 for adults ≥18 years/CVAQC for children <18 years

k Hematology: white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), red cell distribution width (RDW), platelets, neutrophils, lymphocytes, monocytes, eosinophils and, basophils

l Chemistry panel: serum electrolytes (phosphorus, calcium, sodium, chloride, bicarbonate and potassium), blood glucose (only at screening), creatine phosphokinase (CPK), lactate dehydrogenase (LDH)

m Kidney function: Creatinine, blood urea nitrogen (BUN) and uric acid

n Liver function: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), alkaline phosphatase (AP), total protein (TP), albumin, gamma glutamic transpeptidase (γGT, GGT), cholesterol (CHOL) (only at screening)

o Blood 60 minutes after surgery and first urine sample that occurs after 60 minutes post-surgery

p Only in patients with positive antibody response at Week 24

q Urinalysis: Microscopic or multistick strip urinalysis for protein, blood and ketones

r Urine pregnancy test if applicable for women of childbearing potential will be performed at Day -28 and Day -1 and must be negative

s Assessment performed before dilatation

t Assessment performed after dilatation

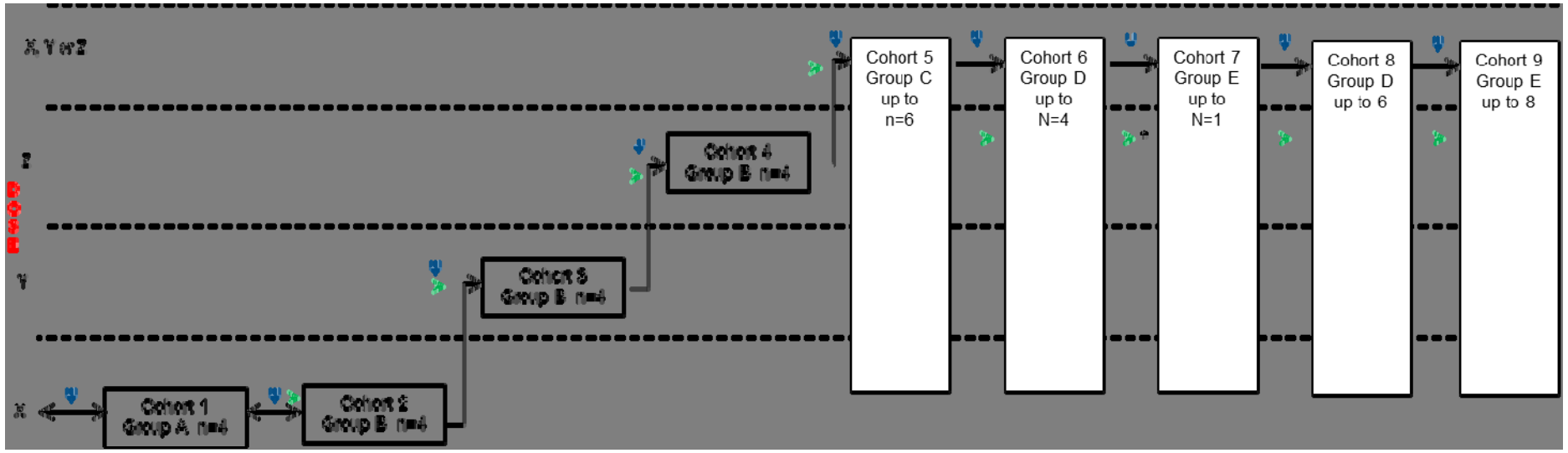
u OCT and infrared images, required for the centralized review, must be performed on day -28 (the first day of the screening visit, if screening is conducted over several days). The OCT volume maps and montaged infrared reflectance images must be forwarded to the reading center within 2 days of collection during screening visit as instructed in the MOP.

v OCT is to be performed prior to Microperimetry at Screening (Day -28) to obtain the OCT overlay to determine the location of the anatomical fovea.

w Fundus photography and FAF screening images must be submitted to the reading center as required in the MOP within 14 days of the planned surgery date.

x To be repeated just in case of re-screening, if previous screening was earlier, than 38 days before surgery.

4 STUDY FLOW DIAGRAM



5 INTRODUCTION AND RATIONALE

Stargardt macular degeneration (SMD), (which is also known as fundus flavimaculatus or Stargardt disease) was described in 1909 by Karl Stargardt, an ophthalmologist in Strasbourg. It is the most common form of inherited juvenile macular degeneration and affects approximately one in 10 000 worldwide with around 26 000 sufferers in the United States.

SMD is characterized by a deterioration of central vision, and the presence of bilateral atrophic appearing foveal lesions, eventually leading to legally defined blindness most commonly in children and young adults (VA of ≤20/200) (2).

This disease is nearly always inherited as an autosomal recessive trait that produces a severe form of macular degeneration, similar to age-related macular degeneration (AMD), but which begins in childhood; it is the most common autosomal recessive juvenile onset macular dystrophy (2). Less than 1% of cases may result from a dominant mode of inheritance. The autosomal recessive trait for SMD in affected children means that both parents were carriers, having 1 mutated gene for the disease paired with one normal gene. Children where both parents are carriers have a one in 4 chance of inheriting both the mutated genes (one from each parent) leading to Stargardt disease (3, 4).

Carriers are unaffected. The gene which is mutated in patients with autosomal recessive SMD was isolated and identified by Allikmets and colleagues (5). The gene identified is a retina-specific ABC transporter (6) (ABCR) gene, part of the subfamily adenosine triphosphate (ATP)-binding cassette (ABC) transporters (ATP-binding cassette, sub-family A, member 4 [ABCA4], also known as ABCR).

SAR422459 is a gene therapy product developed by Oxford BioMedica (UK) Ltd, designed to introduce the correct ABCA4 cDNA to photoreceptors (PR) and thereby attenuate and possibly reverse the pathophysiology which leads to SMD.

SAR422459 is a non-replicating, recombinant lentiviral vector derived from the genome of the nonprimate lentivirus, equine infectious anemia virus (EIAV). SAR422459 contains approximately 10% (861 nucleotides) of the wild type EIAV genome and there are no functional viral proteins or viral coding regions in the recombinant EIAV vector. This LentiVector® technology platform for gene delivery is currently in use in an on-going Phase I/II studies for Parkinson's disease wet age-related macular degeneration and retinitis pigmentosa associated with Usher syndrome, type 1B.

5.1 THERAPEUTIC GENES

In 1997, the gene for SMD, coding for a member of the ABC transporter family was isolated and characterized (4, 7, 8).

The ABCA4 gene encodes for a ~250 kDa ATP-binding cassette transporter localized to the disk margins of vertebrate PR outer segments and is involved in the transport of toxic by-products of the visual cycle out of the PRs. The ABCA4 gene is relatively large containing 50 exons which may explain its susceptibility to frequent mutations (9, 10). The ABCA4 (ABCR) protein is organized as 2 tandem-arranged halves, each containing a trans-membrane segment, followed by a large extracellular domain, a multi-spanning membrane domain and a nucleotide binding domain (11, 12).

Expression of the ABCA4 gene is restricted to retinal rod and cone PRs and the Abcr4 protein is localized to the rim and incisures of outer segment discs, where it is present at a molar ratio of approximately 1:120 with rhodopsin (9, 13, 14). Abcr4 has been implicated in the active transport of retinoid compounds across the outer segment disk membrane following the photo-activation of rhodopsin and requires the presence of ATP (15).

Disease-associated ABCA4 alleles show an extraordinary heterogeneity with over 400 currently identified mutations most of which represent missense substitutions. In SMD the mutant ABCR protein is unable to fully perform its transport function leading to progressive irreversible loss of central vision and delayed dark adaptation due to degeneration of PRs and the underlying retinal pigmented epithelium (RPE) within and near the macula. The degeneration of the PRs thought to be secondary to the loss of RPE due to the accumulation of an age related pigment lipofuscin containing toxic by-products of the visual cycle including elevated levels of diretinoid-pyridinium-ethanolamine (A2E).

5.2 CLINICAL PATHOLOGY

Stargardt Macular Degeneration, caused by mutations in the ABCA4 gene is inherited as an autosomal recessive trait, is the most frequent cause of juvenile macular degeneration. There is variation in the clinical course of the disease but typically central visual failure begins in childhood with later onset of peripheral visual constriction in some cases. The consequence of the condition is frequently legal blindness.

SMD pathophysiology is characterized by the accumulation of lipid rich subretinal deposits (lipofuscin) that frequently appear as yellowish-tinted flecks on ophthalmoscopic examination. As the disease progresses, atrophy of the RPE develops with subsequent loss of the adjacent PRs.

Symptoms of SMD usually appear before age 20, but may present as early as age 5. Diagnosis is initially characterized by sensitivity to glare, even during overcast days and there is decreased central vision, peripheral vision is maintained. The disease may also manifest with wavy vision, blind spots and blurriness. Patients may also notice difficulty with reading and seeing in dim light before being referred to an ophthalmologist for diagnosis. However, the disease is often misdiagnosed, or not diagnosed in the first few years of onset, and this may be the result of little evidence of the disease being found during eye examinations. The deterioration in vision is variable and can decrease rapidly (especially in children) (16). By age 50, approximately half of all SMD subjects who were being studied in clinical trials had visual acuities that had deteriorated to 20/200 or worse (17).

5.3 DIAGNOSIS AND MONITORING OF SMD

In early stages of SMD the macula may appear normal, resulting in a delay in diagnosis. Characteristic changes occur with disease progression which aid diagnosis.

In latter stages, SMD is often diagnosed in patients who exhibit bilateral visual loss, following the observation of characteristic atrophic-appearing macular lesions surrounded by yellowish-white legions or flecks. The appearance of a “beaten-metal” macula in conjunction with the appearance of flecks is typical of SMD (18).

Despite the early work performed by Fishman and colleagues classification of phenotypic subtypes in SMD has been problematic because neither duration of disease, nor the extent and distribution of fundus lesions correlate well with retinal function (19, 20). However, there appears to be good concordance with respect to electrophysiological attributes and on this basis SMD can be divided broadly into 3 groups:

- Patients with normal scotopic ERG and photopic ERG abnormalities.
- Patients that have preserved scotopic but abnormal photopic ERG.
- Patients with abnormal scotopic and photopic ERG.

Patients with normal scotopic and photopic ERG abnormalities tend to have better VA and preserved peripheral visual fields over the course of the disease than patients that have preserved scotopic but abnormal photopic ERG or abnormal scotopic and photopic ERG. Despite there being overlap between the groups, patients with preserved scotopic and photopic ERG b-wave activity tend to have better VA (1). It is not known whether these differences represent different stages of the disease or are related to the nature of the mutation of the ABCR gene (21).

Due to the heterogeneity of this disease, there is considerable overlap in clinical phenotype of SMD whilst electrophysiological, morphological or clinical predictors of outcome are still to be established. In the current study the clinical criterion of VA will be used in conjunction with ERG to assess overall pan-retinal function and act as a measure for advancement of SMD to select patients for the early study groups (A-C). For the final study group (D), a number of imaging modalities and functional assessments will also be used throughout the study to document disease prior to treatment, monitor ocular safety and any signs of treatment benefit.

SMD is a complex retinal degenerative disease with variable disease presentation and progression. In the present study, in addition to routine ophthalmic examinations, a number of modalities will be used to monitor safety and any signs of bioactivity. Each technology has value in identifying disease severity and monitoring progression, but as each has intrinsic limitations others can complement, ERG to detect the electrophysiology of the retina, FAF to track lipofuscin accumulation and RPE atrophy, OCT will visualize cross sectional retinal structure, perimetry will give a measure of retinal function and adaptive optics will visualize cone PR morphology.

Regular measurements combining these techniques throughout the study will ensure the treated eye is effectively monitored for safety and may detect any early signs of bioactivity in this patient population.

5.4 NON PHARMACOLOGICAL TREATMENT

Although current research shows that patients with SMD may be able to slow the progression of the disease by wearing UV-protective sunglasses, avoiding both exposure to bright light and high intake in vitamin A, there are currently no approved therapies that can treat SMD either by attenuating or halting its progression. As the pathophysiology is now being understood in molecular detail and the disease has been attributed to mutations within the ABCA4 gene, the most obvious approach to preventing or halting disease progression is through gene therapy.

5.4.1 Gene transfer

SAR422459 uses a nonprimate lentiviral vector system based on the EIAV which has been developed as a vector for therapeutic application (22). SAR422459 is pseudotyped with the vesicular stomatitis virus G (VSV-G) protein that allows entry into many cell types but following subretinal delivery transduction is limited to the RPE cells and PR and to a lesser extent other cells of the inner neural retina. Gene marker studies using EIAV-based vectors have demonstrated that expression of the gene product persists for at least 16 months in the mouse eye and due to the integrative nature of the EIAV vector, gene expression is likely to last much longer.

SAR422459 is a novel self-inactivating, EIAV vector (EIAV CMV ABCA4) which encodes the ABCA4 gene driven by the cytomegalovirus (CMV) constitutive promoter.

This same EIAV vector system is also used in the production of other gene therapy products currently under development including ProSavin®, which is in clinical development in France (NCT00627588 EudraCT: 2007-001109-26) Retinostat (NCT01301443) and UshStat (NCT01505062).

5.4.2 SAR422459 formulation

The SAR422459 product is presented as a frozen liquid formulation, stored at ≤-70°C. The composition of the product is shown in Table 1. The product is formulated [redacted]

A target dose of $6x10^6$ ($\geq 1.8x10^6$ to $<1.8x10^7$ TU/mL) will be produced which corresponds to undiluted material from the manufacturing process.

Table 1 - Components of the undiluted investigational medicinal product

Name of Ingredients	Quantity	Function	Reference to Standards
Active Substance: SAR422459	≥1.8x10^6 to <1.8x10^7 TU/mL Target strength: 6x10^6 TU/mL	Active	
[redacted]	[redacted]	[redacted]	EP/USP EP/USP EP/USP EP/USP EP, BP, JP EP

EP: European Pharmacopeia; USP: US Pharmacopeia; BP: British Pharmacopeia; JP: Japanese Pharmacopeia

Final formulation buffer: [redacted]

5.4.3 Mechanism of action

SAR422459 is an EIAV-based lentiviral vector product aimed at introducing the normal ABCA4 cDNA which encodes for the relatively large functional ATP-binding cassette transporter, ABCR protein in the PR outer segments, thereby restoring normal cellular function and attenuating vision loss associated with SMD.

Due to the relatively large size of the ABCA4 cDNA, it is expected that lentiviral vectors, that can accommodate large inserts (~8-9 kb), will be well suited to effective gene delivery to treat SMD.

5.5 SUMMARY OF PROOF OF PRINCIPLE NON-CLINICAL STUDIES

Details of all non-clinical studies performed to date can be found in the SAR422459 Investigator Brochure (IB).

5.5.1 Pharmacology studies

Overall conclusion of the Pharmacology studies:

- The subretinal delivery EIAV CMV ABCA4 vector SAR422459 leads to expression of ABCR protein in the PR and RPE cells in the *Abca4*$^{-/-}$ knockout (KO) mouse model. To date we have not observed any negative impact of expressing ABCR in the non-target RPE cells. This will be further assessed in the combined good laboratory practice (GLP) toxicology and biodistribution studies in rabbits and non-human primates (NHP).

- Subretinal administration of EIAV CMV ABCA4 vector expressing human ABCR protein significantly reduces the accumulation of A2E/isoA2E, the primary component of lipofuscin, in the *Abca4*$^{-/-}$ mouse model.
- The 12-month efficacy data from the *Abca4*$^{-/-}$ mice injected with SAR422459 (EIAV CMV ABCA4) provides proof of principle for the use of EIAV vectors expressing ABCA4 as a long-term therapeutic strategy to treat patients with SMD.

5.5.2 Pharmacokinetic studies

A series of pharmacokinetic studies have been performed in vivo to assess gene transfer and biodistribution. Following subretinal delivery of the EIAV lentiviral vector gene delivery and expression is observed most evidently in rod and cone PRs and retinal pigment epithelial cells in both mice, rabbits and 3 different NHP species; cynomolgus macaques, baboons and rhesus macaques. Further details of these studies can be found in the IB.

5.5.3 Toxicology studies

Non-clinical toxicology studies have been performed to assess acute and chronic effects of SAR422459. The studies demonstrate no significant findings and provide safety data for the proposed clinical dose levels. Full details of these studies can be found in the IB.

5.6 RATIONALE FOR STUDY

The primary objective of the present study is to assess the safety and tolerability of ascending doses of SAR422459 in patients with SMD. The secondary objective is to evaluate for possible biological activity.

This is a First in Man (FIM), Phase I/IIa open-label, paired-eye, dose escalation study to enable the treatment of sufficient number of patients in this rare indication to establish a safe and active dose level. The data from this study will facilitate the appropriate design of efficacy studies in a Phase II/III clinical development program.

5.6.1 Rationale for SAR422459

There is currently no marketed safe and effective therapy for SMD. As the pathophysiology is now being understood in molecular detail and the disease has been attributed to mutations within the ABCA4 gene, the most likely successful route to preventing or halting disease progression is through gene therapy. SAR422459 is a lentiviral vector therapy which delivers the normal ABCA4 cDNA and so is able to restore retinal transport function preventing build-up of the non-degradable toxic lipofuscin component A2E. Effective PR cell transduction and gene expression has been demonstrated in mice and non-human primates following subretinal delivery of the EIAV lentiviral vector.

5.7 RATIONALE FOR INJECTION INTO THE EYE

The eye is an ideal target organ for gene therapy.

- Local gene therapy is ideal for the eye since it is anatomically separated from the rest of the body and creates a natural barrier between itself and surrounding tissues. Therefore, it is unlikely that the SAR422459 vector would gain access to and affect tissues other than the eye.
- The eye is easily accessible to the surgeon compared to other organs, both in terms of administering the treatment and in terms of evaluating the effect.
- The treatment approach is designed to correct the underlying genetic abnormality. Administration of SAR422459 directly into the eye via subretinal injection provides a convenient means of delivering the normal *ABCA4* cDNA to restore retinal transport function and resulting in a permanent restoration of ABCR protein function in photoreceptors.

5.8 RATIONALE FOR UNILATERAL ADMINISTRATION

In this study, one study eye will be selected. If both eyes are eligible for the study, the worse eye, as per investigator judgment, will be selected. For Cohorts 6-9, the centralized review will advise on the choice of the study eye if both eyes are clinically similar. The rationale for unilateral administration is to minimize the risk to the less advanced eye and thus minimize any risk to the patient's remaining vision. For patients in Cohorts 1-4 with advanced SMD the study eye will have a maximum BCVA of 20/200. In Cohort 5 with slightly less advanced SMD the study eye will have a maximum BCVA of 20/100. Cohort 6 and 8 will enroll patients with a much less advanced stage of the disease with a minimum BCVA of 20/200 or better in the worse eye at the time of the screening exam. Cohort 7 and 9 will enroll pediatric patients with even less advanced stage of the disease with a minimum BCVA of 20/100 or better in the worse eye at the time of the screening exam.

5.9 RATIONALE FOR THE CLINICAL DOSE

The rationale for the clinical dose is based on the number of transducing units delivered per eye in a fixed volume of formulation buffer. Using ocular allometric scaling and information from the published literature (Table 2) it was anticipated that a volume of 100 µL of SAR422459 could be safely subretinally dosed to both rabbits and NHPs without the need for vitrectomy (which is technically difficult in these species). Therefore, a total volume of 100 µL was used to deliver SAR422459 subretinally in the rabbit and NHP GLP combined toxicology/biodistribution studies. Absorption and retinal re-attachment was complete by 1-2 weeks following subretinal administration in NHP and by 4 weeks in the rabbit, there were no observed long-term morphological changes to the retinal structures examined at 4 and 6 weeks post-dosing. The relative difference in ocular volume between rabbit, NHP and human is around 3-fold, therefore a total volume of up to 300 µL will be delivered subretinally in the FIM study following a partial vitrectomy.

Table 2 - Allometric scaling of approximate ocular volumes and safe subretinal injection volumes

Species	Approximate axial ocular diameter (cm)	Approximate orbital volume (cm^3)	Relative ocular volume as compared to mouse	Safe maximal subretinal volume (µL)	Allometric scale-up based on size relative to mouse safe volumes
Mouse	0.34 (23)	0.16	-	2 (24)	-
Rat	0.64 (22, 25)	1.1	7	10	5
Rabbit	1.5 (26)-1.6 (27)	5 (28)-14.1	88	100 (29)	50
Macaque	1.7 (30)	20.6	129	100 (31)-150 (32)	50-75
Human	2.4 (32)	57.9	362	1000 (33, 34)	500

The dose selection for the FIM study was based on the MTD used in the rabbit and NHP GLP combined toxicology/biodistribution studies.

The MTD in the rabbit that was used in the GLP safety study is 1.4 x 10^6 TU/eye. The MTD in the NHP that was used in the GLP safety study is 4.7 x 10^5 TU/eye. Based on the average 3-fold ocular allometric scaling of ocular volume between rabbit/NHP and the human eye the expected MTD in man is 1.4 x 10^6 TU/eye up to 4.2x10^6 TU/eye based on the MTD in the NHP and rabbit, respectively.

In the current study, injected doses are below the MTD predicted by the rabbit toxicology data and are either below or almost equivalent to the MTD predicted in the NHP studies.

5.9.1 Summary of dosing regimens

The design is a dose escalation in terms of viral vector particles (transducing units, [TU]), in a fixed volume. The study will evaluate 3 target dose levels of SAR422459 1.8 x 10^5 TU/eye (1:10), 6 x 10^5 TU/eye (1:3), 1.8 x 10^6 TU/eye (undiluted) in a volume of 300 µL. As production process results in certain variability of strength - doses per measured strength vary from 0.48x10^5 to 4.5x10^6 TU/eye). Details of the formulation are provided in Table 1.

5.10 RATIONALE FOR DOSING INTERVALS

SAR422459 will be administered unilaterally on one occasion only per patient in this study. Patients with the most advanced disease will be included in the early cohorts; subsequent cohorts will include patients with less advanced macular degeneration and pediatric patients in the last cohort. In the first cohorts (Cohorts 1-4), allowing 21 days between dosing patients and 28 days between cohorts will permit adequate time to assess short-term safety prior to dose escalation or the inclusion of patients with less advanced disease. In addition, the long-term safety data (approximately 6 months) from the patients with advanced disease dosed early in the study (Cohorts 1-3) will be available at the time of treating the later cohorts (Cohorts 5, 6 and 7).

Prior to the inclusion of pediatric patients, the DSMB will review all safety data including the available data from all cohorts after the last patient of Cohort 5 has completed 12 weeks of follow-up after having been dosed. An interim report including all available safety data, preliminary efficacy data and the recommendations from the DSMB will be submitted to the regulatory authorities and institutional review boards/ethics committees for approval before enrolling pediatric patients (<18 years). Following the dosing of the first pediatric patient a 28 day interval will be observed prior to the dosing of the second pediatric patient. Thereafter, subsequent pediatric patients may be enrolled consecutively.

5.11 RATIONALE FOR TARGET PATIENT POPULATION

It is inappropriate to administer a gene therapy investigational product to healthy normal volunteers. Therefore when determining an initial patient population in which to assess the safety and tolerability of SAR422459 careful consideration was given to identifying a patient population with the optimal risk:benefit profile. Data from clinical and non-clinical studies have demonstrated that the lentiviral vector system is safe and well tolerated. Therefore the potential risk to patients is limited to the possible effects of the administration of the normal human ABCA4 gene directly into the retina.

Three phenotypic subtypes of SMD have been identified based upon ERG attributes (Lois et al. 2001, (1):

- Category 1: Severe pattern ERG abnormality with normal scotopic and [photopic] full-field ERG.
- Category 2: Severe pattern ERG abnormality with loss of photopic function but normal scotopic and full-field ERG.
- Category 3: Severe pattern ERG abnormality with loss of both photopic and scotopic function.

Four patient groups with a differing level of advancement of SMD will be included in this study.

- Group A: Patients (18 years or older) with advanced SMD, VA ≤20/200 in the worst eye and severe cone-rod dysfunction with no detectable or severely abnormal full-field ERG responses. These will be patients with severe pattern ERG abnormality and loss of both photopic and scotopic function, with loss of photopic responses to no more than 70% of the category 3 ERG criteria in the Lois et al. classification, and very poor VA.
- Group B: Patients (18 years or older) with SMD, VA ≤20/200 in the worst eye with abnormal full-field ERG responses. These will be patients with very abnormal pattern ERG and loss of both scotopic and photopic responses, with loss of photopic responses to no more than 85% of the category 3 ERG criteria in the Lois et al. classification, and very poor VA.
- Group C: Patients (18 years or older) with SMD, VA ≤20/100 in the worst eye with abnormal full-field ERG responses. These will be patients with severe pattern ERG abnormality and loss of both photopic and scotopic function, and have photopic b-wave amplitude within the range of category 3 criteria in the Lois et al. classification. These patients will also have more preserved VA.

