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LFG316

Protocol No. CLFG316A2204

A randomized, active-controlled, open-label, multiple-dose, proof-of-concept study of intravitreal LFG316 in patients with active non-infectious intermediate-, posterior-, or panuveitis requiring systemic immunosuppressive therapy

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Table of contents

Table of contents 2
List of tables 6
List of figures 6
List of abbreviations 7
Glossa1y of terms 9

Corporate Confidential Information

Protocol synopsis 25
Assessment schedule 32
1 Introduction 36
1.1 Background 36
1.2 Study purpose 46
2 Study objectives 47
2.1 Prima1y objectives 47
2.2 Seconda1yobjectives 47

Corporate Confidential Information

3 Investigational plan 48
3.1 Study design 48
3.2 Rationale of study design 52
3.3 Rationale of dose/regimen, dmation of treatment 53
3.4 Rationale for choice of comparator 54
3.5 Risk / Benefit for this study 54
3.6 Purpose and timing ofinterim analyses/design adaptations 55
4 Population 56
4.1 Inclusion cliteria 56
4.2 Exclusion criteria 57
4.2.1 Interpretation ofl aborato1y and electrocardiogram results 58
5 Treatment. 59
5.1 Investigational treatment 59
5.1.1 Bio-batch Retention samples 59
5.2 Treatment aims 59
5.3 Treatment assignment 59

5.4 Treatment masking 59
5.5 Treating the patient 59
5.5.1 Patient numbering 59
5.5.2 Dispensing the study treatment. 60
5.5.3 Supply, storage and tracking of study treatment 60
5.5.4 Instrnctions for prescribing and taking of study treatment 61
5.5.5 Permitted dose adjustment 61
5.5.6 Rescue 62
5.5.7 Concomitant, pennitted, and prohibited treatments 63
5.5.8 Prohibited treatment 64
5.5.9 Tapering schedule for oral co1ticosteroids 64
5.5.10 Discontinuationof study treatment and premature subject withdrawal 65
5.5.11 Emergency unblinding of treatment assignment. 66
5.5.12 Study completionand post-study treatment. 66
6 Visit schedule and assessments 67
6.1 Dietary, fluid and other restrictions 67
6.2 Patient demographics/other baseline characteristics 67
6.3 Treatmentexposure and compliance 68
6.4 Efficacy / Pharrnacodynamic assessment 69
6.4.1 Vitreous haze 69
6.4.2 Anterior Chamber cells 69
6.4.3 Chorioretinal lesions 69
6.4.4 Papillitis 69
6.4.5 Vasculitis 69
6.4.6 Visual acuity 69
6.4.7 Optical coherence tomography (sd-OCT) 69
6.4.8 Total CS 70
6.5 Safety 70
6.5.1 Physical examination 70
6.5.2 Vital signs 71
6.5.3 Height and weight 71
6.5.4 Laborato1y evaluations 71
6.5.5 Electrocardiogram (ECG) 72
6.5.6 Pregnancy 72
6.5.7 Meal Record 72
6.5.8 Chest X-ray 72

6.5.9 Ocular assessments ... 73
6.6 Pharmacokinetics ... 74
6.6.1 PK Blood Collection and Processing ... 74
6.6.2 Urine Collection and processing ... 74
6.6.3 Pha1macokinetic analytical method(s) ... 74
6.7 Other assessments ... 75
6.7.1 Health-related quality of Life ... 75

CorporateConfidentialInformation

7 Safety monitoring ... 76
7.1 Adverse events ... 76
7.2 Serious adverse event repmt ing ... 78
7.3 Pregnancies ... 78
7.4 Data Monitoring Committee ... 79
8 Data review and database management ... 79
8.1 Site monitoring ... 79
8.2 Data collection ... 79
8.3 Database management and quality control ... 80
9 Data analysis ... 80
9.1 Analysis sets ... 80
9.2 Subject demographics and other baseline characteristics ... 81
9.3 Treatments (study dmg, rescue medication, other concomitant therapies, compliance) ... 81
9.4 Analysis of the p1imaiy vai·iable(s) ... 81
9.4.1 Response rate ... 81
9.5 Analysis of secondaly vai·ables ... 81
9.5.1 Efficacy / Pharm aco d ynamics ... 81
9.5.2 Safety ... 82
9.5.3 Health-related quality of Life ... 82

Corporate Confidential Information

9.5.7 PK/PD ... 83

Corporate Confidential Information

9.6 Sample size calculation ... 83
9.7 Power for analysis ofkey secondaiy variables ... 83

CorporateConfidential Information

10 Ethical considerations 84
10.1 Regulatory and ethical compliance 84
10.2 Informed consent procedures 84
10.3 Responsibilities of the investigator and IRB/IEC 84
10.4 Publication of study protocol and results 85
11 Protocol adherence 85
11.1 Protocol Amendments 85
12 References 86
13 Appendix 1: Blood collection log: blood sampling schedule for safety, PG, PK, PD, and immunogenicity 88
14 Appendix 2: Sample labeling and shipping information 89
14.1 Sample labeling 89
14.2 Sample shipment instructions 90
14.2.1 Instructions for shipment of PK, PD, PG, and immunogenicity samples to the central lab 91
14.2.2 Instructions for shipment of PK, PD, and immunogenicity samples from central lab to the bioanalytical lab 91

List of tables

Table 1-1 LFG316 Completed Studies 40
Table 1-2 Adverse events by treatment condition from study CLFG316A2101 ..41
Table 1-3 Adverse events by treatment condition from study CLFG316A2102 (n=24)....41
Table 1-4 Summa1y of Adverse Events from CLFG3l6A2201 42
Table 1-5 System Organ Class and Adverse Events Observed in CLFG316A2202....43
Table 1-6 Incidence of Ocular Adverse Events Obse1v ed in Subjects in CLFG316A2202 43
Table 1-7 Incidence of Fatal Adverse Events Obse1ved in Subjects in CLFG316A2203-Part A....44
Table 1-8 Incidence of non-fatal ocular Serious Adverse Events Obse1v ed in Subjects in CLFG316A2203-Pa1iA....44
Table 1-9 Mean PK parameters of total LFG316 46
Table 3-1 Overall study scheme....51
Table 5-1 Pe1mitted and concomitant therapies....64
Table 5-2 Prednisone tapering schedule (100 to 10 mg/day prior to Day 1 of study) 65
Table 6-1 Vitreous haze scoring....69
Table 6-2 Anterior chamber cell grading 69

