Amended Clinical Trial Protocol 08

US1/001/10 - Study TDU13600

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

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Amended Protocol 8		07 August 2018, Version 1 (electronic 3.0)
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Amended Protocol 8 07 August 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

Summary of main changes:

- Additional 6 patients added to Part A (dose finding) to test additional dose levels

  Rationale: Due to variability observed in previous batch strength, patients in Cohort 3 have received different doses when calculated by measured strength. While strength remained within specification, one patient has received $0.33x10^6$ TU/eye dose, while the two following patients (treated with a new batch) received $2.4x10^6$ TU/eye dose. Following DSMB review additional safety data in Part A was requested. Next two dose levels based on dilution from the measured batch strength will be investigated. This will provide additional safety information and improve dose selection for Parts B and C.

- Adding mention of a diluent for IMP

  Rationale: dilution is needed to administer above mentioned additional dose levels.

- Inclusion criteria modified to better define target population

  Rationale: Following new natural history data and DSMB recommendations, BCVA lowest threshold and minimal EZ zone area is added in order to select patients with some residual photoreceptor zone and some visual function, who could benefit more from treatment. ERG is removed from inclusion criteria since it does not appear to provide additional benefit for selection of the target population.

- Prophylactic glucocorticoid schedule added as mandatory after surgery and IMP injection

  Rationale: anti-inflammatory regimen is added to decrease the risk of intraocular inflammation following the subretinal injection procedure. This modification is agreed with DSMB following two cases of uveitis classified as serious adverse events following subretinal injection of lentiviral vectors (one case in this study, the other with another project using the same lentiviral vector technology). The DSMB, in agreement with study Investigators, reviewed the cases and recommended the modification of the protocol with regard to glucocorticoids in order to reduce the occurrence of post-operative ocular inflammation.

- Additional list of ophthalmic AESIs added for better safety.

  Rationale: additional list of ophthalmic AESIs will permit early reception of these safety events in sponsor's safety database, with more detailed data reported. This will ensure earlier monitoring for potential safety signals.

- Simplifying retinotomy description

  Rationale: this will allow better adaptation of retinotomy and IMP injection to individual patients, with respect to lesion size and target retinal areas.

- Correction of baseline definition:

  Rationale: definition of baseline was provided to use the data most close to the treatment for more precise evaluation of treatment-emergent safety events and efficacy signals

Other minor changes are also implemented to facilitate operational conduct, clarify or eliminate inconsistencies.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Whole document	UshStat / UshStat® replaced with SAR421869	UshStat® was previous name.
DOCUMENT HISTORY	Added, including a table and the sentence stating the amendment is substantial.	Template applied.
OVERALL RATIONALE FOR THE AMENDMENT	Added, for Amendment 8.	Template applied.
Section 17 APPENDICES	Appendix E added: History of protocol amendments. Summary of rationales for previous amendments moved to Appendix E (were at the beginning, before table of contents).	Template applied.
Section 1 SYNOPSIS + Section 6.2 SECONDARY ENDPOINTS + Section 9.3.3 Screening Clinical and Laboratory/Diagnostic Measurements Day -28 + Section 9.3.4 Baseline Clinical Laboratory/Diagnostic Measurements Day -1 + Section 9.3.7 Follow-up Procedures	Secondary (Biological Activity) Endpoints: - 'Contrast sensitivity' added - 'CVAQC (when possible)' added to endpoint 'Visual function questionnaire VFQ 25'.	For better biological activity evaluation.
Section 9.3.11.2 Contrast sensitivity	Additional section (refer to Appendix D).	
Section 17 APPENDICES	Appendix D added: Low-Contrast Sloan Letter Chart Testing.	
Section 9.3.11.11 Visual Function Questionnaire (VFQ-25)	Details on CVAQC added.	
Section 1 SYNOPSIS (Study design, Study dosing schedule, and Study population) + Section 7 STUDY DESIGN + Section 8 STUDY POPULATION	Number of patients in cohorts of Part A and Part B; dose by measured strength added for Part A; number of patients to complete the study.	Additional patients to test additional dose levels based on dilution from the measured batch strength; to provide additional safety information and improve dose selection for Parts B and C.
Section 2 STUDY SCHEDULE	Additional table for Cohorts 3b, 3c, 4, and 5.	Clarification and consistency.
Section 3 STUDY DIAGRAM	Diagram changed.	
Section 4.4 SAR421869 DRUG DEVELOPMENT	Diluent added in components, specification on dilution.	For dilution (measured batch strength).
Section 9.2.4 SAR421869 preparation	One sentence deleted.	Details provided in Pharmacy manual.
Section 10 STUDY MATERIALS 10.1 SAR421869; 10.1.1 Packaging and Labelling; 10.1.2 Storage and Disposition of Study Medications	Specifications added.	For dilution.
Section 1 SYNOPSIS (Study design, Study dosing schedule)	Precision of age of pediatric patients in Part C.	Clarification.
Section 4.12 RATIONALE FOR DOSING INTERVALS	Number of patients of Cohort 4 (Part B) - Precision of age of pediatric patients in Part C.	
Section 4.14 RATIONALE FOR INCLUSION OF CHILDREN AND ADOLESCENTS	Number of patients of Cohort 4 (Part B).	
Section 6 ENDPOINTS (1st paragraph)	Specification on baseline (before surgery).	Definition of baseline to use the data most close to the treatment for more precise

Section # and Name	Description of Change	Brief Rationale
		evaluation of safety and efficacy.
Section 1 SYNOPSIS + Section 8.2 ENTRY CRITERIA	Entry criteria: 2 inclusion criteria added for all cohorts; specific inclusion criteria added for Cohorts 3b and 3c (Part A), Cohort 4 (Part B), and Cohort 5 (Part C).	Specific inclusion criteria to better define target population (to select patients with some residual photoreceptor zone and some visual function; ERG removed from inclusion criteria).
Section 9.2.2 Intraocular injection + Section 9.2.3 Positioning the subretinal bleb	Details on retinotomy provided in study manuals.	Better adaptation of retinotomy and IMP injection.
Section 9.2.2 Intraocular injection + Section 9.3.13 Postsurgical ophthalmological adverse events	Specifications on prophylactic glucocorticoid schedule added, wording of anti-inflammatory protocol adapted.	Modification with regard to glucocorticoids in order to reduce the occurrence of postoperative ocular inflammation.
Section 9.3.5 Re-screening	Additional section.	To facilitate operational conduct.
Section 9.3.11.1 Best-Corrected Early Treatment Diabetic Retinopathy Study (ETDRS) Visual Acuity	Addition of ETDRS testing as back-up of EVA (electronic visual acuity) testing.	To facilitate operational conduct.
Section 11.5 ADVERSE EVENTS OF SPECIAL INTEREST + Table 'Summary of adverse event reporting instructions' in Section 11.6 GENERAL GUIDELINES FOR REPORTING ADVERSE EVENTS	AESIs added.	Additional list of ophthalmic AESIs added for better safety.
Section 13 DATA MANAGEMENT AND STATISTICAL ANALYSES 13.4 SAFETY ENDPOINTS 13.4.1 Adverse events	Addition of a specific grouping for ocular inflammatory events.	For better safety evaluation.
Section 13 DATA MANAGEMENT AND STATISTICAL ANALYSES 13.6 OTHER MEASURES 13.6.2 Withdrawals	One sentence deleted.	Consistency.
Section 1 SYNOPSIS + Section 13.7 INTERIM ANALYSIS STATISTICAL ANALYSES SPECIFIC TO THE DSMB MEETINGS	Specifications on interim analyses.	Clarification.
Throughout	Minor editorial and document formatting revisions.	Minor, therefore have not been summarized.

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LIST OF ABBREVIATIONS

AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
AMD:	age related macular degeneration
AST:	aspartate aminotransferase
BCVA:	best-corrected visual acuity
BP:	blood pressure
BUN:	blood urea nitrogen
cDNA:	complimentary deoxyribonucleic acid
CFR:	code of federal regulations
CHOL:	cholesterol
CPK:	creatinine phosphokinase
CRF:	case report form
CRO:	contract research organization
CS:	clinically significant
CVAQC:	cardiff visual ability questionnaire for children
DSMB:	data safety monitoring board
EC:	Ethics Committee
ECG:	electrocardiogram
EIAV:	equine immune anemia virus
ERG:	electroretinogram
EVA:	electronic visual acuity
EZ:	ellipsoid zone
FAF:	fundus autofluorescence
FDA:	U.S Food and Drug Administration
FIM:	first in man
GATE:	german adapting thresholding estimation
GCP:	good clinical practice
GGT:	gamma glutamic transpeptidase
GLP:	good laboratory practice
HCT:	hematocrit
HGB:	hemoglobin
HIV:	human immunodeficiency virus
HR:	heart rate
ICH:	International Conference on Harmonization
IMP:	Investigational Medicinal Product
IOP:	intraocular pressure
IRB:	International Review Board
ISCEV:	International Society for Clinical Electrophysiology of Vision

LDH:	lactate dehydrogenase
MCH:	mean corpus hemoglobin
MCV:	mean corpus volume
MTD:	maximum tolerated dose
MYO7A:	myosin 7a gene
NCS:	not clinically significant
NEI:	national eye institute
NHP:	non human primate
OCT:	optical coherence tomography
OXB:	oxford biomedica ltd
PCR:	polymerase chain reaction
PI:	principal investigator
PT:	prothrombin time
PTT:	partial prothrombin time
RBC:	red blood cells
RDW:	red cell distribution width
RP:	retinitis pigmentosa
RPE:	retinal pigment epithelium
RPE-65:	retinal pigment epithelium protein - 65
SAE:	serious adverse event
SD-OCT:	spectral domain OCT
SITA:	swedish interactive thresholding algorithm
SKP:	semi-automated kinetic perimetry
SUSAR:	suspected unexpected serious adverse reaction
TBIL:	total bilirubin
TP:	total protein
[redacted]	[redacted]
TU:	transducing unit
USA:	United States of America
USH1B:	usher syndrome type 1b
VFQ-25:	visual function questionnaire -25

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 US1/001/10 - TDU13600.

Signed _____

Name _____

Date _____

1 SYNOPSIS

Official Title	A Phase I/IIa Dose Escalation Safety Study of Subretinally Injected SAR421869, Administered to Patients with Retinitis Pigmentosa Associated with Usher Syndrome Type 1B
Clinical Phase	I/IIa
Study Objectives	
Primary Objectives	To evaluate the safety and tolerability of ascending doses of subretinal injections of SAR421869 in patients with Usher syndrome Type 1B.
Secondary Objective	To evaluate for possible biological activity of SAR421869.
Study Endpoints	
Primary Safety Endpoints	The incidence of adverse events over a 12-month period following a single intraocular dose of SAR421869. Clinically important changes from baseline in the following safety assessments. • Best-corrected visual acuity (BCVA). • Slit-lamp examination. • Indirect ophthalmoscopy. • Fundus photography. • Intraocular Pressure (IOP). • Optical Coherence Tomography (OCT). • Laboratory parameters. • Vital signs. • Concomitant medications. • Physical examinations.
Secondary (Biological Activity) Endpoints	To determine a delay in retinal degeneration following subretinal injection of SAR421869, through changes in function relative to the untreated contralateral eye utilizing the following retinal analytical techniques: • Best-corrected visual acuity (BCVA). • Contrast sensitivity. • Indirect ophthalmoscopy. • Visual function questionnaire VFQ-25 / CVAQC (when possible). • Full dilated slit-lamp examination. • Fundus photography - Pan-retinal photomontage. • Visual field testing: Semi-automated Kinetic Perimetry (SKP) and Full-Field German Adaptive Thresholding Estimation (GATE) Static Perimetry, and microperimetry. • Autofluorescence. • Electroretinogram (ERG). • Optical coherence tomography (OCT).
Other Endpoints	• SAR421869 distribution in the blood and urine assessed by polymerase chain reaction (PCR). • Humoral antibody response to SAR421869 administration. • Hematology, biochemistry, urinalysis and other laboratory data will be measured at various time points throughout the study.

Study Design

This is a Phase I/IIa open label dose escalation study of subretinally injected SAR421869 in patients with retinitis pigmentosa (RP) associated with Usher Syndrome Type 1B. In this study at least three doses of SAR421869 will be evaluated over five patient cohorts. The study is separated into a dose escalation phase, Part A, followed by a two part dose extension phase at the maximum tolerated dose, Parts B and C.

Part A will evaluate at least 3 ascending dose levels of SAR421869, in 300 µL of vehicle. A total of at least 15 patients ≥18 years of age will be entered: 3 patients in Cohorts 1 and 2 and at least 9 patients in Cohort 3. An interval of 21 days between dosing the first and subsequent patients will be observed in Cohorts 1-3 in order to assess the safety. If DSMB requires additional patients – total up to 24 may be included in Part A.

After dosing the last patient in each of the first three cohorts, the patients will be followed for 28 days to ensure there are no dose-limiting toxicities. If after a minimum interval of 28 days from dosing the last patient of the previous cohort, the safety and tolerability is considered satisfactory by the DSMB, then patients in the next cohort will be dosed.

If the safety and tolerability of SAR421869 is considered satisfactory by the DSMB in Part A of the study, the study will proceed to Part B.

In Part B (Cohort 4), 6 patients ≥18 years of age will be treated at the maximum tolerated dose (MTD) determined from Part A, to further characterize the risk: benefit profile of SAR421869. These patients will be enrolled in parallel.

Part C (Cohort 5) provides the opportunity to extend the study to include pediatric patients 6-17 years of age treated at the MTD. Prior to the inclusion of pediatric patients, the DSMB will review all safety data including the data from Part B, three months after all 6 patients in cohort 4 have 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 review, before up to 6 patients 6-17 years will be included in Part C of the study (Cohort 5).

All patients will be followed for 48 weeks. After this period they will enter an open-label safety study for long-term follow-up. Patients will attend visits at a minimum interval of one visit every 6 months for assessments that will include ophthalmological examinations and recording of adverse events for 240 weeks (5 years).

In addition, the investigator will conduct visits/contact the patient by telephone for a subsequent 10 years at a minimum interval of once a year to monitor delayed adverse events.

In the event that a patient dies during the study then consent for post-mortem will be sought from the patient's family. In the event of development of an infection that is classified as an important medical event, particularly any opportunistic infection or onset of an autoimmune condition, effort will be made to collect data regarding the infectious agent and the outcome of the relevant investigations to characterize the autoimmune disease.

Study Dosing Schedule

Part A

Cohort	Age (yr)	Number of patients	Subretinal Injection		
			Vector total dose per eye		Volume
			by target strength (TU/eye)*	by measured strength (TU/eye)**	
1	≥18	3	$1.4x10^5$	$2.1x10^4$	300 µL
2	≥18	3	$4.7x10^5$	$1.1x10^5$	300 µL
3a	≥18	1	$1.4x10^6$	$0.33x10^6$	300 µL
3a	≥18	2	$1.4x10^6$	$2.4x10^6$	300 µL
3b	≥18	3	-	$0.33x10^6$	300 µL
3c	≥18	3	-	$1.4x10^6$	300 µL

Part B

Cohort	Age (yr)	Number of patients	Subretinal Injection	
			Vector total dose per eye	Volume
4	≥18	Up to 6	MTD	300 µL

Part C

Cohort	Age (yr)	Number of patients	Subretinal Injection	
			Vector total dose per eye	Volume
5	6-17	Up to 6	MTD	300 µL

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

Study Population

All patients must have a clinical and molecular diagnosis of RP caused by MYO7A mutations.

The results of the gene mutation analysis will be collected in the study database provided that written results are made available to the site, and participants (patients and/or the patient's parent[s]/legal guardian[s]) would give consent to record the results. Twenty seven to 36 patients will complete the study. The protocol accommodates the possibility of several screen failures due to the rigorous inclusion and exclusion criteria. It is anticipated that up to three additional patients may need to be enrolled during the study to replace those who fail to complete the first six months of follow-up appointments.

Entry Criteria

Main Inclusion Criteria

For the purpose of this study 1 month is equivalent to 28 days.

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

- Signed and dated written informed consent must be obtained from the patient (or assent in the case of minors from their legal guardian/representative), in accordance with the local regulations.
- Clinical and molecular diagnosis of Retinitis Pigmentosa associated with Usher syndrome Type 1B, caused by at least one pathogenic MYO7A mutation on both alleles, confirmed by direct sequencing and co-segregation analysis within the patient's family.
- Patients must have suitable verbal, auditory and/or tactile sign language communication (in the opinion of the investigator) as to allow written informed consent to be obtained.
- Females of childbearing potential must have a negative urine pregnancy test at screening and at baseline, and agree to use an effective form of contraception such as the contraceptive pill or intra uterine device for at least three months following SAR421869 administration, or be surgically sterile or postmenopausal, with the last menstrual period being over two years prior to enrolment.
- Males of reproductive potential must agree with their partner to use two forms of contraception, including one barrier method for at least three months following SAR421869 administration if their partner is of childbearing capacity, or must be surgically sterile.
- Patients enrolled in France must be affiliated to or benefit from a social security regimen.
- Patients must agree to not donate blood, organs, tissues or cells for at least three months following SAR421869 administration.

<u>Part A</u>

Specific Inclusion Criteria Cohorts 1, 2 and 3a

- ≥18 years of age.
- Concentric constriction of kinetic visual field centrally in the worse seeing-eye equating to a horizontal visual field diameter of ≤20 degrees, measured through the center of the visual field grid. The visual field constriction will be

measured by Semi-automated Kinetic Perimetry (SKP) and the degrees of constriction will be confirmed by centralized independent assessment of the SKP data.

- No detectable rod-derived amplitudes on the full field electroretinogram performed to ISCEV standards.

Specific Inclusion Criteria Cohorts 3b and 3c

- ≥18 years of age.
- Concentric constriction of kinetic visual field centrally in the worse seeing-eye equating to a horizontal visual field diameter of ≤20 degrees, measured through the center of the visual field grid. The visual field constriction will be measured by Semi-automated Kinetic Perimetry (SKP) and the degrees of constriction will be confirmed by centralized independent assessment of the SKP data.
- Patients with a baseline BCVA >20/200 in both eyes.
- Patients with subfoveal Retinal Pigment Epithelium (RPE) intact and Ellipsoid zone ≥1mm (in any dimension on OCT evaluation).
- 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.

Part B

Specific Inclusion Criteria Cohort 4

- ≥18 years of age
- Concentric constriction of kinetic visual field centrally in the worse seeing-eye equating to a horizontal visual field diameter of ≤ 20 degrees, measured through the center of the visual field grid. The visual field constriction will be measured by Semi-automated Kinetic Perimetry (SKP) and the degrees of constriction will be confirmed by centralized independent assessment of the SKP data.
- Visual field loss in the worse seeing-eye that is equivalent to ≥30% reduction from normal sensitivity volume (decibel-steradian) on full-field GATE Static Perimetry using the size V (1.7°) test target. The percentage reduction in normal sensitivity volume will be confirmed by centralized independent assessment of the data.
- Patients with a baseline in both eyes BCVA >20/200.
- Patients with subfoveal Retinal Pigment Epithelium (RPE) intact and Ellipsoid zone ≥1mm (in any dimension on OCT evaluation).
- 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.

Part C

Specific Inclusion Criteria Cohort 5

- 6-17 years of age.
- Concentric constriction of kinetic visual field centrally in the worse seeing-eye equating to a horizontal visual field diameter of ≤ 20 degrees, measured through the center of the visual field grid. The visual field constriction will be measured by Semi-automated Kinetic Perimetry (SKP) and the degrees of constriction will be confirmed by centralized independent assessment of the SKP data.
- Visual field loss in the worse seeing-eye that is equivalent to ≥30% reduction from normal sensitivity volume (decibel-steradian) on full-field GATE Static Perimetry using the size V (1.7°) test target. The percentage reduction in normal sensitivity volume will be confirmed by centralized independent assessment of the data.
- Patients with a baseline BCVA >20/200.
- Patients with subfoveal Retinal Pigment Epithelium (RPE) intact and Ellipsoid zone ≥1mm (in any dimension on OCT evaluation).
- All eligible patients must demonstrate an ability to understand, reasonably well cooperate to perform required study procedures as judged and confirmed by the study Investigator.

Exclusion Criteria

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

- Presence of significant ocular abnormalities in the study eye that in the opinion of the investigator would preclude the

planned surgery, effective safety follow-up, or interfere with the interpretation of study endpoints (eg, glaucoma, corneal or significant lens opacities, pre-existing uveitis, intraocular infection, choroidal neovascularization).