- Group D: Patients (from 6 years to 26 years old) with symptomatic early or childhood-onset SMD (age at disease onset <18 years), and VA ≥20/200 in both eyes at the time of the screening visit anticipated to experience rapid deterioration in visual function and/or retinal structure.
- Group E: Patients (from 6 years to 17 years old) with symptomatic SMD and VA ≥20/100 in both eyes at the time of the screening visit anticipated to experience rapid deterioration in visual function and/or retinal structure.

Patients thus treated in the first cohort will have advanced disease with the most severe loss of photopic retinal function on ERG and very poor VA. Therefore, whilst this patient group is unlikely to experience any significant clinical benefit from treatment in terms of improvement in BCVA, any deleterious local effects of SAR422459 will be detectable through regular safety monitoring. Following clinical experience in patients with advanced disease a further 3 cohorts (Cohorts 2-4) in patients with less advanced disease will be evaluated.

In Cohorts 2-4, all patients will have less advanced disease but will still have extensive retinal involvement, abnormal ERG and very poor VA. These patients still may have islets of functional retina and may receive clinical benefit from treatment with SAR422459.

The dose evaluation phase and identification of a MTD or the highest dose tested will be completed. The dose of $4.5x10^6$ TU per measured strength was administered in 4 patients in Cohort 6 and up to 1 patient in Cohort 7, it will be down-escalated in subsequent cohorts for better safety. Cohorts 1-5 included patients with less advanced disease with abnormal ERG and reduced VA.

Cohort 6 and 8 will include symptomatic patients (from 6 years to 26 years old) with SMD who are anticipated to experience rapid deterioration in visual function and/or retinal structure, with VA of ≥20/200 in both eyes at the time of the screening visit. The previous cohorts must have demonstrated acceptable safety and tolerability in the patients with more advanced disease prior to treatment of this patient group.

Cohort 7 and 9 will enroll pediatric patients (from 6 to 17 years old) with SMD who are anticipated to experience rapid deterioration in visual function and/or retinal structure, with VA of ≥20/100 in both eyes at the time of the screening exam - population expected to benefit most from this type of treatment, based on natural history data on SMD (35). In case patients pass eligibility criteria in both Cohort 6 and Cohort 7, they will be included in Cohort 7; the patients, who match criteria of Cohorts 8 and 9, will be enrolled into Cohort 9.

6 OBJECTIVES

6.1 PRIMARY OBJECTIVES

To assess the safety and tolerability of ascending doses of SAR422459 in patients with SMD.

6.2 SECONDARY OBJECTIVE

To evaluate for possible biological activity of SAR422459.

7 ENDPOINTS

For all endpoints with repeated measures, the primary time point will be considered the Week 48 visit unless otherwise specified. Last available measures before surgery will be considered as baseline value.

7.1 PRIMARY ENDPOINTS

The primary endpoint will be considered the Week 48 visit.

- The incidence and severity of treatment emergent adverse events.
- Clinically important changes from baseline in the following safety assessments:
  - Best-corrected visual acuity,
  - Slit lamp examination,
  - Fundoscopy/Indirect ophthalmoscopy,
  - Fundus photography (color and infrared reflectance),
  - Intraocular pressure,
  - Microperimetry,
  - Full-field static perimetry,
  - Full-field kinetic perimetry,
  - Optical coherence tomography,
  - Electroretinogram,
  - Laboratory parameters,
  - Vital signs,
  - Concomitant medications.

7.2 SECONDARY ENDPOINTS

Secondary Endpoints

- To determine a delay in retinal degeneration following subretinal injection of SAR422459 through changes from baseline in visual function and retinal structure relative to the untreated contralateral eye utilizing the following retinal analytical techniques:

  For visual function:
  - Best-corrected visual acuity,
  - Microperimetry,
  - Full-field static perimetry,
  - Full-field kinetic perimetry.

For retinal structure:

- Optical coherence tomography,
- Fundus autofluorescence.

7.2.1 Immunology

Humoral response to SAR422459 vector components.

7.2.2 Laboratory parameters

Hematology, biochemistry, urinalysis and other laboratory data will be measured at various time points throughout the study. Values will be flagged as High or Low if outside the laboratory normal range. Out of range values will be assessed as clinically significant (CS) or not clinically significant (NCS) by the investigator. Clinically significant out of range values will be recorded as AEs. Blood for immunology and blood for PCR will also be taken at multiple time points throughout the study, as will urine samples for biodistribution assessment.

7.2.3 Other safety parameters

Other safety parameters (vital signs, physical examination) will be measured. New abnormalities will be recorded under adverse events.

7.2.4 Exploratory efficacy parameters

Contrast sensitivity will be performed using the Sloan Low Contrast Acuity Chart. Reading speed and visual function questionnaires (visual function questionnaire-25 [VFQ-25]/25-item Cardiff visual ability questionnaire for children [CVAQC-25]) will be recorded in patients when possible and if the age of the patient allows. Multifocal ERG and adaptive optics are performed only in Cohorts 1-5 and not required for Cohorts 6-9.

7.2.5 Concomitant medication

Changes to concomitant medication will be recorded at all visits.

7.3 BIODISTRIBUTION ENDPOINT

SAR422459 distribution in the blood and urine assessed by polymerase chain reaction (PCR). For Cohorts 1-5 blood samples will be taken at Day -28 (Screening), Day 0 (60 minutes post-surgery), Day 1, Weeks 1, 2, 4, 12, 24, 36 and 48 and urine samples will be taken at Day -28 (Screening), Day 0 (60 minutes post-surgery), Day 1 and Weeks 1 and 2. For Cohorts 6-9 blood samples will be taken at Day -28 (Screening), Day 0 (60 minutes post-surgery), Day 1, Weeks 1, 4, 12, 24, and 48 and urine samples will be taken at Day -28 (Screening), Day 0 (60 minutes post-surgery), Day 1 and Week 1 only.

7.4 OTHER MEASURES

7.4.1 Patient characteristics

During screening, height, weight, sex, vital signs, inclusion/exclusion criteria, medical history (including reproductive status, clinical symptoms of SMD and treatment history), electrocardiogram (ECG), chest X-ray and anesthesia assessment will be recorded.

8 STUDY DESIGN

This is a Phase I/IIa, open-label, dose escalation study of subretinally injected SAR422459 in patients with SMD. In this study, 3 doses of SAR422459 will be evaluated over 6 patient cohorts with 5 groups of patients. The first 4 cohorts will evaluate the dose escalation phase of the study and will each consist of 4 patients. Cohorts 5, consisting of 6 patients, Cohorts 6, consisting of 4 patients and Cohort 7, having 1 patient each, receive the highest dose tested from the dose escalation phase. Cohorts 8 and 9-and will be treated with intermediate dose de-escalated from previous cohorts and evaluate the safety and biological activity of SAR422459. It is considered to be more probable to detect biological activity from the Cohorts 6-9 patients which are patients at a less advanced stage of the disease.

One study eye will be selected. If both eyes are eligible for the study, the worse eye, as per investigator judgment, will be selected. The centralized review will advise on the choice of the study eye if both eyes are clinically similar.

Five groups of patients (groups A, B, C, D and E) will be recruited to this study. The advancement of disease for groups A, B and C will be defined according to BCVA and ERG recordings, whereas group D will have less advanced disease as determined by clinical parameters (please see Section 5.11 for further information):

- Group A: Patients (18 years or older) with advanced SMD, VA ≤20/200 in the worst eye and severe cone-rod dysfunction with no detectable or severely abnormal full-field ERG responses.
- Group B: Patients (18 years or older) with SMD, VA ≤20/200 in the worst eye with abnormal full-field ERG responses.
- Group C: Patients (18 years or older) with SMD, VA ≤20/100 in the worst eye with abnormal full-field ERG responses.
- Group D: Patients (from 6 years to 26 years old) with symptomatic early or childhood-onset SMD (age at disease onset <18 years), and VA ≥20/200 in both eyes at the time of the screening visit anticipated to experience rapid deterioration in visual function and/or retinal structure.
- Group E: Patients (from 6 years to 17 years old) with symptomatic SMD, 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.

An independent data safety monitoring board (DSMB) will be convened to monitor safety and will meet regularly either at face-to-face meetings or by teleconference once the first patient has been enrolled. Based on accrual of the data, the committee will comprehensively review the safety and tolerability of the treatment for each individual patient and make the decisions regarding dose escalation, study continuance and recommended amendments to the protocol.

Four group A patients will receive SAR422459 at the lowest dose level SAR422459, 1.8 x 10^5 TU/eye (1:10), Cohort 1). An interval of 21 days between dosing 2 consecutive patients will be observed in order to assess the safety and tolerability of SAR422459 in these patients.

If after a minimum interval of 28 days after the 4th patient has been dosed, the safety and tolerability of group A at the lowest dose is considered satisfactory by the DSMB then 4 Group B patients will also be enrolled into Cohort 2. These patients will also receive SAR422459, 1.8 x 10^5 TU/eye (1:10) (the same dose of SAR422459 as dose Cohort 1), an interval of 21 days between dosing 2 consecutive patients will be observed.

If after a minimum interval of 28 days the safety and tolerability of group B in Cohort 2 is considered satisfactory by the DSMB the dose of SAR422459 will be escalated and 4 Group B patients will be enrolled into dose Cohort 3 and receive the SAR422459 dose of 6x10^5 TU/eye (1:3). An interval of 21 days between dosing 2 consecutive patients will be observed.

If after a minimum interval of 28 days from dosing the 4th patient of group B in Cohort 3, the safety and tolerability of SAR422459 is considered satisfactory by the DSMB then the dose of SAR422459 will be escalated to the maximal dose 1.8x10^6 TU/eye (undiluted), and 4 Group B patients will be enrolled into the next dose cohort (Cohort 4). An interval of 21 days between dosing 2 consecutive patients will be observed.

If after a minimum interval of 28 days from dosing the 4th patient of Group B in Cohort 4, the safety and tolerability is considered satisfactory by the DSMB then 6 Group C patients will be enrolled into the next dose cohort (Cohort 5) and receive SAR422459 at the MTD or the highest dose tested (either SAR422459 1.8 x 10^5 TU/eye (1:10), 6 x 10^5 TU/eye (1:3) or 1.8 x 10^6 TU/eye (undiluted) in a volume of 300 µL).

For Cohort 5, an interval of 21 days between dosing the first patient and second patient will be observed; subsequent patients may be enrolled in parallel.

If after a minimum interval of 28 days from dosing the last patient of Cohort 5, the safety and tolerability is considered satisfactory by the DSMB then adult patients will be enrolled in Cohort 6 (Group D) and receive SAR422459 at the MTD or the highest dose tested.

Prior to the inclusion of pediatric patients, the DSMB will review all safety data including the available data from all cohorts after at least 4 patients of Cohort 5 has completed 12 weeks of follow-up after having been dosed. An interim report including all available safety data, preliminary efficacy data, analysis of benefit/risk balance of enrolling pediatric patients (with regard to US 21 CFR Part 50 Subpart D ‘Additional Safeguards for Children in Clinical Investigations’ for FDA specifically and the recommendations from the DSMB will be submitted for approval to the regulatory authorities and institutional review boards/ethics committees, before enrolling pediatric patients (<18 years). Additional patients’ data may be submitted to the DSMB review, if requested.

Group D (Cohort 6) plans to enroll and treat symptomatic patients (from 6 years to 26 years old) with early or childhood-onset SMD (age at disease onset <18 years) and VA ≥20/200 in both eyes at the time of the screening visit anticipated to experience rapid deterioration in visual function and/or retinal structure.

An interval of 28 days between dosing of the first and second pediatric patients will be observed. Thereafter, subsequent pediatric patients may be enrolled consecutively. DSMB reviews will be done as previewed in the Charter of DSMB.

Group E (Cohort 7) plans to enroll and treat symptomatic patients (from 6 and 17 years old) with SMD and VA ≥20/100 in at least one eye at the time of the screening visit, anticipated to experience rapid deterioration in visual function and/or retinal structure. If patient is eligible in both – Cohorts 6 and 7, she/he will be included in Cohort 7).

Cohort 7 will receive SAR422459 at the highest dose tested.

Cohort 8 will be treated with the 1.5 $x10^6$ TU measured strength dose and will enroll patients corresponding to Group D criteria: (from 6 years to 26 years old; early or childhood onset symptomatic SMD and VA ≥20/200 in both eyes at screening; rapid deterioration).

Cohort 9 will be treated with 1.5 $x10^6$ TU measured strength dose and will enroll patients corresponding to Group E criteria (from 6 years to 17 years old; symptomatic SMD and VA ≥20/100 in both eyes at screening; rapid deterioration. If patient is eligible in both – Cohorts 8 and 9, she/he will be included in Cohort 9).

DSMB review of available data will be performed before starting treating patients younger than 16 years.

For Cohorts 6 to 9, to ensure consistency across sites, a centralized review of baseline study assessments will be performed pre-operatively for the purpose of providing a recommendation on the area of retina to be targeted for the subretinal injection to optimize the treatment benefit.

Table 3 - Summary of cohorts of patients and dose levels

Cohort	Group	Subretinal Injection				
		No of patients	**Dilution factor**	**Dose by target strength** (TU/eye)*	**Dose by measured strength**** (TU/eye)	**Volume**
1	A	4	1:10	$1.8x10^5$ TU	$0.48x10^5$ TU	300 µL
2	B	4	1:10	$1.8x10^5$ TU	$0.48x10^5$TU	300 µL
3	B	4	1:3	$6x10^5$ TU	$3.6x10^5$ TU	300 µL
4	B	4	undiluted	$1.8x10^6$ TU	$0.99x10^6$ TU	300 µL
5	C	6	undiluted	$1.8x10^6$ TU (highest dose targeted)	$0.99x10^6$ TU	300 µL
6	D	4	undiluted	$1.8x10^6$ TU (highest dose targeted)	$4.5 x10^6$ TU (highest dose tested)	300 µL

Cohort	Group	Subretinal Injection				
		No of patients	**Dilution factor**	**Dose by target strength** (TU/eye)*	**Dose by measured strength**** (TU/eye)	**Volume**
7	E	1	undiluted	$1.8x10^6$ TU (highest dose targeted)	$4.5 x10^6$ TU (highest dose tested)	300 µL
8	D	Up to 6	1:3	-	$1.5 x10^6$ TU	300 µL
9	E	Up to 8	1:3	-	$1.5 x10^6$ TU	300 µL

Note: * - calculated from target product strength; ** - calculated from dilution (as applicable) of measured strength

The patients will all be followed up for 48 weeks. After this period they will enter an open-label safety study (LTS13588) and undergo long-term follow-up visits including ophthalmological examinations and recording of adverse events.

8.1 STUDY SITES

The study is multicenter with sites in EU and the USA. Selected sites will have the necessary experience to perform the subretinal injection procedure in children and adults and the capability to handle gene therapy products.

9 STUDY POPULATION

Patients with SMD meeting all of the study inclusion criteria and none of the exclusion criteria will be recruited following EC/IRB and regulatory approval.

9.1 ENTRY CRITERIA

9.1.1 Main inclusion criteria

Patients must meet ALL of the following criteria to be considered for enrolment into this study:

1. Signed and dated written informed consent obtained from the patient and/or the patient's legally acceptable representative, if applicable, in accordance with the local regulations.
2. Diagnosis of SMD, with at least one pathogenic mutant ABCA4 allele on each chromosome, confirmed by direct sequencing. Gene mutation analysis results conducted prior to signing the informed consent may be used provided that the analysis was conducted by a CLIA (Clinical Laboratory Improvement Amendments) certified laboratory, written results are provided to the site, and participants (patients and/or the patient's parent[s]/legal guardian[s]) give consent to utilize the results. For patients genotyped during the screening period results demonstrating a pathogenic mutant ABCA4 allele on each chromosome must be documented prior to the administration of SAR422459.
3. Women of childbearing potential must have a negative pregnancy test at Day -1 and agree to use an effective form of contraception for at least 3 months such as the contraceptive pill or intra uterine device, or be surgically sterile or postmenopausal, with the last menstrual period being over 2 years prior to enrolment (partners of study patients must agree to use barrier contraception for at least 3 months after SAR422459 administration).
4. Males must agree with their partner to use 2 forms of contraception, including one barrier method for at least 3 months following SAR422459 administration if their partner is of childbearing potential, or must be surgically sterile.
5. Patients must agree to not donate blood, organs, tissues or cells for at least 3 months following SAR422459 administration
6. Patients enrolled in France must be affiliated to or benefit from a social security regimen.

9.1.2 Specific inclusion criteria Patient Group A

- Patients (18 years or older) with advanced SMD.
- VA $\leq$20/200 in the worst eye.
- Severe cone-rod dysfunction with no detectable or severely abnormal full-field ERG responses.

9.1.3 Specific inclusion criteria Patient Group B

- Patients (18 years or older) with SMD.
- VA ≤20/200 in the worst eye.
- Abnormal full-field ERG responses.

9.1.4 Specific inclusion criteria Patient Group C

- Patients (18 years or older) with SMD.
- VA ≤20/100 in the worst eye.
- Abnormal full-field ERG responses.

9.1.5 Specific inclusion criteria Patient Group D

- Symptomatic patients (from 6 years to 26 years old) with early or childhood-onset SMD (age at disease onset <18 years) with at least one pathogenic mutant ABCA4 allele on each chromosome confirmed by direct sequencing and co-segregation analysis within the patient's family.
- Visual acuity of ≥20/200 in both eyes at the time of the screening visit.
- Patients are anticipated to experience rapid deterioration in visual function and/or retinal structure as determined by an annual progression rate in at least one of the following parameters occurring in at least one eye (assessments recorded up to 2 years prior to the screening visit date may be considered to document evidence of rapid deterioration):
  - Loss of ≥1 line of Snellen visual acuity (equivalent to 5 ETDRS letters),
  - Reduction in macular mean sensitivity of ≥1.2 dB as assessed by microperimetry,
  - Reduction in macular mean sensitivity of ≥5 dB or reduction in hill of vision by >14 dB-sr as assessed by static perimetry,
  - Enlargement in the area of macular RPE atrophy by fundus autofluorescence at a rate of ≥0.5 mm^2,
  - Enlargement in the area of central macular retinal thinning/photoreceptor loss by ocular coherence tomography at a rate of ≥0.5 mm^2.
- All eligible patients must demonstrate an ability to understand, willingness to cooperate and ability to reliably perform required study procedures as judged and confirmed by the study investigator.

9.1.6 Specific inclusion criteria Patient Group E

- Symptomatic patients (between 6 years and 17 years old) with early or childhood-onset SMD with at least one pathogenic mutant ABCA4 allele on each chromosome confirmed by direct sequencing and co-segregation analysis within the patient's family.
- Visual acuity of ≥20/100 in both eyes at the time of screening visit.

- Patients are anticipated to experience rapid deterioration in visual function and/or retinal structure as determined by an annual progression rate in at least one of the following parameters occurring in at least one eye (assessments recorded up to 2 years prior to the screening visit date may be considered to document evidence of rapid deterioration):
  - Loss of ≥1 line of Snellen visual acuity (equivalent to 5 ETDRS letters),
  - Reduction in macular mean sensitivity of ≥1.2 dB as assessed by microperimetry,
  - Reduction in macular mean sensitivity of ≥5 dB or reduction in hill of vision by >14 dB-sr as assessed by static perimetry,
  - Enlargement in the area of macular RPE atrophy by fundus autofluorescence at a rate of ≥0.5 mm^2,
  - Enlargement in the area of central macular retinal thinning/photoreceptor loss by ocular coherence tomography at a rate of ≥0.5 mm^2.
- All eligible patients must demonstrate an ability to understand, willingness to cooperate and ability to reliably perform required study procedures as judged and confirmed by the study investigator.

9.1.7 Exclusion criteria

Presence of ANY one of the following criteria will exclude patients from being enrolled into the study:

1. Pre-existing eye conditions that would preclude the planned surgery or interfere with the interpretation of study endpoints: glaucoma or other primary optic neuropathy that has resulted in significant visual field loss, corneal or significant lens opacities, active uveitis, retinopathy and maculopathy (other than that from Stargardt disease) that in the opinion of the investigator is causing significant visual loss, myopia greater than 8 diopters spherical equivalent.
2. Cataract surgery with intraocular lens implantation within 6 months of enrolment.
3. Aphakia or prior vitrectomy in the study eye.
4. Concomitant systemic diseases including those in which the disease itself, or the treatment for the disease, can alter ocular function. For instance malignancies whose treatment could affect central nervous system function, diabetes, juvenile rheumatoid arthritis or sickle cell disease.
5. Any intraocular surgery (other than study procedure) or laser in either eye planned within 6 months of Day 0.
6. Any contraindication to pupil dilation in either eye.
7. Any known allergy to any component of the delivery vehicle or diagnostic agents used during the study (eg, fluorescein, dilation drops), or medications planned for use in the peri-operative period particularly topical, injected or systemic corticosteroids.
8. Any injectable intravitreal treatment to the treated eye or intravitreal device in the treated eye within 6 months prior to screening.

9. Any periocular injections of corticosteroids to the treated eye within 4 months prior to screening.
10. Laboratory test abnormalities or abnormalities in electrocardiogram, chest X-rays that in the opinion of the PI would make the patient unsuitable for participation in the study.
11. Significant intercurrent illness or infection during the 28 days prior to enrolment.
12. Pre-menopausal or non-surgically sterile women who are unwilling to use an effective form of contraception such as the contraceptive pill or intrauterine device.
13. Men or women who do not agree to use barrier contraception according to the inclusion criteria.
14. Alcohol or other substance abuse.
15. Contraindications to use of anesthesia (local or general, as appropriate).
16. Concurrent anti-retroviral therapy that would inactivate the investigational agent
17. History of any investigational agent within 28 days prior to SAR422459 administration.
18. Participation in a prior ocular gene transfer therapy study, other than the TDU13583 study.
19. Enrolment in any other clinical treatment study, for any condition, including those relating to SMD, throughout the duration of the SAR422459 TDU13583 study participation.
20. Current or anticipated treatment with anticoagulant therapy or the use of anticoagulation therapy within the 4 weeks prior to surgery.
21. A past medical history of HIV or hepatitis A, B or C infection.
22. Inability to comply with the demands of the study.
23. Women who are pregnant or are breastfeeding.
24. History or signs consistent with unilateral amblyopia (strabismic, anisometropic or stimulus deprivation).

9.2 WITHDRAWAL CRITERIA

Once SAR422459 has been administered into the eye it cannot be removed, therefore patients are unable to withdraw from the study treatment. However, an individual may withdraw consent for any study related procedures at any time throughout the study, and this will not affect the standard of care (SOC) they receive. Patients withdrawing from follow-up monitoring before the primary endpoints have been established 6 months after surgery may be replaced. Regardless of the reasons for withdrawal below, the sponsor commits to follow the patient for the complete duration of the trial.

Individual patients may also be withdrawn under the following circumstances:

- The patient requests early discontinuation.
- Investigator's request (eg, if the investigator considers that the patient's health is compromised by remaining in the study or the subject is not sufficiently co-operative).
- The patient is lost to follow-up (all attempts will be made to locate patients lost to follow-up).

Any patient that is withdrawn from the study will be encouraged to enroll in a long-term follow-up study. Long-term follow-up in gene transfer research allows for the collection of important information on the long-term safety and effects of the study treatment. The long-term follow-up study (LTS13588) will last for up to 15 years. If the patient withdraws/is withdrawn from the study prematurely, the Week 48 procedures should be completed, if possible.

The long-term safety follow-up will be described in a separate protocol which will be submitted to regulatory agencies and Institutional Review Boards/Ethics Committees for approval.

The open-label follow-up study has been designed to capture the essential safety data pertinent to gene therapy follow-up, as well as key efficacy assessments, whilst providing the patient with a degree of flexibility for minimizing inconvenience. The long-term follow-up protocol will also permit patients to receive alternative treatment during their participation while allowing for safety follow-up.

9.3 STUDY STOPPING CRITERIA

The following is to be considered stopping enrollment:

- Prolonged anterior chamber inflammation and/or prolonged posterior chamber inflammation continuing without signs of resolution 28 days after SAR422459 administration.