List of figures

List of abbreviations

AC	Anterior chamber cells
AE	Adverse event
ALT	Alanine transaminase
AMD	Age-related macular degeneration
AREDS	Age-Related Eye Disease Study
AST	Aspaliate trnnsaminase
AUC	Area under the concentration time curve
-hCG	Beta human chorionic gonadotropin
B:MI	Body mass index
bpm	Beats per minute
BUN	Blood urea nitrogen
CFR	(United States) Code of Federal Regulations
CK	Creatine kinase
CSR	Clinical study rep01t
eCRF	Electrnnic case report / record form
EDC	Electronic data capture
	ColJ)Orate Confidential Information
ETDRS	Early treatment in diabetic retinopathy study
FAF	Fundus autofluorescence
FDA	Food and Drng Administration
FSH	Follicle stimulating hormone
GA	Geographic atrophy
GCP	Good clinical practice
GLP	Good laboratory practice
IB	Investigator's brochure
IMT	Immuno-Modulat01y Therapy
IRB	Institutional Review Board
IV	Intravenous(ly)
IVT	Intravitreous(ly), intravitreal(ly)
LC/MS	Liquid chromatography/mass spectrometry

LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
MAC	Membrane attack complex
MFC	Multifocal choroiditis
mmHg	Millimeters of mercury
MRSD	Maximum recommended staiting dose
NOAEL	No-observed adverse effect level
NIU	Non-infectious intermediate- , posterior- or panuveitis
PD	Phan nacodynamics
PG	Phan nacogenomic s
pH	Negative log hydrogen ion concentration
PK	Pharmacokinetics
PRN	Pro re nata (as needed)
RBC	Red blood cell/c01puscle
RPE	Retinal pigment epithelium
SAE	Serious adverse event
sd-OCT	Spectral domain ocular coherence tomography
SUSAR	Suspected unexpected serious adverse reaction
TME	Translational Medicine expe1i
VEGF	Vascular Endothelial Growth Factor
WBC	White blood cell
WHO	World Health Organization
WOCBP	Women of child bearing potential

Glossary of terms

Screening	Point/time of subject/patient entry into the study; the point at which informed consent must be obtained (i.e., prior to sta1ting any of the procedures described in the protocol)
Emollment	Point/time of subject/patient randomisation into the study / assignment of a randomization number.
Investigational drng	The study chu g whose propert ies are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug".
Phase	A major subdivision of the study tin1eline; begins and ends with major study milestones such as, Screening, or Study Completion.
Treatment Period	A minor subdivision of the study timeline that divides phases into smaller functional segments, i.e., the time starting from Baseline prior first study drug administration until the last day prior the next Baseline, or the Study Completion visit.
Premature subject/patient withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments. At this time all study chug administration is discontinued. Study Completion assessments must be completed.
Study chug	Any chu g administered to the subject as pa.rt of the req uired study procedures; includes investiga.tiona l ch11g and any control and comparator chu gs.

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Protocol synopsis

LFG316

Title of study: A randomized, active-controlled, open-label, multicenter proof-of concept study of intravitreal LFG316 in patients with active non-infectious intermediate-, posterior-, or panuveitis requiring systemic immunosuppressive therapy

Objectives:

Primary objective(s)

- To assess the effect of intravitreal LFG316 Corporta e Co n fid en t i al Inf o n nat i on on t h e p rotocol - d efin e d, Day 85 re sponse ra t e i n t he s t udy eye of patients who meet the inclusion criteria.

Secondary objective(s)

- To assess the safety and tolerability of intravitreal LFG316 (5 mg q 4 weeks x 3 doses) in patients who meet the inclusion criteria. Corporate Confidential Info1mation

- To assess the effect of intravitreal LFG316 Corporate Confidential Information on vitreous haze as measured on the Nussenblatt scale, ETDRS visual acuity, macular edema, presence or absence of chorioretinal lesions, and anterior chamber cells score in the study eye of patients who meet the inclusion criteria, and compare these between Baseline and Days 2, 8, 15, 29, 43, 57, and 85. Corporate Confidential Information

- To evaluate the serum concentrations of total LFG316 and total CS during the course of the study.

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Study Design:

Approximately 24 patients with active NIU, in at least one eye, requiring intensification of systemic immunosuppressive therapy will be enrolled and randomized in a 2:1 ratio to receive intravitreal LFG316 Corporate Confidential Information . Throughout the study, the fellow eye may be treated as needed; except that certain systemic medications are prohibited (see Section 5.5.7 and Section 5.5.8). There will be 1 screening and 8 scheduled visits over 85 days for a total of 9 site visits for all patients.

Assessments are listed in the Assessment schedule. Efficacy assessments (ocular assessments and photos) will be conducted by personnel masked to the treatment assignment. Low molecular weight non-steroidal immunosuppressive medications are allowed up to the baseline day as long as the dose has not changed in the 3 weeks prior to baseline, except for corticosteroid doses which may change.

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Patient Safety

Safety assessments will include ocular evaluations, adverse events, and serious adverse events. Cumulative safety listings will be reviewed by the Principal Investigator and the Novartis Medical Director periodically during the study, and *ad hoc* when necessary.

Population:

Approximately 24 patients with active NIU requiring intensification of systemic immunosuppressive therapy will be enrolled.

Inclusion/Exclusion criteria:

Full inclusion / exclusion criteria are presented in Section 4.1 and Section 4.2, respectively.

Key inclusion criteria:

- Male or female patients 18 years or older.
- Active NIU, in at least one eye, as defined below, in patients requiring intensification of systemic immunosuppressive therapy;
  - Vitreous haze at least 1+ on the scale of Nussenblatt et al 1985, or
  - Chorioretinal lesions due to uveitis *(chorioretinal lesions due to infectious uveitis will exclude the patient)*
  - Patients who present with a flare and who are at the time of the enrollment on systemic corticosteroid or non-steroidal immunosuppressants will have their therapy tapered or stopped, respectively, at the time of intravitreal LFG316 administration.
- Visual acuity (ETDRS method) of 20 letters (20/400 Snellen equivalent) or better in the study eye.
- Female patients must not be pregnant or lactating and must, unless post-menopausal, use effective contraception as specified in Section 4.1 of this protocol.
- Ability to provide informed consent and comply with the protocol.

Key exclusion criteria:

- Uveitis so severe that, in the investigator's judgment, it is too risky to test an experimental drug.
- Bilateral uveitis for which, in the opinion of the investigator, systemic immunosuppressive therapy is required to manage the inflammation in the fellow eye; use of local therapy in the fellow eye is acceptable and not an explicit exclusion (See Section 5.5.7 for acceptable concomitant treatments)
- Uncontrolled glaucoma or ocular hypertension in either eye, defined as an intraocular pressure (IOP) >30 mmHg while on medication for the specific condition
- Forms of uveitis that may spontaneously resolve such as multiple evanescent white dot syndrome (MEWDS).
- In the opinion of the investigator clinically significant abnormality in screening laboratory results or electrocardiogram.
- In the study eye, cataract that is expected to interfere with study conduct or require surgery during the study.
- History of infectious uveitis or endophthalmitis in either eye.
- History of retinal detachment
- Patients taking corticosteroids or other systemic immunosuppressive medication for any other disease (e.g., asthma or other autoimmune disease) where the tapering of the immunosuppressant would not be safe because of the risk of exacerbation of the extraocular disease
- Any biologic immunosuppressive agent given via intravitreal, intravenous or subcutaneous route within 4-12 months of screening depending on the agent.