- Any pre-existing factor or past history of eye disease in children that may predispose to an increased risk of surgical complications in the study eye (eg, trauma, previous surgery, uveitis, congenital, developmental or structural abnormalities).
- Concomitant systemic diseases including those in which the disease itself, or the treatment for the disease, can alter ocular function (eg, malignancies, diabetes, juvenile rheumatoid arthritis or sickle-cell disease).
- Any ocular surgery including laser and cataract surgery with intraocular lens implantation, aphakia or prior vitrectomy, in the study eye within 6 months of screening.
- Any contraindication to pupil dilatation in either eye.
- Treatment with intravitreal, subtenon, or periocular steroid within 4 months of the screening visit.
- 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 during the peri-operative period, particularly topical, injected or systemic corticosteroids.
- Life-threatening illness.
- Alcohol or other substance abuse.
- Laboratory test abnormalities or abnormalities in electrocardiogram or chest X-ray that, in the opinion of the principal investigator, are clinically significant and would make the patient unsuitable for participation in the study.
- Intercurrent illness or infection 28 days prior to SAR421869 administration.
- Contraindications to use of anesthesia (local or general, as appropriate).
- Concurrent anti-retroviral therapy that would inactivate the investigational agent.
- 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.
- Pregnant or breastfeeding women.
- Males or females who do not agree to use barrier contraception as specified in the inclusion criteria.
- History of any investigational agent within 28 days prior to SAR421869 administration.
- Participation in a prior gene transfer therapy study.
- Enrolment in any other clinical study, for any condition, including those relating to Usher syndrome Type 1B, throughout the duration of the SAR421869 study.
- Current or anticipated treatment with anticoagulant therapy or the use of anticoagulation therapy within the four weeks prior to surgery.
- Long term treatment with systemic corticosteroids within 28 days prior to the screening visit or ongoing systemic corticosteroid treatment at screening or on Day -1.
- Current treatment with immunosuppressant therapies.
- A history of malignancy within a five year period or have had a positive cancer screening test within a one year period of the screening visit.
- Past medical history of HIV, or hepatitis A, B or C.
- Inability to comply with the study protocol.

Statistical Analysis

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

Due to a small number of patients 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.

BCVA and perimetry measurements are subject to broad intra-individual variability. The baseline value used for statistical analysis of these measures will be an average of all values obtained before surgery.

Interim Analysis

No formal interim analysis is planned in this study. A review of data will be conducted on all available safety data and any available preliminary efficacy/activity data up to the 3-month time point for Cohort 4 patients. This review, consisting of descriptive statistics and exploratory figures will be used to provide data to the regulatory authorities and IRB/ethics committees before pediatric patients are enrolled in Cohort 5. Formal statistical tests will not be performed as part of this analysis.

2 STUDY SCHEDULE

2.1 FOR COHORTS 1-3A

	Pre-SAR421869	Days			Weeks						
	-28	-1	0 Surgery	Day 1	1	2	4	12	24	36	48[k]
Visit Windows	**+10 days**	**-7 days**	**N/A**	**N/A**	**±3 days**	**±3 days**	**±3 days**	**±14 days**	**±14 days**	**±14 days**	**±14 days**
SAR421869 administration			X								
Entry Criteria	X										
Informed consent/assent	X										
Medical history	X										
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Anesthesia assessment	X										
Height	X										
Weight	X										
Vital signs [c]	X	X	X	X	X	X	X	X	X	X	X
ECG	X [o]										
Chest X-ray	X [o]										
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	X	X		X	X	X	X	X	X	X	X
Autofluorescence	X						X	X	X		X
OCT [p]	X	X		X	X	X	X	X	X	X	X
Perimetry (SKP, GATE, microperimetry)[a]	X [m]	X [n]				X	X	X	X	X	X
Fundus photography [b]	X		X	X		X	X		X	X	X
Multifocal and full Field ERG	X								X		X
VFQ-25		X [o]									X [o]
Hematology [d]	X	X [o]		X [o]			X [o]		X [o]		X [o]
Chemistry panel [e]	X	X [o]		X [o]			X [o]		X [o]		X [o]
Kidney function [f]	X	X [o]					X [o]		X [o]		X [o]
Liver function [g]	X	X [o]		X [o]			X [o]		X [o]		X [o]
Coagulation [h]	X	X [o]									

	Pre-SAR421869										
	Days				Weeks						
	-28	-1	0 Surgery	Day 1	1	2	4	12	24	36	48[k]
Visit Windows	**+10 days**	**-7 days**	**N/A**	**N/A**	**±3 days**	**±3 days**	**±3 days**	**±14 days**	**±14 days**	**±14 days**	**±14 days**
Urinalysis[i]	X	X[o]		X[o]			X[o]		X[o]		X[o]
Blood for PCR	X		X[j]	X	X	X	X	X	X	X	X
Blood for Immunology		X[o]					X	X	X	X[q]	X[q]
Urine for PCR	X		X[j]	X	X	X	X	X	X	X	X
Urine pregnancy test	X[o]	X[o,l]					X[o]	X[o]	X[o]	X[o]	X[o]
Adverse events	X	X	X	X	X	X	X	X	X	X	X

Notes:

a. BCVA, Semi-automated Kinetic Perimetry (SKP), full field German Adaptive Thresholding Estimation (GATE) static perimetry and microperimetry will be performed 3 times during screening period; once at the screening visit (Day -28) and on two occasions at baseline (Day -1).

b. A photomontage will be taken at the screening visit and Week 48 only.

c. Vital signs: blood pressure (BP, lying down), heart rate (HR) and temperature taken and recorded before SAR421869 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.

d. 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, basophils.

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

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

g. 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).

h. Coagulation: prothrombin time (PT), partial thromboplastin time (PTT) at screening and baseline only.

i. Urinalysis: Microscopic urinalysis for protein, blood, ketones.

j. Blood and where possible urine sample 60 minutes after surgery.

k. Week 48 or early termination procedures.

l. Visit window does not apply to urine pregnancy test; must be negative on Day -1.

m. Semi-automated Kinetic Perimetry conducted at screening visits Day -28 may be repeated prior to Day -1 if requested by the centralized independent assessor.

n. Semi-automated Kinetic Perimetry will be conducted twice at baseline (Day -1)

o. In subjects of <18 years only investigations may be omitted unless considered clinically indicated.

p. Infra-red fundus montage to be performed at each visit.

q. Only in patients with a positive antibody response at Week 24.

2.2 FOR COHORTS 3B, 3C, 4, 5

	Pre SAR421869									
	Days				Weeks					
	-28 (screening visit)	-1 (baseline visit)	0 Surgery	Day 1	1	2	4	12	24	48
Visit Windows	**+10 days**	**-7 days**	**N/A**	**N/A**	**±3 days**	**±3 days**	**±3 days**	**±14 days**	**±14 days**	**±14 days**
SAR421869 administration			X							
Entry Criteria	X	X ***								
Informed consent/assent	X									
Medical history	X									
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Anesthesia assessment	X	X ***								
Height	X									
Weight	X	X ***								
Vital signs [c]	X	X	X	X	X	X	X	X	X	X
ECG	X [o]	X ***								
Chest X-ray	X [o]	X ***								
Physical examination	X	X ***								X
BCVA [a]	X	X		X	X	X	X	X	X	X
Contrast sensitivity (before dilatation)	X	X						X	X	X
Slit lamp examination	X	X		X	X	X	X	X	X	X
Intraocular pressure	X	X		X	X	X	X	X	X	X
Fundoscopy	X	X		X	X	X	X	X	X	X
Autofluorescence	X						X	X	X	X
OCT [p]	X	X		X	X	X	X	X	X	X
Perimetry (SKP, GATE, microperimetry)[a]	X [m]	X [n]				X	X	X	X	X
Fundus photography [b]	X		X	X		X	X		X	X
Intraoperative video-recording (intra-operative OCT, where available)			X							
Multifocal and full Field ERG	X									X
VFQ-25/ CVAQC (when possible)*		X [o] *								X [o]
Hematology [d]	X	X [o] **		X [o]			X [o]		X [o]	X [o]
Chemistry panel [d]	X	X [o] **		X [o]			X [o]		X [o]	X [o]
Kidney function [f]	X	X [o] **					X [o]		X [o]	X [o]
Liver function [g]	X	X [o] **		X [o]			X [o]		X [o]	X [o]
Coagulation [h]	X	X [o] **								
Urinalysis [i]	X	X [o]		X [o]			X [o]		X [o]	X [o]
Blood for PCR	X		X [j]	X	X	X	X	X	X	X

	Pre SAR421869									
	Days				Weeks					
	-28 (screening visit)	-1 (baseline visit)	0 Surgery	Day 1	1	2	4	12	24	48
Visit Windows	**+10 days**	**-7 days**	**N/A**	**N/A**	**±3 days**	**±3 days**	**±3 days**	**±14 days**	**±14 days**	**±14 days**
Blood for Immunology		X [o]					X	X	X	X [q]
Urine for PCR	X		X [j]	X	X	X	X	X	X	X
Urine pregnancy test	X [o]	X [o, l]					X [o]	X[§]	X[o]	X[o]
Adverse events	X	X	X	X	X	X	X	X	X	X

Notes:

a BCVA, Semi-automated Kinetic Perimetry (SKP), full field German Adaptive Thresholding Estimation (GATE) static perimetry and microperimetry will be performed 3 times during screening period; once at the screening visit (Day -28) and on two occasions at baseline (Day -1).

b A photomontage will be taken at the screening visit and Week 48 only.

c Vital signs: blood pressure (BP, lying down), heart rate (HR) and temperature taken and recorded before SAR421869 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.

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

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

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

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

h Coagulation: prothrombin time (PT), partial thromboplastin time (PTT) at screening and baseline only.

i Urinalysis: Microscopic urinalysis for protein, blood, ketones.

j Blood and where possible urine sample 60 minutes after surgery.

k Week 48 or early termination procedures.

l Visit window does not apply to urine pregnancy test; must be negative on Day -1.

m Semi-automated Kinetic Perimetry conducted at screening visits Day -28 may be repeated prior to Day -1 if requested by the centralized independent assessor.

n Semi-automated Kinetic Perimetry will be conducted twice at baseline (Day -1).

o In subjects of <18 years only investigations may be omitted unless considered clinically indicated.

p Infra-red fundus montage to be performed at each visit.

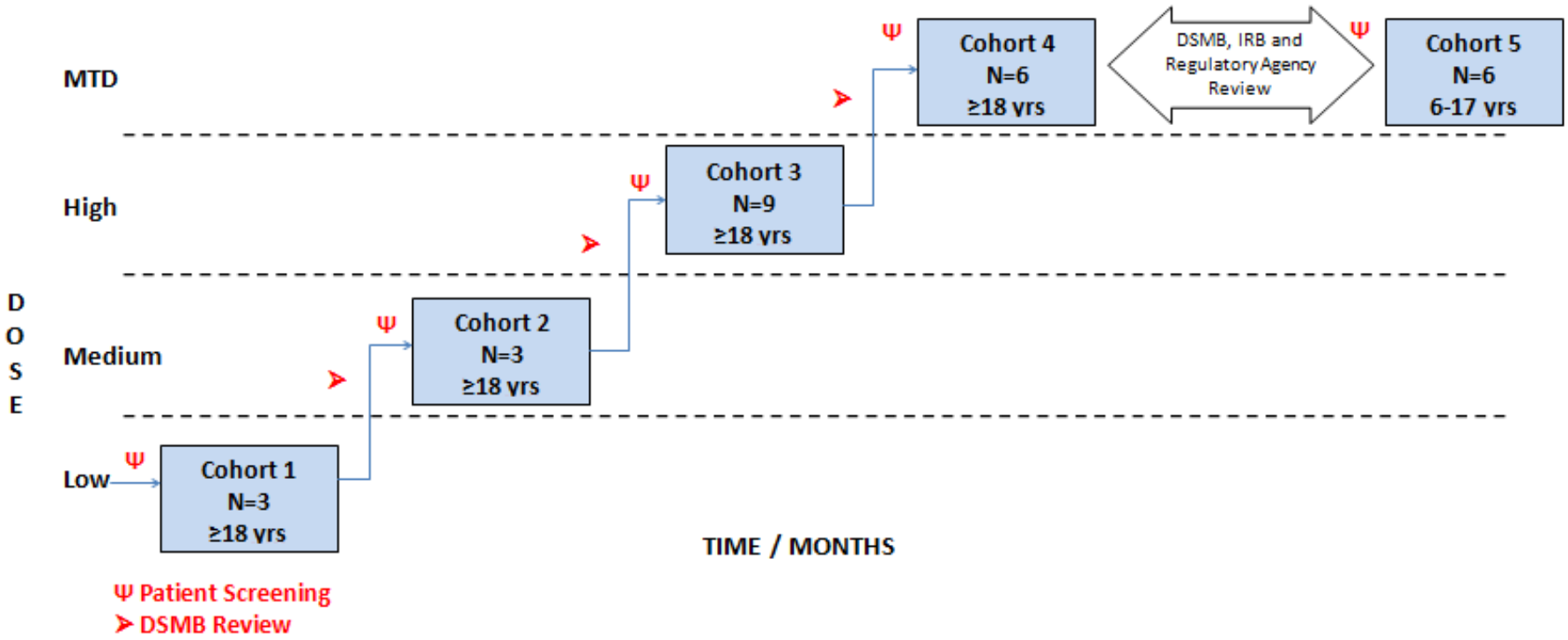
q Only in patients with a positive antibody response at Week 24

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

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

****- anesthesia assessment and physical examination will be repeated if outside 28 days or Day -1 window. Weight, ECG, chest X-ray and additional physical examination may be repeated by request of anesthesiologist atrescreening.*

3 STUDY DIAGRAM



4 INTRODUCTION AND RATIONALE

Usher syndrome is characterized by sensorineural hearing loss and retinitis pigmentosa (RP). It accounts for the majority of the deaf-blindness population and between 8-33% of individuals with RP (**1**). The disease is named after the British ophthalmologist Charles Usher, who examined the pathology and transmission of the illness in 1914 on the basis of 69 cases (**2**). The prevalence of Usher syndrome ranges from 3.6 to 6.2 per 100,000 in the US and European populations (**3**, **4**, **5**, **6**, **7**).

Usher syndrome is inherited in an autosomal recessive pattern and is classified into subtypes called Usher 1, 2 and 3 in order of decreasing severity of deafness. Usher 1 and 2 are the more common forms. People with Usher 1 syndrome are congenitally profoundly deaf and have vestibular dysfunction as well as prepubertal onset of retinitis pigmentosa leading to blindness. Babies with Usher syndrome Type 1 are usually slow to develop motor skills such as walking.

Usher syndrome Type 1B which accounts for 30-50% of Usher syndrome Type 1 (prevalence of ~1 per 100,000 people in the population [**3**, **4**, **5**]) is caused by a mutation in the gene coding for the unconventional myosin (motor) protein (MYO7A [**8**]). Myosin VIIa is expressed in the hair cells of the cochlea in the ear and the retinal pigment epithelial and photoreceptor cells of the retina, two tissues known to be affected in Usher syndrome Type 1B patients (**9**, **10**). In addition, myosin VIIa is also expressed in the olfactory epithelium, brain, choroid plexus, intestine, liver, kidney, adrenal gland, testis, and lymphocytes (**11**). In the ear, myosin VIIa plays a role in the development and maintenance of inner ear structures such as hair cells (stereocilia) which transmit sound and motion signals to the brain. Loss of normal myosin VIIa function leads to disorganized development of the hair cell structure causing congenital profound deafness and vestibular dysfunction. While the molecular basis of retinal degeneration in Usher syndrome Type 1B patients is not completely understood, loss of normal myosin VIIa function leads to photoreceptor degeneration from the outer periphery to the macula.

The earliest symptom associated with RP in Usher syndrome Type 1B patients is most commonly night blindness; this is considered a hallmark of the disease and can become apparent from the age of about 10 years. For example, patients might report difficulties with tasks at night or in dark places, such as trouble walking in dimly lit rooms, difficulties seeing in low light, at dusk, or in foggy conditions. Peripheral vision is gradually lost in the first instance leading to a restriction of the visual field (tunnel vision), which then generally progresses to complete blindness. They may also report a prolonged period of time needed to adapt from light to dark. Peripheral vision loss is often asymptomatic; however some patients notice a reduction in visual acuity and report it as tunnel vision. Although the therapeutic window for Usher syndrome Type 1B is large in terms of the retinal pathology, with sight gradually being lost from birth (diagnosis from about 10 years), the earlier the correct MYO7A gene can be delivered, the greater the potential for preventing further peripheral and central vision loss.

SAR421869 (previously named UshStat) is an EIAV-based lentiviral vector product aimed at introducing the normal MYO7A cDNA which codes for the relatively large functional myosin VIIa protein (2215 amino acids) into the photoreceptors and RPE cells, thereby restoring normal cellular function in both cell types and attenuating vision loss associated with Usher syndrome Type 1B. Due to the relatively large size of the MYO7A cDNA, it is expected that lentiviral vectors which can accommodate larger inserts (~8-9 kb) will be well suited for effective gene delivery to treat Usher syndrome Type 1B.

SAR421869 will be dosed on one occasion subretinally to patients who have been genotyped for this syndrome and in whom there is residual vision.

4.1 CLINICAL PATHOLOGY

Usher syndrome is a rare genetic disorder which is responsible for a significant proportion of deaf-blindness. Usher syndrome is inherited in an autosomal recessive pattern and is classified into subtypes called Usher syndrome Type 1, Type 2 and Type 3 (USH1, USH2 and USH3) in order of decreasing severity of deafness. USH1 and USH2 are the more common forms.

People with USH1 are usually born deaf and often have difficulties in maintaining their balance owing to problems in the vestibular system. Babies with USH1 are usually slow to develop motor skills such as walking.

By contrast, people with USH2 typically have mild to severe non-progressive hearing loss from birth and normal vestibular response (**1**). USH3 is similar to USH2, except the onset is later (**12**), hearing loss is progressive and vestibular function deteriorates (**1**). While differences in auditory and vestibular function are the main features used to distinguish between different types of Usher syndrome, retinitis pigmentosa (RP) is present in all three types (**12**).

These subtypes have been designated on the basis of the mutated gene that causes them, although they cannot be differentiated on a clinical basis (**12**). Thirty to fifty percent of USH1 patients are affected by Usher syndrome Type 1B (USH1B) (**13**). USH1B is caused by mutations in the unconventional myosin VIIa gene (MYO7A), which is one of the five genes identified among the 7 loci known in Usher syndrome Type 1 (**12**). This gene codes for the unconventional myosin (motor) protein (myosin VIIa), which is present in a variety of tissues. Myosin VIIa displays a critical function in the ear and eye, where the myosin plays a role in the development and maintenance of inner ear structures such as hair cells (stereocilia), which transmit sound and motion signals to the brain. Alterations in this gene can cause an inability to maintain balance (vestibular dysfunction) and hearing loss. Loss of normal myosin VIIa function in the eye leads to photoreceptor degeneration from the outer periphery to the macula.

In the eye, mutant myosin VIIa results in defective motility of both phagosomes and melanosomes, suggesting that myosin VIIa plays a role in the intracellular transport of these organelles. The phagosomes result from phagocytosis of the photoreceptor outer segment tips (**14**) as part of the renewal of the photoreceptor disk membranes, a critical process for the viability of photoreceptor cells (**15**).

The role of the melanosomes in the RPE cells is not fully understood, but may involve light absorption, a possible contribution to phagosome digestion, and protection against lipid peroxidation and the formation of cytotoxic oxiranes from resultant ingestion of photoreceptor outer segment phospholipids (**16**).

Over 90% of the ocular myosin VIIa protein is found in RPE cells of normal retinas. Mutations that affect the normal function of these genes can result in RP and vision loss. The therapeutic window for Usher syndrome Type 1B is potentially large in terms of the retina, with sight gradually being lost from birth (diagnosed at approximately 10 years) to beyond 40 years of age, although the earlier the delivery of the correct MYO7A gene can be performed, the greater the potential for preventing further vision loss (**4**, **12**).

4.2 DIAGNOSIS AND MONITORING OF USHER SYNDROME TYPE 1B

The earliest symptom in Usher's Retinitis Pigmentosa (RP) is most commonly night blindness and this is considered a hallmark of the disease. Patients might report difficulties with tasks at night or in dark places, such as trouble walking in dim lit rooms, difficulties seeing in low light, at dusk, or in foggy conditions. They may also report a prolonged period of time needed to adapt from light to dark. Peripheral vision loss is often asymptomatic; however, some patients notice this vision loss and report it as tunnel vision.

On examination, Snellen visual acuity can vary from 20/20 to light perception, but it is usually preserved until late in the disease. While the retina can appear unaffected in early stages of the disease, typical key findings include mid-peripheral retinal hyperpigmentation, optic nerve pallor, atrophy of the RPE in the mid periphery of the retina and retinal arteriolar attenuation.