Criteria for suspending enrolment or further study conduct are defined in the DSMB charter and all events will be reviewed by the DSMB.

In the event that enrollment is terminated, all patients who have been dosed with SAR422459 will continue to be followed up as per protocol until the Week 48 visit has been completed. Patients will be encouraged to enroll in a long-term follow-up study. Long-term follow-up in gene transfer research allows for the collection of important information on the long-term safety and effects of the study treatment. The long-term follow-up study (LTS13588) will last for up to 15 years.

9.4 DOSE-LIMITING TOXICITIES

Dosing will stop if a dose-limiting toxicity is encountered in a dosing cohort. Events that constitute a dose-limiting toxicity will be defined in the DSMB charter. Dose limiting toxicities will include:

- Severe or persistent ocular inflammation.;
- Other significant ocular toxicity (eg, large retinal detachment, evidence of direct toxicity).
- Other systemic toxicities (eg, acute allergic reaction).
- Any safety issue that has been identified that adversely changes the benefit/risk balance to study participants.

10 TREATMENT PLAN AND METHODS

10.1 ALLOCATION OF TREATMENTS

10.1.1 Dose escalation

Patients will be allocated to treatment in the order in which they are enrolled into the study.

Dose escalation or progression to the next patient cohort will be based on safety from the patients of the previous cohorts, including events such as the presence and severity of manifested clinical signs and symptoms, laboratory tests including clinical chemistry, hematology, urinalysis and antibodies. The DSMB will thoroughly review and discuss the results from the previous cohort(s) before proceeding with any subsequent dose escalation. All patients in the previous cohort must be observed for a minimum of 28 days before additional participants receive drug at the next dose level.

10.2 STUDY MEDICATION ADMINISTRATION

10.2.1 Hospitalization

Hospitalization is not required but may be necessary for the subretinal injection procedure for convenience of some patients. Patients will not take anything by mouth for a minimum of 8 hours prior to the ocular surgery.

10.2.2 Subretinal injection procedure

After informed consent is completed, patients will have baseline assessments and eligibility will be confirmed. For Cohorts 6 to 9, a centralized review of baseline study assessments will be performed pre-operatively for the purpose of providing a recommendation on the area of retina to be targeted for the subretinal injection to optimize the treatment benefit.

Eligible patients will be scheduled for surgery, the study eye will be marked prior to entering the operating room and once in the operating room the study eye will be reconfirmed.

Surgery will be performed under general anesthesia or waking sedation at the surgeon's discretion, with additional periocular/retrobulbar injections according to surgeon and anesthesiologist preferences. Surgery will be performed under sterile conditions in accordance with hospital operating room protocols, according standard practice of subretinal injections and following recommendations of Study Manuals.

Following the administration of SAR422459, the fundus will be examined by fundoscopy/indirect ophthalmoscopy and scleral depression to look for peripheral retinal tears. If there are any peripheral retinal tears, they will be treated with cryopexy and a fluid-air exchange or other appropriate technique at the judgment of the surgeon. The vitreous cavity may be filled with the appropriate tamponade at the discretion of the surgeon.

To explore further the treatment effect (safety and biological activity) at the bleb level during the procedure, intraoperative photos and, where available, video of the surgery and/or intra-operative OCT will be collected. Following the procedure the surgeon will prepare a retinal drawing showing the location of the bleb in order to define as precisely as possible the area of the bleb and consequently, the zone of cell transduction. Materials documenting the subretinal bleb location will be forwarded to the reading center. In the event that the subretinal injection is not placed in an area recommended by the central review at the completion of the procedure the surgeon will make a note in the study source documents indicating the rationale for the location of the subretinal bleb.

The eye will be patched and the patient will be taken to the post-operative observation area.

For each patient, the following protocol required anti-inflammatory regimen including antibiotics and corticosteroid medications must be administered to reduce the possibility of clinically significant intraocular inflammation after subretinal injection procedure.

- **Two hours prior to the subretinal injection procedure - administer:**
  - **In Children:** one dose of intravenous methylprednisolone 1 mg/kg for patients ≥50 kg or 0.5 mg/kg for patients <50 kg. Maximum corticosteroid dose not to exceed 80 mg for children <16 years,
  - **In Adults:** one dose of intravenous methylprednisolone 1 mg/kg.
- **Immediately following the completion of the subretinal injection procedure:**
  - At the discretion of the surgeon, a subconjunctival injection of corticosteroids (eg Dexamethasone 5 to 10 mg) and/or a subconjunctival injection of antibiotics may be given.
- **Starting (post-operative) Day 1 administer/initiate:**
  - **In Children:** oral prednisone 1 mg/kg/day for patients ≥50 kg or 0.5 mg/kg/day for patients <50 kg daily for 5 days, then reduce dose to 0.5 mg/kg/day for patients ≥50 kg or 0.25 mg/kg/day for patients <50 kg daily for 5 days, then reduce dose by 10 daily until the corticosteroid taper is complete. Maximum corticosteroid dose not to exceed 80 mg for children <16 years,
  - **In Adults:** oral prednisone 1 mg/kg/day for 5 days, then reduce dose to 0.5 mg/kg/day for 5 days, then reduce dose by 10 mg daily until the corticosteroid taper is complete,
  - Topical broad-spectrum antibiotic (eg, ofloxacin, ciprofloxacin, moxifloxacin, trimethoprim-polymyxin B or similar) QID for 7-10 days,
  - Topical prednisolone acetate 1% (or similar) 4 times a day (QID) for 7-10 days, then 3 times a day (TID) for 7-10 days, then 2 times a day (BID) for 7-10 days, then once daily (QD) for 7-10 days. (Note: The frequency of the topical corticosteroid drops and the timing for the start of the taper may be adjusted as needed in response to the patient's manifestation of post-operative inflammation with the goal of resolving the post-operative ocular inflammatory response within 28 days after the surgical procedure),

- A topical steroid ointment (eg, sterdex, tobradex or similar) may also be given at bedtime (qhs) for 7-10 days at the discretion of the surgeon.

Intraocular inflammation worsening during the course of treatment with the protocol defined anti-inflammatory regimen (see Section 10.3.27 Post Surgical Ophthalmological Adverse Events) or persisting or occurring after the completion of the above protocol defined anti-inflammatory regimen must be recorded as a post-surgical adverse event.

For the management of intraocular inflammation persisting or occurring after the completion of the above protocol defined anti-inflammatory regimen or worsening during the course of the regimen see Section 10.3.27 Post-surgical Ophthalmological Adverse Events.

10.2.3 Positioning of the subretinal bleb

In all patients, the site for subretinal injection will be selected as to ensure that the existing VA will not be impaired and the treated retinal area can be easily monitored for safety after SAR422459 administration. Group A will have advanced disease and very poor VA. In this group encroachment of the injection bleb to the central macula will be permitted as it is unlikely it will further impair VA. However, groups B, C, D and E will have less advanced disease with better acuity and group E will include pediatric patients.

Prior to surgery, the position of the subretinal bleb will be determined based on the baseline clinical evaluation, fundus imaging and visual field testing. Clinical evaluation and fundus imaging will be used so that the subretinal bleb can be positioned to avoid area(s) of outer retinal atrophy. Perimetry will be used so that the bleb avoids area(s) with normal retina sensitivity.

Patient Group A: The bleb will be allowed to extend into the central macula. If the surgeon determines that the bleb is not forming in the correct position, he/she can choose to stop infusing and create another retinotomy. This can be done up to twice until the full volume has been delivered.

Patient Group B and C: The positioning of the bleb will be determined pre-operatively based upon visual field testing and in an area of retina that has diminished but recordable retinal sensitivity. An extramacular bleb will be created at the macular boundary. The bleb may extend into the macula but the central macula will not be detached.

Patient Group D and E: Recommendation of the bleb location will be made by the centralized review for the purpose of optimizing the treatment benefit and minimizing the risk to existing VA.

10.2.4 SAR422459 preparation

SAR422459 will be provided in 100 µL aliquots in 0.3 mL type I borosilicate glass ‘V’ vials with a butyl stopper and aluminum crimp seal. Each vial of SAR422459 will be issued in a white plastic tamper evident container secured in packaging. The vial and plastic tamper-evident container will be labeled appropriately.

Further details of the preparation of SAR422459 for administration are provided in the study pharmacy manual.

10.2.5 SAR422459 administration

All disposable surgical supplies; including gloves, masks, gowns, dressings and swabs used during the surgical procedure will be destroyed by incineration according to hospital policy at the end of the operation. The first dressings removed from the patient's wounds following surgery will also be disposed of by incineration or local equivalent in accordance with the local hospital policy on genetically modified materials.

10.2.6 Post-surgical monitoring

Post-surgical monitoring will be conducted according to SOC according to the clinical sites usual protocols.

Before the patient is discharged, blood and urine samples will be obtained for PCR assay for viral particles.

10.3 SPECIFIC PROCEDURES

Ophthalmic procedures will be conducted on both the treated and untreated eye at all visits.

10.3.1 Screening/baseline procedures

A screening log must be maintained for all patients screened for entry to the study, reasons for screen failure will be documented.

Patient screening will take place in the 28 days prior to SAR422459 administration. Full-field Kinetic and Static perimetry and BCVA will be performed during the screening period. As these measures are subject to broad intra-individual variability, they may be repeated during the screening period to determine the patient's reliability in the performance of these psychophysical assessments.

A pan-retinal photomontage image will be taken at screening to document the whole retina prior to the beginning of the study.

At screening, a 7-field fundus photos series will be taken of each eye to document the whole retina. At subsequent visits a standard 50˚ photograph centered on the macula and including the optic nerve will be obtained to document the appearance of the posterior pole with specific emphasis on recording the area of the retina that will be or was treated. Images should be evenly illuminated, well focused and free of artifacts (please see the Technical Manual of Procedures for more details). If opacities of the anterior ocular structures compromise image quality, an external red-reflex image focused on the iris plane should also be taken.

Screening procedures are detailed in the study schedule in Section 3.

10.3.2 Screening clinical and laboratory/diagnostic measurements

The following assessments are required 28 ± 10 days prior to administration of SAR422459. If necessary, the screening assessments can be carried out over several days. Screening urine pregnancy tests must be negative.

- Informed consent
- Entry criteria
- Demographic data
- Genotyping
- Medical history
  - Clinical symptoms of SMD
  - Treatment history
  - Past medical history of HIV, hepatitis A, B or C infection will be evaluated.
  - Reproductive status
- Concomitant medications
- Pre-operative assessments
  - Anesthesia assessment
  - Height
  - Weight
  - Vital signs
  - Electrocardiogram (ECG)
  - Chest X-ray
  - Physical examination
- Ophthalmological examination
  - BCVA
  - Contrast sensitivity - Cohorts 6-9 only
  - Reading speed (when possible) - Cohorts 6-9 only
  - Slit lamp examination
  - Intraocular pressure (IOP)
  - Fundoscopy/indirect ophthalmoscopy
  - FAF
  - OCT
  - Infra-red imaging - Cohorts 6-9 only

  - Microperimetry
  - Full-field kinetic and static perimetry
  - Full-field ERG
  - Multifocal ERG (Cohort 1-5)
  - Adaptive optics (Cohort 1-5)
  - Fundus photography
- Laboratory samples
  - Hematology
  - Chemistry panel
  - Kidney function
  - Liver function
  - Coagulation
- Urinalysis
- Urine pregnancy test for women of childbearing potential
- Blood for PCR
- Urine for PCR
- Adverse events (since consent).

10.3.3 Screening clinical laboratory/diagnostic measurements Day -1

The following assessments must either be completed on Day-1 or in the preceding 7 days with the exception of the urine pregnancy test that must be negative on Day -1.

- Concomitant medications
- Vital signs
- Ophthalmological examination
  - BCVA
  - Contrast sensitivity- Cohorts 6-9 only
  - Slit lamp examination
  - Intraocular pressure (IOP)
  - Fundoscopy/indirect ophthalmoscopy
  - FAF
  - OCT
  - Infra-red imaging

- Microperimetry
- Full-field kinetic and static perimetry
- Fundus photography
- Multiphocal ERG (Cohort 1-5)
- Full-field ERG
- Adaptive optics (Cohort 1-5)
- Reading speed (when possible)
- VFQ-25/CVAQC-25 (when possible)

- Clinical laboratory samples
- Urinalysis
- Urine pregnancy test for women of childbearing potential
- Blood for immunology
- Adverse events

10.3.4 Re-screening

Re-screening will be allowed once within 90 day period from initial informed consent, in case patient was eligible by all inclusion – exclusion criteria, but was not treated. Previous evaluation of rapid deterioration will be accepted. All other eligibility criteria need to be reviewed. Patient will undergo a baseline visit (if was not done) or repeat it within a 7 day period before surgery. Additional (standard) examinations/ tests can be needed during such visit:

- laboratory tests of hematology, chemistry panel, kidney function, liver function and coagulation will be repeated if done earlier than 38 days before surgery, or - by a request of anesthesiologist.
- anesthesia assessment will be repeated if outside of the Day-28 to Day-1 window before surgery. Weight, ECG, chest X-ray may be repeated by a request of anesthesiologist.

10.3.5 Surgery

The following assessments are performed on the day of surgery.

- SAR422459 administration.
- Fundus photography will be performed in the operating room during surgery. This will be post bleb placement and will record the position of the bleb relative to the retinal anatomy
- Where available, intraoperative video recording of the surgical procedure and/or intraoperative OCT will also be performed.
- Vital signs 30 and 60 minutes after surgery

- Blood 60 minutes after surgery and first urine sample that occurs after 60 minutes post-surgery
- Adverse events
- Concomitant medications

10.3.6 Follow-up procedures

Patient follow-up visits are outlined in the study schedule in Section 3.

10.3.7 Follow-up Day 1 clinical and laboratory/diagnostic measurements

- Concomitant medications
- Vital signs
- Ophthalmological examination
  - BCVA
  - Slit lamp examination
  - Intraocular pressure (IOP)
  - Fundoscopy/indirect ophthalmoscopy
  - OCT
  - Fundus photography
- Clinical laboratory samples (except coagulation and kidney function) (for Cohorts 1-5 only)
- Blood for PCR
- Urine for PCR
- Urinalysis
- Adverse events

10.3.8 Follow-up Week 1, 2, 4, 12, 24, 36 and 48 clinical and laboratory/diagnostic measurements (visit at Week 36 is not performed in Cohorts 6 and 9)

- Concomitant medications
- Vital signs
- Ophthalmological examination
  - BCVA
  - Contrast sensitivity (Weeks 12, 24 and 48) - Cohorts 6 to 9 only
  - Slit lamp examination
  - Intraocular pressure (IOP)

- Fundoscopy/indirect ophthalmoscopy
- FAF:
  - Cohorts 1-5: Weeks 4, 12, 24 and 48 only
  - Cohorts 6-9: Weeks 4,12, 24 and 48 only
- Infrared reflectance imaging:
  - Cohorts 6-9: Weeks 12, 24 and 48
- OCT:
  - Cohorts 1-5: at each visit
  - Cohorts 6-9: at each visit
- Microperimetry:
  - Cohorts 1-5: Weeks 2, 4, 12, 24, 36 and 48 only
  - Cohorts 6-9: Weeks 4, 12, 24, and 48 only
- Full-field Kinetic and Static Perimetry
  - Cohorts 1-5: Weeks 2, 4, 12, 24, 36 and 48 only
  - Cohorts 6-9: Weeks 12, 24, and 48 only
- Fundus photography:
  - Cohorts 1-5: Weeks 2, 4, 24, 36 and 48 only
  - Cohorts 6-9: Weeks 2, 4, 24 and 48 only
- Full-field ERG:
  - Cohorts 1-5: Weeks 4, 12, 24 and 48 only
  - Cohorts 6-9: Week 48 only
- Multifocal ERG:
  - Cohorts 1-5: Weeks 4, 12, 24 and 48 only
- Adaptive optics:
  - Only for Cohorts 1-5 (Weeks 12, 24, 36 and 48 only)
- Reading speed
  - Cohorts 1-5: Week 48 only
  - Cohorts 6-9: Week 48 only, when available
- VFQ-25/CVAQC-25:
  - Cohorts 1-5: Week 48 only
  - Cohorts 6-9: Week 48 only, when available

- Clinical laboratory samples (except coagulation) (Weeks 4, 24 and 48 only)
- Urinalysis (Weeks 4, 24 and 48 only)
- Blood for PCR
  - Cohorts 1-5: Week 1, 2, 4, 12, 24, 36 and 48
  - Cohorts 6-9: Week 1, 4, 12, 24 and 48

- Urine for PCR
  - Cohorts 1-5: Week 1 and 2
  - Cohorts 6-9: Week 1 only
- Blood for immunology:
  - Cohorts 1-5: Week 4, 12 and 24. For patients with positive antibody response at Week 24, additional blood sampling will be performed at Week 36 and 48.
  - Cohorts 6-9: Week 4, 12 and 24. For patients with positive antibody response at Week 24, additional blood sampling will be performed at Week 48.
- Adverse events
- Physical examination (Week 48 only)

10.3.9 Samples for PCR

Blood samples for PCR are required to be taken at the Screening visit (28 Days prior to surgery) and at the following visits post-administration of SAR422459; 60 minutes after surgery, Day 1, Weeks 1, 2, 4, 12, 24, 36 and 48. In Cohorts 6-7, blood samples are not required at Week 2 and Week 36.

Urine samples for PCR are required to be taken at the Screening visit (28 Days prior to surgery) and at following visits, Day 0 (first urine sample that occurs after 60 minutes post-surgery), Day 1 and Weeks 1 and 2 only. In Cohorts 6-7, urine samples are not required at Week 2.

The processing of blood samples for PCR analysis will be performed at the designated hospital by a person designated by the PI. The samples will be labeled with the patient number, date of collection and visit number. They will then be stored in the freezer at ≤-70°C prior to shipment to the Sponsor designated company for analysis. The shipment of samples will be on dry ice. The Sponsor clinical project manager or designee will be notified at least 24 hours in advance of any shipment.

10.3.10 Samples for immunology

Samples for immunology are required to be taken at the baseline visit (Day -1) and at the following visits post administration of SAR422459; Weeks 4, 12 and 24 (and Week 36 for Cohorts 1-5). In patients with positive antibody response at Week 24, additional blood sampling will be performed at Week 36 and 48 for Cohorts 1-5 and only at Week 48 for Cohorts 6-7.

The processing of the blood samples for immunology analysis will be performed at the designated hospital by a person designated by the PI. The samples will be labeled with the patient number and initials, date of collection and visit number. They will then be stored in the freezer at ≤-70°C prior to shipment to the Sponsor designated company for analysis. The shipment of samples to the Sponsor designated company will be on dry ice. The Sponsor clinical project manager or designee will be notified at least 24 hours in advance of any shipment.

Blood samples collected for immunology will be analyzed using either ELISA and/or Western blot analysis.

Future use of samples

For subjects who have consented to it, the samples that are unused or left over after testing may be used for other research purposes (excluding genetic analysis) related to ophthalmology.

These sample(s) will be transferred to a Sanofi site (or subcontractor site) and will be handled and stored at a secure site specialized for such investigations under the responsibility of the sponsor up to 15 years after completion of the final report of the main clinical. Thereafter, all samples will be destroyed.

10.3.11 Ophthalmological assessments

Ophthalmological assessments will be carried out by certified individuals at the study site. As far as possible, for each patient, assessments will be performed by the same individual at each visit. Technical details of all ophthalmological assessments will be provided in the investigator site file. All findings will to be documented in the source documentation and the appropriate electronic Case Report Form (eCRF).

Studies have shown that a number of psychophysical measures and imaging modalities provide a sensitive method of monitoring disease progression and response in SMD.

10.3.12 Best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) Visual Acuity

A BCVA examination will be performed using the EVA (electronic VA) testing system according to the recommended protocol. Early Treatment Diabetic Retinopathy Study (ETDRS) chart testing will be used as a back-up in case the EVA is not functioning or available. In such cases the same method used to record BCVA at the screening visit for a given patient should be used throughout the study.

For young patients, not knowing to read letters - adapted equivalent charts will be used BCVA evaluation. Use of such charts for rapid deterioration for inclusion will be agreed with Sponsor beforehand, loss equivalent to Snellen / ETDRS criteria will be established for each chart.

10.3.13 Contrast sensitivity

A contrast sensitivity assessment will be performed using the Sloan Low Contrast Letter acuity chart according to the recommended protocol/manual. In low vision patients, functional vision, eg, the ability to recognize faces and read moderate size print and the orientation and mobility capacities were better correlated to contrast sensitivity levels than visual acuity measurements. (36, 37). The 100%, 2.5%, and 1.5% contrast level Sloan Low Contrast Acuity charts will be used for testing. Contrast sensitivity in the study will be tested on each eye separately; it is not required to test both eyes together. For detailed instructions see Appendix D.

Special other charts may be used for young patients not knowing to read letters.

10.3.14 Slit lamp examination

Slit lamp examination will be performed using the investigator's standard procedure.

This procedure will be the same for all patients examined. Observations will be made to indicate the absence or presence of findings for ocular adnexa, anterior and posterior segments. Intraocular inflammation will be graded using a standard scale (see Appendix A).

10.3.15 Fundoscopy/indirect ophthalmoscopy

Dilated fundoscopy/indirect ophthalmoscopic will be performed according to the investigator's standard practice. Investigators will specifically document the presence or absence of retinal detachment, retinal tears or holes, subretinal hemorrhage, exudation, fluid or fibrosis. Additional observations will also be documented.

10.3.16 Intraocular pressure measurement

Applanation tonometry is the preferred method to be used for IOP measurements after dilation, however, for Cohorts 6-9, Tonopen or noncontact methods are acceptable. The same method of IOP measurement must be used in each subject throughout the study.

10.3.17 Optical coherence tomography

OCT is a non-invasive technique that provides high resolution axial images of the retina. A low coherence infrared source is used to image the retina and a portion of coherent backscattered light is detected using an optical interferometer (38). Depth and intensity information can be captured digitally to visualize the structural morphology of the intraretinal layers. Spectral domain OCT (SD-OCT) is the most advanced method available and provides high resolution, rapid scanning, high repeatability and the capacity for transverse scans and the 3-dimentional mapping of single retinal layers (39). Macular thickness, subretinal fluid, and other architectural OCT features provide useful information on the transverse and axial location of retinal lesions.

OCT will be performed after dilation using the Spectralis SD-OCT imaging system (Heidelberg Engineering) to evaluate the cross-sectional anatomy of the macula and document areas of retinal atrophy.

10.3.18 Fundus photography

Fundus photography (color and infrared reflectance images) remains an invaluable tool to record the characteristics of the retina at any one stage of the disease and is used in combination with other imaging modalities (eg, autofluorescence) to accurately map the appearance of atrophy.

To document the retinal anatomy after adequate dilation, a suitable fundus camera, (Zeiss FF4 series and the Topcon TRC-50EX or similar) will be used to collect color fundus photos, whereas, the Heidelberg Spectralis OCT capable of collecting infrared reflectance images will be used.

10.3.19 Electroretinogram

Full-field electroretinography (ERG) measures the electrical responses of various cell types in the retina, including the PRs, inner retinal cells bipolar and amacrine cells, and the ganglion cells. It is a non-invasive technique in which electrodes are placed on the cornea and the skin near the eye. During a recording, the patient's eyes are exposed to standardized light stimuli and the resulting ERG signal is displayed showing the time course of the signal's amplitude. The ERG is composed of electrical potentials contributed by different cell types within the retina, and the stimulus conditions (flash or pattern stimulus, whether a background light is present, and the colors of the stimulus and background) can elicit stronger response from certain components.

If a flash ERG is performed on a dark-adapted eye (scotopic), the response is primarily from the rod system and flash ERGs performed on a light adapted eye (photopic) will reflect the activity of the cone system. With sufficiently bright flashes, the ERG will contain an ‘a-wave’ (initial negative deflection) followed by a ‘b-wave’ (positive deflection). The leading edge of the a-wave is produced by the PRs, while the remainder of the wave is produced by a mixture of cells including PRs, bipolar, amacrine and Mueller cells.

A full-field electroretinogram will be conducted after dilation using the standard procedure according to the ERG Standardisation Committee of the International Society for Clinical Electrophysiology of Vision (ISCEV). Stimulus protocols for both scotopic and photopic function will be performed.

Multifocal electroretinography will be performed using the multifocal ERG according the manufacturers protocol.