- Any intraocular surgery, intravitreal injection, periocular injection, or laser photocoagulation to the study eye within 90 days prior to dosing.

Investigational and reference therapy:

Approximately twenty-four (24) patients will be enrolled and will be randomized 2:1 to either LFG316 (n=16) Corporate Confidential Infonnation

LFG316 will be administered to patients randomized to LFG316 on days 1, 29 and 57.

Corporate Cont1ctentl a l 1nt01mat1on

- LFG316 solution for injection **is a** liquid solution provided in vials containing

Rescue to Conventional Therapy throughout the study:

Study drug will be discontinued and conventional therapy instituted for any patient that meets the following criteria in the study eye:

- Loss of >10 letters in best corrected visual acuity (BCVA) at any visit, as compared to baseline that, in the opinion of the investigator, is due to worsening of uveitis.
- Active vitritis, anterior chamber inflammation, or chorioretinitis at least 28 ±3 days after their last dose that, in the opinion of the investigator, is significantly worse as compared to the previous visit and requires alternate therapy
- Unilateral flare in fellow / non-study eye which does not respond to local treatment (including ozurdex® implant) or bi latera l flare in both eyes which require the intensificationof systemic immunosuppressivetherapy.

Concomitant medications/Significant non-drug therapies:

Intravitreal administration involves certain protocol-specified anesthetics and antibiotics. See the full protocol for a complete list of concomitant, permitted, and prohibited medications.

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Primary endpoint: response rate at Day 85, LFG316 treatment arm.

A response will be defined by any one of the following criteria in the study eye:

- An improvement of 2 or more steps in vitreous haze, relative to baseline. For the purpose of "step" calculation, 0.5 shall count as one of the increments. Thus, improvement from a score of 2 to 0.5 or from 1 to 0 would constitute a 2-step improvement **or,**
- An improvement of 10 or more letters in visual acuity, relative to baseline **or**
- An improvement of 2 or more steps in anterior chamber cells, relative to baseline , **or**
- Resolution of chorioretinal lesions as determined by the investigator, **or**
- Change in central retinal thickness from baseline to Day 85 of 50 micrometer

Remission (complete response) will be defined as any patient who has a vitreous haze score of O or 0. 5 in the stud y e ye , w ho has an anter ior chamber cell score of O and no chor ioretinal les ions in the study eye and is off all immune modulatory therapy (systemic, corticosteroids and topical), without any worsening of uveitis during the trial.

Secondary endpoints:

- Mean changes in BCVA, vitreous haze score, AC cell score, and central retinal thickness on Days 2, 8, 15, 29, 57 and 85 for both eyes of all patients.
- Mean changes in BCVA, vitreous haze score, AC cell score, and central retinal thickness in LFG316 responders on Days 169, 253, and/or 281 (EOES)
- Percentage of eyes that respond (as per responder criteria) on days 2, 8, 15, 29, 57.
- AE and SAE rates on days 2, 8, 15, 29, 57 and 85 for all patients

Sample size determination

The target sample size for this study is approximately 24 patients, randomized in a 2:1 ratio

Power calculations are not based upon a comparison between LFG316 Corporate Confidential Info1mation but rather on the null hypothesis that the response rate in the LFG316 arm (p_{LFG}) will not diffe r from the lower bound of the expected C01porate Confide ntia l fufo n nat ion response rate which is assumed to be 60%. With 16 patients in the LFG316 arm, the null hypothesis $H_0: p_{LFG} \leq 0.60$ will be rejected in favor of $H_1: p_{LFG} > 0.60$, if 11 / 1 6 patients in the sample are responders. Such a rejection rule has 17% false positive rate (incorrectly reject H_0 when it is true) and 45% (80%, 92%) power to correctly reject H_0 when the true p_{LFG} is 70% (80%, 85%).

Analysis methods

The 90% confidence intervals for the proportion of responders at Day 85 in the LFG316 as well as the 90% confidence interval for the difference in response rates will be reported. The response rates at other time points (e.g., at Days 15, 29, 57) will be analyzed similarly.

Summary statistics for the secondary endpoints and their changes from baseline will be provided by treatment group and visit/time. A longitudinal analysis of the secondary PD endpoints may be performed if deemed relevant. Graphical displays of mean time profiles may be constructed as appropriate.

Descriptive statistics of safety data will be provided by treatment group. Adverse events will also be analyzed by treatment group. Ocular adverse events will be separately listed and analyzed by study eye vs. fellow eye.

Assessment schedule

Study phase	J g> c u en	Treatment Period								Treatment extension for LFG316 Responders				c..,,,,.c.
	Day - 14 lo -1	Day 1	Day 2 (+1 day)	Day 8 (±1 day)	Day 1 5 (+/-1 .-bv\	Day 29 (+/-3 .-bvsl	Day 43 (+/-3 days)	Day',! (+/-3days)	Day 85" (± 3 days)	PRN	Day 169 (+/-5 days)	PRN	Day253 (+/-5 davsl	Day281 (+/-5 days)
Visit flumbers	5	N 5	M 5	5	5	U) 5	5	5	Visi t 9 or 777		5			
Informed Consent	X													
CorporateConfidential Information	X													
Inclus ion /Excu sion cr iteria	X													
Relevantmedical historv / Curren t medical conditions	X													
Den-vv>r nhv	X													
Ocular historv	X													
ECG	X								X					X
I><an,tifis and HIV historv	X													
Ak:ohol abuse and dn deoendence historv	X													
Smokino hist= •	X													
Phvsical exarrina1ion	X								X					X
Laboratory Safety Tests; incl hematology. blood cherristry and urinalvsis	X								X					X
P"" nancv lest (obtained ore-dose)	X(serum	X (urinel				X (urinel		X (urine)	X (urinel		X (urine)		X (urinel	X (urinel
Roctv hei<Jht	X													
Roctv v.eiaht	X								X	X	X	X	X	X
Il<xiv ,.....,,,,,ture	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood aressure / Puse rate	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study co etion information														X
Comnen1s	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ACM!rse Ew nts (cantured followina initial dose adrrinistrationl		X	X	X	X	X	X	X	X	X	X	X	X	X
SAEs (captureduponsigning ICF until4v.ecksfollov.ing final 'Asit)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concorri1ant rnedsfTheraoies	X	X	X	X	X	X	X	X	X	X	X	X	X	X
LFG316 Intra"1real Dose adrrinistration(sh.fv <Ne onlvl'->A		X				X		X	X'	X'		X'	x 2,J	
		Oc •- ••••~												
P K sa ecollection (pre-dose)		X	X		X	X	X	X	X	X	X	X	X	X
PD /total C5l samnt<> collection Cor e-dosel		X	X		X	X	X	X	X	X	X	X	X	X
Corporate ConfidentialInfonnation	X									-	,___-	- -	--	,___-