The electroretinogram (ERG) is the most critical diagnostic test for RP because it provides an objective measure of rod and cone function across the retina and is sensitive to even mild photoreceptor impairment.

The full field ERG in RP typically shows a marked reduction of both rod and cone signals, although rod loss generally predominates. 'a' and 'b' waves are reduced since the primary site of disease is at the photoreceptors or RPE. The ERG is usually abnormal by early childhood, and is characterized by severe and selective loss of rod function occurring with varying degrees of cone abnormality.

Progressive loss of peripheral vision is a major symptom along with visual acuity changes; therefore, perimetry is the most useful measure for ongoing follow-up care of patients with RP. Goldmann (kinetic) perimetry is recommended, as it can more easily detect progressive visual field changes. Mid-peripheral scotomas develop early in RP. These visual field defects can join together to form a ring scotoma. Patients can go on to develop constricted visual fields or tunnel vision. Some patients progress to legal blindness with their peripheral vision limited to less than 20°, while their central vision remains intact (**17**, **18**, **19**). The term "legal blindness" is defined by the US federal statute as a central visual acuity of 20/200 or less in the better seeing-eye with the use of a correcting lens (**20**). An eye which also has a limitation in the fields of vision such as the widest diameter of the visual field subtends an angle no greater than 20 degrees shall also be considered as having a central visual acuity of 20/200 or less, even if the eye has an actual visual acuity of 20/20. Hence, a visual field less than 20° is also defined as legally blind.

In this 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, fundus autofluorescence (FAF) and optical coherence tomography (OCT) will visualize lipofuscin accumulation and cross-sectional retinal structure, respectively, and perimetry to assess visual fields.

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.

4.3 PHARMACOLOGICAL TREATMENT

There are currently no approved treatment options for RP associated with Usher syndrome Type 1B gene defect. Early diagnosis of the condition is seen as a key factor, since the earlier it is diagnosed, the sooner a child can begin special educational training programs to manage the loss of hearing and vision, such as orientation and mobility training, and learning sign language and Braille. In conjunction with the effects of congenital deafness and vestibular dysfunction, a patient's vision will inevitably deteriorate in time until he or she is blind. This means that RP associated with Usher syndrome Type 1B gene defect has a progressively debilitating effect on a patient's life from birth.

For RP associated with Usher syndrome Type 1B, there are no therapies that stop disease progression or restore lost visual function. Therapeutic approaches are restricted to slowing down the degenerative process by sunlight protection, treating complications (cataract and macular edema), and helping patients to cope with the social and psychological impact of blindness (**21**).

Gene Transfer

SAR421869 is a gene therapy product designed to introduce the corrective MYO7A gene to photoreceptors and supporting RPE cells, thereby attenuating the deterioration in vision caused by RP associated with Usher syndrome Type 1B. SAR421869 is a non-replicating, recombinant lentiviral vector derived from the genome of the non-primate lentivirus 'Equine Infectious Anemia Virus' (EIAV).

The EIAV vector contains only 10% (861 nucleotides) of the wild type EIAV genome. There are no functional viral proteins or viral coding regions in the recombinant EIAV vector, thus ensuring that no viral sequences are expressed in the recipient patient.

4.4 SAR421869 DRUG DEVELOPMENT

SAR421869

The SAR421869 product and [redacted] ~~is~~ are both presented as a frozen liquid formulation that must be stored at ≤-70°C.

The product is shown in Table 1.

A target strength of $4.7x10^6$ TU/mL will be produced which corresponds to undiluted material from the manufacturing process. Additional lower dosage strengths will be prepared from this material by dilution.

Table 1 - Components of the Medicinal Product

Product description	Quantity	Function	Reference to Standards
Active Substance: SAR421869	≥6.0x105 to <1.5x107 TU/mL Target strength:4.7x106 TU/mL	Active	
[redacted]	[redacted]	[redacted]	

Once SAR421869 is completely thawed, the appearance is a "turbid or clear colorless suspension free from particulates". Upon thawing of [redacted] the appearance is a clear colorless solution, having no visible particulates. More detail information is provided in the study pharmacy manual.

Mechanism of Action

The protein encoded by the SAR421869 vector is the unmutated form of human myosin VIIa. Myosin VIIa protein has been localized to connecting cilium in photoreceptors and the apical processes of the RPE. Myosin VIIa protein is always co-localized with cilia, which indicates a role in maintaining axonemal structures or function. A defect in axonemal transport of rhodopsin has been suggested as a cause of RP. Consequently, mutations that affect the MYO7A gene can result in RP and vision loss. SAR421869 is a lentiviral vector product aimed at introducing normal MYO7A cDNA which codes for the relatively large functional myosin VIIa protein (2215 amino acids) in the RPE cells and photoreceptors, thereby restoring normal cellular function in both cell types and attenuating vision loss associated with Usher syndrome Type 1B.

Lentiviral vectors are advantageous for gene therapy applications for several reasons: they deliver genes stably and permanently into the genome of transduced cells in vivo, they are capable of transducing non-dividing cells and can carry large expression cassettes (**22**).

4.5 SUMMARY OF PROOF OF PRINCIPLE NONCLINICAL STUDIES

Full details of the non-clinical studies performed with SAR421869 can be found in the Investigator Brochure.

Pharmacology Studies

Shaker1 mice provide the only currently available in vivo model of Usher syndrome Type 1B. These mice lack a functional myosin VIIa protein, are deaf and have vestibular dysfunction. Exposing shaker1 mice to similar light intensities to those experienced by a typical Usher syndrome Type 1B patient leads to photoreceptor rod degeneration over a 6- to 12-month period. Other retinal abnormalities in the shaker1 mouse include accumulation of opsin in the cilium and translocation defects in alpha transducin across the cilium. In the RPE the motility of both phagosomes and melanosomes are also defective. Pharmacology studies following subretinal administration of EIAV lentiviral vector (SAR421869) coding the normal human MYO7A gene has demonstrated:

- SAR421869 vector shows expression of myosin VIIa protein in the photoreceptors of shaker1 mice, a genetic model of Usher syndrome Type 1B.
- SAR421869 vector restored apical melanosome localization in RPE cells of shaker1 mice.
- SAR421869 vector reduced opsin levels in the connecting cilia of photoreceptors in shaker1 mice to levels seen in wild type mice.
- SAR421869 vector restored the light sensitivity of photoreceptors in shaker1 mice to mediate alpha-transducin translocation from the outer segments to the inner segments in response to light exposure.

Pharmacokinetic Studies

The investigations into the pharmacokinetic profile of SAR421869 have focused on what cell types are transduced by the vector following subretinal injection, the profile of the target therapeutic proteins and whether the product escapes from the ocular compartment, the target organ.

Since there are no MYO7A knockout models in rabbits and NHPs, EIAV-based lentiviral vectors similar to SAR421869 expressing reporter genes coding for either β-galactosidase (LacZ) or green fluorescent protein (GFP), were used to identify retinal cell types that are transduced by the vector. Following subretinal delivery of the EIAV lentiviral vector, gene delivery and expression was most evident in rod and cone photoreceptors and Retinal Pigment Epithelial (RPE) cells in mice, rabbits and three different NHP species; namely Cynomolgus macaques, baboons and Rhesus macaques.

The biodistribution of SAR421869 in the Rhesus macaque was shown to be confined to the ocular compartment following subretinal dosing. Extensive biodistribution and vector shedding studies with similar EIAV ocular products (RetinoStat® and SAR422459) in rabbits and Rhesus macaques also demonstrated that vector DNA was primarily located in the retina/choroid and sclera, and absent in all non-ocular tissue by the end of the study.

Toxicology Studies

Non-clinical GLP toxicology studies have been performed to assess acute and long-term effects of SAR421869 in the Rhesus macaque. Single subretinal injections of SAR421869 at a dose level of $9.08x10^5$ TU/eye into the right eye followed by a 3-month (92-day) observation period resulted in ocular findings of anterior chamber inflammation/anterior uveitis with concomitant transient decreases in IOP, vitreal opacities, retinal opacities, retinal edema/haze and retinal vessel congestion. No signs of toxicity were noted at the level of the retina and most changes were to be expected with the subretinal dosing procedure. All noteworthy ocular findings resolved during the 3-month observation period, with the exception of vitreous/retinal opacities and pigment changes in the retina/choroid. The results of this study are consistent with a transient and dose-related inflammation response that has been seen with other EIAV-based lentiviral vector products when dosed subretinally in the eyes of Rhesus macaques in GLP regulatory safety studies. Overall, the studies demonstrate no significant findings and provide safety data for the proposed clinical dose levels.

4.6 RATIONALE FOR STUDY

This is a Phase I/IIa, first in man, dose escalation study with a one-year follow-up duration, designed to assess whether SAR421869 is safe, well tolerated and efficacious in patients with moderate to severe RP associated with Usher syndrome Type 1B.

Evaluation of a safe and effective dose of SAR421869 in this study will enable optimum dose identification and further characterization of the safety profile in the target population in Phase II/III efficacy studies.

4.7 RATIONALE FOR SAR421869

Usher syndrome Type 1B is a severely debilitating disease resulting in significant hearing loss at birth and progressive blindness. There are no treatments currently available and none in development.

The underlying cause of the retinal pathology of Usher syndrome Type 1B is mutations in the unconventional myosin VIIa gene (MYO7A). It is believed that by replacing the mutated gene in the RPE, with the corrected gene using SAR421869, that this deficiency will be corrected, and that the treatment of RP associated with Usher syndrome Type 1B with SAR421869 will result in a substantial alteration of the pathophysiology of the disease leading to attenuation of the deterioration in vision which is associated with the syndrome.

4.8 RATIONALE FOR INJECTION INTO THE EYE

The eye is a suitable target organ for gene therapy due to the following:

- 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 SAR421869 directly into the eye provides a convenient means of delivering the normal MYO7A cDNA and so is able to restore retinal transport function resulting in a longer duration of effect, or permanent restoration of myosin VIIa protein function.
- The eye is easily accessible to safety monitoring using multiple methodologies.

4.9 RATIONALE FOR PROPOSED SUBRETINAL INJECTION SITE

In patients with RP, there exists a transition zone between normal and abnormal retina that can be defined readily on spectral domain OCT. The reduction in visual sensitivity in the transitional zone correlates well with the progressive increase in retinal degeneration, and particularly a decrease in outer nuclear layer (ONL) thickness. This zone contains normal and degenerating photoreceptors with both normal and abnormal sensitivity, and thus is a good candidate region for localized gene therapy, and to perform the retinotomy and SAR421869 bleb placement in Usher Syndrome 1B patients.

The transition zone is detectable in very early disease with the least severely affected definable region beginning at about 3 mm from the center of the fovea and extending outward, with the most severe region beyond about 8-9 mm from fixation. In more advanced stages, the first transition region begins about 2 mm or less from the fovea and the rest of the regions of transition are collapsed such that abnormally thinned outer nuclear layer (ONL) occurs by 2 to 4 mm eccentricity and the region of greatest abnormality of outer retinal layer (that of extensive retinal remodeling with profound loss or absence of photoreceptors as well as absence of sensitivity), would be reached within 5 mm or less distance from the fovea (23).

In Part A of the study patients will have a visual field in the worse seeing-eye that subtends ≤20 degrees on the retina. This visual field is equivalent to 3-6 mm from the center of the fovea and in the center of the transition zone of these patients. Subretinal injection in this region will be widely separated from the fovea, thus minimizing any risk to central visual acuity, but will also be in a region of the transition zone that may improve in function and where SAR421869 may give benefit.

In Parts B and C of the study patients will have much less restricted visual fields and the transitional zone will be wider (approximately 3-9 mm around the fovea) ensuring the risk to central visual acuity is further minimized by performing the subretinal injection even more distant from the fovea, but still maintaining the possibility to show benefit of SAR421869.

In addition, the placement of the retinotomy site and subretinal injection nasal to the optic disc will minimize the risk to foveal retinal function. The optic disc and superior and inferior nerve fiber layers extending from the disc will form an anatomical buffer between the injection site and the fovea, further minimizing the possibility of foveal extension and thus risk to central vision.

4.10 RATIONALE FOR UNILATERAL ADMINISTRATION

In this study the contralateral non-administered eye will act as the control (ie, intra patient control) as well as the untreated areas of the study eye. The more severely affected of the two eyes will be injected. This is done with the intention of minimizing risk to the less affected eye and thus reducing risk to the patient's remaining vision.

4.11 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 SAR421869 could be safely subretinally dosed to NHPs without the need for vitrectomy (which is technically difficult in these species). Therefore, a total volume of 100 µL was used to deliver SAR421869 subretinally in the NHP GLP combined toxicology/biodistribution study. Absorption and retinal re-attachment was complete by 1-2 weeks following subretinal administration in NHP and there were no observed long term morphological changes to the retinal structures examined at 12 week post dosing. The relative difference in ocular volume between NHP and human is around 3-fold, therefore a total volume of up to 300 µL will be delivered subretinally in this FIM study following a vitrectomy using standard ophthalmic surgical approaches.

The dose selection for the FIM study was based on the maximum tolerated dose (MTD) used in the NHP GLP combined toxicology/biodistribution studies. The MTD is defined as reversible inflammation that resolves to grade 1+ aqueous cell and flare scores within 2 weeks of dosing with no chronic degraded view of the fundus, sustained perivascular sheathing, or white exudates over the optic disc and fovea at 2 weeks. In addition, there should be no elevation in intraocular pressure over the observation period or general wellbeing of the animals. The MTD in the NHP was determined to be around 9.08×10^5 TU/eye. Based on the average 3-fold ocular allometric scaling of ocular volume between NHP and the human eye the expected MTD in man is 2.72×10^6 TU/eye.

The first dose in man is equivalent to 1.4×10^5 TU/eye, the second dose equivalent to 4.7×10^5 TU/eye and the highest dose planned will be undiluted SAR421869 which is equivalent to 1.4×10^6 TU/eye. All three of these dose levels are below the MTD in the NHP. Escalation to the next dose level only occurs following the review of the safety data on the preceding dose cohort by an independent safety data monitoring board, (DSMB), who advise on the progress of the SAR421869 development program.

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

Species	Approximate axial ocular diameter (cm)	Approximate orbital volume (cm3)	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 (24)	0.16 (25)	-	2	-
Rat	0.64 (26)	1.1	7	10	5
Rabbit	1.5 (27)-1.6 (28)	5 (29)- 14.1	88	100 (30)	50
Macaque	1.7 (31)	20.6	129	100 (32)–150 (33)	50-75
Human	2.4 (34)	57.9	362	1000 (35),(36)	500

4.12 RATIONALE FOR DOSING INTERVALS

A single unilateral dose of SAR421869 will be administered to each study patient who completes screening. Patients with advanced RP will be included in Cohorts 1, 2 and 3. Cohort 4 (MTD adults) and Cohort 5 (MTD including pediatric patients) will include patients with less advanced RP. In the non-clinical studies bleb resolution, vector clearance and gene expression have all occurred within two weeks post administration. Therefore, allowing 21 days between dosing individual patients (Cohorts 1-3) and 28 days between patient cohorts (Cohorts 1-4), will permit adequate time to assess short-term safety, including ocular inflammation and post-operative complications prior to dose escalation or the inclusion of adult patients with less advanced disease.

Thus, prior to dose escalation there will be up to 4 month safety data on the first patient, up to three months on the second and up to one month safety data on the third patient in the preceding cohort. These data will permit assessment of the short-term safety profile during the dose escalation part of the study. In addition, the long-term safety data (approximately 12-14 months) from patients with advanced disease dosed in the first three cohorts of the study will be available at the time of treating the final, less severely affected patient groups (Cohorts 4 and 5).

Prior to the inclusion of pediatric patients ≥6 years of age (Cohort 5), the DSMB will review all safety data, including data from Parts A and B, three months after all 6 patients in Cohort 4 have 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 review, before patients 6-17 years of age can be enrolled into Part C of the study.

4.13 RATIONALE FOR TARGET PATIENT POPULATION

The patient population in the study will all have genetically confirmed RP due to Usher syndrome Type 1B and be selected using clinical, psychophysical and electrophysiological criteria. Molecular genetic diagnosis of RP associated with Usher syndrome Type 1B will be confirmed by direct sequencing and co-segregation analysis within the patient's family caused by at least one pathogenic mutation on each of the MYO7A alleles. It is well established, that as a clinical entity Usher syndrome Type 1B may be caused by a spectrum of mutations in MYO7A. However different mutations do not have any significant influence on the clinical presentation and no statistically significant difference in visual function (**34**).

In the USA the federal definition of blindness is a reduction in central visual acuity to 20/200 or less in the better eye with the use of a correcting lens. However, an eye that has limitation of visual fields such that the widest diameter of the visual field subtends an angle no greater than 20 degrees is considered legally blind, the equivalent to a central visual acuity of 20/200 or less (**37**, **38**).

Although RP is cited as a disease that causes legal blindness, studies have shown that less than 0.5% of patients have lost all vision in both eyes (**39**). However, more recent data has shown that, of patients with Usher syndrome Type 1, 38% have a visual acuity of 20/40 in at least 1 eye and 38% a visual acuity of 20/200 or worse in both eyes (**15**). This disparity is due to RP being a disease of the peripheral retina with the reduction in vision, at least in the early stages of disease, being due to visual field restriction rather than deterioration of central visual acuity.

Grover et al. evaluated the distribution of visual field loss using kinetic perimetry and classified the Usher Type 1 patients into one of 5 distinct phenotypes on the basis of field defects (**40**).

Phenotype 1: Normal

Phenotype 2: Presence of partial or complete ring scotoma, the latter either completely or incompletely extending into the periphery

Phenotype 3: Concentric central field loss with a remaining peripheral island less than one half of the field circumference

Phenotype 4: Marked concentric loss (≤10 degrees)

Phenotype 5: No visual field – blind.

Usher syndrome Type 1B is a disease of the peripheral retina, with foveal sparing at least in the early stages of the disease. Sparing of the central vision means that visual acuity can be preserved until relatively late in the disease, with the probability of a patient being classified as legally blind due to impairment of visual acuity of 25% at 52 years, 60% at 61 years and 75% at 71 years. Furthermore, in some of these cases the reduction in central retinal sensitivity is due to local lesions, such as RPE defects or the sequellae of chronic cystoid macular edema, that are not directly related to the underlying molecular defect in the Usher disease process or by dense cataract, which is associated with Usher syndrome Type 1 in the advanced stages.

Concentric visual field loss which makes a major contribution to the reduction in retinal sensitivity and the underlying marked abnormality of retinal electrophysiology can be detected early in the disease using perimetry and ERG, respectively. Loss in peripheral visual fields thus makes a major contribution to the prevalence of legal blindness in the Usher syndrome Type 1 population. Loss of peripheral field sensitivity occurs earlier in the disease and progresses more rapidly with a probability of 25% at 42 years, 50% at 52 years and 75% at 56 years.

Generally the visual field reduction becomes substantial in the second and third decades of life. Taking the classification of Grover et al., and relating it to the temporal progression of the disease, it has been possible to distinguish three phases in the pathogenesis of Usher syndrome Type 1. In addition to increasing severity, phases 1, 2, and 3 also show a tendency for age dependence occurring between 1-20 years, 20-50 years and after 50 years of age, respectively (**41**).

Phase 1: Characterized by a pathological ERG, but no major visual field losses. Visual acuity can be normal.

Phase 2: Increased loss of peripheral vision and some visual acuity loss.

Phase 3: Major loss in visual acuity and severe visual field restriction.

The progression to legal blindness is thus significantly age-dependent and it is estimated that the prevalence of legal blindness in the Usher syndrome Type 1B population is between 12-17%. However, due to the relationship between disease progression and age, the relative contribution of peripheral visual field restriction to overall reduction in retinal sensitivity and progression to legal blindness, is greater in the early phases than that of central visual acuity loss. The outcome of this disparity is that patients can be classified as legally blind on the basis of markedly reduced peripheral vision but retain a good degree of central visual acuity.

In the current study the patient population selected in Part A (Cohorts 1-3) have a specific peripheral visual field restriction (≤20 degrees) set for the worse seeing-eye. It is expected that the patient peripheral visual field will also be severely constricted in the better eye, but the study does not require any specific criteria in the better eye. The Part A patient population may therefore not be legally blind, as defined by the US federal statute, based on the status of the better seeing-eye. They will broadly fall into field phenotypes 4-5, or phase 3 of disease progression.

Patients to be enrolled in Parts B and C (Cohorts 4 and 5) of the current study will broadly fall into Phase 2 or Phenotype 3 of the classification.

In patients with Usher syndrome Type 1B, regions of structurally and functionally normal retina are definable along-side areas of severe laminopathy and visual loss. Visual loss in Usher syndrome type 1 is predictably related to a decline in retinal outer nuclear layer thickness (ONL) caused by photoreceptor damage and loss, with a resulting gliotic response.