10.3.20 Perimetry

Semi-automated Kinetic Perimetry (SKP) and Full-field Static Perimetry are non-invasive, psychophysical tests that can rapidly and accurately assess the visual fields and create a detailed map of the retina documenting any scotoma and the level of retinal function at individual loci. SKP allows greater standardization, control, and documentation of how the testing is performed, and minimizes the variability normally observed when different perimetrists test the same patient. Analysis will be performed at a central reading center.

The technique of static perimetry has been optimized specifically for glaucoma, however has also been shown to be appropriate for retinal disease (40). Using the German Adaptive Threshold Estimation (GATE) strategy (41) and radially oriented, centrally condensed grids that extend from 50° nasally to 80° temporally, the entire full-field is captured. The centrally condensed grid captures detail of sensitivity boundaries and gradients within the central portion of the field and thus, can more precisely define remaining visual field in advanced disease. The differential luminance sensitivities are exported digitally to the central reading center for computation and modeling to create a “Hill of Vision”, which is a volumetric estimate of retinal function.

Perimetry will be performed prior to dilation using the Haag Streit Octopus 900 (Semi-automated Kinetic Perimetry (SKP) and Full-Field GATE Static perimetry).

Full-field Kinetic and Static perimetry and BCVA will be performed during the screening period. As these measures are subject to broad intra-individual variability, they will be repeated to during the screening period to determine the patient's reliability in the performance of these psychophysical assessments.

10.3.21 Microperimetry

Microperimetry will be performed on the MP1 following dilation. The MP1 provides a quantitative assessment of fixation by tracking fundus movements while the patient looks steadily at the fixation target. The MP1 can also accurately map a scotoma by delineating the absolute or relative non-seeing areas within the visual field. This is accomplished by projecting a light stimulus onto the patient's retina until it becomes visible to the patient. With the MP1 it is possible to monitor the evolution of a disease and the exact changes it effects on a patient's vision over the long-term, because follow-up examinations are automatically performed in previously examined areas.

10.3.22 Fundus Autofluorescence imaging

Fundus autofluorescence imaging of the retina will be performed following dilation to document the distribution of lipofuscin and degenerative geography using the Spectralis system (Heidelberg Engineering). Fundus autofluorescence (FAF) is a non-invasive imaging technique to visualize lipofuscin, particularly in the parafoveal area.

Abnormally increased FAF suggests RPE dysfunction, while decrease FAF indicates RPE atrophy and PR death (42). Images are acquired using a confocal laser ophthalmoscope system effectively gathering light from a single focal plane and eliminating autofluorescence from sources anterior to the retina (43). Studies of early SMD have consistently demonstrated abnormal FAF with a wide variation in the pattern and degree of retinal involvement. This technique can detect areas of atrophy that may be missed by fundus photography and is therefore useful for detection and monitoring of early disease (40).

Early detectable disease is characterized by diffusely increased FAF in the posterior pole and is followed by more focal involvement in the parafoveal region. In late disease, FAF decreases due to RPE dysfunction and PR degeneration and death (44).

Although FAF intensity cannot be directly correlated with lipofuscin accumulation, due to absorption of fluorescence by a number of ocular structures (45) and variability in detecting systems (46) it remains a useful tool in conjunction with other imaging modalities to document the retinal geography in macular degenerative disease.

10.3.23 Adaptive optics

Adaptive optics is a non-invasive technique in which a light–illuminated ophthalmoscope system or a scanning laser ophthalmoscope utilizes a deformable mirror to form a high resolution image of the retina capable of imaging individual cones and other cellular structures (47). Images from patients with inherited retinal degenerative conditions have shown irregular cone mosaic patterns, increased cone spacing and reduced density and hyper-reflective areas in regions of atrophy compared to normal. Adaptive optics can be used in inherited retinal degenerative disease to identify both normal and abnormal areas of cone mosaic. However due to limitations of the technique identification and estimation of cone spacing is reliably quantified only where the cone mosaic can be identified unambiguously. Adaptive optics (Cohort 1-5 only) is often used in conjunction with SD-OCT to ensure the expected laminar appearances of the PR inner and outer layer in the SD-OCT cross section corresponds to the adaptive optics image.

10.3.24 Reading speed

Reading speed is a good predictor of everyday visual function. As VA tests are poor predictors of the real-world function, performance-based tests (eg, reading speed measurements) can be used for the determination of visual function. Thus, standard charts have been developed in order to evaluate reading acuity as well as reading speed (Appendix E). Print size is defined as the height of a lower case x and progresses logarithmically from one phrase to another. With these reading charts it is possible to determine reading speed with high reliability and a good reproducibility of the reading acuity evaluations (48). VFQ-25 and reading speed assessment will also provide data regarding the effect of the disease process on the quality of life of patients in the current study. For Cohorts 6-9 reading speed will be performed prior to dilation when possible.

10.3.25 Visual Function Questionnaires VFQ-25/CVAQC-25

An individual's own perception of quality of life is perhaps one of the most meaningful measures of that individual's level visual function. The National Eye Institute (NEI) Visual Function Questionnaire (VFQ-25) was developed to measure vision-specific health-related quality of life.

The VFQ-25 assess difficulty with near vision activities, difficulty with distance vision activities, limitations in social functioning due to vision, role limitations due to vision, dependency on others due to vision, mental health symptoms due to vision, future expectations for vision, driving difficulties, pain and discomfort in or around the eyes, limitations with peripheral vision and color vision. The VFQ-25 questionnaire was developed from patient focus groups representing a diverse set of visual conditions, the intention being to develop a scale that can be generalized to all patients with vision deficits, regardless of cause. Across the range of developmental conditions (cataract, glaucoma, AMD, and diabetic retinopathy), as well as other conditions as diverse as corneal diseases and vascular occlusions of the retina, NEI-VFQ scores vary in the expected direction with differences in visual performance and disease state. For Cohorts 6-9 visual function questionnaires will be performed at sites when possible. Interviewer-administered versions of the instruments will be used in the study; interviewers will read the questionnaire to the patient and record only the patient’s response (without interpretation). Each questionnaire is composed of 25 items each.

The Visual Function Questionnaire-25 (VFQ-25) from the National Eye Institute will be administered to adult patients (≥18 years old). This patient-reported outcome (PRO) instrument measures the influence of visual impairment on quality of life of adult with eye diseases.

The Cardiff Visual Ability Questionnaire for Children (CVAQC) will be administered to children aged 6 to <18 years old. This PRO instrument measures the self-perceived visual ability in visually impaired children and young people aged 6 to 18 years. The 25-item Cardiff Visual Ability Questionnaire for Children (CVAQC) is a short, psychometrically robust and a self-reported instrument that works to form a unidimensional scale for the assessment of the visual ability in children and young people with a visual impairment. A list of 121 items was generated from 13 focus groups with children and young people with and without a visual impairment. A long 89-item questionnaire was piloted with 45 visually impaired children and young people using face-to-face interviews. Rasch analysis was used to analyze the response category function and to facilitate item removal ensuring a valid unidimensional scale. The validity and reliability of the short questionnaire were assessed on a group of 109 visually impaired children (58.7% boys; median age 13 years) using Rasch analysis and intraclass correlation coefficient (ICC). The final 25-item questionnaire has good validity and reliability as demonstrated by a person separation index of 2.28 and reliability coefficient of 0.84. The items are well targeted to the subjects with a mean difference of -0.40 logit between item and person means, and an ICC of 0.89 demonstrates good temporal stability (49).

10.3.26 Medication, adverse event and concomitant medication review

Review of concomitant medication and adverse events will be conducted by an ophthalmologist/designee at all visits.

10.3.27 Post-surgical ophthalmological adverse events

Patients who develop post-surgical complications such as intraocular inflammation and raised IOP should be treated according to local standard of care procedures.

Intraocular inflammation worsening during the course of treatment with the protocol defined anti-inflammatory regimen (see Section 10.2.2 Subretinal Injection) or persisting or occurring after the completion of the protocol defined anti-inflammatory regimen must be recorded as a post-surgical ophthalmological adverse event.

In this setting the treatment and follow-up of the patient will be at the discretion of the investigator, guided by the severity and longevity of the inflammation, in an effort to minimize the risk of loss of visual function as a result of the ongoing inflammatory process. In the situation where the intraocular inflammation is clinically worsening the presence of an intraocular infection should be excluded.

Treatment with high dose, oral corticosteroids (1 mg/kg/day for patients ≥50 kg; 0.5 mg/kg/day for patients <50 kg; maximum dose not to exceed 80 mg/day for children <16 years) is recommended for any patient manifesting worsening intraocular inflammation (eg, ≥2+ for anterior chamber cells, ≥2+ vitreous haze and/or cells, the presence of vitreous snowballs or retinal vasculitis). In such cases, the oral corticosteroids should be continued until the ocular inflammation is resolved and then tapered as appropriate.

Raised IOP greater than 30 mmHg must be recorded as a post-surgical adverse event and may be treated with IOP lowering drops with the patient reviewed within a week. If the IOP remains greater than 25 mmHg another pressure lowering drop will be added and the patient reviewed again within a week. This sequence will be repeated until the IOP remains below 25 mmHg. For increases in IOP occurring while the patient is receiving topical steroids per the recommended protocol defined anti-inflammatory regimen, consideration may be given to reducing the frequency of the topical steroids if the intraocular inflammation is controlled.

10.3.28 Clinical laboratory tests

Clinical laboratory safety tests will be performed in a clinical laboratory. Urinalysis may be performed by microscope in a clinical lab or using a multistick strip for protein, blood and ketones. Urine pregnancy tests may be performed at the site using a licensed test (dipstick).

For blood assays, microvolumes and micro-assays should be used, whenever possible. In principle, general and / or local anesthesia should be used as appropriate for painful and/or invasive procedures.

Timing of sampling should be coordinated as far as possible to avoid repeat procedures and to avoid repeat sampling during the day in order to minimize pain and distress, and the risk of iatrogenic complications. Sampling should be performed by trained staff. The number of attempts for sampling should be limited. It is recommended that after one unsuccessful attempt, another experienced person take over the procedure. The trial-related blood loss (including any losses in the maneuver) should not exceed 3 % of the total blood volume during a period of 4 weeks and should not exceed 1% at any single time (50).

The following clinical laboratory tests will be performed.

Serum chemistry

- Calcium
- Chloride
- Phosphorous
- Bicarbonate
- Potassium
- Sodium
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase (ALP)
- Gamma glutamic transpeptidase (GGT)
- Lactate dehydrogenase (LDH)
- Creatine Phosphokinase (CPK)
- Blood urea nitrogen (BUN)
- Uric acid
- Creatinine
- Total bilirubin
- Glucose
- Albumin
- Total protein
- Cholesterol

Hematology

- White blood cell (WBC) count with differential
- Red blood cell (RBC) count
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils
- Hematocrit
- Hemoglobin
- Platelet count
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean corpuscular volume (MCV)
- Red Cell Distribution Width (RDW)

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Blood
- Bilirubin
- Microscopy including WBC/high power field (HPF), RBC/HPF

Pregnancy test (females of childbearing potential only)

- Urine human chorionic gonadotropin (hCG)

Other safety tests

- Coagulation parameters: prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen

10.3.29 Flexibility of assessment data capture

A certain degree of flexibility is required for capturing the data at the various time points throughout the study primarily as not all tests can be carried out on the same day to reduce burden of the study on the patient and investigator availability and time. In addition if a patient is not well enough to undertake a certain test on a given day it may need to be postponed. The following time windows for carrying out the tests are shown below. If tests are performed outside of this then a protocol deviation form must be completed explaining the reason for the delay in the test or if the assessment has not been done.

- Screening (Day -28) tests may be performed up to 38 days prior to surgery.
- Baseline (Day -1) tests may be performed up to 7 days prior to surgery.
- Re-screening new baseline visit may be performed if needed - up to 7 days prior to surgery.
- Weeks 1, 2 and 4 tests may be performed ±3 days of the scheduled visit.
- Follow-up visits for Weeks 12, 24, 36 and 48 may be performed ±14 days of the scheduled visit (Week 36 for Cohort 1-5 only).

10.3.30 Surgery video-recording and intra-operative OCT

In addition to intraoperative photographs, to explore further the treatment effect (safety and biological activity) at the bleb level, video of the surgery and/or intra-operative OCT will be collected, where the equipment is available, in order to define as precisely as possible to the area of the bleb and consequently the zone of cell transduction.

For the patients already enrolled, if video-recording of the surgery was obtained, the patient will be asked to consent to allow the video to be collected and used for analysis.

11 STUDY MATERIALS

11.1 SAR422459

SAR422459 will be supplied by the Sponsor. All patients will be injected with SAR422459 via a subretinal route. Surgery will be performed under general anesthesia or waking sedation at the surgeon's discretion, with additional periocular/retrobulbar injections according to surgeon and anesthesiologist preferences.

All healthcare staff handling SAR422459 must wear an apron, gloves, mask and protective goggles. All materials contaminated with SAR422459, eg, syringes, swabs, bandages, must be destroyed by incineration in accordance with hospital policy on genetically modified materials. Certificates of Destruction must be completed and copies maintained in the Study File. Healthcare staff that are pregnant or suspect that they are must not administer or handle SAR422459.

[redacted]

Details of SAR422459 [redacted] and their proper handling will be provided in a pharmacy manual available at the clinical site.

11.1.1 Packaging and labeling

Packaging and labeling will be in accordance with the Directive 2003/94/EC Good Manufacturing Practice (GMP) Annex 13 and The Code of Federal Regulations, specifically 21CFR Part 211.

SAR422459 will be provided in 0.1 mL aliquots in 0.3 mL type I borosilicate glass 'V' vials with a butyl stopper and aluminum crimp seal. Each vial of SAR422459 will be issued in a white plastic tamper evident container secured in packaging. The vial and plastic tamper-evident container will be labeled appropriately.

[redacted]

11.1.2 Storage and disposition of study medications

SAR422459 [redacted] ~~is~~ a frozen liquid formulation, stored at ≤-70°C, in aliquots of 0.1 mL [redacted], respectively. SAR422459 must be stored in a locked ≤-70°C freezer in the hospital pharmacy. It must be stored in such a way that it cannot be mixed up or confused with other medications, be they clinical study supplies or medicines for routine clinical use. The locked ≤-70°C freezer must be monitored daily and any deviations in temperature above -70°C reported to the Sponsor via the study coordinator within 72 hours, or prior to clinical use.

Dispensing will be documented by completing a log with the date of dispensing and the patient details. Used and unused vials should be returned to the hospital pharmacy (or in accordance with local standard operating procedures) and stored in labeled biohazard bags prior to reconciliation by the study monitor. Where local procedures require immediate destruction of used and unused vials, the process will be witnessed, signed and documented on a destruction log.

At each visit, the clinical study monitor will review the drug-dispensing log and reconcile it with the unused vials/destruction log.

11.1.3 Precautions/Overdose

There is no known method of vector removal from the eye should an error occur during SAR422459 administration.

11.2 OTHER STUDY SUPPLIES

Electronic case report forms will be used in this study (see Section 15.2 below). The PI and Co-Investigators must keep all study supplies and documentation in a secure place.

12 OBLIGATIONS OF THE INVESTIGATOR REGARDING SAFETY REPORTING

12.1 ADVERSE EVENT DEFINITION

An adverse event (AE) is any untoward medical occurrence in a patient that develops or worsens in severity during the conduct of a clinical study of a pharmaceutical product and does not necessarily have a causal relationship to the investigational product. This can, therefore, be any unfavorable and unintended physical sign, symptom, or laboratory parameter that develops or worsens in severity during the course of the study, whether or not considered related to the investigational product.

All AEs must be described in the appropriate section of the eCRF and their seriousness and putative relationship (causality) to the study medication and/or protocol procedures noted. Adverse events are recorded following signature of the informed consent; this is to ensure that any adverse events associated with the screening procedures are captured.

12.2 RELATIONSHIP OF AN ADVERSE EVENT TO THE INVESTIGATIONAL PRODUCT/PROTOCOL PROCEDURE

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product.

An event will be considered “not related” to use of the investigational product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the investigational product and the onset of the event (eg, the event occurred either before, or too long after, administration of the investigational product for it to be considered product-related).
- A causal relationship between the investigational product and the event is biologically implausible (eg, death as a passenger in an automobile accident).
- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease related event).

An event not meeting any of the above definitions for “not related” will be considered “related” to the investigational product.

“Associated with the use of the drug” means that there is a reasonable possibility” that the event may have been caused by the product under investigation (ie, there are facts, evidence, or arguments to suggest possible causation).

12.3 SEVERITY OF AN ADVERSE EVENT

For each AE, the severity must be recorded as one of the following:

- Mild: Discomfort noticed but does not interfere with the patient's daily routines (an annoyance).
- Moderate: Some impairment of function, not hazardous to health (uncomfortable or embarrassing).
- Severe: Significant impairment of function, hazardous to health (incapacitating).

12.4 SERIOUS ADVERSE EVENT DEFINITION

Adverse events are classified as either serious or non-serious.

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or

  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event

  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent 1 of the other outcomes listed in the definition above.

  Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

  - Intensive treatment in an emergency room or at home for:
    - Allergic bronchospasm
    - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc.)
    - Convulsions (seizures, epilepsy, epileptic fit, absence fit, etc.).

- Development of drug dependence or drug abuse
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study or aggravated during the study (only if judged unusual/significant by the investigators in oncology studies)
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases)
- Suspected transmission of an infectious agent: if any suspected transmission of an infectious agent via a medicinal product (eg, product contamination).

Elective surgeries

For the purpose of this protocol, the following conventions will apply for SAE reporting of elective surgery:

- A pre-scheduled elective procedure or a routinely scheduled treatment is not to be considered an SAE, even if the subject is hospitalized, provided the site stipulates that:
  - The condition requiring the pre-scheduled elective procedure or routinely scheduled treatment was present before and did not worsen or progress between the patient's consent to participate in the clinical study and the time of the procedure or treatment
  - The pre-scheduled elective procedure or routinely scheduled treatment is the sole reason for admission and intervention
  - Any untoward medical event occurring during the pre-scheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

12.5 ADVERSE EVENTS OF SPECIAL INTEREST

An adverse event of special interest AESI) is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added or removed during a study by protocol amendment. Reporting guidelines for AESIs are provided in Section 12.6.2.

The following AEs are considered as AESI. This list includes all the AESI defined by Sanofi for any program, although these events have not been observed with SAR422459.

- Acute hypersensitivity/ anaphylaxis
- Pregnancy of a female subject occurring at any time after treatment with SAR422459. Pregnancy occurring in a female partner of a male subject if within 3 months of her male partner treatment with SAR422459.

  The pregnancy will be qualified as an SAE only if it fulfills 1 of the seriousness criteria (see Section 12.4).

  Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.
- Symptomatic overdose (serious or non-serious) with IMP
  - An overdose (accidental or intentional) with the IMP is an event suspected by the investigator or spontaneously notified by the patient and defined as at least 30% more than the intended dose or if the dose is administered in less than half the recommended duration of administration.

    Of note, asymptomatic overdose has to be reported as a standard AE.
- Increase in alanine transaminase (ALT) (see the "Increase in ALT" flow diagram in Appendix C of the protocol).
- In addition to the aforementioned AESI, the following adverse events are defined as project specific AESIs:
  - Infection, particularly any opportunistic infection
  - Immunological reactions (eg, new incidence or exacerbation of rheumatologic or other autoimmune disorder)
  - New incidence or exacerbation/recurrence of a hematological disorder
- Ocular AESIs:
  - AEs that cause a decrease in VA of ≥15 ETDRS letters or ≥ +0.3 LogMAR (compared with baseline or the VA assessment at the latest visit) lasting >1 week or 2 successive visits.
  - AEs that require surgical intervention (eg, conventional surgery, vitreous tap or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight.
  - AEs associated with severe intraocular inflammation (ie, >2 step increase in anterior chamber cells and flare or a >2 step increase in Vitreous Haze).
  - AEs that, in the opinion of the Investigator, may require medical intervention to prevent permanent loss of sight.

In the event that a patient enrolled in the study experiences any of the above project specific AESIs, blood samples for PCR and/or immunological analysis will be taken to investigate the involvement of IMP.

12.6 GENERAL GUIDELINES FOR REPORTING ADVERSE EVENTS

- All AEs, regardless of seriousness or relationship to IMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the CRF.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s).
- The investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor. Patients who experience an ongoing SAE or an AESI, at the pre-specified study end-date, should be followed until resolution, stabilization, or death and related data will be collected. The duration of post-study follow-up and reporting of AEs will be until recovery.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.

12.6.1 Instructions for reporting serious adverse events (SAE)

In the case of occurrence of an SAE, the Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.

- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.
  - SEND (within 24 hours, preferably by fax or e-mail) the signed and dated corresponding page(s) in the case report form to the representative of the monitoring team whose name, fax number, and e-mail address appear on the clinical trial protocol.
  - ATTACH the photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
  - All further documentation should be sent to the monitoring team within 24 hours of knowledge. In addition, every effort should be made to further document within the week (7 days) following initial notification any serious adverse event that is fatal or life threatening.

Any SAE brought to the attention of the investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

12.6.2 Guidelines for reporting adverse events of special interest (AESI)

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 12.6.1, even if not fulfilling a seriousness criterion, using the corresponding pages of the CRF (to be sent) or screens in the e CRF.

Instructions for AE reporting are summarized in Table 4 below.

Table 4 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Complementary Form	Other specific forms
Adverse Event (nonSAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious Adverse Event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 12.4	Yes	Yes	No
Adverse Event of Special Interest	Expedited (within 24 hours)	Acute hypersensitivity/ anaphylaxis	Yes	Yes	No
		Pregnancy	Yes	Yes	Yes
		Symptomatic overdose	Yes	Yes	No
		ALT≥3 ULN (if baseline ALT<ULN) and ALT≥2 x baseline (if baseline ALT≥ULN)	Yes	Yes	Yes
		Infection, particularly any opportunistic infection	Yes	Yes	No

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Complementary Form	Other specific forms
		Immunological reactions (eg, new incidence or exacerbation of rheumatologic or other autoimmune disorder)	Yes	Yes	No
		New incidence or exacerbation/recurrence of a hematological disorder	Yes	Yes	No
		Ocular AESI	Yes	Yes	No

12.6.3 Guidelines for management of specific laboratory abnormalities

As for any study protocol conducted by Sanofi with any investigational medicinal products, decision trees for the management of certain laboratory abnormalities are provided in Appendix C.

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices:

- Neutropenia
- Thrombocytopenia
- Acute renal insufficiency
- Suspicion of rhabdomyolysis

12.7 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, IECs/IRBs as appropriate and to the investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected [please refer to the IB].

Any other AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered unexpected.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

12.8 PATIENT WITHDRAWALS FROM THE STUDY

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records check. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up may jeopardize the public health value of the study. If possible, the patients should be assessed using the Week 48 procedures defined above. Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. Preferably the patient should withdraw consent in writing and, if the patient or the patient's representative refuses or is physically unavailable, the site should document and sign the reason for the patient's failure to withdraw consent in writing.

If an AE leads to patient withdrawal, the patient will be followed up until the AE is resolved. All efforts will be made to encourage the patient to continue in the study and the long-term follow-up.

Withdrawal from the study and reason for withdrawal must be documented in the eCRF.

13 DATA SAFETY MONITORING BOARD

13.1 ROLE

An independent Data Safety Monitoring Board (DSMB) will be formed to undertake an ongoing review of the data from the study, the primary role of the DSMB is to ensure the protection and safety of patients participating in the study. The DSMB will review the general progress and conduct of the study and assist in resolving any issues that may arise. The composition and responsibilities, together with the agreed schedule for reviewing data will be detailed in a guidance document (DSMB Charter), approved and signed by all members of the committee. The members of this committee will include appropriately qualified medical and if needed statistical personnel.

13.2 RESPONSIBILITIES

- Monitor and review safety data of patients participating in the study and advise on study termination as appropriate
- Recommend whether to dose escalate after the patients in each cohort have been dosed
- Recommend the termination of the study if unforeseen safety issues occur which alter the risk assessment of the study
- Provide advice on any other matters as deemed necessary for the safe conduct of the study

Detailed responsibilities of the DSMB are provided in the DSMB charter.

14 DEVELOPMENT SAFETY UPDATE REPORTS

The Sponsor will make provision for a harmonized International Birth date for SAR422459; this will serve as a data lock point from which all development safety update reports will be generated. This will be the date of the first regulatory authority protocol approval.