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Ocular Assessment schedule

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Study phase	Screening Vis it	Treatment Period							End of Study (EOS)[3]	C01porate Confidentia1 Informatio n			
	D-14 to -1	Day 1	Day 2 (+1)	Day 8 (+1)	Day 15 (+/-1)	Day 29 (+/3)	Day 43 (+/3)	Day 57 (+/-3)	Day 85[4] (± 3 day)	PRN	Day 169 (+/-5 days)	PRN	Day 253 (+/-5 days)
Visit Numbers	Visit 1	Visit 2	Visi t 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9 or 777[1]		Visit 10		Visit 11
Best corrected visual acuity (ETDRS)	ou[1]	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
Intraocular pressure(IOP)	OU	ou[2]	OU	OU	OU	ou[2]	OU	ou[2]	ou[3]	ou[2]	ou[2]	ou[2]	ou[2]
;:,,n lamp oiomlcroscopy	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
Spectral domain ocular coherence tomography (sd-OCT)	OU	OU				OU		OU	OU		OU		OU
Dilated ophthalmoscopy	OU	ou[2]	ou[2]	ou[2]	OU	ou[2]	OU	ou[2]	ou[2]	ou[2]	ou[2]	ou[2]	ou[2]
Color fundus photo	OU					OU		OU	OU	OU	OU	OU	OU
Standardized Vitreous Haze Score	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
Anterior Chamber cells	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
Chorioretinal lesions (absenUpresent per PI)	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU
Macular edema due to u iti s (absenUpresent per P I\	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU	OU

1. OU--both eyes and all assessments will be done pre-dose

PI: Principal Investigator

2. Patients receiving LFG316 will have dilated ophthalmoscopyto verify perfusion of the retinal vessels in the study eye immediately after each LFG316 injection. IOP should be checked approximately 30 minutes followinQ each LFG316 intravitreal injection in the study eve (SE).

1 Introduction

1.1 Background

Uve itis refers to approximately 25 different disorders characterized by the presence of intraocular inflammation. The major causes of uveitis are infections, systemic immune-mediated disease and autoimmune syndromes confined primarily to the eye (Pan et al 2014). These diseases are not confined to the uveal tract, comprised of the iris, cilia1y body and choroid, but may also include the retina, retinal vessels and other stmctures (Jabs 2008). Uveitis is the 5th leading cause of visual impainnent and blindness in the United States (Pan et al 2014) and responsible for 10% of blindness worldwide (Jabs 2008). Epidemiological studies rep01ied that the incidence of uveitis in the general population varies between 17 and 52 cases per 100,000 people per year with a prevalence of approximately 38 to 714 cases per 100,000 in the population (Miserocchiet al 2013).

In Western countiies, anterior uveitis accounts for at least 50% of all cases of uveitis, posterior uveitis for 15-30% (Wakefieldand Chang 2005), and intermediate and panuveitis for the balance. The cmTen t conventiona l tl'eatment for non-infectious intermediate-posterior and panuveitis includes local and systemic co1ticosteroids with or without the addition of co1ticosteroid-sparing immunomodulato1y therapy. Although these therapeutic options are effective in suppressing the inflammation,m ug related co-morbidities and toxicities limit the use.

Noninfectious uveitis is thought to result from inappropriate activation of the immune system and is often associated with systemic autoimmune or autoinflammat01y diseases , however when no such disease is present these cases are te1med idiopathic. Considering the immune mediated natme of uveitis, co1t icosteroids are typically the first line of therapy for noninfectious uveitis. The route and dose of co1t icosteroids depend on the severity of the uveitis and whether the ocular inflammation is confined to the anterior segment (ie, anterior uveitis or iritis), the posterior segment (ie, inte1mediate-, posterior-uveitis) or both (ie, panuveitis). Local steroids, which often cause glaucoma and cataract, can be attempted, but systemic steroids are usually necessa1y to control the disease. Many cases of uveitis are not controlled with c01t icosteroids alone, or the dose of c01t icosteroids required to persistently suppress inflammation is higher than the Cushing threshold (about 8-10 mg prednisone equivalent/day). In such cases, one or more steroid-sparing immunosuppressivem u gs are used, many of which are used off-label. Many of these steroid sparing therapies, including the commonly used methotrexate, take weeks to achieve full efficacy. Cyclosporine has a more rapid onset of activity, but at therapeutic levels is commonly associated with other co-morbidities such as nephrotoxicity and hype1tension, requiring frequent monitoring. Thus, there is an unmet need for highly effective rescue therapy for patients with acute or relapsing disease, precluding the need for high dose co1ticosteroid therapy or prolonged systemic biologic therapy (Hazirolan and Pleyer 2013).

The complement system is pait of the innate immune defense mechanism and is involved in modulating various immune and inflammatory respo nses (Yanget al 2012). Within the eye, complement plays an important role in the generation and maintenance of tolerogenic/ suppressive antigen-presenting cells (APCs). By regulating the production/expression of immune mediators, the complement system is required to mount the antigen specific CD4+ T-cell-mediated immune responses that cause inflammation in the eye (Jha et al 2010). Recent studies have demonstrated that complement system activation is critical for the development of autoimmune uveoretinitis. Both local (intravitreal) and systemic suppression of the host's complement system with an anti-CS antibody was shown to completely inhibit the development and progression of an antigen specific T-cell mediated murine model (experimental autoimmune uveitis, EAU) of intraocular inflammation (Copland et al 2010).

Under norm al condi tions, the complement system is active at baseline level and tightly regulated by vai·ious complement regulatory proteins (CRegs) such as complement factor H (CFH). CFH is one of the most important regulators in the alternative complement pathway and is involved in the pathogenesis of immunological diseases. Recent studies suggested that variants in the CFH gene are associated with several immune-mediated diseases. Activated complement, due to loss of CRegs regulation by CFH, might cause self-tissue damage in sensitive organs like the eyes. *In vivo* studies have revealed that human RPE cells can synthesize and express CFH, and upregulated secretion of CFH by RPE can suppress the development of EAU (Yanget al 2012). In previous studies by Yang and Ng, it has been found that polymorphisms in the *CFH* gene ai·e assoc iated with the development of neovascular age-related macular degeneration (AMD) as well as anterior uveitis in females (Yang et al 2011; Ng et al 2008). In addition, *CFH* polymorphisms have also been found to be associated with other immune-mediated diseases such as multi.focal choroiditis, hemolytic-uremic syndrome (HUS) and glomernlonephritis.