Full-field Static Perimetry has been extensively used to evaluate visual field loss. It is accurate and reproducible and has the advantage of detecting retinal sensitivity and thus the degree of retinal damage in any one region. Furthermore, sensitivity measured by static perimetry has been shown to correlate with morphological changes observed using SD OCT in the transitional zone in Usher syndrome Type 1 (**42**).

In this study full-field GATE Static Perimetry will be used to help identify the patient populations and during follow-up for safety monitoring as well as detection of any signs of bioactivity. GATE is a new, fast, full thresholding algorithm which is considerably faster than the 4-2-1 strategy, yet gives comparable results (**43**).

In Part A of the study, patients will be required to have severe visual field constriction (evaluated by SKP). Patients will broadly be expected to have visual field loss in the worse seeing-eye that is equivalent to ≥50% reduction from normal sensitivity volume on full-field GATE Static Perimetry.

In Parts B and C of the study patients will have less advanced disease. Due to early foveal sparing in Usher syndrome type 1B, patients will not be selected on central visual acuity (since this will be near minimally affected), but instead on the restriction in visual fields. Patients in these groups will have some visual field loss. To reflect this, the criterion of a visual field loss in the worse seeing-eye that is equivalent to ≥30% reduction from normal sensitivity volume on full-field GATE Static Perimetry has been selected.

These parameters are consistent with the clinical and morphological findings that can be expected to be observed in the advanced population selected for Part A of the study, and less severe patients to be included in Parts B and C.

4.14 RATIONALE FOR INCLUSION OF CHILDREN AND ADOLESCENTS

The opportunity for intervention is potentially large in terms of the retina in Usher syndrome Type 1B, with sight gradually being lost from birth to beyond 40 years of age. Once the neural retina has degenerated it is very unlikely that any function can be restored with current therapies. Therefore, the earlier the delivery of a normal MYO7A gene can be performed, the greater the potential for preventing further deterioration of visual function (**2**, **10**).

From 6 years of age the human eye is fully developed, thus inclusion of children from 6 years of age will allow evaluation of SAR421869 in this important population without the need to change dose, volume, method or technical difficulty of administration. Appropriate measures will be implemented to minimize any pain or discomfort associated with study procedures in children, including SAR421869 administration under general anesthesia and where necessary in-patient hospitalization for post-operative management.

In a recent study in Leber Congenital Amaurosis patients aged 8 years and older have been included. This study evaluated subretinally injected adeno-associated virus vector expressing the RPE-65 gene, the greatest benefit in terms of improvement in vision was seen in the younger patients. This therapy is now being studied in patients of 3 years and older to further evaluate the population and define the optimal time for intervention in the natural history of the disease to maximize benefit (www.clinicaltrials.gov Trial Identifiers NCT00749957 and NCT00999609). Given that Usher syndrome Type 1B is also an incurable inherited retinal degeneration disease starting from a young age, it was considered appropriate to enroll patients <18 years of age since SAR421869 may also demonstrate greater benefit in this younger population. However, the initial evaluation of the safety of SAR421869 will be in adults.

Prior to the inclusion of children/adolescents into the study, the DSMB will review all safety data, including data from Part B, three months after all 6 patients in Cohort 4 have 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 review, before children/adolescents can be enrolled.

Patient Informed Consent for Adults and Children

People with Usher 1 syndrome are congenitally profoundly deaf and have vestibular dysfunction as well as prepubertal onset of retinitis pigmentosa leading to blindness. The subject will be required to have at least one effective form of communication in order to obtain and provide informed consent or assent to participate in the study. This can be verbal, auditory, written and or tactile communication. Tactile signing is a common means of communication used by people with both a sight and hearing impairment and is based on a standard system of Deaf Manual Signs. No specific method of tactile sign language is prescribed in this protocol. The tactile sign language often used by people who first lose their hearing and later their sight is hand-over-hand signing where the receiver's hands are placed lightly upon the back of the hands of the signer to read the signs through touch and movement. The sign language used in hand-over-hand signing is often a slightly modified version of the local Sign Language. Several other versions of tactile sign language exist such as Tracking, Tactile Fingerspelling and Braille signing.

5 OBJECTIVES

5.1 PRIMARY OBJECTIVE

To evaluate the safety and tolerability of ascending doses of subretinal injections of SAR421869 in patients with Usher syndrome Type 1B.

5.2 SECONDARY OBJECTIVE

To evaluate for possible biological activity of SAR421869.

6 ENDPOINTS

All patients enrolled into this study will be followed for one year. For all endpoints with repeated measures, the primary time point will be considered the 12-month visit unless otherwise specified. BCVA and perimetry measurements are subject to broad intra-individual variability therefore the baseline value used for these measures will be an average of all the values obtained before surgery. For all other endpoints - last available measures before surgery will be considered as baseline value.

6.1 PRIMARY ENDPOINT

The incidence of adverse events over a 12-month period following a single intraocular dose of SAR421869.

Clinically important changes from baseline (Day -28) in the following safety assessments:

- Best-corrected visual acuity (BCVA).
- Slit lamp examination.
- Indirect ophthalmoscopy.
- Fundus photography.
- Intraocular pressure (IOP).
- Optical coherence tomography (OCT).
- Laboratory parameters.
- Vital signs.
- Concomitant medications.
- Physical examinations.

6.2 SECONDARY ENDPOINTS

The primary time points will be considered the 6- and 12-month visits.

To determine a delay in retinal degeneration following subretinal injection of SAR421869 through changes in function relative to the untreated contralateral eye utilizing the following retinal analytical techniques:

- Best-corrected visual acuity (BCVA).
- Contrast sensitivity.
- Indirect ophthalmoscopy.
- Visual function questionnaire VFQ-25/ CVAQC (when possible).
- Full dilated slit-lamp examination.
- Fundus photography – Panretinal photomontage.

- Visual field testing: Semi-automated Kinetic Perimetry (SKP) and Full-Field German Adaptive Thresholdings Estimation (GATE) Static Perimetry, and microperimetry.
- Autofluorescence.
- Electroretinogram (ERG).
- Optical coherence tomography (OCT).

Adverse Events

The number and severity of any adverse events associated with SAR421869 administration will be assessed at each time point.

Immunology Endpoint

Humoral antibody response to SAR421869 administration.

Clinical Laboratory Tests

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. CS out of range values will be recorded as adverse events. 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.

Biodistribution Endpoint

SAR421869 distribution in blood and urine will be assessed by polymerase chain reaction (PCR).

7 STUDY DESIGN

This is a Phase I/IIa, open-label, dose escalation study of subretinally injected SAR421869 in patients with Usher's RP. In this study at least three doses of SAR421869 will be evaluated over five patient cohorts stratified by disease severity and age. The study is separated into a dose escalation phase, Part A followed by a two part dose extension phase at the maximum tolerated dose, Parts B and C.

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 decisions regarding dose escalation, study continuance and recommended amendments to the protocol.

Part A will evaluate at least 3 ascending dose levels of SAR421869, in 300 μL of vehicle. A total of at least 15 patients (≥18 years of age) will be entered: 3 patients in Cohort 1 and 2 and at least 9 patients in Cohort 3. An interval of 21 days between dosing the first and subsequent patient will be observed in Cohorts 1-3 in order to assess safety. The DSMB will recommend whether to dose escalate following review of the data one month after all three patients have been dosed in each cohort in Part A. If DSMB requires additional patients – total up to 24 may be included in Part A.

If the safety and tolerability of SAR421869 is considered satisfactory by the DSMB in Part A and to further characterize the risk: benefit profile of SAR421869, the study will proceed to Part B, where 6 patients ≥18 years of age with less severe disease (Cohort 4) may be treated at the maximum tolerated dose determined from Part A, these patients may be enrolled in parallel.

The DSMB will review all safety data including the data from Parts A and B three months after all patients in Cohort 4 have been dosed. An interim report including all available safety data and preliminary efficacy data will be submitted to the regulatory authorities and institutional review boards/ethics committees for review, before up to 6 patients 6-17 years of age can be enrolled in Part C of the study (Cohort 5). Patients enrolled into Part C will be treated at the MTD determined from Part A of the study and further characterized in Part B of the study.

It is anticipated that up to three additional patients may need to be enrolled during the study to replace those who fail to complete the first six months of follow-up appointments.

All patients will be followed for 48 weeks. After this period they will enter an open-label safety study for long-term follow-up. Patients will attend visits at a minimum interval of one visit every six months for assessments that will include ophthalmological examinations and recording of adverse events for 240 weeks (5 years).

In addition, the investigator will conduct visits/contact the patient by telephone for a subsequent 10 years at a minimum interval of once a year to monitor delayed adverse events.

The long-term follow-up of patients in the current study will be described in a separate protocol.

In the event that a patient dies during the study then consent for a post-mortem will be sought from the patient's family. In the event of development of an infection that is classified as an important medical event, particularly any opportunistic infection or onset of an autoimmune condition, effort will be made to collect data regarding the infectious agent and the outcome of the relevant investigations to characterize the autoimmune disease.

Table 3 - Study Design and Dosing Schedule

Part A

Cohort	Age (yr)	Number of patients	Subretinal Injection		
			Vector total dose per eye		
			by target strength (TU/eye)	by measured strength (TU/eye)**	Volume
1	≥18	3	$1.4x10^5$	$2.1x10^4$	300 µL
2	≥18	3	$4.7x10^5$	$1.1x10^5$	300 µL
3a	≥18	1	$1.4x10^6$	$0.33x10^6$	300 µL
3a	≥18	2	$1.4x10^6$	$2.4x10^6$	300 µL
3b	≥18	3	-	$0.33x10^6$	300 µL
3c	≥18	3	-	$1.4x10^6$	300 µL

Part B

Cohort	Age (yr)		Subretinal Injection	
		Number of patients	Vector total dose per eye	Volume
4	≥18	Up to 6	MTD	300 µL

Part C

Cohort	Age (yr)		Subretinal Injection	
		Number of patients	Vector total dose per eye	Volume
5	6-17	Up to 6	MTD	300 µL

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

Alternative Treatment following SAR421869 Administration

The re-administration of SAR421869 has not currently been assessed in nonclinical studies.

To safeguard patients, SAR421869 will not be available to those who have previously received SAR421869 until and unless appropriate nonclinical data are available. Repeat administration will not be permitted to any patient without prior approval of relevant national regulatory authorities, ethics committees (ECs) and institutional review boards (IRBs), and even then it would be the subject of a separate formal clinical research protocol.

8 STUDY POPULATION

All patients must have a clinical and molecular diagnosis of RP caused by MYO7A mutations.

The results of the gene mutation analysis will be collected in the study database provided that written results are made available to the site, and participants (patients and/or the patient's parent[s]/legal guardian[s]) would give consent to record the results.

Twenty seven to 36 patients will complete the study. The protocol accommodates the possibility of several screen failures due to the rigorous inclusion and exclusion criteria.

Patients with differing disease severity and/or ages will be recruited, as defined by entry criteria.

8.1 PATIENT RECRUITMENT

Patients will be recruited from the hospitals' Usher syndrome Type 1B patient population following IEC/IRB and regulatory approval.

This is a multicenter study with sites in the USA and EU. The selected sites have extensive experience in ophthalmic surgery, intraocular injections and handling of gene therapy products.

8.2 ENTRY CRITERIA

Main Inclusion Criteria

For the purposes of this study 1 month is equivalent to 28 days.

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

1. Signed and dated written informed consent must be obtained from the patient (or assent in the case of minors from their legal guardian/representative), in accordance with the local regulations.
2. Clinical and molecular diagnosis of Retinitis Pigmentosa associated with Usher syndrome Type 1B, caused by at least one pathogenic MYO7A mutation on both alleles, confirmed by direct sequencing and co-segregation analysis within the patient's family.
3. Patients must have suitable verbal/auditory and/or tactile sign language communication (in the opinion of the investigator) as to allow written informed consent to be obtained.
4. Females of childbearing potential must have a negative pregnancy test at screening and at baseline, and agree to use an effective form of contraception such as the contraceptive pill or intra uterine device for at least three months following SAR421869 administration, or be surgically sterile or postmenopausal, with the last menstrual period being over two years prior to enrolment.

5. Males of reproductive potential must agree with their partner to use two forms of contraception, including one barrier method for at least three months following SAR421869 administration if their partner is of childbearing capacity, or must be surgically sterile.
6. Patients enrolled in France must be affiliated to or benefit from a social security regimen.
7. Patients must agree to not donate blood, organs, tissues or cells for at least three months following SAR421869 administration.

Part A

Specific Inclusion Criteria Cohorts 1, 2 and 3a

- ≥18 years of age.
- Concentric constriction of kinetic visual field centrally in the worse seeing-eye equating to a horizontal visual field diameter of ≤20 degrees, measured through the center of the visual field grid. The visual field constriction will be measured by Semi-automated Kinetic Perimetry (SKP) and the degrees of constriction will be confirmed by centralized independent assessment of the SKP data.
- No detectable rod-derived amplitudes on the full field electroretinogram performed to ISCEV standards.

Specific Inclusion Criteria Cohort 3 subgroups 3b and 3c

- ≥18 years of age.
- Concentric constriction of kinetic visual field centrally in the worse seeing-eye to ≤20 degrees measured through the center of the visual field grid. The visual field constriction will be measured by Semi-automated Kinetic Perimetry (SKP) and the degrees of constriction will be confirmed by centralized independent assessment of the SKP data.
- Baseline BCVA >20/200 in both eyes.
- Subfoveal Retinal Pigment Epithelium (RPE) intact and Ellipsoid zone ≥1mm in any dimension. This will be confirmed by centralized independent assessment of the OCT.
- Ability to understand, willingness to cooperate and ability to reliably perform required study procedures as judged and confirmed by the study Investigator.

Part B

Specific Inclusion Criteria Cohort 4

- ≥18 years of age.
- Concentric constriction of kinetic visual field centrally in the worse seeing-eye equating to a horizontal visual field diameter of ≤20 degrees, measured through the center of the visual field grid. The visual field constriction will be measured by Semi-automated Kinetic Perimetry (SKP) and the degrees of constriction will be confirmed by centralized independent assessment of the SKP data.

- Visual field loss in the worse seeing-eye that is equivalent to ≥30% reduction from normal sensitivity volume (decibel-steradian) on full-field GATE Static Perimetry using the size V (1.7°) test target. The percentage reduction in normal sensitivity volume will be confirmed by centralized independent assessment of the data.
- Screening BCVA >20/200.
- Subfoveal Retinal Pigment Epithelium (RPE) intact and Ellipsoid zone ≥1mm in any dimension. This will be confirmed by centralized independent assessment of the OCT.
- ability to understand, willingness to cooperate and ability to reliably perform required study procedures as judged and confirmed by the study Investigator.

Part C

Specific Inclusion Criteria Cohort 5

- 6-17 years of age.
- Concentric constriction of kinetic visual field centrally in the worse seeing-eye equating to a horizontal visual field diameter of ≤20 degrees, measured through the center of the visual field grid. The visual field constriction will be measured by Semi-automated Kinetic Perimetry (SKP) and the degrees of constriction will be confirmed by centralized independent assessment of the SKP data.
- Visual field loss in the worse seeing-eye that is equivalent to ≥30% reduction from normal sensitivity volume (decibel-steradian) on full-field GATE Static Perimetry using the size V (1.7°) test target. The percentage reduction in normal sensitivity volume will be confirmed by centralized independent assessment of the data.
- Screening BCVA >20/200.
- subfoveal Retinal Pigment Epithelium (RPE) intact and Ellipsoid zone ≥1mm in any dimension. This will be confirmed by centralized independent assessment of the OCT.
- ability to understand, reasonably well cooperate to perform required study procedures as judged and confirmed by the study Investigator.

Exclusion Criteria

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

1. Presence of significant ocular abnormalities in the study eye that in the opinion of the investigator would preclude the planned surgery, effective safety follow-up, or interfere with the interpretation of study endpoints (eg, glaucoma, corneal or significant lens opacities, pre-existing uveitis, intraocular infection, choroidal neovascularization).

2. Any pre-existing factor or past history of eye disease in children that may predispose to an increased risk of surgical complications in the study eye (eg, trauma, previous surgery, uveitis, congenital, developmental or structural abnormalities).

3. Concomitant systemic diseases including those in which the disease itself, or the treatment for the disease, can alter ocular function (eg, malignancies, diabetes, juvenile rheumatoid arthritis or sickle cell disease).

4. Any ocular surgery including laser and cataract surgery with intraocular lens implantation, aphakia or prior vitrectomy, in the study eye within 6 months of screening.

5. Any contraindication to pupil dilatation in either eye.

6. Treatment with intravitreal, subtenon, or periocular steroid within 4 months of the screening visit.

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 during the peri-operative period, particularly topical, injected or systemic corticosteroids.

8. Life-threatening illness.

9. Alcohol or other substance abuse.

10. Laboratory test abnormalities or abnormalities in electrocardiogram or chest X-ray, that in the opinion of the principal investigator, are clinically significant and would make the patient unsuitable for participation in the study

11. Intercurrent illness or infection 28 days prior to SAR421869 administration.

12. Contraindications to use of anesthesia (local or general, as appropriate).

13. Concurrent anti-retroviral therapy that would inactivate the investigational agent.

14. 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.

15. Pregnant or breastfeeding women.

16. Males or females who do not agree to use barrier contraception as specified in the inclusion criteria.

17. History of any investigational agent within 28 days prior to SAR421869 administration.

18. Participation in a prior gene transfer therapy study.

19. Enrolment in any other clinical study, for any condition, including those relating to Usher syndrome Type 1B, throughout the duration of the SAR421869 study.

20. Current or anticipated treatment with anticoagulant therapy or the use of anticoagulation therapy within the four weeks prior to surgery.

21. Long-term treatment with systemic corticosteroids within 28 days prior to the screening visit or ongoing systemic corticosteroid treatment at screening or on Day -1.

22. Current treatment with immunosuppressant therapies.

23. A history of malignancy within a five year period or have had a positive cancer screening test within a one year period of the screening visit.

24. Past medical history of HIV, or hepatitis A, B or C.

25. Inability to comply with the study protocol.

8.3 WITHDRAWAL CRITERIA

Once SAR421869 has been administered it cannot be removed, therefore patients are unable to withdraw from the study treatment. However, an individual may withdraw consent from any study related procedures at any time throughout the study and this will not affect the standard of care they receive.

Individual patients may also be withdrawn under the following circumstances:

- The patient experiences a serious or severe adverse event that prevents him/her from continuing.
- The patient incurs a significant protocol violation. Withdrawal will be judged by the Investigator and the Medical Monitor on a case by case basis.
- The patient requests early discontinuation.
- Request of the Sponsor.
- Investigator's request (eg, if the Investigator considers that the patient's health is compromised by remaining in the study or the patient 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 early from the study will be encouraged to consent to an open-label, long-term follow-up study. If the patient withdraws or 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/Independent 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.

8.4 STUDY STOPPING CRITERIA

The following are considered stopping criteria:

- Prolonged anterior chamber inflammation and/or prolonged posterior chamber inflammation continuing without signs of resolution 28 days after SAR421869 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 of early study termination all patients who have been dosed with SAR421869 will continue to be followed up as per protocol.

8.5 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.

9 TREATMENT PLAN AND METHODS

9.1 ALLOCATION OF TREATMENTS

Dose Escalation Part A

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 in the three patients of the previous cohort, 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 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.

Dose Extension (MTD) Parts B and C

The Maximum Tolerated Dose to be used in Parts B and C (Cohorts 4 and 5) of the study will be determined from the dose escalation phase (Part A). Cohort 4 will include only adult patients (≥18 years or older) with less advanced RP, while Cohort 5 will provide the opportunity to include pediatric patients 6-17 years of age. Before pediatric patients can be enrolled into the study, the DSMB will review all safety data including the data from Part B, three months after all patients in Cohort 4 have been dosed. An interim report including all available safety data and preliminary efficacy data will be submitted to the regulatory authorities and institutional review boards/ethics committees for review prior to the enrolment of pediatric patients.

9.2 STUDY MEDICATION ADMINISTRATION

9.2.1 Hospitalization

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

9.2.2 Intraocular Injection

After informed consent is completed, patients will have baseline assessments and eligibility will be confirmed. Eligible patients will be scheduled for surgery, which will be performed under anesthesia. The study eye will be the eye that in the opinion of the investigator, in consultation with the patient, is the worse seeing eye. In order to select the worse eye the investigator will review the patient historic and Day -1 visual acuity and visual field data and also consider which eye is dominant and any preferences shown by the patient. 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.