15 DATA MANAGEMENT AND STATISTICAL ANALYSES

15.1 SAMPLE SIZE ESTIMATES

This is an exploratory study the primary objective of which is to evaluate safety and, as a secondary objective, to estimate the biological activity. No formal sample size calculation has been performed.

15.2 STATISTICAL ANALYSES

Due to the small number of patients to be enrolled in this study the data will be analyzed by descriptive statistics and exploratory figures. A statistical analysis plan will be finalized prior to database lock. It is envisaged that analyses will be performed on all available data. However, it may be necessary for specific data points to be excluded if not considered reliable.

Baseline values will be defined as the last available values collected at study visits (eg, Day -28 or Day -1) preceding the date of study treatment.

15.3 SAFETY ENDPOINTS

15.3.1 Adverse events

The number and percentage of patients with treatment emergent adverse events (ie, started or increased in severity after the patient received study treatment and includes abnormal lab results, ECGs etc.) will be summarized. The adverse events recorded prior to SAR422459 administration will not be summarized and will be separated from the adverse events that are recorded post SAR422459 administration in the final listings.

An overall summary will include the number and percentage of patients with:

- A fatal AE (death).
- At least 1 serious AE.
- At least 1 severe AE.
- At least 1 related AE.
- Without any AEs.

An additional table will show the number and percentage of patients with treatment emergent adverse events broken down by System Organ Class, High Level Term and Preferred Term. Related AEs will be summarized separately.

15.3.2 Ophthalmological safety endpoints

Changes in other safety endpoints will be summarized at each visit; in addition, where appropriate, individual profile plots and mean plot of changes in the variable against time will be presented. The primary end points will be considered the 48 week (12-month) visit; the individual change at this end point will be plotted against dose received.

15.3.3 Secondary endpoints

Secondary endpoints will be summarized at each visit; in addition, where appropriate, individual profile plots and mean plot of changes in the variable against time will be presented. The secondary end points will be considered the 24 week (6-month) and 48 week (12-month) visit; the individual change at this end point will be plotted against dose received.

15.3.4 Immunology endpoint

The number and percentage of patients with antibody response to SAR422459 administration at all time points will be tabulated.

15.3.5 Laboratory parameters

Hematology, biochemistry and other laboratory data will be listed at each time point by treatment group and, for appropriate values, will be flagged as ‘High’ or ‘Low’ if outside the laboratory normal range. Shift tables for key laboratory parameters out of normal range will be presented for the assessed visits.

An additional listing will be provided for those patients who have laboratory values that are abnormal and considered to be clinically significant. Laboratory values that become abnormal will also be recorded as an adverse event.

15.3.6 Other safety parameters

All other safety parameters (vital signs, physical examination, ECG) will be listed by patient, treatment assignment, and cohort. New abnormalities will be recorded and summarized under adverse events.

15.3.7 Concomitant medication

Concomitant medication will be listed by patient, cohort, and study visit.

15.4 BIODISTRIBUTION ENDPOINT

The number and percentage of patients with SAR422459 detected in the blood and urine by polymerase chain reaction (PCR) at all time points will be tabulated.

15.5 OTHER MEASURES

15.5.1 Patient characteristics

Patient demographic (height, weight, sex, reproductive status) data will be summarized by cohort.

The number of patients meeting each inclusion/exclusion criteria will be tabulated. Medical history, treatment history, chest x-ray and anesthesia assessment will be listed.

15.5.2 Withdrawals

The number (%) of patients who withdraw from the study over time, along with their reasons for withdrawal, will be tabulated.

15.5.3 Deaths

All deaths occurring during the study and its follow-up period will be listed and included in the adverse events summary.

15.6 ELECTRONIC CASE REPORT FORMS AND DATA COLLECTION

Data must be transcribed from the patient's notes and entered onto the eCRF completely, legibly and in a timely fashion by the PI or his designees. He will also verify that all the data contained on these forms are accurate and will sign the forms once they are completed.

Copies of anonymized supporting documentation such as ECG recordings, X-rays etc. necessary to support regulatory submissions and reports will be provided to and will remain the property of the Sponsor and must be available for review and retrieval by the Sponsor or Contract Research Organization (CRO) staff at any time. The Investigators are requested to enter data promptly onto eCRFs in order to facilitate review, monitoring, and correction of eCRFs in a timely fashion.

Any subsequent alterations to the data must be made by striking out the previous entry with a single line and by writing the new value next to it. All such change must be initialed and dated by the PI (or his designee). Whiting or scribbling out of errors is not acceptable.

When the monitor reviews the eCRFs, certain queries may arise. These will be tracked and documented in the eCRF along with the resolution.

15.7 DOUBLE-BLINDED CODES

Double-blind codes are not required as only one treatment is administered in all patients.

15.8 INTERIM ANALYSIS

No formal interim analysis is planned.

An independent DSMB will:

- Monitor and review safety data of patients participating in the study and advise on study termination as appropriate
- Recommend whether to dose escalate after the patients in each cohort have been dosed
- Recommend the termination of the study if unforeseen safety issues occur which alter the risk assessment of the study
- Provide advice on any other matters as deemed necessary for the safe conduct of the study

At a minimum the following individual data and mean data will be plotted against time following surgery:

- Adverse events and concomitant medications will be listed
- Laboratory results
- Humoral antibody response and vector distribution data
- BCVA
- IOP
- Slit lamp examination and fundoscopy data

Furthermore for Cohorts 6-9, a review of the data by the sponsor and the investigators will be regularly planned (every 6 months) in order to ensure to capture any signal of biological activity. Following these meetings, discussion with health authorities could be requested.

16 ETHICAL CONSIDERATIONS

16.1 PATIENT INFORMATION LEAFLETS AND INFORMED CONSENT FORMS

All patients invited to participate in a clinical study are entitled to make their decision based on the maximum amount of information available at the time. In order to make the choice, they will be given a written document written in clear concise lay language in their native tongue to read. The document will previously have been approved by the relevant ethics committee (EC) or institutional review board (IRB) and may be updated as new important information becomes available that may affect a patient's willingness to participate or continue in the study.

This document will inform potential patients about the nature of the indication and the drug, its efficacy and safety profile in animals and man, the human experience to date and the route of administration. It will also outline the numbers of patients in the study and the steps of the protocol as they will apply to the individual, including number of visits, venipunctures and other invasive procedures and types of measurements to be performed so that the individual has a clear understanding of the risks, inconveniences and benefits that may accrue from the study. Participants (both male and female) must understand the need for reliable contraception if appropriate.

The individual must be made aware that he/she may refuse to join the study or may withdraw at any time without prejudicing further medical care which is covered by the Sponsor clinical trial insurance in the event of a mishap. A contact with whom suspected trial related injuries may be discussed will also be detailed. Individuals must also know that their personal hospital records may be reviewed in confidence by the Sponsor (or CRO) staff and by Regulatory Authorities from time to time and that personal information about them will be held on a confidential database. Conditions for ensuring the security and confidentiality of the database should be explained.

Consent must be recorded in writing after the patient has had adequate time to reflect on the information and to ask further questions if need be. The consent form must be signed and dated by the patient (and/or by the patient's legally acceptable representative, if necessary) and then countersigned by the Investigator or delegate. A copy of the signed consent form may need to be presented to each of the various hospital departments participating in the study.

Local regulations need to be followed to ensure compliant consent procedure by patients/parents/legal guardians as applicable, re-consent, if needed with the change of age and necessary archiving of relevant documents.

16.2 ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD REVIEW

Prior approval must also be obtained by the relevant IRB of the local hospital. The EC/IRB will conform to the standards of ICH E6, EU Directives 2001/20/EC and 2005/28/EC or the Code of Federal Regulations, specifically 21 CFR Part 56. The EC/IRB will be provided with copies of the protocol, any amendments, patient information and consent forms for review. EC/IRB approval must always be recorded in writing. The approval documents should clearly identify the protocol by title and an EC/IRB identifying number, identify the committee members present when the approval was granted and list any required amendments with the reasons for them. If a protocol is refused approval, the reasons will be given in writing. Amendments and refusals will be notified to all other committees considering the study and refusals will be notified to relevant Regulatory Authorities. The EC/IRB will review ongoing studies at appropriate intervals.

The study will not begin and study supplies will not be shipped to the site until written approval is received by the Sponsor. The EC/IRB will also provide a list of its members, their affiliations and its written procedures if requested by the Sponsor as part of the pre study documentation. The EC/IRB must keep records of all its procedures and decisions for at least 3 years after completion of the study and make them available on request to representatives of regulatory authorities.

17 REGULATORY REQUIREMENTS AND SPONSOR/INVESTIGATOR OBLIGATIONS

This study will be conducted in accordance with the GCP Guidelines as issued by the International Conference for Harmonisation (ICH 135/95, 1996), the Declaration of Helsinki the Code of Federal Regulations Title 21 (see Appendix B), EU Directives 2001/20/EC and 2005/28/EC. These documents will be provided in the site study file. To ensure compliance with the guidelines, the study will be audited by third parties including independent auditors and possibly Regulatory Authorities. The Investigators agree, by written consent to this protocol, to co-operate fully with compliance checks by allowing access to all documentation by authorized individuals.

The study may not begin and clinical study supplies will not be shipped until the Sponsor receives relevant regulatory and ethics written approvals.

17.1 STUDY INITIATION

It is essential that all personnel concerned with the study understand their duties and responsibilities fully. In order to facilitate this process, site initiation visits will be conducted by the Sponsor or designee prior to first patient recruitment and after EC/IRB has been obtained. It is expected that all personnel involved will attend this meeting and will familiarize themselves with the protocol, the eCRF and the principles of GCP which will be implemented during the study.

17.2 MONITORING

The purposes of clinical study monitoring are to verify that the rights and wellbeing of patients are protected, that reported study data are accurate, complete and verifiable from source documents and that the conduct of the study is in accordance with current GCP and regulatory requirements. In order to assist with the collection in a timely fashion of accurate, verified data which are in accordance with the protocol, monitors will visit the study sites regularly. They will audit source documents and compare them with data contained in the eCRF. If inconsistencies occur, these queries will be answered by the investigator. The monitors will also check patient accrual, drug dispensing logs, lists of persons to whom clinical study related activities have been delegated, relevant communications with family physicians, fridges and other equipment where necessary. They will also visit associated laboratories to ensure their continuing compliance with the protocol and with GCP and deal with any problems arising in the course of the study. The investigator and others involved in the study must make adequate time available to be present at these visits.

17.3 DOCUMENTATION AND RECORD KEEPING

Essential records must be retained by the study site for at least 5 years after the last approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region OR at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

No records may be destroyed or moved without the Sponsor written permission. The Sponsor will archive and retain all documents pertaining to the study for the lifetime of the product under investigation and final study reports will be kept for a further 5 years.

17.4 CLINICAL STUDY REPORT

This clinical study will be summarized by the Sponsor (or designated CRO) and a final audited report must be retained on file. This report will include discussions of the study objectives, methodology, findings, and conclusions. The PI will be asked to review and comment on the draft report and will be required to sign the final version. In a multi-center study, other investigators will be provided with a copy of the final report for their information. This report must be archived with all other study related documents.

17.5 TERMINATION OF THE STUDY

The study may be terminated at any time at the request of regulatory agencies, the EC/IRB or the PI. The study may be terminated at any time by the Sponsor on the basis of any safety concern, inadequate enrolment or developments in a related study or program which would challenge the clinical and ethical justification for continued enrolment.

The study may be terminated prematurely by the investigator by giving 30 days written notice. The Sponsor retains the right to terminate the study immediately upon written notice. If a clinical study is terminated early for whatever reason, the investigator will return all samples, supplies, and CRFs to the Sponsor and will notify the EC/IRB. Whichever party terminates the study will provide a written statement as to the reason for the termination. The Sponsor (or CRO) will notify Regulatory Authorities as appropriate of premature terminations.

At the end of a clinical study, investigators must return to the Sponsor (or CRO) all unused clinical trial supplies and loaned equipment unless other arrangements have been made.

Study completion is defined as the date when the final patient has completed their final visit for the study.

In the event that enrollment is terminated, all patients who have been dosed with SAR422459 will continue to be followed up as per protocol until the Week 48 visit has been completed. Patients will be encouraged to enroll in a long-term follow-up study. Long-term follow-up in gene transfer research allows for the collection of important information on the long-term safety and effects of the study treatment. The long-term follow-up study (LTS13588) will last for up to 15 years.

17.6 COMPENSATION FOR MEDICINE-INDUCED INJURY AND INDEMNIFICATION REQUIREMENTS

The Sponsor will purchase and maintain no fault compensation for clinical trial insurance sufficient to meet local regulatory requirements. In the event of a proven investigational product-induced injury, proof of guilt or negligence will not be required. Settlements will be decided by arbitration and the decision of the arbitrator will be final.

17.7 PUBLICATION AND COMMUNICATION

The Sponsor actively encourages publication of clinical trial data in reputable peer reviewed journals. Authorship will be discussed and agreed in advance.

In this context, no submission for publication and/or written and/or oral disclosure regarding the results of the Study shall be made by the Investigator without prior written consent of the Sponsor. Therefore, the Investigator agrees to:

- Submit the draft of any proposed publication and communication to the Sponsor at least sixty (60) days prior to submission for publication communication.
- Submit the draft of any proposed abstract to the Sponsor at least thirty (30) days prior to submission for publication.

As the Study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, first presentation (including any oral presentation) or publication of the results of the Study shall be made only as part of a publication of the results obtained by all sites performing the Protocol.

17.8 PROTOCOL AMENDMENTS

All items in this protocol must be followed exactly. If any deviations occur, they must be documented and explained. If an amendment is required, this will be enacted through a formal documented protocol amendment procedure and must receive approval from all the authorities who approved the original protocol. The approved amendment will be distributed to all protocol recipients with instructions to append them to the protocol (or a revised protocol will be issued).

18 REFERENCES

1. Lois N, Holder GE, Bunce C, Fitzke FW. Phenotypic subtypes of Stargardt macular dystrophy-fundus flavimaculatus. Arch ophthalmol. 2001;119:359-69.

2. Walia S, Fishman GA. Natural history of phenotypic changes in Stargardt macular dystrophy.Ophthalmic Genet.2009;30(2):63-8.

3. Bither PP, Berns LA. Dominant inheritance of Stargardt's disease.J Am Optom Assoc.1988;59:112-7.

4. Zhang K. The ABCR Gene in Recessive and Dominant Stargardt Diseases: A Genetic Pathway in Macular Degeneration. Genomics.1999;60:234-7.

5. Allikmets R, Shroyer NF, Singh N, Seddon JM, Lewis RA, Bernstein PS, et al. Mutation of the Stargardt disease gene (ABCR) in age related macular degeneration. Science.1997;277:1805-7

6. Allikmets et al. A photoreceptor cell-specific ATP-binding transporter gene (ABCR) is mutated in recessive Stargardt macular dystrophy.Nat. Genet.1997;15:236-46.

7. Dean M, Hamon Y, Chimini G. The human ATP-binding cassette (ABC) transporter superfamily.J. Lipid Res.2001;42:1007-17

8. Nasonkin I, Illing M, Koehler MR, Schmid M, Molday RS, Weber BH, et al. Mapping of the rod photoreceptor ABC transporter (ABCR) to 1p21-p22.1 and identification of novel mutations in Stargardt's disease.Hum. Genet.1998:10221-6.

9. Sun H, Smallwood PM, Nathans J. Biochemical defects in ABCR protein variants associated with human retinopathies. Nat. Genet. 2000;26:242-6.

10. Shroyer NF. In Vivo Fundus Autofluorescence in Macular Dystrophies, Human Mol. Genet. 2001;10:2671-8.

11. lling M, Molday LL, Molday RS. The 220-kDa Rim Protein of Retinal Rod Outer Segments Is a Member of the ABC Transporter Superfamily, J. Biol. Chem. 1997;272:10303-10.

12. Bungert S, Molday LL, Molday RS. Membrane Topology of the ATP Binding Cassette Transporter ABCR and Its Relationship to ABC1 and Related ABCA Transporters identification of N-linked glycosylation sites. J. Biol. Chem. 2001;276:23539-46.

13. Azarian SM, Travis GH. The photoreceptor rim protein is an ABC transporter encoded by the gene for recessive Stargardt's disease (ABCR). FEBS Lett. 1997;409:247-52.

14. Sun H, Nathans J. Stargardt's ABCR is localised to the disc membrane of retinal rod outer segments, Nat. Genet. 1997;17:15-6.

15. Beharry S, Zhong M, Molday RS. N-Retinylidene-phosphatidylethanolamine is the Preferred Retinoid Substrate for the Photoreceptor-specific ABC Transporter ABCA4 (ABCR), J. Biol. Chem. 2004;279:53972-9.

16. Hammer R, Sunnes JS. Report for Foundation Fighting Blindness. Oct 2002.

17. Foundation for Fighting Blindness 2009 www.ffb.ca

18. Windsor RL, Windsor LK. Understanding Stargardt Disease. Vision World Wide. 2004; http://www.visionww.org/drswindsor-stargardt.htm

19. Fishman GA. Fundus flavimaculatus A clinical classification. Arch Ophthalmol. 1976;94:2061-7.

20. Von Ruckmann A, Fitzke FW, Bird AC. In Vivo Fundus Autofluorescence in Macular Dystrophies. Arch Ophthamol.1997;115:609-15.

21. Lois N, Holder GE, Fitzke FW, Plant C, Bird AC. Intrafamilial variation of phenotype in Stargardt macular dystrophy-Fundus flavimaculatus. Invest Ophthalmol Vis Sci. Bird 1999;40:2668-75.

22. Rohill JB, Mitrophanous KA, Martin-Rendon E, Ellard FM, Radcliffe PA, Mazarakis ND, et al. Design, production, safety, evaluation, and clinical applications of nonprimate lentiviral vectors. Meth. Enzymol. 2002;346:466-500.

23. Remtulla S, Hallet PE. A Schematic Eye For The Mouse, And Comparisons With The Rat. Vis. Res. 1985;25:21-31.

24. Timmers AM, Zhang H, Squitieri A, Gonzalez-Pola C. Subretinal Injections In Rodent Eyes: Effects On Electrophysiology And Histology Of Rat Retina. Mol. Vis. 2001;7:131-7.

25. Hughes. A Schematic Eye For The Rat. Vis. Res. 1979;19:569-88.

26. Bozkir G, Bozkir M, Dogan H, Aycan K, Güler B. Measurements of axial length and radius of corneal curvature in the rabbit eye. 1997 Acta Medica Okayama. 1997. 51:9-11.

27. Liu JH, Farid H. Twenty-four-hour change in axial length in the rabbit eye. Invest. Ophthamol. Vis. Sci. 1998;39:2796-9.

28. Sarnet BG. Eye and orbital size in the young and adult. Ophthalmologica. 1982;185:74-89.

29. Covance study #7175-107; Pilot feasibility study of subretinal dosing techniques in rabbits.

30. Wiesel TN, Raviola E. Increase in axial length of the macaque monkey eye after corneal opacification. Invest. Ophthamol. Vis. Sci. 1979;18:1232-6.

31. Covance study #7175-106. Twelve week range finding study with a single subretinal injection of RetinoStat in Cynomolgus macaques.

32. Le Meur G, Weber M, Péréon Y, Mendes-Madeira A, Nivard D, Deschamps JY, et al. Postsurgical Assessment and Long-term Safety of Recombinant Adeno-Associated Virus–Mediated Gene Transfer Into the Retinas of Dogs and Primates Arch Ophthalmol. 2005;123:500-6.

33. Jacobson SG, Boye SL, Aleman TS, Conlon TJ, Zeiss CJ, Roman AJ, et al. Safety in nonhuman primates of ocular AAV2-RPE65, a candidate treatment for blindness in Leber congenital amaurosis. Human Gene Therapy. 2006;17:845-58.

34. Bainbridge JW, Smith AJ, Barker SS, Robbie S, Henderson R, Balaggan K, et al. Effect of gene therapy on visual function in Leber's congenital amaurosis. N. Engl. J. Med. 2008;358:2231-9.

35. Brun-Strang C, Piscopo A, Buggage R, Milce J, Sellami R. Natural History of Stargardt Disease: Patients' profile at clinical diagnosis. Poster presentation number: 1487 - B0168, ARVO 2017.

36. Lennerstrand G, Ahlström CO.Contrast sensitivity in macular degeneration and the relation to subjective visual impairment. Acta Ophthalmologica. 1989;67:225-33.

37. Balcer LJ, Baier ML, Cohen JA, Kooijmans MF, Sandrock AW, Nano–Schiavi ML, et al. Contrast letter acuity as a visual component for the Multiple Sclerosis Functinal Composite. Neurology. 2003;61(10):1367-73.

38. Polodeanu AG, Rosen RB. Combinations in techniques in imaging the retina with high resolution Prog Retin Eye Res. 2008;27:464-99.

39. Forte R, Cennamo GL, Finelli ML, De Crecchio G. Comparison of time domain stratus OCT and spectral domain SLO/OCT for the assessment of macular thickness and volume. Eye. 2009;23:2071-8.

40. Jansonius NM, Nevalainen J, Selig B, Zangwill LM, Sample PA, Budde WM, er al. mathematical description of nerve fiber bundle trajectories and their variability in the human retina. Vision Res. 2009;49(17):2157-63.

41. Schiefer U, Pascual JP, Edmunds B, Feudner E, Hoffmann EM, Johnson CA, et al. Comparison of the New Perimetric GATE Strategy with Conventional Full-Threshold and SITA Standard. Strategies Invest Ophthalmol Vis Sci. 2009.50:488-94.

42. Lois N, Halfyard AS, Bird AC, Fitzke FW. Quantitative evaluation of fundus auto fluorescence imaged "in vivo" in eyes with retinal disease. Br J Ophthalmol. 2000;84:741-5.

43. Sharp PF, Mannivannan A, Xu H, Forrester JV. The scanning laser ophthalmoscope – a review of its role in bioscience and medicine. Phy Med Biol. 2004;49:1085-96.

44. Cideciyan AV, Aleman TS, Swider M, Schwartz SB, Steinberg JD, Brucker AJ, et al. Mutations in the ABCA4 result in the accumulation of lipofuscin before slowing of the retinoid cycle: a reappraisal of the human disease sequence. Hum Mol Genet. 2004;13:525-34.

45. Delori FC, Goger DG, Dorey CK. Age-related accumulation and spatial distribution of lipofuscin in RPE of normal subjects. Invest Ophthalmol Vis Sci. 2001;42(8):1855-66.

46. Bellmann C, Rubin GS, Kabanarou SA, Bird AC, Fitzke FW. Fundus auofluorescence imaging compared with different confocal scanning laser ophthalmoscopes. Br J Ophthalmol. 2003;87:1381-6.

47. Martin JA, Roorda A. Direct and non-invasive assessment of parafoveal capillary leukocyte velocity. Ophthalmology. 2005;112:2219-24.

48. Radner W, Willinger U, Obermayer W, Mudrich C, Velikay-Parel M, Eisenwort B. A new reading chart for simultaneous determination of reading vision and reading speed. Universitätsklinik für Augenheilkunde und Optometrie, Wien, Austria Klin Monbl Augenheilkd. Sep 1998;213(3):174-81.

49. Khadka J, Ryan B, Margrain TH, Court H, Woodhouse JM. Development of the 25-item Cardiff Visual Ability Questionnaire for Children (CVAQC). British Journal of Ophthalmology. 2010;94(6):730-5.

50. Ethical considerations for clinical trials on medicinal products with the paediatric population - Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use.

51. Glazer LC, Dryja TP. Understanding the etiology of Stargardt's disease. Ophthalmol Clin North Am.2002 Mar;15(1):93-100.

52. Weleber RG. Stargardt's macular dystrophy. Arch Ophthalmol.1994 Jun;112(6):752-4.

53. Fujinami K, Lois N, Davidson AE, Mackay DS, Hogg CR, Stone EM, et al. A longitudinal study of stargardt disease: clinical and electrophysiologic assessment, progression, and genotype correlations. Am J Ophthalmol 2013 Jun;155(6):1075–88.

54. McBain VA, Townend J, Lois N. Progression of retinal pigment epithelial atrophy in Stargardt disease. Am J Ophthalmol. 2012 Jul;154(1):146–54.

55. Zahid S, Jayasundera T, Rhoades W, Branham K, Khan N, Niziol LM, et al. Clinical Phenotypes and Prognostic Full-Field Electroretinographic Findings in Stargardt Disease. Am J Ophthalmol 2013 Mar;155(3):465–73.