In patients with non-infectious intermediate and posterior uveitis, an association with the specific rs800292 (CFH 184 G/A) polymorphism was identified and showe d a recessive effect (GG/AG versus AA genotype; odds ratio (95% CI) was 2.74 (1.13-6.62)). In addition, the frequency of can iers of the G allele was significantly higher in uveitis patients than in controls (Yang et al 2012). This inform ation, comb ined with non-clinical EAU results and the considerable unmet need in noninfectious uveitis, has prompted the hypothesis that complement inhibition will be beneficial in this patient; the present study will test this hypothesis.

1.1.1.1 Relevant data summary

Table 1-1 LFG316 Completed Studies

Study	Design	Route of Administration	Doses	N
Corporate Confidential Info1mation				
CLFG316A2102	A single-ascending dose Safety and tolerance, PK/PD study in age-related macular degeneration	IVT	Co1porate Confidential Informa tion	24; 24 LFG316
CLFG316A2201	A multiple dose Safety and tolerance PK/PD study in neovascular age- related macular degeneration	IV		4; 4 LFG316
CLFG316A2202	Multiple dose Safety and tolerance PK/PD study in neovascular age- related macular degeneration	IVT		45; 30 LFH316 15 Sham

CLFG316A2102

This was a single ascending dose study conducted to assess the safety and tolerability, as well as PK and PD of **intravitreally** administered LFG316 in patients with advanced AMD.

Overall, There were no drng related adverse events, deaths, serious adverse events, or discontinuations. Table 1-3 below summari zes the top 5 most frequently repo1ted adverse events obse1ved in this study. Conjunctiva! hemonhage was the most frequently reported ocular AE which can be attributed to the intravitreal injection procedure. None of the AEs were dose dependent or suspectedto be related to the study drng. There was no increase in total *CS* or inhibition of alternative complement pathway activity. Anti-LFG316 antibodies were not detected in this study. The remaining safety assessments (e.g. vital signs, ECG, etc) and ocular assessments showedno clinically significantchanges.

Table 1-3 Adverse events by treatment condition from study CLFG316A2102 (n=24)

	LFG316 N=6 n (%)	LFG316 N=6 n (%)	LFG316 N=6 n (%)	LFG316 N=6 n (%)	Total N=24 n (%)
Pat ients with AE(s)	6 (100)	6 (100)	3 (50)	4 (67)	19 (79)
Conjunctiva! haemorrhage	2 (33)	5 (83)	2 (33)	2 (33)	11 (46)
Eye pain	2 (33)	0	1 (17)	2 (33)	5 (21)
Eye irritation	1 (17)	2 (33)	1 (17)	0	4 (17)
Lacrimation increased	1 (17)	1 (17)	1 (17)	0	3 (12)
Vitreous detachment	1 (17)	0	0	1 (17)	2 (8)

Source: CLFG316A2102 CSR, Table 14.3.1-1.1

CLFG316A2201

This study was a multicenter, multiple dose, 2-cohmt trial to assess the safety, tolerability, phaimacokinetics, phaimacodynamics, and efficacy of intravenous (IV) LFG316 in patients with neovascular age-related macular degeneraiton. Novartis terminated this study and stopped recrnitment after 4 subjects had been randomized to the c,..,...Camda,ml..... treatment aim. The decision to terminate the study was not due to any safety signal with LFG316. It was based upon a consideration of the repmted number of patients with meningococcal infection and uncleai· risk of death due to meningitis noted after repeated dosing with Soliris® (Ec ulizumab), which is an approved antibody against complement factor 5 *(C S)* for the treatment of pai·oxysmal nocturnal hemoglobinuria and atypical hemolytic syndrome. See Table 1-4 for a summaiy of adverse events.

Table 1-4 Summary of Adverse Events from CLFG316A2201

	10 mg/kg LFG316 N=4
Patients with at least 1 AE	4 (100)
Anaemia	1 (25)
Eye pain	1 (25)
Lacrimation increased	1 (25)
Photophobia	1 (25)
Visual acuity reduced	1 (25)
Vitreous detachment	1 (25)
Vitreous floaters	1 (25)
Otitis media	1 (25)
Diabetes mellitus	1 (25)
Chronic obstructive pulmonary disease	1 (25)
Dyspnea	1 (25)

Source: CLFG316A2201 CSR, Table 14.3.1-1.1

CLFG316A2202

This study was a repeat-dose Proof-of-Concept study in patients with neovascular (wet) AMD. This study used a multicenter, randomized study design to assess the efficacy, safety, tolerability, and sernm phaimacokinetics of 3 successivedoses of intravitreally administered LFG316. Forty-five (45) subjects were randomized in a 2:1 ratio to either LFG316 "-""".....,...,.....intravitreal injection (30 subjects) or to sham injection. There were no differences between the 2 treatment aims in the rate or use of rescue therapy with anti-VEGF on Day 85: the number of subjects who required anti-VEGF rescue therapy was 18 (62.1%) and 10 (66.7%) in the LFG316 and sham-injection aims, respectively. The mean (± SD) anti-VEGF rescue therapy rate up to Day 85 was 0.10 (± 0.097) and 0.08 (±0.078)retreatment per week in the LFG316 and sham-injectionaims, respectively(15 subjects)for total of 3 doses.

fu patients with neovascular (wet) AMD, monthly treatment with LFG3 l 6 eo,p.m.c.., IVT was well tolerated with similar safety profile in both treatment groups. None of the AEs resulted in discontinuation from the study. No deaths or drug-related SAEs were rep01ted. See Table 1-5 and Table 1-6 for Systemic and Ocular Adverse Events respectively.