A standard 20- or 23-gauge 3 port pars plana vitrectomy will be performed. If achievable, a posterior vitreous detachment will be induced and the posterior hyaloid will be removed from the posterior retinal surface at least to include the anticipated retinotomy site.

The posterior retina will be examined and the appropriate site for subretinal injection will be identified. Additional details on retinotomy will be provided in study manuals. The final positioning of the retinotomy and subretinal bleb will be determined by the surgeon.

The retina will be approached with a needle loaded with SAR421869. A hydraulically-induced retinotomy will be created and a subretinal bleb created. 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.

At the discretion of the surgeon an air-fluid exchange may be undertaken.

Following the administration of SAR421869, the fundus will be examined by 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 will be done. The vitreous cavity may be filled with the appropriate tamponade at the discretion of the surgeon.

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.

- **Immediately following the completion of 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.
  - 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 mg 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 three times a day (TID) for 7-10 days, then two 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 9.3.12 Medication, Adverse Event and Concomitant Medication Review) 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 post-surgical anti-inflammatory regimen or worsening during the course of the regimen see Section 9.3.12 Specific Procedures - Medication, Adverse Event and Concomitant Medication Review

9.2.3 Positioning of the Subretinal Bleb

The placement of the retinotomy site and subretinal injection will be detailed in study manuals.

9.2.4 SAR421869 Preparation

SAR421869 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 SAR421869 will be issued in a white plastic tamper proof container secured in packaging. The vial and plastic tamper-evident container will be labelled appropriately.

Further details of the preparation of SAR421869 for administration are provided in the study pharmacy manual.

9.2.5 SAR421869 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.

9.2.6 Post-Surgical Monitoring

Vital signs will be documented 30 and 60 minutes after the end of surgery. After 60 minutes, if the patient is feeling well and able to tolerate food and drink, he/she will be discharged. Before discharge, blood and urine samples will be obtained for PCR assay for viral particles.

9.2.7 Concurrent Treatments

Concurrent treatments for any concurrent diseases are permitted in this protocol and will be recorded in the CRF.

9.2.8 Study Conduct Specific to Children and Adolescents

It is important to note that children and adolescents will not be enrolled in the current study unless data from adult patients treated with SAR421869 demonstrate that the risk is justified by an anticipated benefit to the patients.

The process of informed assent of children/ adolescents and the consent of their parents, guardians or other legal representatives will ensure that all parties understand the unique risks associated with gene therapy as well as the specific risks associated with ocular gene therapy. Moreover, the process will ensure that all parties understand the risks of participating in early clinical research where the safety and efficacy of a therapy may not have been fully established. The management of children and adolescents will be approached on an individual patient basis within the constraints of the protocol and the necessary procedures and monitoring to ensure safety. The patient and parents/legal guardians will be fully informed and consulted at all stages of the research and concerning all decisions regarding the management of the individual during subsequent follow-up.

Signed and dated written informed consent must be obtained from the patient (or assent in the case of minors from their legal guardian/representative), in accordance with the local regulations.

As in adults, the following procedures will be followed when including children and adolescents in the protocol:

- To ensure effective monitoring of both vector and product, biodistribution and immunology samples will be collected at the same intervals as in adult patients.
- Children and adolescents will enter the open label long-term follow-up protocol designed to monitor the long-term safety of patients treated with SAR421869.

Appropriate measures will be implemented to minimize any pain or discomfort associated with study procedures in children, including administering SAR421869 under general anesthesia if necessary, and where appropriate providing in-patient hospitalization for postoperative management.

- The administration of SAR421869 to children of less than 12 years will be under general anesthesia with neuromuscular paralysis and controlled ventilation.
- Postoperative nausea and vomiting will be managed proactively through prophylactic use of anti-emetics.

- Perioperative analgesia will be administered (eg, subtenon lidocaine block), at the time of surgery and oral post-operative analgesia will be available to minimize any discomfort.
- The surgeons and anesthesiologists will be experienced in pediatric ocular surgery and anesthesia.
- The ophthalmic monitoring procedures included in this protocol are non- invasive and as such involve minimal discomfort to the patient. Pupil dilatation is necessary for effective examination and this can result in some sensitivity to light. In general, these examinations are well tolerated and in this vulnerable group any discomfort will be kept to a minimum.
- Particularly for the younger age patients, hospitalization may be necessary for some procedures, which would normally be managed in an out-patient setting for adults. Accommodation and logistic assistance will be provided to family members/care givers to ensure they can be close to children in the event of hospitalization.
- Routine phlebotomy for safety laboratory blood samples will be kept to a minimum. All routine safety bloods will be taken at screening. However, subsequent hematology and chemistry evaluations will be as clinically indicated and at the discretion of the investigator. Blood draws will be performed by personnel adequately trained and knowledgeable in phlebotomy techniques in pediatric patients.
- Chest X-ray and ECG will not be required at screening unless considered clinically indicated by the investigator or anesthesiologist (non-compulsory investigations in children are indicated in Section 3).

9.3 SPECIFIC PROCEDURES

It is important to note that children and adolescents will not be enrolled in the current study unless data from adult patients treated with SAR421869 demonstrate that the risk is justified by an anticipated benefit to the patients.

9.3.1 Screening/Baseline Procedures

A screening log must be maintained for all patients screened for entry to the study with reasons for screen failure/not entering the study documented.

Patient screening will take place in the 28 days prior to SAR421869 administration.

During screening, height, weight, sex, reproductive status, inclusion/exclusion criteria, clinical symptoms of Usher syndrome Type 1B, medical history, treatment history, ECG, chest X-ray and anesthesia assessment (as appropriate) will be recorded.

Details of the screening procedures are detailed in the study schedule in Section 2.

9.3.2 Screening Clinical and Laboratory/Diagnostic Measurements

SKP (study part A) or full-field GATE Static Perimetry (study Parts B&C) data from Day -28 will be reviewed by a centralized independent assessor to evaluate patient study eligibility, with regards to the visual field of the worse seeing-eye. If in the assessor's opinion the Day -28 results are borderline in regards to the patients eligibility status then the test may be repeated, the retest will be conducted prior to Day -1.

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

Details of the screening procedures are detailed in the study schedule in Section 2.

Following the completion of SAR421869 administration to the first three patients in the trial (Cohort 1, dose level 1) the fourth patient (Cohort 2, dose level 2) may commence screening prior to a decision being reached by the investigator, the Sponsor and independent data monitoring committee to increase the dose of SAR421869. Similarly, screening by anticipation may be initiated for all subsequent cohorts.

9.3.3 Screening Clinical and Laboratory/Diagnostic Measurements Day -28

The following assessments are required 28 (visit window +10 days) days prior to administration of SAR421869.

- Entry criteria.
- Informed consent/assent.
- Medical history.
- Anesthesia assessment.
- Height.
- Weight.
- Vital signs.
- ECG (not unless clinically indicated in <18 years old).
- Chest X-ray (not unless clinically indicated in <18 years old).
- Physical examination.
- Ophthalmological examination:
  - BCVA (procedure to be performed up to three times in total at screening, once at this visit),
  - Contrast sensitivity,
  - Slit-lamp examination,
  - Intraocular pressure (IOP),
  - Fundoscopy,
  - Autofluorescence,
  - ERG (multifocal and full field),
  - OCT including an infra-red imaging montage,

  - Semi-automated Kinetic Perimetry (SKP) full-field German Adaptive Thresholding Estimation (GATE) Static Perimetry and Microperimetry (procedures to be performed up to three times in total during screening, at least once at this visit),
  - Fundus photography – including a photomontage.
- Clinical laboratory samples.
- Urinalysis.
- Pregnancy test (not unless clinically indicated in <18 years old).
- Blood for PCR.
- Urine for PCR.
- Adverse events.
- Concomitant medications.

9.3.4 Baseline 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 (not unless clinically indicated in <18 years old).

- Vital signs.
- Ophthalmological examination:
  - BCVA (procedure to be performed up to three times at screening, twice at this visit),
  - Contrast sensitivity,
  - Slit-lamp examination,
  - Intraocular pressure (IOP),
  - Fundoscopy,
  - OCT including an infra-red imaging montage,
  - SKP, full-field GATE static perimetry and microperimetry (procedures to be performed at least twice and up to three times during screening),
  - VFQ25 questionnaire / CVAQC (when possible).
- Clinical laboratory samples (not unless clinically indicated in <18 years old).
- Urinalysis (not unless clinically indicated in <18 years old).
- Pregnancy test (not unless clinically indicated in <18 years old).
- Blood for immunology.
- Adverse events.
- Concomitant medications.

9.3.5 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. All eligibility criteria need to be reviewed. Patient will undergo a baseline visit (if was not done) or repeat it within a 7 days 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 and physical examination will be repeated if outside of the Day -28 to Day -1 window before surgery. Weight, ECG, chest X-ray and additional physical examination may be repeated by a request of anesthesiologist.

9.3.6 Surgery

The following assessments are performed on the day of surgery:

- 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, the following assessments will be performed:
  - Surgery video-recording,
  - and/or intra-operative OCT.
- Vital signs 30 and 60 minutes after surgery
- Blood and where possible urine for PCR 60 minutes after surgery.
- Adverse events.
- Concomitant medications.

9.3.7 Follow-up Procedures

Patient follow-up visits are outlined in the study schedule in Section 2.

9.3.7.1 Follow-up Day 1 Clinical and Laboratory/Diagnostic Measurements

- Vital signs
- Ophthalmological examination:
  - BCVA,
  - Slit-lamp examination,
  - Intraocular pressure (IOP),
  - Fundoscopy,
  - OCT including an infra-red imaging montage,
  - Fundus photography.

- Clinical laboratory samples (except coagulation and kidney function ([not unless clinically indicated in <18 years old]).
- Blood for PCR.
- Urine for PCR.
- Urinalysis (not unless clinically indicated in <18 years old).
- Adverse events.
- Concomitant medications.

9.3.7.2 Follow-up Week 1, 2, 4, 12, 24 and 48 Clinical and Laboratory/Diagnostic Measurements

- Vital signs.
- Physical examination (Week 48 only).
- Ophthalmological examination:
  - BCVA,
  - Contrast sensitivity (Weeks 12, 24, 36 and 48 only),
  - Slit-lamp examination,
  - Intraocular pressure (IOP),
  - Fundoscopy,
  - Autofluorescence (Weeks 4, 12, 24 and 48 only),
  - OCT including an infra-red imaging montage,
  - SKP, full-field GATE static perimetry and Microperimetry (Weeks 2, 4, 12, 24, 36 and 48 only),
  - Fundus photography (Weeks 2, 4, 24, 36 and 48 only),
  - Fundus photomontage (Week 48 only),
  - ERG (Weeks 24 and 48 only),
  - VFQ25 questionnaire (Week 48 only) / CVAQC (when possible, 48 week only).
- Clinical Laboratory Samples (except coagulation, at Weeks 4, 24 and 48 only, not in <18 years old unless clinically indicated).
- Urinalysis (Weeks 4, 24 and 48 only), (not unless clinically indicated in <18 years old).
- Pregnancy test (Weeks 4, 12, 24, 36 and 48 only), (not unless clinically indicated in <18 years old).
- Blood for PCR.
- Urine for PCR.
- Blood for Immunology (For all the patients at Weeks 4, 12, and 24 only). 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 returns to baseline in these patients (the need for sample collection beyond Week 48 (if needed) would be collected in the long term safety study.
- Adverse events.
- Concomitant medications.

9.3.8 Samples for PCR

Blood and Urine samples for PCR are required to be taken at screening and at follow-up visits post administration of SAR421869; 60 minutes after surgery, Day 1, Weeks 1, 2, 4, 12, 24, 36 and 48.

The processing of the blood samples for PCR analysis will be performed at the designated hospital by a person designated by the PI. The samples will be labelled 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. 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.

Urine and blood samples will be analyzed using PCR to assess the presence of vector RNA and/or DNA.

9.3.9 Samples for Immunology

Samples for immunology are required to be taken at baseline (Day -1) and at the following follow-up visits post administration of SAR421869: Weeks 4, 12, and 24.

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 labelled 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. 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.

Blood samples collected for immunology will be analyzed by the Sponsor designated company using Western blot analysis or ELISA.

9.3.10 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.

Your sample(s) will be transferred to a Sanofi site (or subcontractor site). Your sample(s) 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.

9.3.11 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 be documented in the source documentation and the appropriate CRF.

Studies have shown that a number of imaging modalities provide a sensitive method of monitoring disease progression and response in retinal dystrophies.

9.3.11.1 Best-Corrected Early Treatment Diabetic Retinopathy Study (ETDRS) Visual Acuity

A BCVA examination will be performed using the EVA (electronic visual acuity) 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.

9.3.11.2 Contrast sensitivity

A contrast sensitivity assessment will be performed using the Sloan Low Contrast Letter acuity chart. 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 (**23**, **44**). The 100%, 2.5%, and 1.25% contrast level Sloan Low Contrast Acuity charts will be used for testing. For detailed instructions see Appendix D.

Contrast sensitivity is not to be measured using both eyes.

9.3.11.3 Slit-Lamp Examination

Slit-lamp examination will be performed using the investigator's standard procedure. This procedure will be the same for all subjects 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.

9.3.11.4 Fundoscopy

Dilated funduscopic examination 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.

9.3.11.5 Intraocular Pressure Measurement

Applanation tonometry will be used for IOP measurements.

9.3.11.6 Optical Coherence Tomography

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. 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. Macular thickness, subretinal fluid, and other architectural OCT features provide useful information on

the transverse and axial location of retinal lesions. Optical coherence tomography (OCT) will be performed using the Spectralis SD-OCT imaging system (Heidelberg Engineering) to evaluate the cross-sectional anatomy of the macula and document areas of retinal atrophy. The Spectralis system will also be used to collect infra-red images for the infrared imaging montage.

9.3.11.7 Fundus Photography

Fundus photography 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, auto fluorescence) to accurately map the appearance of the atrophy. A suitable fundus camera, (Zeiss FF4 series and the Topcon TRC-50EX or similar) will be used to document the retinal anatomy. At screening a seven field retinal photomontage will be taken to document the whole retina and standard photographs at subsequent visits (at the 35°setting to document the appearances of the macula and posterior pole) with specific emphasis on recording the treated area of the retina.

9.3.11.8 Electroretinogram

Full field electroretinography (ERG) measures the electrical responses of various cell types in the retina, including the photoreceptors, 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 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 dim 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. In response to 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 photoreceptors, while the remainder of the wave is produced by a mixture of cells including photoreceptor inner segments, bipolar, amacrine, and Mueller cells.

A full field electroretinogram will be conducted using the standard procedure according to the ERG Standardization 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 VERIS multifocal ERG according to the manufacturer’s protocol.

9.3.11.9 Perimetry

Semi-automated Kinetic Perimetry (SKP) and Full-field German Adapative Thresholding Estimation (GATE) 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 scotoma and the level of retinal function at specific regions. Compared to manual Goldmann kinetic perimetry, Semi-automated Kinetic Perimetry (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.

Full-field Static Perimetry assesses the sensitivity of the entire field of vision through estimation of thresholds at specific loci determined by the number of test locations and the pattern of the grid. The Swedish Interactive Thresholding Algorithm (SITA) fast strategy for static perimetry was initially optimized specifically for glaucoma, however, a new fast strategy, GATE, has been shown to be appropriate for retinal disease. Using the GATE strategy and radially-oriented, centrally condensed grids that extend from 56° 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 for computation and modelling to create a “Hill of Vision”, from which volumetric estimates of retinal function can be measured for the entire Hill of Vision or any subregion therein.

Perimetry (both Semi-automated Kinetic Perimetry (SKP) and Full-field GATE Static perimetry) will be performed using the Haag Streit Octopus 900 perimeter.

Microperimetry will also be performed on the MP1. 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.

9.3.11.10 Autofluorescence Imaging

Autofluorescence imaging of the retina will be performed 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 photoreceptor death (**38**). Images are acquired using a confocal laser ophthalmoscope system effectively gathering light from a single focal plane and eliminating AF from sources anterior to the retina (**39**).

9.3.11.11 Visual Function Questionnaire (VFQ-25)

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

The VFQ-25 assesses 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.

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 17 years. The 25-item Cardiff Visual Ability Questionnaire for Children (CVAQC) is a short, psychometrically robust and a selfreported 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 (**45**).

9.3.12 Medication, Adverse Event and Concomitant Medication Review

Review of concomitant medication and adverse events will be conducted by a physician at all visits and be recorded in the electronic CRF and reported as required.

9.3.13 Post-surgical ophthalmological adverse events

Patients who develop post-surgical complications such as ocular 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 9.2.2 Intraocular 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.

9.3.14 Clinical Laboratory Tests

Clinical laboratory safety tests will be performed in a clinical laboratory. Urine pregnancy tests may be performed at the site using a licensed test (dipstick).

The following clinical laboratory tests will be performed.

Serum Chemistry

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

Hematology	
White blood cell (WBC) count with differential	Hematocrit
Red blood cell (RBC) count	Hemoglobin
Neutrophils	Platelet count
Lymphocytes	Mean corpuscular hemoglobin concentration (MCHC)
Monocytes	
Eosinophils	Mean corpuscular volume (MCV)
Basophils	Red Cell Distribution Width (RDW)
Urinalysis	
Color	Glucose
Appearance	Ketones
Specific gravity	Blood
pH	Bilirubin
Protein	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

9.4 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 due to 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 at any time up to 37 days prior to Day -1.
- Day -1 (baseline) tests must be performed in the preceding 7 days or on the day of the scheduled visit, with the exception of the urine pregnancy test that must be negative on Day -1 (not unless clinically indicated in <18 years old).
- Day 0 tests must be performed on the day of the scheduled visit.
- 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.

10 STUDY MATERIALS

10.1 SAR421869

SAR421869 will be supplied by the Sponsor. All patients will be injected with subretinal SAR421869 under general anesthesia or waking sedation at the surgeon's discretion, with additional periocular/retrobulbar injections according to surgeon and anesthesiologist preferences.

Adequate vials of SAR421869 will be supplied per patient, depending on dose level.

For certain doses a dilution will be performed by qualified personnel of the site. [redacted] will be supplied for this purpose.

Details of SAR421869 and [redacted] and their proper handling will be provided in a pharmacy manual available at the clinical site.

All healthcare staff handling SAR421869 must wear an apron, gloves, mask and protective goggles. All materials contaminated with SAR421869 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 trial file. Healthcare staff who are pregnant, or suspect that they are, must not administer or handle SAR421869.

10.1.1 Packaging and Labelling

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

SAR421869 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 SAR421869 will be issued in a white plastic tamper evident container secured in packaging. The vial and plastic tamper-evident container will be labelled appropriately.

[redacted] will be provided in 2R Type I borosilicate glass vials with a FluroTec® bromobutyl rubber stopper and aluminum crimp seal. Each vial of [redacted] will be packaged and labelled appropriately.

Investigators and pharmacists should note that the clinical trial supplies may only be used for the clinical trial for which they are indicated. They must not be employed for any other trial, whether of SAR421869 or not, or for any other clinical or nonclinical use.

10.1.2 Storage and Disposition of Study Medications

SAR421869 and [redacted] are frozen liquid formulation, stored at ≤-70°C, in aliquots of 0.1 mL. SAR421869 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 trial 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 trial 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 trial monitor will review the drug-dispensing log and reconcile it with the unused vials/destruction log.

10.1.3 Precautions/Overdose

There is no known method of vector removal from the eye should an error occur during SAR421869 administration.

10.2 OTHER STUDY SUPPLIES

Electronic case report forms will be used in this study (see Data Collection section below). The Principal Investigator and Co-Investigators must keep all study supplies and documentation in a secure place.

11 OBLIGATIONS OF THE INVESTIGATOR REGARDING SAFETY REPORTING

11.1 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 CRF 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.

11.2 RELATIONSHIP OF AN ADVERSE EVENT TO THE STUDY DRUG/PROTOCOL PROCEDURE

The Investigators are 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).

Individual AE/SAE reports will be considered “related” to use of the investigational product if the “not related” criteria are not met.

“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).

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

11.3 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).

11.4 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 one 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, 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 subject'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.

11.5 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 11.6.2

- Acute hypersensitivity/ anaphylaxis
- Pregnancy:
  - Pregnancy of a female subject entered in a study and treated with SAR421869,

  - Pregnancy occurring in a female partner of a male subject within 3 months of male subject's treatment of with SAR421869,
  - The pregnancy will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 11.4),
  - 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% 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).
- Other 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 Log MAR (compared with baseline or the last assessment of VA at the last 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 VH, as described in Appendix A).
  - 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, blood samples for PCR and/or immunological analysis will be taken to rule out involvement of IMP.

11.6 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.