56. Armstrong JD, Meyer D, Xu S, Elfervig JL. Long-term follow-up of Stargardt's disease and fundus flavimaculatus. Ophthalmology.1998;105:448–57.

57. Foundation Fighting Blindness http://www.blindness.org/index.php?option=com_content&view=article&id=53&Itemid=74#vision-fadings

58. Rotenstreich Y, Fishman GA, Anderson RJ. Visual acuity loss and clinical observations in a large series of patients with Stargardt disease. Ophthalmology.2003;110(6):1151–8.

59. Davies M, Ellis S, Adams N, Binley K, Kelleher M, Mitrophanous K. Lentiviral Gene therapies for wet AMD, Stargardt macula dystrophy and Usher Syndrome 1B: Clinical Trial Update ARVO 2014; Poster #3299.

60. Willett K, Bennett J. Immunology of AAV-Mediated Gene Transfer in the Eye. Front Immunol. 2013;4:261

61. He XS, Holmes TH, Zhang C, Mahmood K, Kemble GW, Lewis DB, et al. Cellular immune responses in children and adults receiving inactivated or live attenuated influenza vaccines. J. Virol. 2006 Dec 8;80(23):11756-66.

62. Edwards A, Fishman GA, Anderson RJ, Grover S, Derlacki DJ. Visual Acuity and Visual Field Impairment in Usher Syndrome. Arch Ophthalmol.1998 Feb;116(2):165-8.

63. Bennett J. Immune response following intraocular delivery of recombinant viral vectors. Gene Ther. 2003 Jun;10(11):977-82.

64. Gordon RA, Donszis PB. Refractive development of the human eye. Arch Ophthalmol.1985 Jun;103(6):785-9.

65. Maguire AM, High KA, Auricchio A, Wright JF, Pierce EA, Testa F, et al. Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: a phase 1 dose-escalation trial. Lancet. 2009 Nov;374(9701):1597-605.

66. Balaggan KS, Binley K, Esapa M, MacLaren RE, Igball S, Duran Y, et al. EIAV vector-mediated delivery of endostatin or angiostatin inhibits angiogenesis and vascular hyperpermeability in experimental CNV. Gene Therapy. 2006 Aug;13(15):1153-65

67. Morgan JI, Hunter JJ, Masella B, Wolfe R, Gray DC, Merigan WH, et al. Light-Induced Retinal Changes Observed with High-Resolution Autofluorescence Imaging of the Retinal Pigment Epithelium. Invest Ophthalmol Vis Sci. 2008;49(8):3715-29.

19 APPENDICES

Appendix A Ocular inflammation grading

Slit lamp examination will be performed throughout the study to monitor for ocular inflammation. In addition, BCVA, other clinical examination and the results of other investigations such as FA may also assist in the evaluation.

The objective assessment of inflammation will comprise separate assessment of the anterior segment, vitreous and fundus. Active inflammation only will be assessed and any signs of previous inflammation (eg, premacular fibrosis, healed old choroidoretinal scars will not be included in the evaluation of the severity score.)

Prelimbal injection will be noted as present or absent, no attempt will be made to assign a severity score. Anterior chamber findings will be graded according to cell numbers and the intensity of flare using the widest slit beam and luminescence of the slit lamp. (Pigmented cells and red blood cells will not be counted). See Table 1.

Table 1 - Slit Lamp Examination Grading of Anterior Chamber Cells and Flare

Grade	Cells/field (Field size is 1 mm x 1 mm)
0	≤1 cells/field
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50
Grade	**Description of flare**
0	None
1+	Faint
2+	Moderate (iris and lens detail clear)
3+	Marked (iris and lens detail hazy)
4+	Intense (fibrin or plastic aqueous)

(The standardization of uveitis nomenclature [SUN] working group. J Ophthalmol 2005;140:509-516)

Vitreous haze, if present is the most reliable sign of intraocular inflammation and the main indicator of response to treatment. Vitreous haze is can be determined using fundoscopy (indirect ophthalmoscopy). The scoring system is given in Table 2 but it is important to note that the grading system is subjective only and media, corneal or lens opacities may significantly influence the score.

Table 2 - Grading of Vitreous Haze

Grade	Description	Clinical findings
0	nil	none
1	minimal	posterior pole clearly visible
2	mild	posterior pole detail slightly hazy
3	moderate	posterior pole detail very hazy
4	marked	posterior pole detail barely visible
5	severe	fundal detail not visible

(Neussenblatt RB, Palestine AG, Chan CC et al. Standardisation of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmol 1985; 92:467-471

Inflammation will be assessed by slit lamp examination and fundoscopy at all study visits. The inflammation grading data will be reported and monitored by the DSMB.

Appendix B World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)

55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)

59th WMA General Assembly, Seoul, October 2008

A) INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.
2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

A) **BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH**

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C) ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

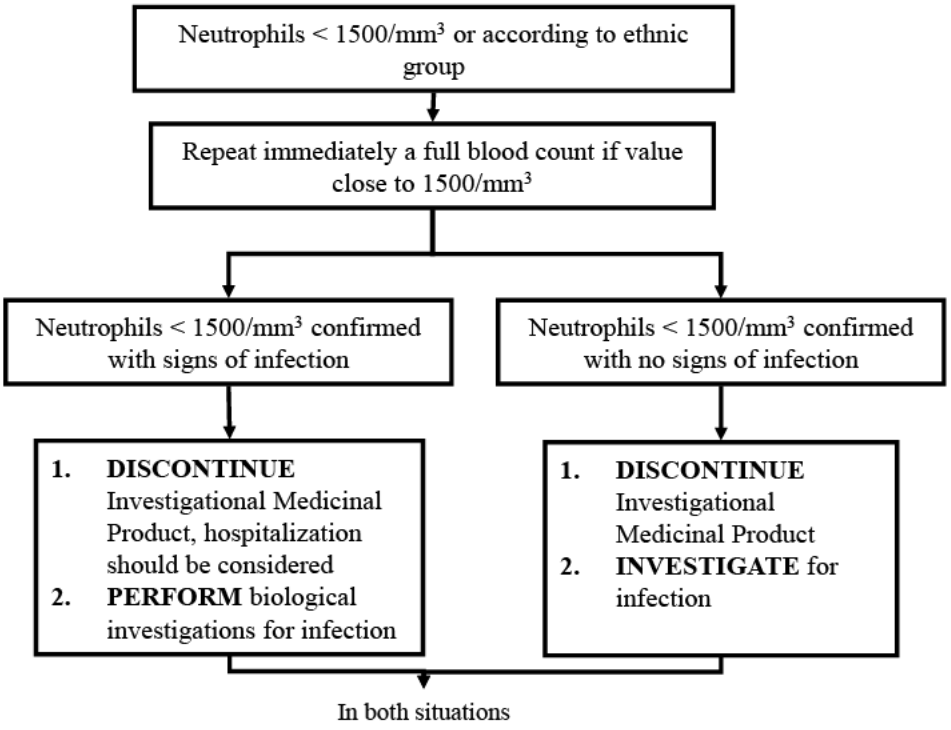
31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
    - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
    - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

22.10.2008

Appendix C General guidance for the follow-up of laboratory abnormalities by Sanofi

This General Guidance is provided by Sanofi as a help to ensure the appropriate documentation of the following laboratory abnormalities if they are observed during the course of the study. It does not infer that these abnormalities have been observed or could be observed using SAR422459.

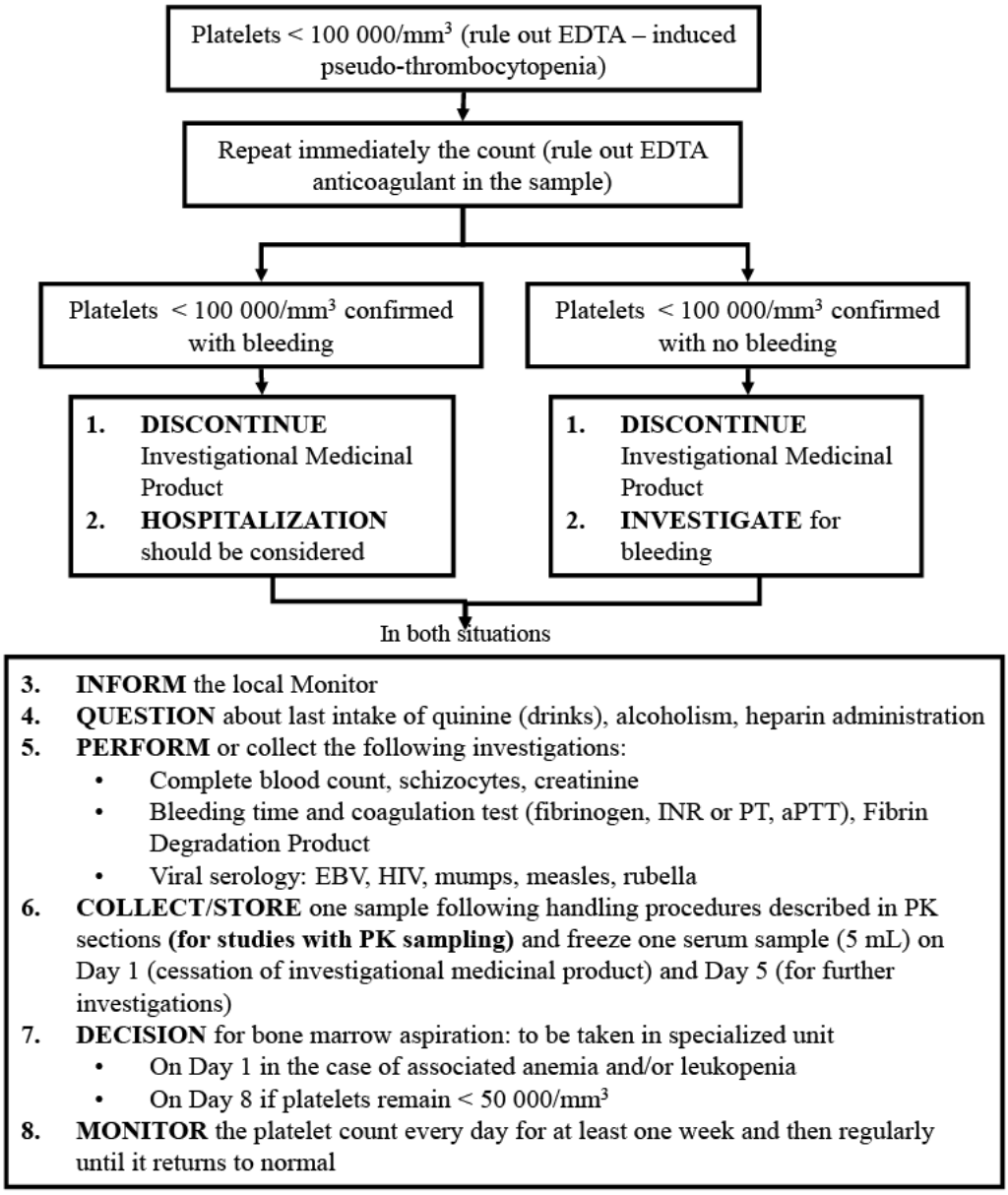
NEUTROPENIA



3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts
   - Serology: EBV, (HIV), mumps, measles, rubella
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)** and freeze one serum sample (5 mL) on Day 1 (cessation of investigational medicinal product) and Day 5 (for further investigations)
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

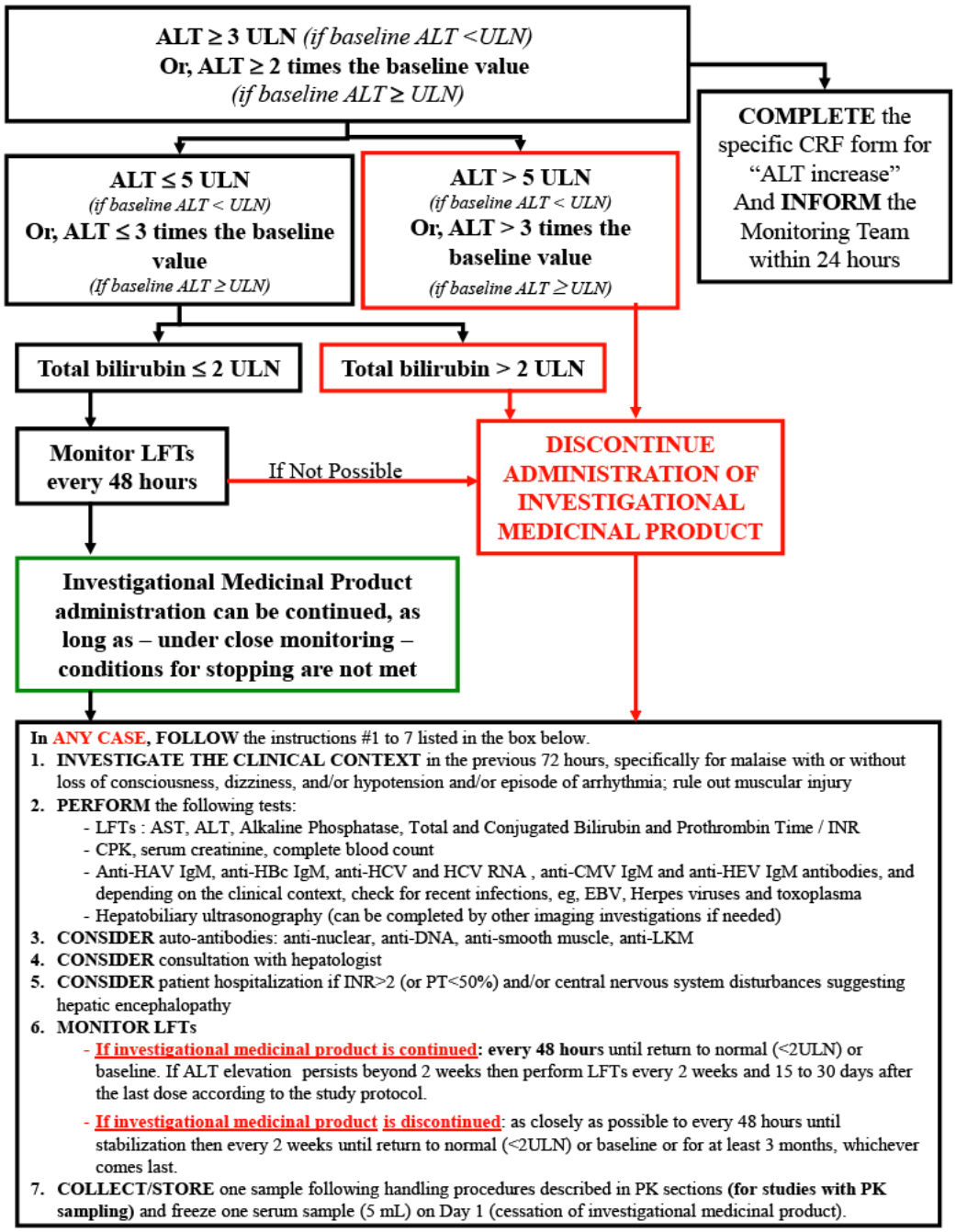
Note:
•The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
•For individuals of African descent, the relevant value of concern is <1000/mm3

THROMBOCYTOPENIA



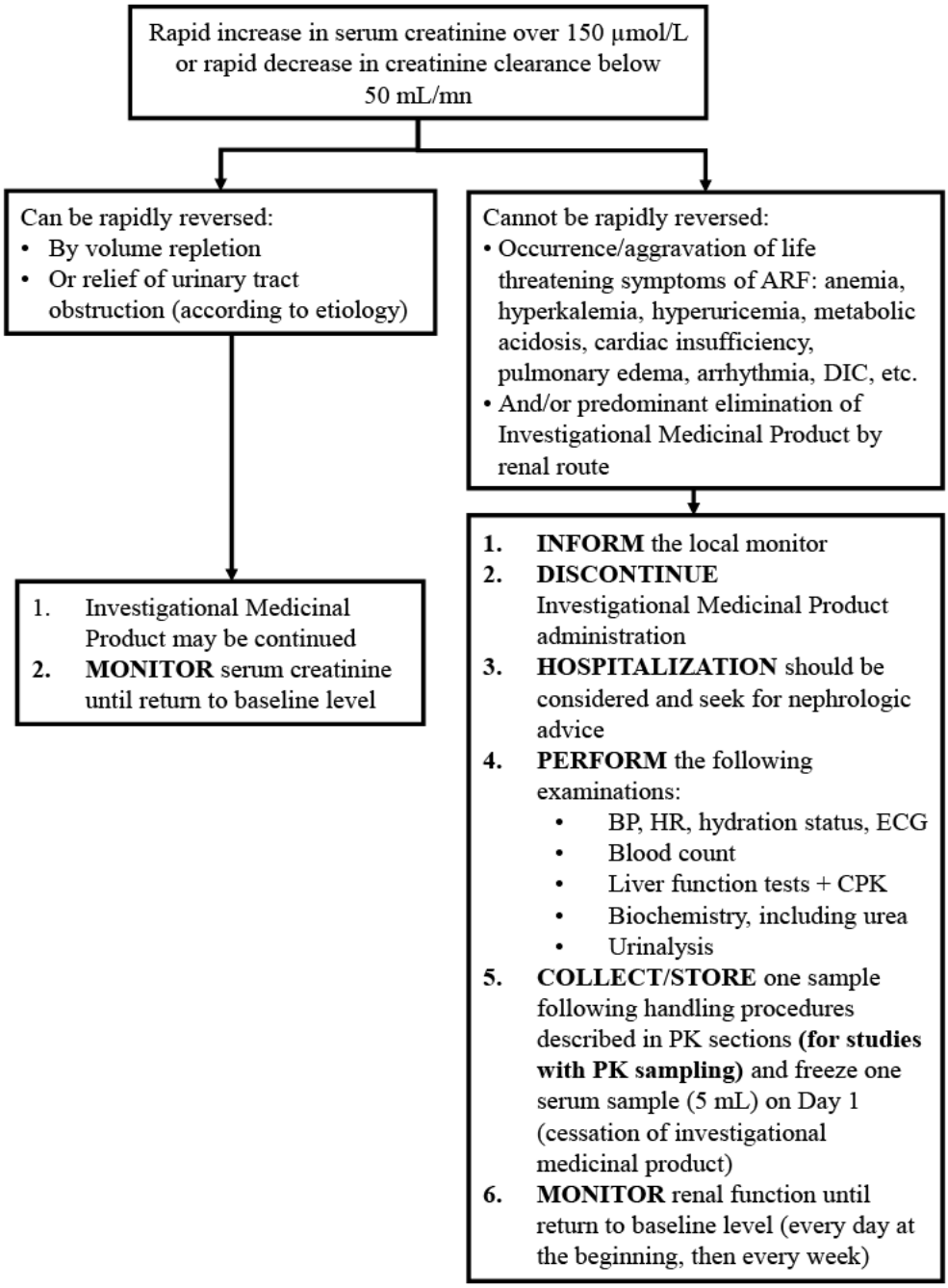
Note:
The procedures above flowchart are to be discussed with the patient only in case described in the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

INCREASE IN ALT

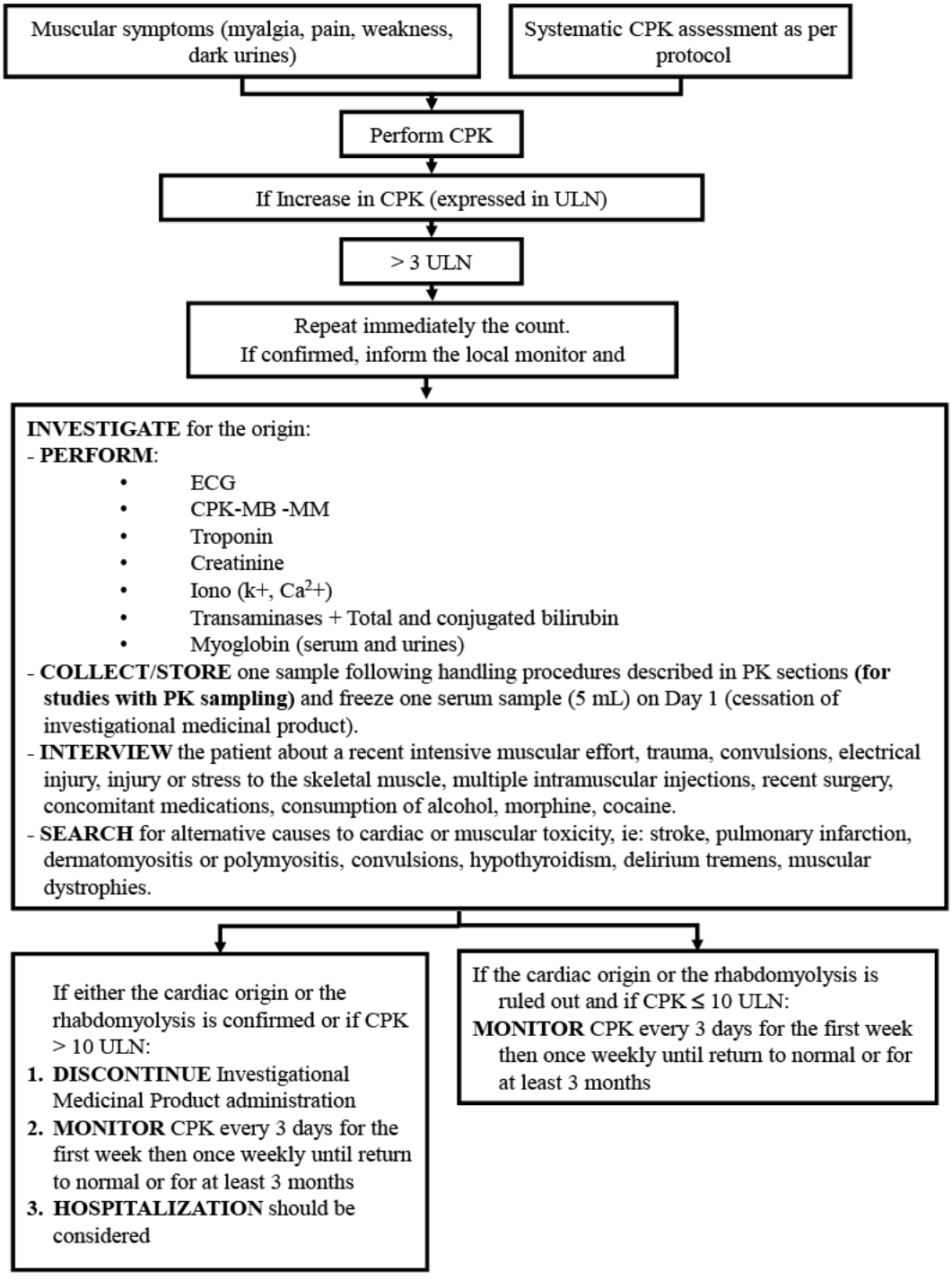


NOTE: ALT ≥3 ULN (IF BASELINE ALT <ULN) OR ALT ≥2 TIMES THE BASELINE VALUE (IF BASELINE ALT ≥ULN) SHOULD BE NOTIFIED WITHIN 24 HOURS TO THE MONITORING TEAM. IN ADDITION, IF ALT <3 ULN MEETS A SERIOUSNESS CRITERION, THE EVENT SHOULD BE NOTIFIED WITHIN 24 HOURS TO THE MONITORING TEAM

ACUTE RENAL FAILURE



SUSPICION OF RHABDOMYOLYSIS



Appendix D Low-Contrast Sloan Letter Chart Testing

The following are instructions for testing patients using the front illuminated Low-Contrast Sloan Letter Charts (LCSLC; Precision Vision, LaSalle, IL). A standardized script with instructions to be read to the patient by the examiner is included below. The examiner should read through the following instructions and practice testing prior to examining study patients.

Preparation and Set-Up:

1. Set room lighting level to 80-100 cd/m2 (equivalent is about 80-100 foot-candles).
2. This level illumination may be achieved in a bright exam room/hallway with fluorescent lighting. Having exact lighting is less important than using the same room/area for each patient/testing session.
3. Place the charts at 2 meters distance from the patient's eyes. An artist's easel or similar device may be used, or use a ledge, stand, or chair to prop the charts perpendicular to the floor. Use a pre-measured string or tape to measure the distance from the patient's eyes (bridge of nose) to the testing charts at the beginning of each testing session (each patient).
4. The 100%, 2.5%, and 1.25% contrast level charts will be used for testing.
5. Patients should wear their usual distance correction for testing (glasses or contact lenses that are used for driving, etc.). The same glasses or contact lenses (same prescription) should be used for each testing session throughout the study.
6. Patients should be asked to read the charts with each eye independently. The eye that is not being tested should be covered with an opaque device.