Table 1-5 System Organ Class and Adverse Events Observed in CLFG316A2202

	LFG316 N=30 n(%)	Sham N=15 n(%)	Total N=45 n(¾)
Patients with at leas t 1 AE	16 (53.3)	9 (60)	25 (55.6)
Infections and infestat ions	6 (20)	4 (26.7)	10 (22.2)
Injury , poiso ning, and procedura l complications	5 (16.7)	1 (6.7)	6 (13.3)
Gastro intest inal disorders	3 (10)	3 (20)	6 (13.3)
Vascular disorders	2 (6.7)	3 (20)	5 (11.1)
Investigat ions	3 (10)	2 (13.3)	5 (11.1)
Nervous system disorders	3 (10)	1 (6.7)	4 (8.9)
Musculoskeletal and connective tissue disorders	2 (6.7)	2 (13.3)	4 (8.9)
Metabolism and nutrition disorders	2 (6.7)	1 (6.7)	3 (6.7)
Immune system disorders	2 (6.7)	1 (6.7)	3 (6.7)
General disorders and administration site conditions	2 (6.7)	**1** (6.7)	3 (6.7)
Cardiac disorders	1 (3.3)	2 (13.3)	3 (6.7)

Source CLFG316A2202 CSR Table 14.3.1-1.1

Table 1-6 Incidence of Ocular Adverse Events Observed in Subjects in CLFG316A2202

	LFG316 N=30 n(%)	Sham N=15 n(%)	Total N=45 n(%)
Pat ients with at leas t 1 AE	10 (33.3)	4 (26.7)	14 (31.1)
Conju nctiva! haemorrhage	6 (20)	1 (6.7)	7 (15.6)

Source CLFG316A2202 CSR Table 14.3.1-1.3

CLFG316A2203:

This is a two-part (A and B) study;

CLFG316A2203-Pa1t A

Part A is an ongoing, multicenter, double masked, randomized, multiple dose study to assess the efficacy, safety, tolerability, and serum pha1macokinetics of intravitreally administered LFG3l 6 (5 mg) in subjects with geographic atrophy. Pait A of the study has recruited the planned number of patients (n = 150), all of whom were randomized to receive monthly intravitreal LFG316 or sham (2:1 respectively) for 18 months. The cut-off date for the following safety rep01t is 8th of May 2015.

Serious adverse events: Dmi ng this study, 5 deaths (4 in the LFG3l6 treatment arm , 1 in the sham control group) have been rep01t ed and are tabulated below (See Table 1-7).

Table 1-7 Incidence of Fatal Adverse Events Observed in Subjects in CLFG316A2203-Part A

Cause of death	Study day	Causality assessment
Severe internal bleeding	87	Not related to study medication
Bladder Cancer	81	Not related to study medication
Acute exacerbation of congestive cardiac failure	200	Not related to study medication
Severe *clostridium difficile* infection	308	Not related to study medication
Deep Vein thrombosis	172	Not related to study medication

Fifty nine non-fatal, non-ocular SAEs were reported by 33 patients. None were deemed to be related to the study medication. For further details on these systemic SAEs please refer to LFG3161B Edition 9-Table5-10.

There were 4 ocular SAEs (Table 1-8). The reduction in visual acuity in the 2 subjects was thought to be related to headache or to worsening of the disease. Two subjects developed endophthalmitis, 1 on day 400 and the other on day 367. The endophthalmiits cases were considered to be procedme related, and were not considered to be related to the study medication. In both cases the identified organism was *Staph. Epidermidis.* The cases occun ed in 2 separate geographical locations and based on the differences in antibiotic resistance, are likely to be due to 2 different strains of *staph epidermidis.* To date over 2000 injections of LFG316 had occun ed, resulting in an incidence of 0.099%. Therefore, the cun ent rate of endophthalmitis per injection of LFG316 is similar to that observed for IVT injections in general (0.03% -0.13%) (Nentwichet al 2014, Bhavsar et *al* 2012). One of the subjects with endophthalmitis was discontinueddue to the SAE.

Table 1-8 Incidence of non-fatal ocular Serious Adverse Events Observed in Subjects in CLFG316A2203-Part A

Study Day	Preferred term	Severity	Eye type
269	Visual acuity reduced	Moderate	Both
401	Endophthalmitis	Moderate	Study
368	Endophthalmitis	Moderate	Study
29	Visual acuity reduced	Severe	Both

Adverse Events:

The most common non-ocular AEs were upper respiratory tract infection which occmTed in 17 subjects (11.3%) and hypertension which occun ed in 13 subjects (8.7%), followed by nausea, pharyngitis and bronchitis in 12 subjects each (8%). None of the AEs were deemed to be related to the study medication.

The most common ocular AE was conjunctiva! hemonhage which occurred in 99 subjects (66%), followed by vitreous floaters (25 subjects; 16.7%), eye pain (19 subjects; 12.7%), foreign body sensation (17 subjects; 11%), and eye irritation (16 subjects; 10.7%). Two subjects discontinued due to developing moderate choroidal neovascularizationin the

study eye. None of the AEs were deemed to be related to the study medication. Instead they were deemed to be related to the study procedure.

CLFG316A2203-Pa1tB

Part B of the study is a single dose, masked, randomized trial to assess the safety, tolerability and sernm pha1macokinetics of intravitreally administered LFG316 in patients with advanced AMD is completed.

Eight patients completed the study (7 receiving LFG316 and 1 receiving sham). One patient discontinued treatment on Day 15 after developing mild subretinal hemonhage. This was deemed to be due to pre-existing condition (neovascular AMD) and not related to the study medication. One patient had 3 SAEs of mild severity on Day 87 of the study. These included atrial fibrillation, gastrointestinal reflux disease and muscle weakness. None of the SAEs were deemed to be related to the study diug. There were no ocular SAEs.

Three patients receiving LFG316 had AEs. These included one patient with moderate corneal dystrophy in both eyes, abno1mal visual acuity test and Charles Bonnet syndi·ome. The patient, who had discontinued on Day 15, also developed conjunctiva! hemonhage on Day 1. The third patient developed conjunctiva! hemonhage and vitreous floaters on Day 1. None of the AEs were deemed to be related to the study medication. Conjunctiva! hemonhage is a known side effect of IVT injections.

Single dose of LFG316 CapamaC la was safe and well tolerated without any diug related adverse events.

1.2 Study purpose

The overall purpose of this study is to assess whether int:ravitreal LFG 316 redu ces int:rao cu lar inflammation in patients with active non-infectious intermediate--, posterior--, or panuveitis (NIU) who require intensification of systemic immunosuppressive therapy. If positive, the results would enable development of a more effective and specific therapy for various f01ms ofNIU.

2 Study objectives

2.1 Primary objectives

To assess the effect of intravitreal LFG316 Corporate Confidential Information on the protocol-defined, Day 85 response rate in eyes of patients who meet the inclusion criteria

The above objective applies to the study eye only. A response will be defined by any **one** of the following criteria in the study eye:

- An improvement of 2 or more steps in vitreous haze, relative to baseline. For the purpose of "step" calculation, 0.5 shall count as one of the increments. Thus, improvement from a score of 2 to 0.5 or from 1 to 0 would constitute a 2-step improvement, or
- An improvement of 10 or more letters in visual acuity, relative to baseline, or
- An improvement of 2 or more steps in anterior chamber cells score, relative to baseline or
- Absence of chorioretinal lesions as determined by the investigator
- Change in central retinal thickness from baseline to Day 85 of 50 micrometer

Remission (complete response) will be defined as any patient who has a vitreous haze score of 0 or 0.5 and who has an anterior chamber cell score of 0 and no chorioretinal lesions in the study eye and is off all immune modulat01y therapy (syste mic, c01ticosteroids and topical), without any worsening of uveitis during the trial.