11.6.1 Instructions for reporting serious adverse events

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 when available (by fax or e-mail) to the monitoring team. 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.

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.

11.6.2 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 11.6.1, 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.

11.6.3 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by the Sponsor 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.

Table 4 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Comple-mentary Form	Other specific forms
Adverse Event (non-SAE, 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 11.4	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
		Any opportunistic infection	Yes	Yes	No

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Comple-mentary 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 AESIs	Yes	Yes	Yes

11.7 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.

11.8 WITHDRAWALS DUE TO ADVERSE EVENTS

Once SAR421869 has been administered it cannot be removed from the eye. A patient may withdraw consent from follow-up monitoring only. If an AE occurs the patient will be followed up until the AE is resolved or has stabilized. As the primary endpoint of this study is safety and tolerability the patient will continue to be monitored.

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

11.9 POST-MORTEM

To obtain vital information about the safety of gene therapy, subjects will be informed that at the time of death, no matter what the cause, permission for a post-mortem will be requested of their families. Autopsies can yield important information that may enable a better understanding of the long-term safety of gene therapy products. In addition to the standard autopsy, samples of major organs will be taken along with biopsy samples from any malignancy associated with the patient's death. PCR and/or immunological analysis will be undertaken by the laboratory designed by the sponsor to rule out involvement of the Investigational Product.

12 DATA SAFETY MONITORING BOARD

12.1 ROLE

An independent Data Safety Monitoring Board (DSMB) will be formed to undertake an ongoing review of 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.

12.2 RESPONSIBILITIES

- Monitor and review safety data of patients participating in the study and advice on study termination as appropriate.
- Recommend whether to dose escalate after the first three 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 trial.
- Provide advice on any other matters as deemed necessary for the safe conduct of the trial.

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

12.3 ANNUAL SAFETY REPORTS

The Sponsor will make provision for a harmonized International Birth date for SAR421869. This date will serve as a data lock point from which all annual safety reports will be generated. This will be the date of the first regulatory authority protocol approval.

13 DATA MANAGEMENT AND STATISTICAL ANALYSES

13.1 SAMPLE SIZE ESTIMATES

This is an exploratory study the primary objective of which is to evaluate safety and estimation of biological activity effects. No formal sample size calculation has been performed.

13.2 STATISTICAL ANALYSES

Due to the small number of patients 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.

13.3 INTERIM ANALYSIS

An interim analysis will be conducted on all available safety data and any available preliminary efficacy data up to the 3 month time point for Cohort 4 patients. The interim analysis, consisting of descriptive statistics and exploratory figures will be used to provide data to the regulatory authorities and IRB/ethics committees before pediatric patients are enrolled in Cohort 5. Formal statistical tests will not be performed as part of the interim analysis.

13.4 SAFETY ENDPOINTS

13.4.1 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 SAR421869 administration will not be summarized and will be separated from the adverse events that are recorded post SAR421869 administration in the final listings.

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.
- Specific grouping will be done for ocular events that are inflammatory in nature.

13.4.2 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 time points will be considered the 48-week (12-month) visit; the individual change at this time point only will plotted against dose received.

13.4.3 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 primary time points will be considered the 24-week (6-month) and 48-week (12-month) visit; the individual change at this time point only will plotted against dose received.

13.4.4 Immunology Endpoint

The number and percentage of patients with antibody response to SAR421869 administration at all time-points will be tabulated.

13.4.5 Laboratory Parameters

Hematology, biochemistry and other laboratory data will be listed at each time point by treatment cohort and, for appropriate values, will be flagged as ‘High’ or ‘Low’ if outside the laboratory normal range.

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.

13.4.6 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.

13.4.7 Concomitant Medication

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

13.5 BIODISTRIBUTION ENDPOINT

- The number and percentage of patients with SAR421869 detected in the blood by urine by polymerase chain reaction (PCR) at all time-points will be tabulated.

13.6 OTHER MEASURES

13.6.1 Patient Characteristics

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

13.6.2 Withdrawals

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

13.6.3 Deaths

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

13.7 INTERIM ANALYSIS STATISTICAL ANALYSES SPECIFIC TO THE DSMB MEETINGS

Below described data will serve as IA (as mentioned in Section 13.3) and will be submitted for DSMB review of Cohort 4. Similar outputs can be used for additional DSMB review, as agreed.

As 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.

13.8 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. The PI or designees will ensure that all CRFs are readable. The PI will also verify that all the data contained on these forms are accurate and will sign a form for each patient after the last study visit to document this approval.

Case report forms and copies of anonymized supporting documentation such as ECG recordings, fluorescein scans, 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 Investigator (or his designee) is requested to enter data promptly into the eCRF in order to facilitate review, monitoring, and correction of CRFs in a timely fashion.

Any subsequent alterations to the source documents must be made by striking out the previous entry with a single line and by writing the new value next to it. All such changes 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. Copies of these query resolution forms will be kept in both the Investigators' and the Sponsor's archive.

The PI will retain a copy of all eCRFs and other study related documents in a secure but accessible place.

13.9 DOUBLE-BLIND CODES

Double-blind codes are not required.

13.10 CRITERIA FOR TERMINATION OF THE TRIAL

The study may be terminated at any time at the request of the regulatory authorities, the IRB/EC or a 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.

14 ETHICAL CONSIDERATIONS

14.1 PATIENT INFORMATION LEAFLETS AND INFORMED CONSENT FORMS

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

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 trial 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 picture of the risks, inconveniences and benefits that may accrue from the trial. 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 trial or may withdraw at any time without prejudicing further medical care and is covered by the Sponsor clinical trial insurance in the event of a mishap. A contact with who 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, Regulatory Authorities and ethics committees 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 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.

14.2 ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD REVIEW

Prior approval must also be obtained by the relevant EC/IRB of the local hospital. The EC/IRB will conform to the standards of ICH E6 and/or the Code of Federal Regulations (CFR), 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. Independent ethics committee 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 three years after completion of the trial and make them available on request to representatives of regulatory authorities.

15 REGULATORY REQUIREMENTS AND SPONSOR/INVESTIGATOR OBLIGATIONS

This study will be conducted in accordance with the GCP Guidelines as issued by the International Conference on Harmonisation (ICH 135/95, 1996), the Declaration of Helsinki and the Code of Federal Regulations Title 21 (Appendix B). 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 trial supplies will not be shipped until the Sponsor receives relevant regulatory and EC/IRB written approvals.

15.1 STUDY INITIATION

It is essential that all personnel concerned with the trial 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 approval has been obtained. It is expected that all personnel involved will attend this meeting and will familiarize themselves with the protocol, the CRF and the principles of GCP which will be implemented during the trial.

15.2 MONITORING

The purposes of clinical trial monitoring are to verify that the rights and wellbeing of human patients are protected, that reported trial 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 CRF. If inconsistencies occur, these queries will be answered by the investigator. The monitors will also check patient accrual, drug dispensing logs, temperature monitoring logs and other equipment as necessary, lists of persons to whom clinical trial related activities have been delegated and relevant communications with family physicians. 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 investigators and others involved in the study must make adequate time available to be present at these visits.

15.3 DOCUMENTATION AND RECORD KEEPING

Essential records must be retained by the trial sites for at least five 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 two years have elapsed since the formal discontinuation of clinical development of the investigational product.

No records may be destroyed or moved without the Sponsor's 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 five years.

15.4 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 PIs will be asked to review and comment on the draft report and will be required to sign the final version. In a multicenter 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.

15.5 TERMINATION OF THE STUDY

The study may be terminated at any time at the request of the regulatory authorities, the Institutional Review Board/Independent Ethics Committee or a 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 an 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 and supplies, 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 his/her final visit for the study.

All patients enrolled to the current study will be encouraged to enter a long-term follow-up study performed under a separate protocol, in which they will be followed intensively for 5 years and then for a maximum of 10 years.

15.6 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 study drug-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.

15.7 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 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, 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.

15.8 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 Health Authorities and Committees, as required. 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).

16 REFERENCES

1. Smith RJH, Berlin CI, Hejtmancik JF, Keats BJB, Kimberling WJ, Lewiset RA, et al. Clinical Diagnosis of the Usher Syndromes. American J. Med. Genetics. 1994,50:32-8.

2. Usher CH. On the inheritance of Retinitis pigmentosa with notes of cases. Royal London Ophthalmol. Hosp. Rep. 1914,19:130-236.

3. Boughman JA, Vernon M, Shaver KA, et al. Usher Syndrome: Definition and Estimate of Prevalence from Two High-Risk Populations. J. Chron Dis. 1983,36(8):595-603.

4. Grøndahl J. Estimation of prognosis and prevalence of retinitis pigmentosa and Usher syndrome in Norway. Clinical Genetics. 1987,31:255-64.

5. Rosenberg T, Haim M, Hauch AM, Parving A. The prevalence of Usher syndrome and other retinal dystrophy-hearing impairment associations. Clinical Genetics. 1997,51(5):314-21.

6. Hope CI, Bundey S, Proops D, Fielder AR. Usher syndrome in the city of Birmingham-prevalence and clinical classifications. Br J Ophthalmol.1997, 81:46-53.

7. Spandau UH, Rohrschneider K. Prevalence and geographical distribution of Usher syndrome in Germany. Graefe's Arch Clin Exp Ophthalmol. 2002,240:495-8.

8. Keats B. Usher Syndrome Type I. GeneReviews. 2010.

9. Hasson T, Heintzelman MB, Santos-Sacchi J, Corey DP, Mooseker MS. Expression in cochlea and retina of mysosin VIIa, the gene product defective in Usher syndrome Type 1B. Proc. Natl. Acad. Sci. 1995, 92:9815-9.

10. Liu Q. Cell Mot Cyto. 1997,37:240-52.

11. Inoue A, Ikebe M. Characterization of the Motor Activity of Mammalian Myosin VIIA. J. Biol. Chem. 2003,278(7):5478-87.

12. Lorenze B. and Preising M. Usher syndrome. Orphanet Encyclopedia. 2004.

13. Hashimoto T, Gibbs D, Lillo C, Azarian SM, Legacki E, Zhang XM. Lentiviral gene replacement therapy of retinas in a mouse model for Usher syndrome Type 1B. Gene Therapy. 2007,14:584-94.

14. Young RW, Bok D. Participation Of The Retinal Pigment Epithelium In The Rod Outer Segment Renewal Process. J Cell Biol. 1969,42(2):392-403.

15. Bok D, Hall MO. The role of pigment epithelium in the etiology of inherited retinal dystrophy in the rat. J Cell Biol. 1971,49:664-82.

16. Schraermeyer U, Heimann K. Current understanding on the role of retinal pigment epithelium and its pigmentation. Pigment Cell Res.1999,12:219-36.

17. Grover S, Fishman GA, Anderson RJ, Tozatti MS, Heckenlively JR, Weleber RG, et al. Visual acuity impairment in patients with retinitis pigmentosa at age 45 years or older. Ophthalmology. 1999,106(9):1780-5.

18. Farrell DF. Unilateral retinitis pigmentosa and cone-rod dystrophy. Clin Ophthalmol.2009,3:263-70.

19. Saihan Z, Webster AR, Luxon L, Bitner-Glindzicz M. Update on Usher syndrome. Curr Opin Neurol. 2009,22(1):19-27.

20. Disability Evaluation Under Social Security. 2.00 Special Senses And Speech – Adult. 2. Definition of statuatory blindness. <http://www.ssa.gov/disability/professionals/bluebook/2.00-SpecialSensesandSpeech-Adult.htm>

21. Hamel C. Retinitis Pigmentosa Orphanet Encyclopedia. 2003, http://www.orpha.net /data/patho/GB/uk-RetinitisPigmentosa.pdf

22. Kong J, Kim SR, Binley K, Pata I, Doi K, Mannik J, et al. Correction of the disease phenotype in the mouse model of Stargardt's disease by lentiviral gene therapy. Gene Therapy. 2008,15(19): 1311-20.

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

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

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

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

27. Bozkir G, Bozkir M, Dogan H, Aycan K, Güler B. Measurements of axial length and radius of corneal curvature in the rabbit eye. Acta Medica Okayama.1997,51(1):9-11.

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

29. Sarnet BG. Eye and Orbital Size in the Young and Adult. Ophthalmologica. 1982, 185:74-89.

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

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

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

33. 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.

34. Oyster. The Human Eye, Raven Press. 1999

35. 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. 2005,17:845-58.

36. 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.

37. Disability Evaluation Under Social Security. 2.00 Special Senses And Speech – Adult. 2. Definition of statuatory blindness. <http://www.ssa.gov/disability/professionals/bluebook/2.00-SpecialSensesandSpeech-Adult.htm>

38. von Rückmann A, Fitzke FW, Bird AC. In Vivo Fundus Autofluorescence in Macular Dystrophies. Arch Ophthalmol. 2010,115(5):609-15.

39. Sharp PF, Manivannan A, Xu H, Forrester JV. The scanning laser ophthalmoscope--a review of its role in bioscience and medicine. Phys. Med. Biol. 2004,49:1085.

40. Grover S, Fishman GA, Anderson RJ, Alexander KR, Derlacki DJ. Rate of visual fields loss in retinitis pigmentosa. Ophthalmology. 1997, 104:460-5.

41. Sadeghi AM, Eriksson K, Kimberling WJ, Sjöström A, Möller C. Longterm visual prognosis in Usher syndrome Types 1 and 2. Acta Ophthalmol Scand. 2006, 84:537-44.

42. Jacobson SG, Aleman TS, Sumaroka A, Cideciyan AV, Roman AJ, Windsor EA et.al. Disease boundaries in the retina of patients with Usher Syndrome caused by MYO7A gene mutations. Inv Ophthalmol & Vis Sci. 2009,50(4);1886-93.

43. 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. Investigative ophthalmology & visual science. 2009,50(1):488-94.

44. 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. 25;61(10):1367-73.

45. 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.

46. Jabs DA, Nussenblatt RB, Rosenbaum JT, Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140(3):509-16.

47. Nussenblatt RB, Palestine AG, Chan CC, Roberge F. Standardisation of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmol. 1985; 92:467-71.

48. Youssef PN, Sheibani N, Albert DM. Retinal Light Toxicity. Eye. 2011,25:1-14.

49. 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.

17 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 1mm x1mm)
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) (**46**)

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) (**47**)

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.

B. 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.

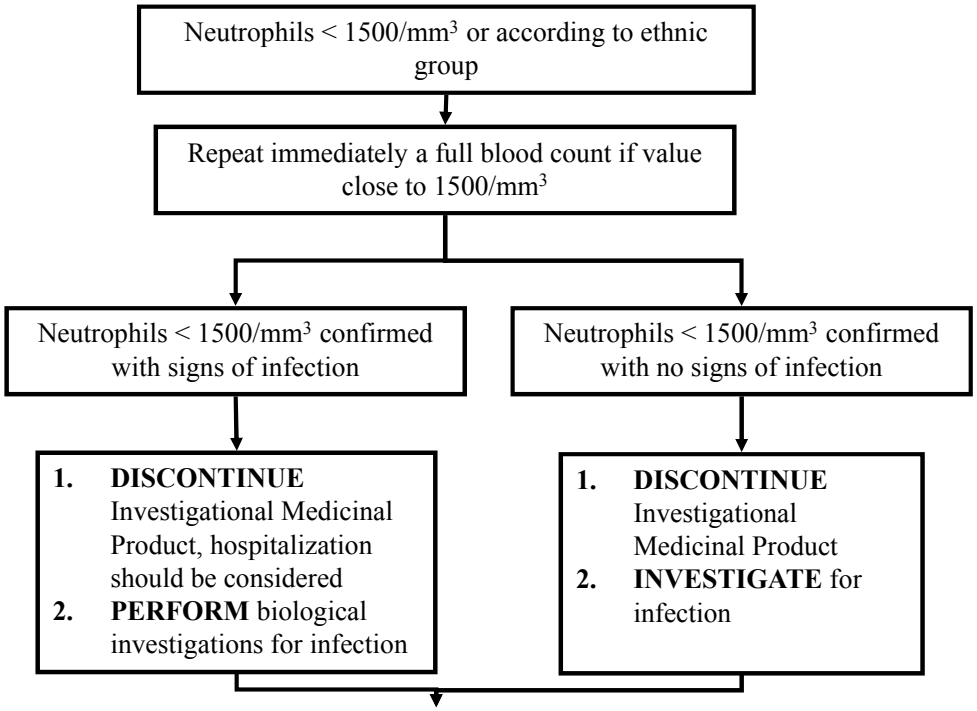
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

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

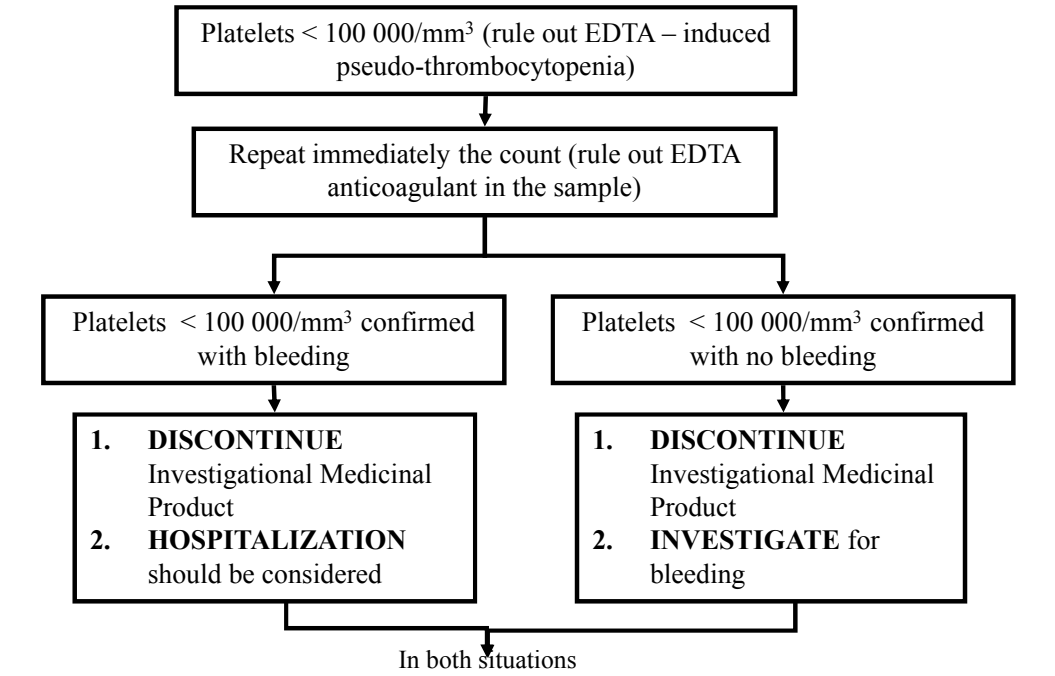
NEUTROPENIA



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

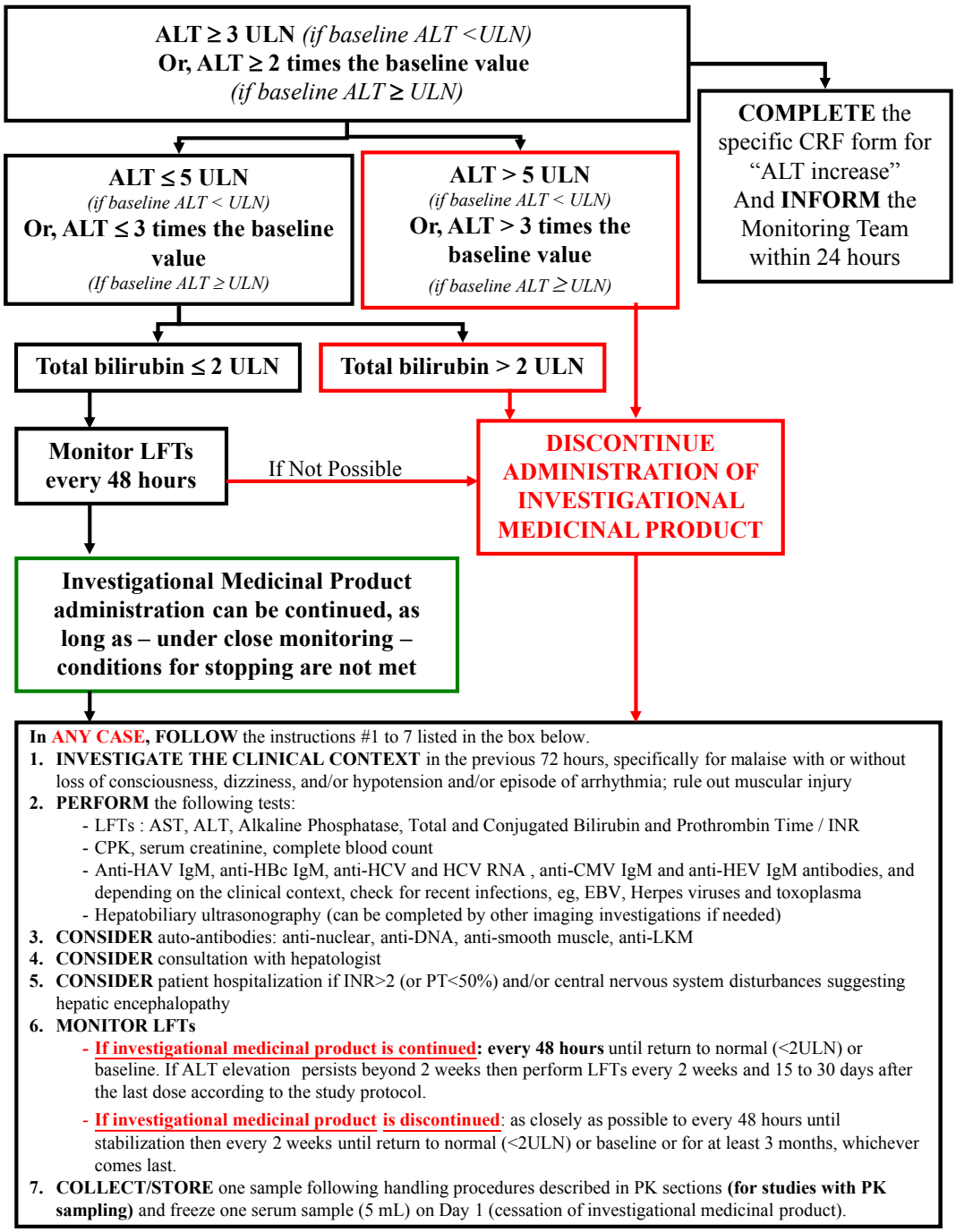
Note:
•The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
•For individuals of African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