Vision Testing

1. Instruct patient to read slowly, letters only, left to right, starting at the top of the chart.
2. Instruct the patient that they are not allowed to re-read any line.
3. The patient is allowed to correct a "mis-speak" of a single letter only if he/she does so before reading the next letter---instruct the patient of this.
4. During the chart reading, PUSH (encourage) the patient until he/she cannot read any letters after being told to guess.
5. The patient must guess at each letter, even if he/she cannot easily read it, until he/she cannot or does not correctly identify any of the 5 letters on a particular line.
6. Stopping Rule: Once the patient cannot or does not correctly identify any of the 5 letters on a line after attempting it, STOP. Go on to the next chart.
7. Test all 3 charts in the same order (100%, 2.5%, 1.25%) for each patient.
8. Scoring the test: During testing, circle all letters read correctly on the data forms for each chart for each eye. Put an "X" through each incorrectly identified letter; leave unattempted letters unmarked.
9. Fill in the number of letters correct at the end of each line of 5 letters. Record the total number of letters correct for each chart at the bottom of the column.

10. If a patient is unable to identify any of the letters correctly on the first line of any of the 3 charts, please indicate this at the top of the data collection form.

Script For Testing to be Read to Patient:

These instructions should be read to the patient once he/she is comfortably seated in front of the charts at 2 meters distance (see above for instructions on Preparation and Set-Up):

1. I am going to show you 3 different eye charts with letters on them. The letters will become increasingly lighter for each chart.
2. For each chart, please begin at the very top of the chart and read each letter slowly, from left to right on each line.
3. If you mis-speak on a letter or feel you have identified it incorrectly, you may correct your response only before you read the next letter.
4. You are not allowed to re-read an entire line.
5. Please try not to lean forward in the chair while reading the letters.

After the first chart (100% chart) has been uncovered, say:

1. You may begin reading the letters.
2. Please start at the top of the chart.

For each chart, allow the patient to continue reading letters until he/she either:

1. Does not identify any of the 5 letters on any given line correctly - say:

You may stop. We will go on to the next chart now.

OR

2. States that they are unable to read any more letters - point to the line which is next for the patient to attempt (use the yellow-tipped pointer only) and say:

Can you read any of the letters on this line?

a) If patient responds no - say: Please guess if you can.

If patient responds that they cannot - say:

You may stop. We will go on to the next chart now.

b) If patient responds yes or begins reading, then continue to record responses until the patient cannot or does not correctly identify any of the 5 letters on a given line.

Stopping Rule: For each chart, once the patient cannot or does not identify any of the 5 letters correctly on a given line, say: You may stop. We will go on to the next chart now.

Please use the yellow-tipped pointer only to point to the charts (pens and fingers may leave marks). The examiner may point to the chart when requested by the patient to indicate the line that they are attempting/should attempt next.

Repeat the above procedure for each of the 3 charts (100%, 2.5%, and 1.25% in that order) with each eye independently.

Appendix E Radner Reading Charts

The "Radner Reading Charts" have been developed on the basis of the concept of "sentence optotypes" for the standardized examination of reading acuity and reading speed. Print sizes are logarithmically scaled (logRAD) to permit statistical analysis, and the results obtained can be compared to other logarithmically scaled vision systems (eg, logMAR).

To guarantee accurate, reproducible and standardized measurements of reading acuity and reading speed at every viewing distance, "sentence optotypes" have been created to minimize the variations between the test items and to keep the geometric proportions as constant as possible at all distances. Through interdisciplinary cooperation, a series of test sentences were developed that are highly comparable in terms of the number of words (14 words), as well as the word length, number of syllables, position of words, lexical difficulty and syntactical complexity. The most similar sentences were statistically selected for the Radner Reading Charts. All testing parameters have been standardized in compliance with EN ISO 8596 and the recommendations of the Committee on Vision of the National Academy of Sciences-National Research Council.

Illumination: 80 - 120 cd/m^2

Testing Procedure:

B) The reading chart is held by the patient; the sentences are covered with a piece of paper.

C) The patient is instructed to uncover the chart sentence by sentence and to read only one sentence per measurement.

D) "Please read the sentences aloud as quickly and accurately as possible. Read each sentence to the end, and do not correct reading errors."

E) "Please uncover the first sentence and start reading." Start the measurement with the stopwatch when the patient starts reading and measure the reading time until the end of the sentence.

F) Write the reading time on the scoring sheet, and record any reading errors on the sheet.

G) Stop criterion: reading time longer than 20 seconds or severe errors.

Reading Speed:

Reading speed in words per minute (w/min) is either calculated on the basis of the number of words in a sentence (=14) and the time (t=seconds) needed to read the sentence. For research or clinical analysis, reading speed can be characterized by 2 parameters: **(a) the maximum reading speed**, and **(b) the mean reading speed**.

Reading Speed (w/min): 14/t(s) x 60 = 840/t(s).

Appendix F Protocol amendment history

Protocol Amendment 11

Please see the protocol amendment 11 attached with details on the rationale and updated changes.

REASON FOR AMENDMENT:

1. Additional Cohort 7 is added to allow a separate analysis of patients 6-17 years of age with visual acuity ≥20/100. Population of such age and vision is a rapidly deteriorating population in Stargardt's macular degeneration natural history - population, who potentially could benefit most from the SAR422459 treatment, so analyzing as separate cohort to evaluate safety and any signals of efficacy is of interest. Total number of planned patients is not changed for the study (ref.: Brun-Strang, ARVO 2017).

2. Inclusion Criterion of the rapid deterioration was reviewed to better define the period of reference assessments and to avoid misinterpretations.

3. Statistical section has a reworded baseline description to use the same for treatment-emergent safety and any efficacy signal assessments, also – additional detail for laboratory test analysis.

Some other minor corrections, clarifications and typos have been performed.

- The Medical Monitor has been changed.
- Definition of severity for AEs has been updated to be consistent with the other Sanofi ophthalmologic gene therapy studies.
- AESI section, including pregnancy criterion, has been updated to match Sanofi standards and eliminate inconsistencies. List of relevant Ocular AESIs has been added.
- It is clarified that in the absence of or due to the dysfunction of the Electronic Visual Acuity (EVA) for the assessment of visual acuity that the Early Treatment Diabetic Retinopathy Study (ETDRS) chart will also be accepted as an alternative assessment tool for visual acuity.
- Radner reading chart instructions have been added as appendix E.
- Rescreening possibility is described.
- Some inconsistencies have been corrected.

Protocol Amendment 10

Please see the protocol amendment 10 attached with details on the rationale and updated changes.

REASON FOR AMENDMENT:

Justification for the change to the protocol defined anti-inflammatory regimen:

Consequent to the occurrence of 2 cases of severe uveitis reported as serious adverse events following administration of the lentiviral vector, the Data Safety Monitoring Board (DSMB), also in agreement with the study investigators, have recommended that the protocol defined anti-inflammatory regimen be modified to include treatment with systemic corticosteroids following the subretinal injection procedure in an effort to reduce the likelihood of additional serious adverse events as a result of post-operative ocular inflammation.

Justification for the new study inclusion criteria:

The following inclusion criteria was added based on the recommendation of the Netherlands Gene Therapy Office after review of the sponsors application to conduct clinical research involving gene therapeutics in the Netherlands: "*Patients must agree to not donate blood, organs, tissues or cells for at least 3 months following SAR422459 administration*".

Other changes:

Other administrative changes have been made to correct inconsistencies and grammatical errors and to clarify, reinforce or highlight the importance of specific protocol sections to aide study site personnel in the proper conduct of the trial.

The back-up plan in using a paper CRF process is revised and completed to more clearly define the process with details.

Protocol Amendment 9

Please see the protocol amendment 9 attached with details on the rationale and updated changes.

The major changes are described below:

Change to the Inclusion/Exclusion Criteria

In sections: Section 1; Section 4.11; Section 7; and Section 8.1.5.

Rationale:

Changes to the specific inclusion criteria for Cohort 6 are made following recommendations from health authorities (the FDA and ANSM) to make the enrollment for the pediatric population more homogeneous by incorporating into the inclusion criteria the parameters for rapid progression suggested by a panel of experts.

The first inclusion bullet point has been revised to more clearly define that we are now only targeting children and young adults with childhood onset disease.

An additional parameter for progression (reduction in hill of vision by > 14 dB-sr as assessed by static perimetry) has been added based on recent data obtained from review of prior cohorts by the reading center.

The statement requiring investigators to document the criteria used to identify patients at risk for progress has been removed as the criteria are now necessary for inclusion and they must be documented in the CRF.

Change to the Study Design for pediatric patients enrolled in Cohort 6

In sections: Section 1; Section 4.10; and Section 7.

Rationale:

In response to a recommendation from ANSM, a 28 day observation period will be imposed between the first and second pediatric patients enrolled in Cohort 6 in order to assess the safety and tolerability of SAR422459 in the pediatric population. Thereafter, subsequent pediatric patients may be consecutively included.

Change in the perioperative medication regimen

In sections: Section 9.2.2; Section 9.3.26.

Rationale:

Per DSMB recommendation, a high dose, tapering course of oral systemic steroids must be given early in subjects in whom there is evidence of more intraocular inflammation than expected following a vitreoretinal procedure, and prophylactically in cases which are complicated by a retinal tear or spillage of vector into the vitreous. This recommendation was made following DSMB assessment of a single reported serious adverse event of granulomatous uveitis that occurred after a patient's subretinal injection procedure which was complicated by a retinal tear.

Other corrections

In sections: Section 2; Section 6.3; Section 9.3.3; Section 9.3.6; Section 9.3.7; Section 9.3.8; and Section 9.3.27.

Rationale:

Some inconsistencies between the study schedule and the main text have been corrected. In fact the study schedule has been modified during the previous amendments and some of the corrections had not been taken into account in the main text.

Protocol Amendment 8

Please see the protocol amendment 8 attached with details on the rationale and updated changes.

The major changes are described below:

- Every occurrence of StarGen™ shall be replaced in the amended protocol by SAR422459

In section(s): Throughout the protocol.

Rationale:

In the original title of Study TDU13583, SAR422459 is referred to as StarGen™ which represents the first nomenclature of this investigational product (IMP). Of note, SAR422459 was initially developed by Oxford BioMedica Ltd. (United Kingdom) and the sponsorship was subsequently transferred to sanofi-aventis Research and Development (Sanofi) on 12 June 2014. Sanofi is now the sole holder of the Investigational New Drug (IND)/Clinical Trial Application (CTA). Therefore, as of 30 June 2015, the Oxford BioMedica trademark name for the SD product (StarGen) has been cancelled and will not be used hereafter.

Change to the Inclusion/Exclusion Criteria

In section(s): Section 1 - Synopsis, Section 4.11 – Rationale for Target Patient Population, Section 7 – Study Design, Section 8 – Study Population, Section 8.1.1 – Main Inclusion Criteria, Section 8.1.5 – Specific Inclusion Criteria Patient Group D

Rationale:

Stargardt disease is a rare, inherited juvenile macular degeneration primarily affecting children and young adults that results in blindness from central vision loss. Currently there is no effective treatment for patients with Stargardt disease. SAR422459 is a gene therapy product in clinical development as a treatment for Stargardt disease to replace the defective *ABCA4* gene in the photoreceptors of affected patients. With the approval of the protocol amendment 6 (dated 12th November 2014) for the ongoing TDU13583 study, the study protocol was changed to allow enrollment of an additional cohort of patients (Cohort 6/Group D) with a less advanced stage of disease, including children (≥6 years of age) to provide an opportunity to evaluate the safety of SAR422459 in a population in which the biological activity of the treatment is also more likely to be observed due to the expected rapid progression of the disease course. Within the protocol amendment 6 the requirements to be completed prior to the inclusion of pediatric patients were detailed: "Prior to the inclusion of pediatric patients, the DSMB will review all safety data including the available data from all cohorts after the last patient of Cohort 5 has completed 12 weeks of follow-up after having been dosed. An interim report including all available safety data, preliminary efficacy data and the recommendations from the DSMB will be submitted to the regulatory authorities and institutional review boards/ethics committees for approval before enrolling pediatric patients (<18 years)". Following the DSMB review of all safety and biological activity data including the available data from all cohorts after the last patient from Cohort 5 had

completed 12 weeks and the benefit-risk profile for SAR422459, the DSMB recommendation is to proceed with the recruitment of children in Cohort 6.

All of the elements fulfilling the predefined requirements for the enrollment of pediatric patients in the ongoing TDU13583 study are now being provided to health authorities and IRBs/HA as an accompaniment to the submission of this protocol amendment.

The rationale for the major changes to the current protocol proposed in this amendment is to make the requisite changes to enable the recruitment of children with Stargardt disease in Cohort 6. Additional rationale for other major changes to the protocol following discussions with investigators and experts includes:

- Clearer definition of the target patient population to be included in Cohort 6 as well as refining the practical guidance to investigators regarding the parameters for determining evidence of ongoing rapid disease progression and predicting risk of rapid deterioration.
- Patients in Cohort 6 will be enrolled consecutively. As patients with Stargardt disease are rare and the targeted patients for Cohort 6 are expected to be rapidly deteriorating, imposing a fixed interval between the enrollment of patients could create a situation where if more than 1 patient meeting the recruitment criteria would be identified within a narrow time window, the subsequent patient(s) could progress and no longer be eligible for the trial until after the required interval had expired. As the safety of SAR422459 highest dose has been defined in the previous cohorts and efforts have been established to minimize the risks for the subretinal injection procedure in children, the is no longer a strong safety rationale to impose a delay between the enrollment of successive patients in the protocol particularly as this may compromise the study enrollment. However, it is anticipated based on the slow enrollment projections for the study that an interval of 21 days or more could reasonably occur between the recruitment of successive patients.
- Clarification regarding availability and use of prior genotyping results: Note, gene mutation analysis could have occurred prior to signing the informed consent and it may be used provided that the analysis was conducted by a certified laboratory, written results are provided to the site, and participants (patients and/or the patient's parent[s]/legal guardian[s]) give consent to utilize the results.
- Based on the Ethical Considerations for Clinical Trials on Medicinal Products with the Pediatric Population, we have streamlined the routine blood draws to minimize blood loss as well as reduce the burden affording the best possible protection for the children.

Perioperative medication regimen

In section(s): Section 9.2.2 – Subretinal Injection Procedure, Section 9.3.26 – Post-Surgical Ophthalmological Adverse Events

Rationale:

Following DSMB recommendations, and consensus among study investigators and surgeons, a common/standardized perioperative medication regimen was developed for the use of perioperative anti-inflammatory agents.

- Duration of the long-term follow up

In section(s): Section 7 Study Design, 16.5 Termination of the Study

Rationale:

The long-term safety follow-up will be described in a separate protocol, LTS13588 where patients will be followed for up to 15 years. This protocol will also be submitted to regulatory agencies and Institutional Review Boards/Ethics Committees for approval.

Reasons for withdrawal

In section(s): 8.2 Withdrawal Criteria

Rationale:

The sponsor commits to following the patient for the complete duration of the trial.

In addition, other changes are listed in the description of changes (next section).

Protocol Amendment 7

Justification

The objective of Amendment 7 is to provide clarification regarding the criteria to be used by Investigators to identify patients anticipated to experience rapid deterioration.

The notion of rapid deterioration is not well described in the literature and neither of the ophthalmic tests performed in the clinical evaluation of Stargardt patients listed below alone have been shown to determine rapid deterioration with utmost certainty, however, the totality of the collected patient information available to the Investigator, in combination with available evidence in literature, and collective experience of the Investigator in managing Stargardt patients, should provide adequate information to enable the Investigator to identify the most appropriate patient for the treatment that meet the inclusion criteria for Group D.

Asymptomatic patients carrying a mutant ABCA4 gene with normal visual function and retinal structure are not eligible for enrollment. The investigators will identify patients anticipated to experience rapid deterioration based on consideration of at least the following data that will be collected and followed during the course of the study: age, family history, genotype, best-corrected visual acuity, ophthalmic examination, fundus photography, fundus autofluorescence, electroretinogram, optical coherence tomography, microperimetry, static and kinetic perimetry. Investigators will be required to document the criteria they used to identify patients at risk of rapid progression.

Protocol Amendment 6

Justification

Significant central vision loss in patients affected by Stargardt's Macular Degeneration (SMD) may occur as early as in the first or second decade. SMD patients ultimately become blind due to the irreversible degeneration of photoreceptors (PR) and retinal pigment epithelial cells in the macula due to the loss of ATP-binding cassette, sub-family A, member 4 (ABCA4) protein function arising from mutations in the ABCA4 gene. While effective gene therapy for SMD promises to restore a normal ABCA4 gene and protein function in viable PR, it is not anticipated that the treatment will restore degenerated cells that are no longer viable. Therefore, the optimal time for intervention with gene therapy in patients with SMD would seem to be before the onset of blindness or advanced macular atrophy.

To date, available clinical data from StarGen and other ocular gene therapy development programs using either the LentiVector® technology or adeno-associated virus platform suggest that ocular gene therapy is safe and well tolerated in treated adults and children. Based on this premise, this protocol amendment proposes extending the safety evaluation of the current protocol to an additional group of patients (Group D/Cohort 6) with a much less advanced stage of the disease that can be observed in adults and children (6 years and older).

Disease course

The progression of SMD is variable over several years before bilateral blindness with an onset (first noticeable symptoms) usually before age 20 (51) but as early as age 5 (52). While no publications report the distribution of disease onset by age groups, articles (53, 54, 55, 56) document that the median age of disease onset is around 20 years with range between 5 to as late as 72 years old.

As observed in a 95-patient study (57), visual acuity (VA) may decrease slowly at first, accelerate and then level off. A survival analysis (58) showed that the median time for patients to progress from VA 20/40 or better in their better seeing eye to 20/200 or worse is: 7 years [95% CI: 5 to 8 years] for patients 20 years or less; 22 years [95% CI: 10-23 years] for patients aged 21to 40 years; 29 years [95% CI: 12-29 years] for patients 41-60 years. This suggests that the rate of central vision decrease could be correlated with disease onset with a younger age at symptoms onset being associated with more rapid vision loss and onset of blindness.

While (distance) VA remains the gold standard for the assessment of visual function, particularly, in clinical trials, for patients with SMD, VA alone may not be the best assessment to define the disease stage or disease course as it reflects only the function of the foveal PRs. Using other clinical assessments such as visual field, microperimetry, electroretinography, fundus autofluorescence, and optical coherence tomography, alone or in combination, shows that evidence of PR and retinal pigmented epithelium (RPE) degeneration and progressive loss of visual function can be observed in SMD patients even if distance VA is maintained.

Treatment expectations

The SMD pathophysiology is due to a defective Rim Protein, a protein encoded by the ABCA4 gene, which causes an accumulation of N-retinylidene-PE in the PR outer segments. N-retinylidene-PE is a precursor of A2E, a major component of lipofuscin. Lipofuscin accumulates in the RPE cells and is toxic to them leading to PRs death secondary to loss of the RPE support function. The treatment objective of gene therapy for SMD is to introduce the correct ABCA4 complementary deoxyribonucleic acid (cDNA) into PRs to halt or slow down the degenerative loss of RPE cells and PRs and, therefore, the loss of visual function. From the current understanding of the pathophysiological process, it is very unlikely that StarGen reverses existing lipofuscin accumulation, and its consequent cell damage. If this assumption is correct, the likelihood to observe biological activity in patients in an advanced stage of the disease is low. Therefore, to enhance the chance of observing biological activity, it has been recommended by experts following a preliminary review of data from Cohorts #1-3 that patients with a much less advanced disease stage must be evaluated.

As an inherited disease, the physiopathological process probably starts at birth although it may remain clinically undetectable for several years; this supports the rationale to initiate a treatment as earlier as possible to limit physiopathological process. Clinical data derived from ongoing clinical trials of gene therapy in inherited ocular disease suggest a better response to treatment in children relative to adults, also supporting the benefit of early treatment.

Safety

From safety and tolerability data collected from Cohorts #1-4, StarGen appears to be safe and well-tolerated. On the 22nd September meeting, the Data Safety Monitoring Board (DSMB) evaluated the safety available data and reviewed the proposed study amendment 6. Following discussion, they recommended continuing the study with the inclusion of patients in cohort 5 and endorsed the study amendment foreseeing the evaluation of StarGen in adults and children with a less advanced stage of SMD.

A 2014 Association of Research in Vision and Ophthalmology (ARVO) abstract concluded that the 4 products using the LentiVector® technology (59) platform (ProSavin in neurological disease and RetinoStat, StarGen and UshStat in ocular diseases) are safe and well tolerated in 54 patients treated to date.

Most of ocular gene therapies currently use Adeno-Associated Virus (AAV) as vector and also appear well tolerated and safe. In 2013, K. Willett and J. Bennett (60) stated ‘Encouragingly, AAV appears safe and effective with clinical follow-up surpassing 5 years in some studies. As disease targets continue to expand for AAV in the eye, thorough and deliberate assessment of immunologic safety is critical. With careful study, the development of these technologies should concurrently inform the biology of the ocular immune response’.

Overall, the experience gained with ocular gene therapies for inherited retinal diseases using either AAV or LentiVector® technology platforms demonstrates the safety ocular gene therapy treatments administered subretinally.

Specific issues related to enrollment of pediatric patients

- **Immune system**

  The immune system in children of 6-18 years can be considered mature and is not expected to respond differently to viral particles or gene product from that of adults. At birth, the cellular immune system is fully developed. The rate of T cell production by the thymus is greatest from birth until puberty. Thus, a diverse T cell repertoire, including T cells selected against 'self' in the thymus, is generated by puberty. Following puberty, the generation of new/naïve T cells decreases with age and although T cell numbers remain stable throughout life, the T cell repertoire diminishes, particularly characterized in the elderly. Hence, a child of age >6 years up until puberty may have a broader repertoire of naïve cells than an 'adult'. This may suggest that this age group may be able to respond to a broader range of antigens ('non-self') than that of adults. Experimental work with influenza vaccines indicated that more influenza-activated T cells were generated in children aged 5 to 9 years than in adults (aged 22 to 49 years) (61). However, the blood/ocular-brain barrier is fully developed and access of T cells remains highly restricted in children >6 years of age as adults. Similarly, various tolerance mechanisms are active within the ocular compartment in both children and adults.

  At birth, the humoral immune system is under developed and remains poor for approximately 6 months. Adult levels of IgM are produced by 12 months; however adult levels of IgG are not reached until 5 years of age when the responses generated in children are equivalent to that in adults.

  There is currently no evidence to suggest that the immune response to vector particles or a gene product in children and adolescents will differ from the adult population. In studies utilizing AAV vectors subretinal injection was well tolerated in children (62). When lentiviral vectors are subretinally injected in mature animals, they have been shown to induce low levels of inflammation that are transient and comparable to those observed with AAV (63). An increased incidence of adverse immunological reactions in children following subretinal delivery of an ocular gene therapy is therefore considered unlikely. To ensure effective monitoring of vector and product in children and adolescents, biodistribution and immunology samples will be collected at the same intervals as in adult patients. In addition, as for the adult population, pediatric patients will be encouraged to enter the long-term, follow-up protocol designed to monitor the long-term safety of patients treated with StarGen.

- **Eye anatomy and surgery procedure**

  From 6 years of age the human eye is fully developed (64), thus inclusion of pediatric patients from 6 years of age will enable evaluation of StarGen in this population using the optimal and safe dose identified in the earlier parts of the study (Cohorts 1-5), without a need for a change in dose, dose volume or method of administration. Given the dose and method of administration will have been deemed to be safe in the first part of the study this approach will minimize any risk of administration to the younger population and provide an effective comparison of the safety of StarGen between the adult and pediatric populations. The risks related to the operative procedure, administration of StarGen in pediatric patients and the management of the complications of subretinal surgery are considered similar to that in adult patients as there is no significant modification in the procedure or factors related to the patient that represent significant differences. Surgery will be performed by experienced ophthalmic surgeons. Appropriate measures will be implemented to minimize any pain or discomfort associated with study procedures in children including administering StarGen under general anesthesia, if deemed necessary, and, where appropriate, providing in-patient hospitalization for postoperative management. General anesthesia in younger children does represent an additional risk compared to local anesthesia; however, the anesthesiologists will be experienced in pediatric anesthesia and specific practices for ocular surgery. Accommodation and logistic assistance will be provided to family members/caregivers to ensure they can be close to children in the event of hospitalization.