2.2 Secondary objectives

- To assess the safety and tolerabilityof intrnvitreal LFG3l 6 CorporateCo nfiden t ia lI nfo rmta ion in pa tients who meet the inclusion criteria. Corporate Confidential lntormation

- To assess the effect of intrnviti-eal LFG3 l 6 CoiporateCon fden t ia l Infonn at io n on vitreous haze as measured on the Nussenblatt scale, ETDRS visual acuity, macular edema, presence or absence of chorioretinal lesions, and anterior chamber cells score in eyes with active NIU, in at least one eye, requiring intensification of systemic immunosuppressive therapy, and compared between Baseline and Days 2, 8, 15, 29, 43, 57, and 85. corporateConiirlentiallnfonnation

- To evaluate the sennn concentrations of total LFG316 and total *CS* during the course of the study.

The above objective applies to the study eye only.

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3 Investigational plan

3.1 Study design

This is a multi-center, randomized, active-controlled, open-label, proof-of-concept study. The study will be canied out at ocular inflammation specialty clinics globally. Approximately 24 patients with active N ill , in at least one eye, requiring intensification of systemic immunosuppressive therapy will be emolled and randomized in a 2:1 ratio to receive intravitreal LFG316 Corporate Confidential Information
Only one eye (designated as the study eye) will be dosed per patient.

Throughout the study, the **fellow eye** (non-sh1dy eye) should be examined and treated at the investigator's discretion (with the exceptions listed in Table 5-1); this study places no restrictions on topical/periocular/intravitreal therapy of the fellow eye. If systemic immunosuppressive therapy is required to treat either eye, patient will be placed on conventional therapy.

Low-molecular-weight non-steroidal immunosuppressive medications are allowed up to the baseline day as long as the dose has not changed in the 3 weeks prior to baseline, except for c01ticoste roid doses for which may change. At baseline, the patient's non-steroidal systemic immunosuppression will be discontinued. If patients are also receiving systemic c01ticoste roids, a rapid tapering schedule will be initiated in conjunction with their first dose ofLFG316 per the tables in Section 5.5.9.

Efficacy assessments (visual acuity and eye exams) will be conducted by a clinician masked to treatment condition. The patient will be instrncted not to divulge his or her treatment condition to this examiner.

Patients randomized to LFG316, will receive three successive int:rav i treal doses on Days 1, 29, and 57. First dose (Day 1) may occur within 14 days of Screening. After the first dose, safety, efficacy, and PK assessments will occur at 7 scheduled visits over a 12-week period.
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However, patients can attend for unscheduledvisits as needed and as determined by the investigator. Patients will be monitored for safety and ocular assessments obtained throughout treatment and follow-up periods. Patienteligibility will be assessed as outlinedin Figure 3-1 below.

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A summa1y of the study visits is shown in Table 3-1 below.

Table 3-1 Overall study scheme

	Screening Period	TreooientPeriod						
Visit	1	2	3	4	5	6	7	8
Day	-14 to -1	1	2	8	1 5	29	43	57
LFG316 5 mg Intravitreal administration (n=16)		X				X		X

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During the screening period (Day -14 to Day -1), eligibility will be verified though applicable ophthalmic/medical histmy, ocular evaluations, vital signs, safety laboratory tests, electrocardiogram, and pregnancy test.

Ocular assessments include:

- Best corrected visual acuity (ETDRS)
- Intraocular pressure (IOP)
- Slit lamp biomicroscopy
- Dilated ophthalmoscopy
- Standardized vitreous haze score (Nussenblatt et al 1985)
- Color fundus photos
- Spectral domain optical coherence tomography (sd-OCT): Study eye unless othe1wise indicated.

- Anterior chamber cells
- Chorioretinal lesions (absent/present per investigator)
- Vasculitis (absent or present per Investigator)
- Presence of chorioretinal infiltrates due to uveitis
- Macular edema due to uveitis (absent or present per Investigator)

If either eye would qualify as the study eye, one eye will be selected as the study eye during the screening period based on the following criteria

- Higher vitreous haze score;
- If not determined by vitreous haze score, then by lower visual acuity;
- If not determined by visual acuity, investigator preference.

At Baseline, vital signs will be checked and compared to eligibility criteria.

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In preparation of the LFG316 IVT injection, personnel from the study clinic should follow the LFG316 preparation and instruction manuals. These are provided separately. Patients randomized to LFG316, will receive [redacted] IVT dose of LFG316. Postdose safety assessments and ocular examination will occur after the IVT injection. PK/PD blood collection will occur prior to dosing. Corporate Confidential Information

Patients will return for scheduled follow-up visits (see Section 3.1), where ocular exams and safety assessments will take place. Safety laboratory studies and ECG will be done at the specified times throughout the trial and at the end-of-study visit.

For assessment details, refer to the Assessment schedule.

3.2 Rationale of study design

This is a randomized, prospecitve, proof-of-concept study of intravitreal LFG316 in patients with active NIU who require intensification of systemic immunosuppressive therapy to manage their disease.

This population has been selected as they may benefit from local anti-CS therapy such as LFG316 and reflect a future patient population for which this compound may be developed. Eligible patients who present with a flare and who are on systemic corticosteroids or non-steroid immunosuppressants will have their therapy tapered or stopped, respectively, at the time of intravitreal LFG316 administration. This discontinuation of systemic immunosuppressive therapy will allow for a true assessment of local LFG316 activity in

controlling the inflammation associated with NIU. Patients who do not respond to IVT therapy can be rescued by the investigator at any time and must be discontinued per protocol if their condition worsens or if they lose vision. Corporate Confide ntial Information

Patients will be monitored for safety and ocular assessments obtained throughout treatment and follow-up periods.

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Women of child-bea In g potential (WOCBP) will be included because women are equally affected by NIU and the disease is most prevalent in patients aged 20 to 50 years, however they need to have effective contraception as explained on Section 4.1.

3.3 Rationale of dose/regimen, duration of treatment

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The treatment duration of 85 days was chosen as the period beyond which lack of response would be confidently interpreted as lack of efficacy; it is based on clinician estimates of the time course of NIU response to conventional therapies. Assessing the plimaly endpoint at Day 85 allows assessment of treatment effect after the patients have received the full benefit of a course ofLFG316 (3 doses).

The treatment interval is based on comparison to the pha1macodynamics of other intravitreal monoclonal antibodies such as ranibizumab and bevacizumab. Siinilar to other intravitreal medications, the appropriate dose and interval will be dete1mined empirica lly in Phase II/III.