THROMBOCYTOPENIA



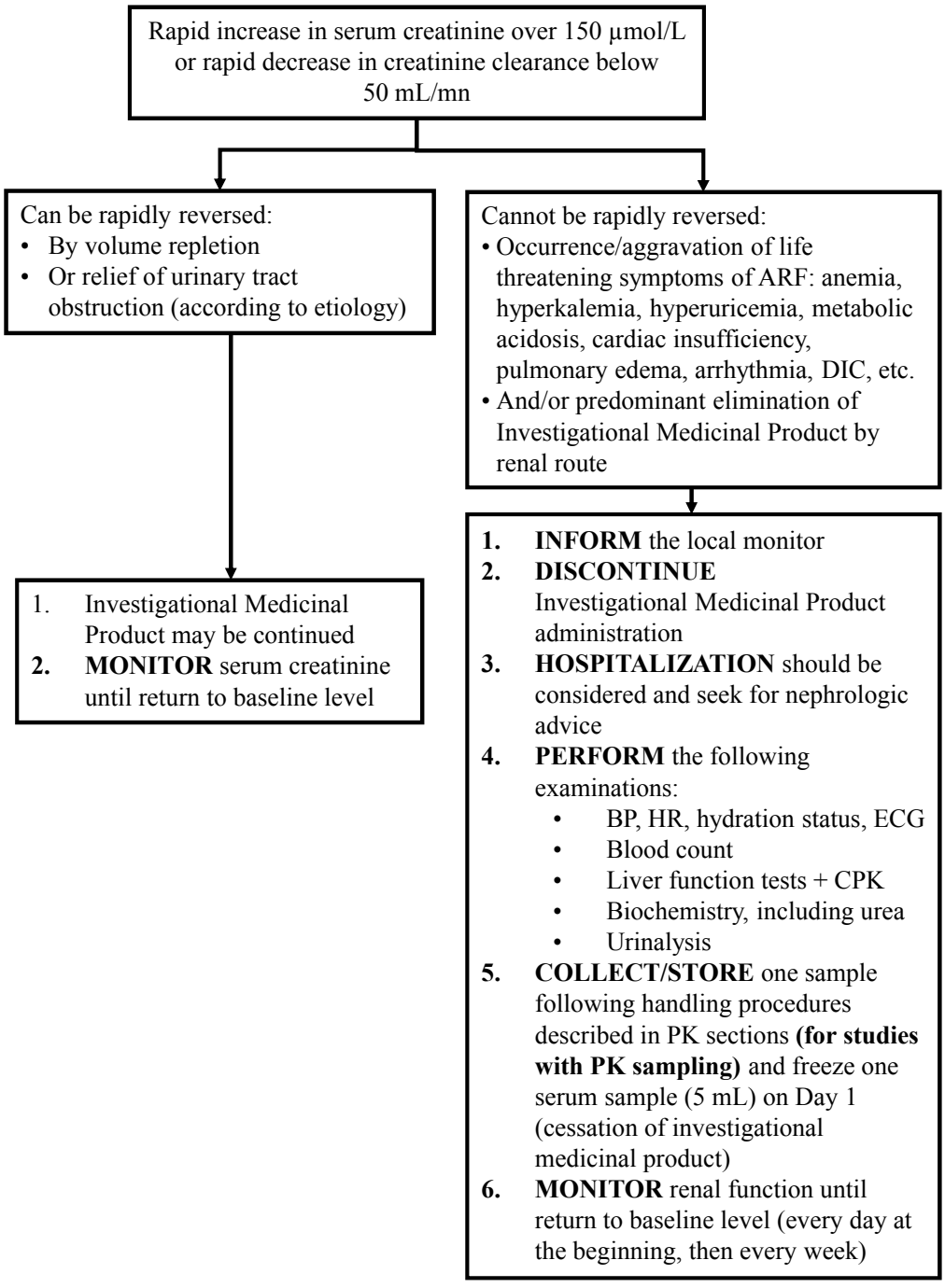
Note:
The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

INCREASE IN ALT

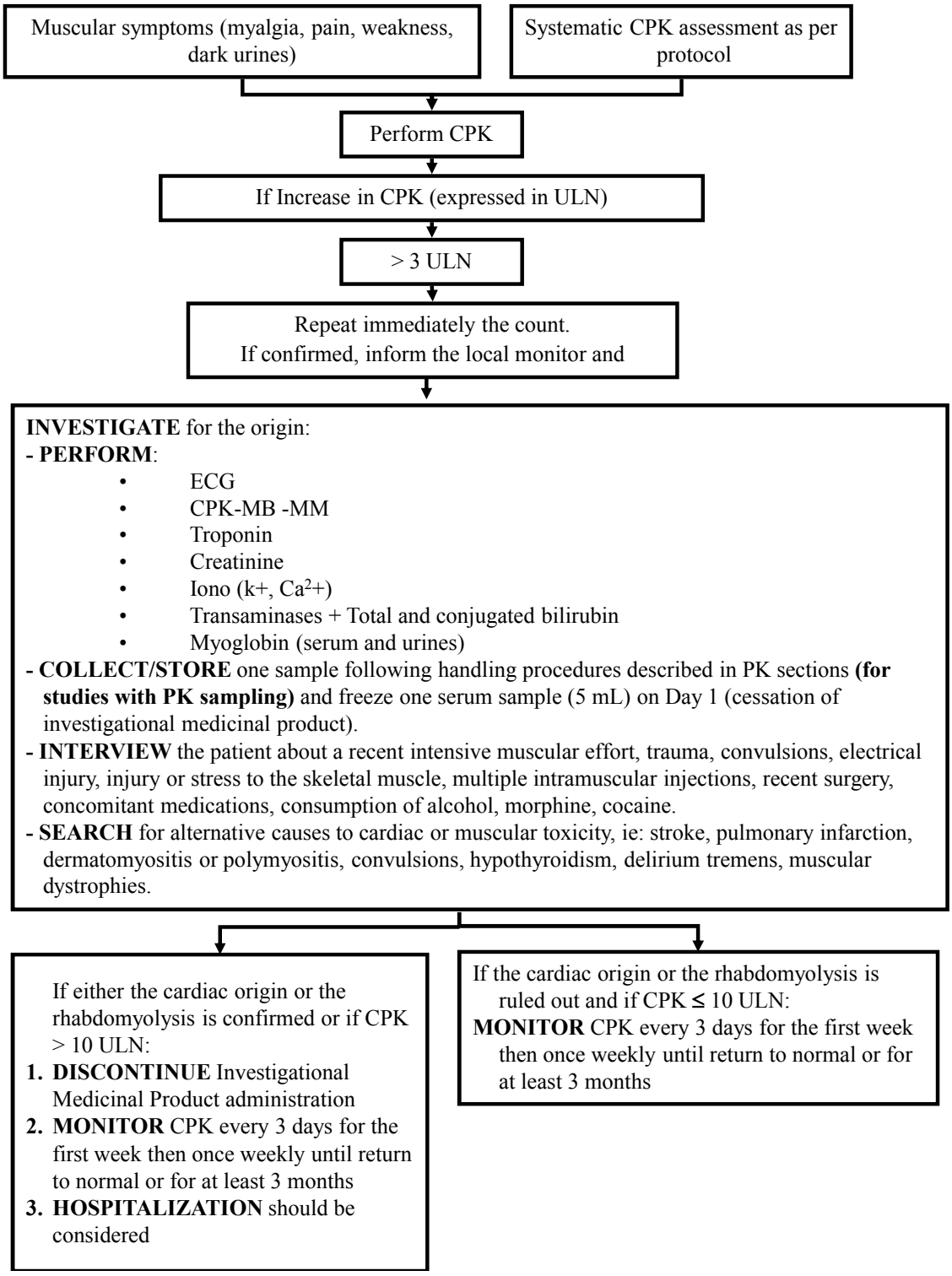


NOTE: ALT ≥ 3 ULN (IF BASELINE ALT < ULN) OR ALT ≥ 2 TIMES THE BASELINE VALUE (IF BASELINE ALT ≥ ULN) SHOULD BE NOTIFIED WITHIN 24 HOURS TO THE MONITORING TEAM. IN ADDITION, IF ALT < 3 ULN MEETS A SERIOUSNESS CRITERION, THE EVENT SHOULD BE NOTIFIED WITHIN 24 HOURS TO THE MONITORING TEAM

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). 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.
2. 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).
3. The 100%, 2.5%, and 1.25% contrast level charts will be used for testing.
4. 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.
5. 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 History of protocol amendments

Protocol Amendment 7 dated September 23, 2015

Justification for change

In Section 1 Synopsis and in Section 7.2 Entry Criteria.

The sentence "Affiliated with the French social security healthcare system (French patients only)" in the Synopsis Main Inclusion Criteria and Section 7.2 which was added as part of Protocol Amendment 2 has now been removed in Protocol Amendment 7 to ensure that there were no country specific restrictions to patient enrolment in this global, multicentre, multinational study.

Justification for change

In Section 8.2 Study Medication Administration and in Section 8.9 Specific Procedures

Based on the DSMB recommendation, a common perioperative medication regimen was developed and aligned with the study investigators and surgeons for the use of perioperative anti-inflammatory agents.

Protocol Amendment 6 dated April 22, 2015

Justification

There were errors in the versioning of protocol amendments (two versions of amendment 4: OXB Amendment 4 dated Jan. 22, 2014; Sanofi Amendment 4 dated April 14, 2014 and Sanofi Amendment 5 dated April 14, 2014 that occurred during the transfer of sponsorship from Oxford Biomedica to Sanofi (Note: Transfer of Sponsorship from Oxford Biomedica to Sanofi occurred on June 12, 2014). Therefore, protocol amendment 6 has been prepared to rectify the above versioning errors, as an administrative remediation. Additionally, the inclusion criteria applying to Cohorts 3, 4 and 5 have been revised to clarify the target populations. On March 13 2015, following evaluation of all safety data to date, the DSMB endorsed the beginning of Cohort 3, endorsed the recommendation to include patients with no detectable rod-derived amplitudes on the full field ERG and for the preparation of Amendment 6 to correct all afore mentioned versioning errors.

Justification for change

The following text has been modified to reflect the need to enroll in subsequent study cohorts patients with adequately advanced disease to minimize the risk of vision impairment while maintaining the likelihood that the remaining photoreceptors would have sufficient residual function to produce the normal MYO7A gene following transduction. While adequately addressing a potential safety concern, the requirement to enroll only patients with no detectable rod-cone derived amplitudes or evidence of severe rod-cone dysfunction on the full field electroretinogram in the study may limit the likelihood to observe early signals of biological activity, the secondary objective of the study, due to the advanced stage of disease

in the enrolled population. Following consultation with experts, the following update to the ERG inclusion criterion for the remaining cohorts to be enrolled was proposed: no detectable rod-derived amplitudes on full field electroretinogram performed to ISCEV standards. This revised criterion would characterize Usher Type 1B patients with advanced retinitis pigmentosa who would also exhibit some evidence of cone dysfunction but does not require that the cone function be so severe that the likelihood of observing a biological effect is reduced. The revised ERG criterion was discussed with the DSMB who has reviewed all available safety data to date in patients treated subretinally with this EIAV lentiviral vector (as UshStat® for Usher Syndrome Type 1B and as StarGen for Stargardt's disease) with no safety concerns. The DSMB endorsed the beginning of Cohort 3 and endorsed the recommendation to include patients with no detectable rod-derived amplitudes on the full field ERG.

Amended text

1. Synopsis - Main Inclusion Criteria - Part B&C, 7. Study Population & 7.2 Entry Criteria – Part B&C

- No detectable rod derived amplitudes on the full field electroretinogram performed to ISCEV standards.

Justification for change

Inclusion criteria added to clarify that patients enrolled in Cohorts 4 and 5 will not meet the definition of legal blindness as determined by visual field constriction.

Added Text

1. Synopsis - Main Inclusion Criteria- Part B & C, 7. Study Population & 7.2 Entry Criteria – Part B&C

- Concentric constriction of kinetic visual field centrally in the worse seeing-eye equating to a horizontal visual field diameter of >20 degrees, measured through the center of the visual field grid. The visual field constriction will be measured by Semi-automated Kinetic Perimetry (SKP) and the degrees of constriction will be confirmed by centralized independent assessment of the SKP data.

Justification for change

The following text was added to exclude breast feeding women from the study.

Added Text

1. Synopsis – Exclusion Criteria & 7.2 Entry Criteria - Exclusion Criteria

- Pregnant or breastfeeding women.

Justification for change

Criterion #23 pertaining to mentally or physically disabled patients has been deleted. Compliance with GCP precludes the need for this exclusion criterion.

Deleted Text

1. Synopsis – Exclusion Criteria & 7.2 Entry Criteria - Exclusion Criteria

- Any physical or mental disability that, in the opinion of the investigator will impair the ability of the patient to provide informed consent/assent or effective safety assessments as specified by the protocol.

Justification for change

The following text was added to include collection of the results of the MYO7A gene mutation documenting patient eligibility for the study.

Added Text

1.Synopsis – Study Population and 7. Study Population

- The results of the gene mutation analysis will be collected in the study database provided that written results are made available to the site, and participants (patients and/or the patient's parent[s]/legal guardian[s]) would give consent to record the results.

Justification for change

The inclusion criteria for study Part A and Part B/C differ in terms of severity of disease. The text was amended to clarify that the efficacy data for part A will be analyzed separately.

Amended Text

1.Synopsis - Statistical Analysis & 12.2 Statistical Analysis

- Note: In addition, analysis of the data from Part A will be provided separately.

Justification for change

Appendix C was deleted since there will be multiple local labs with the addition of new sites in the USA and EU.

Deleted Text

ToC, 1. Synopsis – Exclusion Criteria, 7.2 Entry Criteria - Exclusion Criteria, & 16 Appendices

- Appendix C – Clinical Laboratory Tests.

Justification for change

The following text was updated to revise the time-points for immunology testing and include the possibility of additional immunology blood testing in the event of a positive antibody response. In all patients, immunology blood testing will be performed at -1 day, Week 4, 12, 24 to assess a baseline and 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 returns to baseline in these patients (the need for sample collection beyond Week 48, if needed, would be collected in the long term safety study.

Added Text

2. Study Schedule

- Blood for Immunology : Day -1, Weeks 4, 12, 24, 36 and 48.

8.9 Specific Procedures

- Blood for Immunology : Weeks 4, 12, 24, 36 and 48.

Deleted Text

2. Study Schedule

- Footnote for "Weeks 48i".
- Blood for Immunology - Week 2.

8.9 Specific Procedures

- Blood for Immunology - Week 2.

Justification for change

The following text was amended to clarify the requirement to have at least one effective form of communication in order to obtain and provide informed consent or assent to participate in the study.

Amended Text

3.14. Rationale for Inclusion of Children and Adolescents – Patient Informed Consent for Adults and Children

- People with Usher 1 syndrome are congenitally profoundly deaf and have vestibular dysfunction as well as prepubertal onset of retinitis pigmentosa leading to blindness. The subject will be required to have at least one effective form of communication in order to obtain and provide informed consent or assent to participate in the study. This can be verbal, auditory, written and or tactile

communication. Tactile signing is a common means of communication used by people with both a sight and hearing impairment and is based on a standard system of Deaf Manual Signs. No specific method of tactile sign language is prescribed in this protocol. The tactile sign language often used by people who first lose their hearing and later their sight is hand-over-hand signing where the receiver's hands are placed lightly upon the back of the hands of the signer to read the signs through touch and movement. The sign language used in hand-over-hand signing is often a slightly modified version of the local Sign Language. Several other versions of tactile sign language exist such as Tracking, Tactile Fingerspelling and Braille signing.

Deleted Text in Section 3.14 Rationale for Inclusion of Children and Adolescents– Patient Informed Consent for Adults and Children

- Given that Usher syndrome Type 1B patients are also usually hearing-impaired, it will be a prerequisite that all patients have at least one form of effective communication to enable informed consent. Communication can be verbal, auditory or with the use of tactile sign language. Effective communication will be essential for the consent process and for patient enrolment in the study, since effective measurement of the ophthalmological evaluations requires both patient understanding of the procedure and their active participation. Effective communication is essential to ensure the ophthalmic investigations are conducted to the highest standard to detect signals of safety and benefit.

Justification for change:

Given the progression of RP in these patients we expect that it may be necessary to follow up these patients for more than 1 year to assess efficacy and currently, there are no approved therapies in RP. Also, the statement would likely conflict with exclusion criteria #19.

Deleted Text

6. Study Design

- If UshStat® demonstrates no clinical efficacy in any of the patients after one year following administration then the patients may be offered alternative therapies.

Justification for change

The following text has been updated to include additional European sites.

Amended Text

7.1 Patient Recruitment

- This is a multicenter study with sites in the USA and EU.

Justification for change

The following text has been modified to clarify the process for obtaining the informed consent (ICF).

Amended Text

8.8 Study Conduct Specific to Children and Adolescents

- Signed and dated written informed consent must be obtained from the patient (or assent in the case of minors from their legal guardian/representative), in accordance with the local regulations.

Justification for change

Text amended to clarify study personnel performing blood draws in pediatric patients are adequately trained.

Amended text:

8.8 STUDY CONDUCT SPECIFIC TO CHILDREN AND ADOLESCENTS

- Blood draws will be performed by personnel adequately trained and knowledgeable in phlebotomy techniques in pediatric patients.

Justification for change

The following statement was added to clarify that the sample(s) collected may be used for other research purposes and will be stored for up to 15 years.

Added Text:

8.9 Specific Procedures

- 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.

Your sample(s) will be transferred to a Sanofi site (or subcontractor site). Your sample(s) 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.

Justification for change

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.

Added Text

8.9 Specific Procedures

- Where available, the following assessments will be performed:
  - Surgery video-recording,
  - And/or intra-operative OCT.

Justification for change

Statement added to clarify content of the labeling in accordance with local requirements.

Amended Text

9.1.1 Packaging and Labelling

- Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

Other Administrative Updates

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

Protocol Amendment 5 dated April 14, 2014

Note: Amendment 5 was never submitted to the health authorities during the sponsorship transfer however, the amendment was submitted and approved by the local IRBs/ECs in the USA and France. The following text below captures all of the administrative and content changes pertaining to Sanofi amendment 4 dated April 14, 2014 that were incorporated into the 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 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 in appendices. Criteria for Potentially Clinically Significant Abnormalities for Studies in Children have been added in appendices.

Other Administrative Updates

The protocol has also been reviewed and updated to correct grammatical and administrative errors and harmonize formatting and spelling to US English.

New Sponsor reference numbers have been added.

The names of the PIs in 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 15.7) has been updated, in order to harmonize the text across all the protocols initially generated by Oxford BioMedica Ltd.

Appendix C (Clinical laboratory tests) has been updated to be consistent with the UshStat® US1/002/13 – LTS13619 study.