- **Experience of ocular gene therapy in pediatric patients**

  It is worth noting that recent Phase I/II studies in Leber's Congenital Amaurosis (LCA) conducted in the United States (US) and European Union (EU) enrolled patients as young as 5 years and older (NCT00516477, NCT01496040, NCT00643747). These studies evaluated subretinally injected adeno-associated virus vectors expressing the human gene RPE65 that codes for a normal functional retinal pigment epithelium specific 65 kiloDalton (kDa) protein. In the study reported by Maguire et al. (65), following delivery of the normal functional RPE65 gene, the greatest benefit in terms of improvement in vision was seen in the younger patients. This therapy is now being studied in LCA patients of 3 years and older (NCT00999609) to further evaluate the population and define the optimal time for intervention in the natural history of the disease to maximize benefit.

- **Informed consent process**

  The process of informed assent of pediatric patients and the consent from their parents, guardians or other legal representatives will ensure that all parties understand the unique risks associated with gene therapy and the specific risks associated with ocular gene therapy and the participation in early clinical research where the safety and efficacy of a therapy may not have been fully established.

Inclusion of pediatric patients in the study will only occur upon the recommendation of the DSMB and further to submission of a data package assessing the early benefit/risk profile of StarGen to the competent Health Authorities where the study is conducted.

Summary

Current nonclinical and clinical studies from multiple programs (ProSavin in neurological disease and RetinoStat, StarGen and UshStat in ocular diseases) have demonstrated the safety profile of the lentiviral vectors as a gene therapy platform, as well as the safety of the subretinal injection procedure. The proposed protocol change to allow enrollment of patients with a less advanced stage of disease, including children (≥6 years of age) in an additional cohort will provide an opportunity to evaluate the safety of StarGen in a population in which the biological activity of the treatment is also more likely to be observed due to the expected rapid progression of the disease course. As currently there is no known effective treatment for SMD to alter the inevitable progression to blindness, administering treatment in patients with less advanced stage of the disease offers the promise of maintaining patients at a higher level of visual functioning due to the expected life-long sustained biological activity of StarGen than patients eligible for treatment in previous cohorts. The Sponsor will be closely following Health Authority guidelines for pediatric patient enrollment. Furthermore, inclusion of pediatric patients in the study will only occur upon the recommendations by the DSMB and approval from the competent Health Authorities and IRBs/IECs after the review of adult data and benefit/risk assessment.

Proposed changes to current protocol

Overall, Cohorts 1-4 aimed to demonstrate safety of increasing doses of StarGen and Cohort 5 to confirm the safety profile of the maximum tolerated dose (MTD) or highest dose tested in slightly less severe patients (as displayed in table below) but it is very unlikely that biological activity of StarGen will be demonstrated from Cohorts 1-5 patients since these patients are too advanced in the disease process.

Cohort	Group	No of patients	Vector total dose per eye	Eligibility criteria
1	A	4	$1.8x10^5$ TU	• Patients (18 years or older) with advanced SMD • VA ≤20/200 in the worst eye • Severe cone-rod dysfunction with no detectable or severely abnormal full-field ERG responses
2	B	4	$1.8x10^5$ TU	• Patients (18 years or older) with SMD • VA ≤20/200 in the worst eye • Abnormal full-field ERG responses
3	B	4	$6x10^5$ TU	
4	B	4	$1.8x10^6$ TU	
5	C	up to 12	MTD or the highest dose tested	• Patients (18 years or older) with SMD • VA ≤20/100 in the worst eye • Abnormal full-field ERG responses

TU *Transducing units*
SMD *Stargardt Macular Degeneration*
VA *Visual Acuity*
ERG *Electroretinogram*
MTD *Maximum Tolerated Dose*

In addition to providing additional safety and tolerability data of the MTD or highest dose tested, another potential benefit of adding Group D in Cohort 6 is to provide the opportunity to further investigate the biological activity of StarGen in patients with a less advanced stage of the disease where the likelihood of observing biological activity is more probable. Overall, compared to patients in Groups A-C, Group D patients will be pediatric and adult patients with fairly preserved VA and mildly abnormal or normal full-field ERG responses at baseline in whom a rapid disease progression is expected. Therefore, we propose:

- To decrease the Cohort 5 sample size from up to 12 to up to 6 patients. Although Cohort 5 will provide further information on safety and tolerability of the MTD or highest dose tested, it is considered unlikely that evidence of biological activity will be observed in this cohort due to their advanced disease state. Based on the escalation criteria for previous cohorts, up to 6 additional patients in Cohort 5 will be adequate to confirm the safety and tolerability of the MTD or highest dose tested to allow the evaluation of the dose in adults and children with a much less advanced stage of the disease to be enrolled in Cohort 6.
- To add an additional cohort to the existing 5 cohorts. This Cohort 6/Group D will be enrolling up to 24 adult and pediatric (6 years or older) patients with SMD who are anticipated to experience rapid deterioration in visual function and/or retinal structure in the opinion of the study investigator, with VA of ≥20/100 in the worst eye (study eye) and with mildly abnormal (ie, abnormalities limited to photopic responses) or normal full-field ERG responses.
- Safety and biological data from Cohorts 1-5 will be reviewed by the DSMB, and subsequently, an interim report that includes a benefit/risk balance analysis for enrolling pediatric patients (with regard to US 21 CFR Part 50 Subpart D ‘Additional Safeguards for Children in Clinical Investigations’ for the FDA specifically) and provides a recommendation on the acceptability of commencing enrollment of pediatric patients in Cohort 6 will be submitted for approval by regulatory authorities and institutional review boards/ethics committees (IRB/EC).

Other changes

- **Where available, video-recording of surgery and/or intra-operative optical coherence tomography (OCT)**

To explore further the treatment effect (safety and biological activity) at the bleb level, video of the surgery and/or intra-operative OCT will be collected, where available, in order to define as precisely as possible the area of the bleb and consequently, the zone of cell transduction.

For the patients already enrolled, if a video of the surgery was obtained the patient will be asked to consent to allow the video to be collected and used for analysis.

- **New centers**

It is planned to open new centers in the US and the EU.

- **Centralized review committee**

For Cohort 6, a centralized review committee will be organized to pre-operatively review baseline study assessments for the purpose of providing a recommendation on the area of retina to be targeted for the subretinal injection to optimize the treatment benefit. The committee may also give a recommendation for the choice of the study eye if both eyes are clinically similar. As it is planned to open several new centers in the US and the EU, this committee will contribute to the homogenization in the treatment of the new patients.

- **Addition of time-points for immunology blood testing**
  - In all patients, additional immunology blood testing will be performed at Week 12, to assess the antibody response kinetic and possibly to identify the peak.
  - In patients with positive antibody response at Week 24, additional immunology blood testing will be performed at Week 36 and/or Week 48 to document the antibody response kinetic until the value return to baseline in these patients (therefore a follow-up beyond Week 48 may be needed).
- **For Cohort 6, removal or addition of certain time points of the different assessments**
  - Fundus photography: removal of Week 36 assessments
  - Fundus autofluorescence: removal of Weeks 4 and 12 assessments
  - Optical coherence tomography: removal of Weeks 1, 12 and 36 assessments
  - Full-field kinetic and static perimetry: removal of Weeks 12 and 36 assessments
  - Full-field electroretinogram: removal of Weeks 4 and 12 assessments
  - Multi-focal electroretinogram: removal of Week 12 assessment and addition of Week 2 assessment
  - Microperimetry: removal of Weeks 12 and 36 assessments
  - Adaptive optics: removed from the investigations

- VFQ-25: addition of Week 24 assessment
- Reading speed: addition of Week 24 assessment

- **Addition of secondary endpoints**

New secondary endpoints will be added to evaluate the safety and biological activity at the bleb level.

- **The study eye has been defined**

One study eye will be selected. If both eyes are eligible for the study, the worse eye, as per investigator judgment, will be selected. The centralized review committee may advise on the choice of the study eye if both eyes are clinically similar.

- **Inconsistencies' corrections**

Some inconsistencies have been corrected.

Protocol Amendment 5

Justification

On June 12, 2014, the study sponsorship will be transferred from Oxford BioMedica Ltd. to sanofi. Therefore the protocol is updated to reflect this change of sponsorship.

Amended text

- The header is modified to change the sponsor name, to add the compound code (SAR422459), and the study code (TDU13583), as per the new sponsor coding rules.
- The cover page is updated with the new sponsor related information
- Core text: Oxford BioMedica Ltd. or OXB has been replaced by "the Sponsor" where appropriate

Corrections of a wording mistake

In table 3 in Section 7 and the same table in protocol synopsis, Vector Concentration has been replaced by Vector total dose per eye.

Changes in AESI and SAE process:

Section 11 has been amended to align the protocol with the Sanofi protocol standards as regards to the definition and reporting of adverse events, adverse events of special interest and pre-specified lab abnormalities. Decision trees for standard pre-specified lab abnormalities data ie, neutropenia, thrombocytopenia, acute renal failure, suspicion of rhabdomyolysis and ALT increase have been added as appendices.

Other Administrative Updates

- The protocol has also been reviewed and updated to correct grammatical, administrative errors and harmonize formatting and spelling to US English.
- New Sponsor reference numbers have been added.
- The names of the principal investigators on the cover page have been deleted as per new sponsor rules. A page is added to specify the name of the coordinating investigator, the monitoring team's representative, the new sponsor, and other emergency telephone numbers
- OXB Sponsor signature page has been deleted following the change of Sponsor. As per new Sponsor rules, no Sponsor signature page will be included in the protocol
- The publication policy (Section 16.7) has been updated, in order to harmonize the text across all the protocols initially generated by Oxford BioMedica Ltd.

Protocol Amendment 4

Justification for changes

The following additions/clarifications have been made to protocol version 4.0 and incorporated in protocol version 5.0.

Section 3. Study Schedule and Sections 9.3.6 and 9.3.7

The study schedule and associated sections have been updated to remove Autofluorescence imaging at visits: Day 1 and Weeks 1, 2 and 36. Fundus photography has been removed from visits: Weeks 1 and 12. An infra-red fundus montage has been added to OCT time points to provide comparable information to autofluorescence imaging.

Justification for changes

The Investigators have recommended that the autofluorescence images and colour fundus photography time points are reduced in the early post-operative period, as patients find them difficult to tolerate and the images do not provide accurate data so soon after the surgical procedure. A reduction in autofluorescence imaging and colour fundus photographs also reduces the light exposure that may have a detrimental effect on the retina (66). As an infra-red light source is barely visible to the human eye, is more comfortable for the patient and presents no concerns about retinal light toxicity, a small montage using infra-red imaging will be included as part of the OCT imaging to provide comparable information to the previously specified autofluorescence imaging time points (67). Study schedule footnote '± Infra-red fundus montage to be performed at each visit' has been added to OCT time points.

Section 3. Study Schedule

- An inconsistency between the study schedule and section 9.3.3 has been rectified. Day -1 (baseline) has a visit window of -7 days. In addition, Section 9.3.25 has been updated to be consistent with Section 9.3.3.
- An inconsistency between the study schedule and section 9.3.18 has been clarified. Microperimetry will be performed at scheduled visits requiring Full field Kinetic and Static perimetry. Schedule footnote'*' has been updated to read: "BCVA and perimetry (full-field kinetic and static perimetry) will be performed once at the screening visit (Day -28) and on 2 occasions at baseline (Day -1). Microperimetry will be performed once at visits requiring full-field kinetic and static perimetry"

As a result, section 9.3.2, 9.3.3 and 9.3.7 have been updated to clarify microperimetry time points.

Section 6.2 Biodistribution Endpoint

An inconsistency between section 6.2 and the study schedule has been rectified. Blood samples for PCR will be taken at visits; Day -28, Day 0 (60 minutes post-surgery), Day 1 and Weeks 1, 2, 4, 12, 24, 36 and 48.

Section 9.3.1 Screening/Baseline Procedures

Below cited paragraph has been amended to clarify that only Full-field Kinetic and Static perimetry (not microperimetry) are to be performed in triplicate during screening.

Amended text

Patient screening will take place in the 28 days prior to StarGen™ administration. Full-field Kinetic and Static perimetry and BCVA will be performed on 3 occasions during the screening period, (once at Day -28 and twice at Day -1). These measures are subject to broad intra-individual variability. Thus to ensure eligibility of the patient, an average of the most reliable 2 will be used.

Section 9.3.2 Screening Clinical and Laboratory/Diagnostic Measurements

An inconsistency between section 9.3.2 and the study schedule has been rectified. Day -28 (Screening) has a visit window of ±10 days.

Section 9.3.9 Samples for Immunology

An inconsistency between section 9.3.9 and the study schedule has been rectified. Blood samples for immunology are required to be taken at baseline (Day -1) and Weeks 4 and 24.

Section 9.3.18 Perimetry

Below cited paragraph has been amended to clarify the perimetry requirements during the screening period.

Amended text

Full-field Kinetic and Static perimetry will be performed 3 times during the screening period (once at Day -28 and twice at Day -1). These measures are subject to broad intra-individual variability, thus to ensure eligibility of the patient the most reliable 2 will go forward for analysis by the reading centre. Microperimetry will be performed once at each visit. Follow-up perimetry (micro, full-field kinetic and static) tests will be performed at Weeks 2, 4, 12, 24, 36 and 48/early termination visit.

Following review of the study by the Data Safety Monitoring Board (DSMB), the following section has been added as recommended.

Section 11.3 Adverse Events of Special Interest

AEs of special interest include the following:

- Infection, particularly any opportunistic infection
- Immunological reactions (eg, new incidence or exacerbation of rheumatologic or other autoimmune disorder)
- New incidence or exacerbation/recurrence of a hematological disorder

In the event that a patient enrolled in the study experiences any of the above, blood samples for PCR and/or Immunological analysis will be taken to rule out involvement of Investigational Product.

Section 11.6 Reporting a Serious Adverse Event

The following paragraph has been amended to clarify that the study will comply with ICH GCP and any local pharmacovigilance regulatory reporting requirements.

OBM's pharmacovigilance provider will report all suspected unexpected serious adverse reactions (SUSARs) to the Regulatory Authorities in accordance with ICH GCP, and any local pharmacovigilance regulatory reporting requirements, after the investigator or any agent acting on behalf of the sponsor, or the sponsor being notified of the SUSAR.

Other Administrative Updates

The Protocol has been reviewed and updated to correct grammatical and administrative errors.

Protocol Amendment 3

Justification for changes

The following additions/clarifications have been made to the study protocol in response to review by the French regulatory authority (AFSSAPS)

Section 2. Synopsis (and throughout document)

The Primary Evaluation assessment 'Slit lamp biomicroscopy' has been updated to 'slit lamp examination' throughout the protocol as a point of clarification.

Section 4. Introduction and Rationale (page 23 paragraph 3)

The below cited paragraph has been updated to correct a typographical error; less than 1% of Stargardt cases may result from a dominant mode of inheritance as opposed to 10% previously cited in Protocol version 3.0.

Amended text

This disease is nearly always inherited as an autosomal recessive trait that produces a severe form of macular degeneration, similar to age-related macular degeneration, but which begins in childhood; it is the most common autosomal recessive juvenile onset macular dystrophy. In addition, less than 1% of cases may result from a dominant mode of inheritance. The autosomal recessive trait for SMD in affected children means that both parents were carriers, having 1 mutated gene for the disease paired with 1 normal gene. Children where both parents are carriers have a one in 4 chance of inheriting the both mutated genes (1 from each parent) leading to Stargardt disease.

Section 4.2 Clinical Pathology

This section has been amended to clarify the later onset of peripheral visual constriction compared to central visual failure in SMD patients.

Amended text

SMD, caused by mutations in the ABCA4 gene is inherited as an autosomal recessive trait, is the most frequent cause of juvenile macular degeneration. There is variation in the clinical course of the disease but typically central visual failure begins in childhood together with later onset peripheral visual constriction in some cases. The consequence of the condition is frequently legal blindness.

Section 4.11 Rationale for Target Patient Population

This section has been updated to clarify and more clearly define the patient cohorts in this study. The phenotypic subtypes of Stargardt macular dystrophy are described by Lois et al. (currently ref number 25) and the paper has been appended to the protocol (Appendix D). Updated section also referenced in Section 7. Study Design.

Additional/Amended text

Three phenotypic subtypes of SMD have been identified based upon ERG attributes (Lois et al. 2001, Appendix D):

Category 1: Severe ERG abnormality with normal scotopic and [photopic] full-field ERG.

Category 2: Severe ERG abnormality with loss of photopic function but normal scotopic and full-field ERG.

Category 3: Severe ERG abnormality with loss of both photopic and scotopic function.

Three patient groups 18 years or older with a differing level of advancement of SMD will be included in this study. All 3 patient populations to be studied will be from the most severe category (category 3 of the Lois et al. classification)

- Group A: Patients with advanced SMD, visual acuity ≤20/200 in the worst eye and severe cone-rod dysfunction with no detectable or severely abnormal full-field ERG responses. These will be patients with severe ERG abnormality and loss of both photopic and scotopic function, with loss of photopic responses to no more than 70% of the category 3 ERG criteria in the Lois et al. classification, and very poor visual acuity.
- Group B: Patients with SMD, visual acuity ≤20/200 in the worst eye with abnormal full-field ERG responses. These will be patients with very abnormal ERG and photopic responses, with loss of photopic responses to no more than 85% of the category 3 ERG criteria in the Lois et al. classification, and very poor visual acuity.
- Group C: Patients with SMD, visual acuity ≤20/100 in the worst eye with abnormal full-field ERG responses. These will be patients with severe ERG abnormality, and have photopic B-wave amplitude within the range of category 3 criteria in the Lois et al. classification. These patients will also have more preserved visual acuity.

Patients thus treated in the first cohort will have advanced disease with the most severe loss of photopic retinal function on ERG and very poor visual acuity. Therefore, whilst this patient group is unlikely to experience any significant clinical benefit from treatment in terms of improvement in BCVA, any deleterious local effects of StarGen™ will be detectable through regular safety monitoring. Following clinical experience in patients with advanced disease a further 3 cohorts (Cohorts 2-4) in patients with less advanced disease will be evaluated.

Section 8.2 Withdrawal Criteria

This section has been updated to briefly describe a long term follow-up safety study which will be submitted as a separate protocol to regulatory agencies and ethics committees for approval. Patients taking part in the current study will be encouraged to participate in the follow-up study.

Additional text

Any patient that is withdrawn from the study will be encouraged to consent to an open-label, long term follow-up study. If the patient withdraws/is withdrawn from the study, the Week 48 procedures should be completed if possible.

The long term safety follow-up will be described in a separate protocol which will be submitted to regulatory agencies and Institutional Review Boards/Ethics Committees for approval.

The open label follow-up study has been designed to capture the essential safety data pertinent to gene therapy follow-up, as well as key efficacy assessments, whilst providing the patient with a degree of flexibility for minimising inconvenience. The long term follow-up protocol will also permit patients to receive alternative treatment during their participation whilst allowing for safety follow-up.

Section 9.3.1 Screening/Baseline Procedures

This section has been updated to remove the requirement for 3 ERG assessments during the screening period prior to surgery, this requirement was included in error. Only BCVA and perimetry assessments will now be required in triplicate during screening. ERG assessments will occur once at Day -28 and once at Day -1 per the study schedule.

Amended text

Patient screening will take place in the 28 days prior to StarGen™ administration. BCVA and perimetry will be performed on 3 occasions during the screening period, (once at Day -28 and twice at Day -1). These measures are subject to broad intra-individual variability thus to ensure eligibility of the patient an average value in each case will be used.

Section 9.3.3 Screening Clinical Laboratory/Diagnostic Measurements Day -1

Updated to reduce the number of ERG assessments at visit.

- ERG (Multifocal and Full-Field)

Section 9.3.7 Follow-Up Week 1, 2, 4, 12, 24, 36 and 48 Clinical and Laboratory/Diagnostic Measurements

An ERG assessment has been included at Week 4 at the request of AFSSAPS to assess early signs of safety and biological activity.

- ERG (Weeks 4, 12, 24 and 48 only)

Administrative/other updates

Study Schedule

An inconsistency between the Study Schedule Section 3 and Section 9.3.8 Samples for PCR has been rectified. Blood and where possible urine samples are required to be taken 60 minutes post-surgery.

Section 2.1.1 and 8.1.1 Main Inclusion Criteria

For Inclusion criteria 2 and 3, inconsistencies in wording between both sections have been rectified.

Section 10.1.2 Storage and Disposition of Study Medications

This section has been amended to accommodate local procedures for the destruction of used and unused vials post-surgery.

Amended text

Dispensing will be documented by completing a log with the date of dispensing and the patient details. Used and unused vials should be returned to the hospital pharmacy (or in accordance with local standard operating procedures) and stored in labeled biohazard bags prior to reconciliation by the study monitor. Where local procedures require immediate destruction of used and unused vials, the process will be witnessed, signed and documented on a destruction log.

At each visit, the clinical study monitor will review the drug-dispensing log and reconcile it with the unused vials/destruction log.

Protocol Amendment 2

Justification for changes

The following additions have been made to the study protocol in response to review by the FDA:

Section 4.9 Rationale for the Clinical Dose

The dose selection for the FIM study will be based on the MTD used in the rabbit and NHP GLP combined toxicology/biodistribution studies.

The MTD in the rabbit that was used in the GLP safety study is $1.4x10^6$ TU/eye. The MTD in the NHP that was used in the GLP safety study is $4.7x10^5$ TU/eye. Based on the average 3-fold ocular allometric scaling of ocular volume between rabbit/NHP and the human eye the expected MTD in man is $1.4x10^6$ TU/eye up to $4.2x10^6$ TU/eye based on the MTD in the NHP and rabbit, respectively.

In the current study, the first dose in man is equivalent to $1.8x10^5$ TU/eye, the second dose is equivalent to $6x10^5$ TU/eye and the highest dose will be undiluted StarGen which is equivalent to $1.8x10^6$ TU/eye. All 3 of these dose levels are below the MTD predicted by the rabbit and are either below or almost equivalent to the MTD predicted in the NHP.

Section 6.1.4 Laboratory Parameters and Section 8.1.5 Exclusion Criteria

Blood for immunology and blood for PCR will also be taken at multiple time points throughout the study, as will urine samples for biodistribution assessment.

The normal ranges and the definition of abnormal ranges for screening laboratory tests are now provided in Appendix C and the reference to Appendix C is provided in the Exclusion Criteria item 10 related to laboratory parameters.

Section 8.3 Study Stopping Criteria

Prolonged anterior chamber inflammation and/or prolonged posterior chamber inflammation continuing without signs of resolution 28 days after StarGen administration.

Section 9.2.2 Intraocular Injection

The retinotomy will be temporal to the optic nerve and located outside the major arcade vessels such that the subretinal bleb produced may be expanded towards the macula.

Section 9.2.3 Positioning of the Subretinal Bleb

In all patients, the site for subretinal injection will be selected as to ensure that the existing visual acuity will not be impaired and the treated retinal area can be easily monitored for safety after StarGen™ administration. Group A will have advanced disease and very poor visual acuity. In this group encroachment of the injection bleb to the central macula will be permitted as it is unlikely it will further impair visual acuity. However, groups B and C will have less advanced disease with better acuity. Thus, a more conservative approach will be adopted and the bleb will only extend over the macular boundary to minimize the risk of any visual function impairment.

Prior to surgery, the position of the subretinal bleb will be determined based on the baseline clinical evaluation, fundus imaging, microperimetry and visual field testing.

Protocol Amendment 1

Justification for changes

Following recommendations from the Data Safety Monitoring Board (DSMB) for this study, exclusion criteria 7 has been revised to include any known allergy to topical, injected or systemic corticosteroids.

The DSMB also recommended further guidance on the management of any ocular inflammation.

Changes and additions as follows

Section 2.1.5, Synopsis and Section 8.1.5 Exclusion Criteria

7. Any known allergy to any component of the delivery vehicle or diagnostic agents used during the study (eg, fluorescein, dilation drops), or medications planned for use in the peri-operative period particularly topical, injected or systemic corticosteroids.

Section 9.2.2

Intraocular inflammation may be treated with 1 or a combination of anti-inflammatory medications including topical 1% prednisolone acetate, periocular injection of 20 mg of triamcinolone acetate, and systemic steroids (eg, oral prednisolone 0.5 mg/Kg daily for 10 days or prednisolone 1 mg/Kg daily for 10 days) The choice of medications will be at the treating physicians' discretion and guided by the severity and longevity of the inflammation.