Protocol Amendment 4 dated January 22, 2014

Justification for Amendment 4 changes

The protocol has been amended in response to recommendations from the Agence Nationale de Sécurité du Médicament (ANSM) and Comités de Protection des Personnes (CPP).

Justification for change

The following text has been updated as patients in France will be asked to consent to a post-mortem as part of the study informed consent process.

Amended text

2.5 & 7 Study Design

In the event that a patient dies during the study then consent for post-mortem will be sought from the patient's family, unless the patient has already documented their decision with regards to a post-mortem. The consent of the family is intended to correspond to the patient's wishes with regards to a post-mortem.

11.8 Post-mortem

To obtain vital information about the safety of gene therapy, patients will be informed that at the time of death, no matter what the cause, permission for a post-mortem will be requested of their families, unless the patient has already documented their wishes with regards to a post-mortem.

Justification for change

The following text has been amended to clarify that consent and assent will be obtained in accordance with country specific regulations.

Amended text

2.7.1 & 8.2.1 Main inclusion criteria

1. Signed and dated written informed consent must be obtained from the patient (or in the case of minors from their legal guardian/representative), in accordance with the country specific regulations.

9.8 Study Conduct Specific to Children and Adolescents

Children and adolescents will be asked to assent to the study in accordance with country specific regulations and ICH GCP guidelines.

Justification for change

The following text has been amended to clarify that written communication is a suitable form of communication for the study.

Amended text

2.7.1 & 8.2.1 Main inclusion criteria

Patients must have suitable verbal, auditory, written and/or tactile sign language communication skills (in the opinion of the investigator) as to allow written informed consent to be obtained.

4.15 Patient informed consent

Communication can be verbal, auditory, written or with the use of tactile sign language.

Justification for change

The following text has been updated to include both rod and cone dysfunction in the inclusion criteria

Amended Text

2.7.1. Main Inclusion Criteria, 8. Study Population & 8.2.1 Inclusion Criteria

- No detectable rod-cone derived amplitudes on the full field electroretinogram performed to ISCEV standards.

Justification for change

The following text was added to exclude breast feeding women from the study.

Additional Text

2.7.2 & 8.2.2 Exclusion Criteria

15. Pregnant or breastfeeding women.

Justification for change

The following text has been amended to clarify the exclusion criteria relating to alcohol and substance abuse.

Amended Text

2.7.2 & 8.2.2 Exclusion Criteria

9. A history or state of dependence or addiction to alcohol or drugs.

Justification for change

Criterion #23 has been deleted as it was felt that it could be classed as discriminatory to mentally or physically disabled patients. Compliance with GCP and exclusion criterion 24 preclude the need for this exclusion criterion.

Deleted Text

2.7.2 & 8.2.2 Main exclusion criteria

Any physical or mental disability that, in the opinion of the investigator will impair the ability of the patient to provide informed consent/assent or effective safety assessments as specified by the protocol.

Justification for change

The inclusion criteria for study Part A and Part B/C differ in terms of severity of disease. The text was amended to clarify that the efficacy data for part A will be analysed separately.

Amended Text

2.8 & 13.2 Statistical Analysis

It is envisaged that analyses will be performed on all available data and in addition analysis of Part A data will be provided separately.

Justification for change

The following text was added to clarify the study definition of tactile communication.

Additional Text

4.13. Rationale for Target Patient Population

People with Usher 1 syndrome are congenitally profoundly deaf and have vestibular dysfunction as well as prepubertal onset of retinitis pigmentosa leading to blindness. The subject will be required to have at least one effective form of communication in order to provide informed consent and participate in the study. This can be verbal, auditory, written and or tactile communication. Tactile signing is a common means of communication used by people with both a sight and hearing impairment and is based on a standard system of Deaf Manual Signs. No specific method of tactile sign language is prescribed in this protocol. The tactile sign language often used by people who first lose their hearing and later their sight is hand-over-hand signing where the receiver's hands are placed lightly upon the back of the hands of the signer to read the signs through touch and movement. The sign language used in hand-over-hand signing is often a slightly modified version of the local Sign Language. Several other versions of tactile sign language exist such as Tracking, Tactile Fingerspelling and Braille signing.

Justification for change

The following text was amended to ensure that the blood volume drawn from paediatric patients is appropriate for their body weight.

Amended Text

9.8 Study Conduct Specific to Children and Adolescents

Blood draws will be performed by a dedicated paediatric phlebotomy service, in order to ensure that the volume of blood drawn from paediatric patients is appropriate for their body weight.

Justification for change

The following text was deleted as study specific exceptions to Annex 13 have been granted by ANSM. Detailed information on packaging and labelling is not required in a clinical protocol.

Deleted Text

10.1.1 Packaging and Labelling

Packaging and labelling 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.

Other Administrative Updates:

The Protocol has also been reviewed to update study personnel details and correct grammatical and administrative errors.

Protocol Amendment 3 dated January 31, 2013

Justification for change

To ensure consistency across sites a centralised independent assessor will evaluate patients -28 day visual field data to confirm eligibility (the method of assessing visual field eligibility, Semi-automated Kinetic Perimetry (SKP) for Part A of the study, and full-field GATE static perimetry for Parts B and C, has not been altered). If the patient's visual field restriction at Day -28 is ambiguous then the assessor may request a repeat of the same test prior to Day -1. The independent reviewer's assessment of the results from the retest will determine the patient's eligibility for inclusion in the study. The requirement for the retest to be conducted prior to Day -1 is to allow early confirmation of patient's eligibility and prevent ineligible patients from undergoing further unnecessary study procedures.

References to the patients legal blindness as defined by the US federal statute have been removed from the eligibility criteria, as for a patient to be classed as legally blind in the USA on visual field criteria they must have a maximum visual field of ≤20 degree in the better eye. For this protocol the visual field criteria is set for the worse seeing-eye only.

Amended or Additional Text

2.7.1 & 8.2.1 Entry Criteria

Concentric constriction of kinetic visual field centrally in the worse seeing-eye equating to a horizontal visual field diameter of ≤20 degrees, measured through the center of the visual field grid. The visual field constriction will be measured by Semi-automated Kinetic Perimetry (SKP) and the degrees of constriction will be confirmed by centralized independent assessment of the SKP data.

Visual field loss in the worse seeing-eye that is equivalent to ≥30% reduction from normal sensitivity volume (decibel-steradian) on full-field GATE Static Perimetry using the size V (1.7°) test target. The percentage reduction in normal sensitivity volume will be confirmed by centralized independent assessment of the data.

3. Study schedule

m BCVA, full field static perimetry and microperimetry will be performed 3 times during screening period; once at the screening visit (Day -28) and on two occasions at baseline (Day -1).

k. Semi-automated Kinetic Perimetry conducted at screening visits Day -28 may be repeated prior to Day -1 if requested by the centralized independent assessor.

l. Semi-automated Kinetic Perimetry will be conducted twice at baseline (Day -1).

4.9 Rationale for Proposed Subretinal Injection Site

In Part A of the study patients will have a visual field in the worse seeing-eye that subtends ≤20 degrees on the retina.

4.13 Rationale for Target Patient Population

In the current study the patient population selected in Part A (Cohorts 1-3) has a specific peripheral visual field restriction (≤20 degrees) set for the worse seeing-eye. It is expected that the patient's peripheral visual field will also be severely constricted in the best seeing-eye, but the study does not require any specific criteria in the better eye. The Part A patient population may therefore not be legally blind, as defined by the US federal statute. They will broadly fall into field phenotypes 4-5, or phase 3 of disease progression.

8. STUDY POPULATION

Concentric constriction of kinetic visual field centrally in the worse seeing-eye to ≤20 degrees.

9.9.2 Screening Clinical and Laboratory/Diagnostic Measurements

SKP (study Part A) or full-field GATE Static Perimetry (study Parts B and C) data from Day -28 will be reviewed by a centralized independent assessor to evaluate patient study eligibility, with regards to the visual field of the worse seeing-eye. If in the assessor's opinion the Day -28 results are borderline in regards to the patient's eligibility status then the test may be repeated, the retest will be conducted prior to Day -1.

9.9.3 Screening Clinical and Laboratory/Diagnostic Measurements Day -28

Microperimetry and Static Perimetry (procedure to be performed up to three times in total at screening, once at this visit)

Semi-automated Kinetic Perimetry (to be conducted once at this visit, may be repeated prior to Day -1 if requested by independent assessor)

Justification for change

The following section was deleted as it was not factually correct, BCVA measurements do no impact patient eligibility in this study. In addition amendment 3 changes the perimetry reading used to assess eligibility to be those conducted prior to Day -1.

Deleted Text

9.9.2 Screening Clinical and Laboratory/Diagnostic Measurements

BCVA and perimetry will be performed on three 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.

Justification for change

This section was amended to clarify the perimetry evaluations utilized in the target patient population.

Amended or Additional Text

4.13 Rationale for Target Patient Population

In this study full-field GATE Static Perimetry will be used to identify the patient populations and during follow-up for safety monitoring as well as detection of any signs of bioactivity. GATE is a new, fast, full thresholding algorithm which is considerably faster than the 4-2-1 strategy, yet gives comparable results[44].

In Part A of the study, patients will be required to have severe visual field constriction (evaluated by SKP). Patients will broadly be expected to have visual field loss in the worse seeing-eye that is equivalent to ≥50% reduction from normal sensitivity volume on full-field GATE Static Perimetry.

Justification for change

The following paragraph was added to clarify which of the screening BCVA and perimetry exam results will be used to calculate the baseline value.

Additional Text

2 Synopsis & 6 Endpoints

BCVA and perimetry measurements are subject to broad intra-individual variability. The baseline value used for statistical analysis of these measures will be an average of all values obtained during the screening period.

Justification for change

To ensure consistency across sites when identifying the treatment eye, details of the parameters that will be used to identify the “worse seeing-eye” have been added.

Amended or Additional Text

9.2.2 Intraocular Injection

The study eye will be the eye that in the opinion of the investigator, in consultation with the patient, is the worse seing eye. In order to select the worse eye the investigator will review the patient historic and Day -28 visual acuity and visual field data and also consider which eye is dominant and any preferences shown by the patient.

Justification for change

This section has been amended to clarify the visit window for each study visit.

Amended or Additional Text

9.9.14 Flexibility of Assessment Data Capture

- Screening/baseline (Day -28) tests may be performed at any time up to 37 days prior to Day -1.
- Day -1 tests must be performed in the preceding 7 days or on the day of the scheduled visit, with the exception of the urine pregnancy test that must be negative on Day -1 (not unless clinically indicated in <18 years old).
- Day 0 tests must be performed on the day of the scheduled visit.

Justification for change

The DSMB recommended the addition of the following section.

Additional Text

11.6 Adverse Events of Special Interest

AEs of special interest include the following:

- Recurrent malignancy.
- New malignancy.
- Infection, particularly any opportunistic infection.
- Immunological reactions (eg, new incidence or exacerbation of rheumatologic or other autoimmune disorder).
- New incidence or exacerbation of a neurological disorder.
- New incidence or exacerbation/recurrence of haematological disorder (eg, aenemia).
- Other adverse events (eg, inflammation, ischemia, cardiovascular event.

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.

Justification for change

The AE severity terms were updated to replace references to the impact of AEs on study participation, with references to the impact of AEs on patient general wellbeing. It was felt that this better reflected the actual severity of the AEs.

Amended Text

11.3 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

Justification for change

The following section was amended to clarify the safety follow-up that will be undertaken if a patient dies or suffers an opportunistic infection which participating in the study.

Additional Text

2.5 Synopsis & 7 Study design

In the event that a patient dies during the study then consent for post-mortem will be sought from the patient's family. In the event of development of an infection that is classified as an important medical event, particularly any opportunistic infection or onset of an autoimmune condition, effort will be made to collect data regarding the infectious agent and the outcome of the relevant investigations to characterize the autoimmune disease.

Justification for change

The following text was amended to clarify that as part of the long-term safety follow-up study, patients will only be contacted by telephone if they are unable to attend study visits.

Amended Text

2 Synopsis & 7 Study Design

In addition, the investigator will conduct visits/contact the patient by telephone for a subsequent 10 years at a minimum interval of once a year to monitor delayed adverse events.

Justification for change

The male and female normal lab ranges had been documented incorrectly.

Amended Text

APPENDIX C

Haematocrit Adult	F - <30 or >55 M - <35 or >60	F- 36 - 46 M- 41- 53	%

Justification for change

Addition of information on post-mortem requirements for the study.

Additional Text

11.8 Post-mortem

To obtain vital information about the safety of gene therapy, subjects will be informed that at the time of death, no matter what the cause, permission for a post-mortem will be requested of their families. Autopsies can yield important information that may enable a better understanding of the long-term safety of gene therapy products. In addition to the standard autopsy, samples of major organs will be taken along with biopsy samples from any malignancy associated with the patient's death. PCR and/or Immunological analysis will be undertaken by OXB to rule out involvement of the Investigational Product.

Other Administrative Updates

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

Protocol Amendment 2 dated August 31, 2012

Justification for changes

Due to the addition of a study site in France a requirement for French patients to be affiliated with the French social security system has been added to the inclusion criteria. References to the "Food and Drug administration (FDA)" have been changed to "regulatory authority" throughout the protocol in order to be inclusive of the French regulatory authority.

The study specific EudraCT number has also been added.

Amended or Additional Text

Title Page

EudraCT number: 2012-002574-31

Section 2.7.1 Synopsis Main Inclusion Criteria

6. Affiliated with the French social security healthcare system (French patients only).

Section 8.1 Patient Recruitment

This study is multicentre with sites in the U.S.A, and France. The selected sites have extensive experience in ophthalmic surgery, intraocular injections and handling of gene therapy products.

Section 8.2.1 Main Inclusion Criteria

6. Affiliated with the French social security healthcare system (French patients only)

Justification for changes

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

Amended or Additional Text

Section 11.6. Reporting a Serious Adverse Event

OXB'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.

Justification for changes

The following paragraph has been amended to clarify that routine safety bloods in children and adolescents will only be done if clinically indicated and at the discretion of the investigator.

Amended or Additional Text

Section 9.8 Study conduct specific to children and adolescents

Routine phlebotomy for safety laboratory blood samples will be kept to a minimum. All routine safety bloods will be taken at screening. However, subsequent hematology and chemistry evaluations will be as clinically indicated and at the discretion of the investigator.

Other Administrative Updates

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

Protocol Amendment 1 dated October 20, 2011

Justification for changes

The study design and dosing intervals have been amended in response to review by the Food and Drug Administration (FDA). Part B of the study will consist of patients' ≥18years old (Cohort 4) with less severe disease, that will be treated at the maximum tolerated dose from Part A. The DSMB will review all data from Parts A and B and 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 for review before up to 6 patients ≥6 years or older will be included in Part C of the study (Cohort 5).

The Principal Investigator has 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 (**48**). 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 (**49**). An additional fundus montage will also be included at Week 48.

Since full field and multifocal Electroretinogram (ERG) assessment forms part of the inclusion criteria to determine patient eligibility during the 28-day screening period, the ERG time point has been moved from baseline (Day -1) to the screening visit (Day -28).

Macular edema was included in the exclusion criteria in error. It is not a contraindication to surgery, is often observed on spectral domain OCT in a number of patients with Usher types 1B, and an improvement following treatment would be considered a benefit.

The results of microperimetry will be transitorily affected by retinal elevation in the region of the bleb during the early post-operative period, therefore it is not a good primary safety assessment during this phase. Once the transient effect of the elevated bleb is resolved the microperimetry testing could be considered a secondary biological endpoint.

Amended or Additional Text

The protocol has been updated throughout to include the changes to the patient population for Part B and the addition of Part C.

Section 4.12 Rationale for dosing Intervals

Prior to the inclusion of paediatric patients ≥6 years of age (Cohort 5), the DSMB will review all safety data, including data from Parts A and B, three months after all 3 patients in Cohort 4 have 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 review, before patients ≥6 years of age or older can be enrolled into Part C of the study.

Section 4.13 Rationale for Target Patient Population

Patients to be enrolled in Parts B and C (Cohorts 4 and 5) of the current study will broadly fall into phase 2 or phenotype 3 of the classification.

Sections 6.2 and 2.4 Secondary Endpoints Visual field testing: (Semi-automated Kinetic (SKP) and Full-Field GATE Static Perimetry), and microperimetry.

Section 7.0 and 2.5 Study Design

The DSMB will recommend whether to dose escalate following review of the data one month after all three patients have been dosed in each cohort in Part A.

If the safety and tolerability of UshStat® is considered satisfactory by the DSMB in Part A and to further characterize the risk: benefit profile of UshStat®, the study will proceed to Part B, where 3 patients ≥18 years of age with less severe disease, (Cohort 4) may be treated at the maximum tolerated dose determined from Part A, these patients may be enrolled in parallel.

The DSMB will review all safety data including the data from Parts A and B three months after all 3 patients in Cohort 4 have been dosed. An interim report including all available safety data and preliminary efficacy data will be submitted to the regulatory authorities and institutional review boards/ethics committees for review and consideration, before up to 6 patients ≥6 years of age or older can be enrolled in Part C of the study (Cohort 5). Patients enrolled into Part C will be treated at the MTD determined from Part A of the study and further characterised in Part B of the study.

All patients will be followed for 48 weeks. After this period they will enter an open-label safety study for long-term follow-up visits. Patients will attend visits at a minimum interval of one visit every six months, for assessments that will include ophthalmological examinations and recording of adverse events for 240 weeks (5 years).

Part C

Cohort	Age (yr)		Subretinal Injection	
		Number of patients	Vector concentration	Volume
5	≥6	6	MTD	300 µL

Section 8 Study Population

Three populations of patients with differing disease severity and/or ages will be recruited:

Part C

Patient population to be included in Cohort 5
(a) Patients ≥6 years of age.
(b) Clinical and molecular diagnosis of Retinitis Pigmentosa caused by MYO7A mutations.
(c) Visual field loss in the worse seeing-eye that is equivalent to ≥30% reduction from normal sensitivity.
(d) Electroretinographic evidence of severe rod-cone dystrophy.

Section 8.2.1 and 2.7 Inclusion Criteria

Specific Inclusion Criteria Cohort 4

- ≥18 years of age

Part C

Specific Inclusion Criteria Cohort 5

- ≥6 years of age
- Visual field loss in the worse seeing-eye that is equivalent to ≥30% reduction from normal sensitivity volume (decibel-steradian) on full-field GATE Static Perimetry using the size V (1.7°) test target.
- Evidence of severe rod-cone dysfunction on full-field electroretinogram performed to ISCEV standards.

Section 9.1.2 Dose Extension (MTD) Parts B and C

The Maximum Tolerated Dose to be used in Parts B and C (Cohorts 4 and 5) of the study will be determined from the dose escalation phase (Part A). Cohort 4 will include only adult patients (≥18 years or older) with less advanced RP, while Cohort 5 will provide the opportunity to include paediatric patients ≥6 years of age. Before paediatric patients can be enrolled into the study, the DSMB will review all safety data including the data from Part B, three months after all 3 patients in Cohort 4 have been dosed. An interim report including all available safety data and preliminary efficacy data will be submitted to the FDA and institutional review boards/ethics committees for review prior to the enrollment of paediatric patients.

Section 8.2.2 and 2.7.2 Exclusion Criteria

Presence of significant ocular abnormalities in the study eye that in the opinion of the Investigator would preclude the planned surgery, effective safety follow-up, or interfere with the interpretation of study endpoints (eg, glaucoma, corneal or significant lens opacities, pre-existing uveitis, intraocular infection, choroidal neovascularization).

Section 9.9 Study Procedures and 3. Study Schedule

Autofluorescence has been removed from the visit schedule at Screen Day -1, Day 1, Weeks 1, 2 and 36.

Fundus photography has been removed from the visit schedule at Screen Day -1, Week 1 and 12.

Autofluorescence will be performed at Weeks 4, 12, 24 and 48.

Fundus photography will be performed at Weeks 2, 4, 24, 36 and 48.

Full field and multifocal Electroretinogram (ERG) assessment during the 28 day screening period has been moved from baseline (Day -1) to the screening (Day -28) visit.

An infra-red fundus montage using infra-red imaging will be performed as part of every OCT procedure.

Section 13.3 Interim Analysis

An interim analysis will be conducted on all available safety data and any available preliminary efficacy data up to the 3 month time point for Cohort 4 patients. The interim

analysis, consisting of descriptive statistics and exploratory figures will be used to provide data to the FDA and IRB/ethics committees before paediatric patients are enrolled in Cohort 5. Formal statistical tests will not be performed as part of the interim analysis.

TDU13600 16.1.1 Amended Protocol 08

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	09-Aug-2018 09:54 GMT+0200
	Clinical Approval	09-Aug-2018 12:40 GMT+0200