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3.4 Rationale for choice of comparator

Not applicable.

3.5 Risk/ Benefit for this study

Should int:ravitreal LFG316 be effective in NIU, patients may experience reduced intraocular inflammation and improved vision.

To date, LFG316 has been administered to 153 patients via IVT injection, 90 of whom have received month-ly ea.,,,,,,, LFG316 injections (See Section 1.1.1.6) for up to 18 months with good safety and tolerability. This includes the administration of over 2000 IVT injections. No dmg related toxicity was observed in trials with LFG316 at single doses of up to """""""and with repeat dosing of intravit:real L FG3 1 6 at c_,,.c-o,

IVT administration of LFG31 6 has been shown to result in relatively low levels of sernm antibody concentration and no measurable suppression of semm complement activity (as measured by the Wieslab assay)

Thus, no systemic complement suppression is suspected in the present study with IVT administration.

However, local immunosuppression could in the01y increase the eye ' s suscept ibility to infection, including endophthalmitis. Across all ongoing clinical trials with LFG316, the incidence of endophthalmitis (0.09%) has been similar to the background rate of 0.03% to 0.13% per injection in the general population. With respect to endophthalmitis, the protocol uses cmTent best practices to reduce endophthalmitis rates.

The reportedAEs and SAEs, including deaths, (See Section 1.1.1.6) are in agreement with those expected for the various patient populationsand IVT procedures employed in the administration of LFG316. Per the Reference Safety inf01mation (See investigator brochure) the expected adverse events considered 'Ve1y Common' include conjunctival haemon hage, vitreous floaters, vitreous detachment, and increased lacrimation. Events considered 'Common' include Endophthalmitis and Increased intraocular pressure. The assignment of 'common' for endophthalmitis is based on 2 cases of endophthalmitis observed in 153 patients. Both cases

were due to a common skin pathogen *(staph. Epidennidis).* Overall, these events are most likely associated with the injection procedure and not a specific chug-related toxicity. To monitor patients for these and other unexpected adverse events a comprehensive panel of ocular safety assessments based on the Phase I and Phase II studies with LFG3l 6 as well as that for other of intravitreal medications will be conducted on all patients emolled. The study also includes systemic safety assessments (serum chemistries, hematology, and electrocardiogram) at Screening and end-of-study to fmther profile any systemic changes that could be associated with the patient's disease or trnatment with LFG316.

All IVT injections cany a risk of endophthalmitis, retinal detachment, vitreous or retinal hemonhage, cataract, elevated intraocular pressure, and ocular inflammation. LFG316 itself could cause, in theo1y, adverse effects such as increased risk of endophthalmitis, cataract, elevated intraocular pressure, ocular inflanunation, and retinal toxicity. Patients with NIU are at inherent risk for some of these complications. LFG31 6 could cause existing NIU to worsen. Each of the above outcomes would be apparent on eye exam, and most would cause symptoms that would prompt the patient to seek evaluation.

As with any antibody, LFG3 l 6 may cany the risk of hypersensitiivty and patients should be monitored and managed per local center practice. LFG3l 6 may elicit immunogenicity and the fonnation of anti-LFG316 antibodies; this has not been detected in any LFG316 trials to date.

Regarding women of childbearing potential (WOCBP): to participate in this study, these patients must use effective contraception. Treatment of NIU often requires systemic immunosuppressive therapy with medications in Pregnancy Categories D and X (e.g., mycophenolic acid). By comparison for C5 inhibition with LFG316: inborn deficiency of *CS* target in mice, inborn deficiency in human offspring, and haploinsufficiency in human mothers and fathers have not been associated with reproductive or embryofetal toxicity (Rosenfeldet al 1976; Haeney et al 1980; Cesbron et al 1985; Sanal et al 1992; Delgado-Ce1viiio et al 2005; Lopez-Lera et al 2009; Zerzri et al 2010). Case se1ies on the use of another anti-CS monoclonal antibody, eculizumab, during any or all trimesters of pregnancy have not identified any bi1th defects (Danilov et al 2010). For reasons mentioned above, no systemic effect on the complement cascade is expected.

Overall, patients with NIU are expected to derive a benefit from participating in this trial with LFG3l 6. In the event activity of LFG3l 6 is not sufficient to control the inflammato1ydisease in this patient population, rescue therapy will be implemented per protocol or at the discretion of the investigator to minimize the risk to patient's vision.

3.6 Purpose and timing of interim analyses/design adaptations

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4 Population

The investigator must ensure that all subjects being considered for the study meet the following eligibility criteria. No additional exclusions should be applied by the investigator, in order that the study population will be representative of all eligible subjects.

Subject selection is to be established by checking through all inclusion/exclusion criteria at screening and study baseline. A relevant record (e.g., checklist) must be stored with the source documentation at the study site.

Replacement subjects will be emolled to replace subjects who discontinue the study for reasons other than safety, e.g., useof systemic immunosuppressive therapy to rescue fellow eye.

Deviation from **any** ently criterion excludes a subject from emollment into the study. It is expected that approximately 24 patients with NIU requiring intensification of systemic immunosuppressive therapy will be emolled in the study.

4.1 Inclusion criteria

Patients eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is perf01med.
2. Male or female patients 18 years or older.
3. Active NIU, in at least one eye, as defined below, in patients requiring intensification of systemic immunosuppressive therapy:
   - Viti·eous haze of at least 1+ at screening on the scale of Nussenblatt et al 1985, **or**
   - Chorioretinal lesions due to uveitis (chorioretinal lesions due to infectious uveitis are excluded)
   - Patients who present with a flare and who are at the time of the emollment on systemic c01ticoste roid or non-steroidal immunosuppressantswill have their therapy tapered or stopped, respectively, at the time of intravitreal LFG316 administration.
4. ETDRS visual acuity of 20 letters (20/400) or better in the study eye.
5. Women of child-bearing potential (WOCBP), defmed as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and 7 weeks (5 times the telmi nal half-life) of LFG316.
   Effective contraception methods include:
   - Total abstinence (when this is in line with the prefened and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothe1m al, post-ovulation methods) and withdrawal are not acceptable methods of conti·aception
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confomed by follow up h01mone level assessment
   - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male pa1tner should be the sole pa1tner for that subject

- Banier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK: with spennicidal foam/gel/film/cream/ vaginal suppositol y
- Use of oral, injected or implanted ho1monal methods of contraception or other fo1ms of ho1mona l contraception that have comparable efficacy (failure rate <l %) for example ho1mone vaginal ling or t1ansde1mal ho1mone contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IDS)
- In case of use of oral contraception women should have been stabile on the same pill for a minimum of 3 months before taking study treatment.

6. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

4.2 Exclusion criteria

Patient s fulfilling **any** of the following criteria are not eligible for inclusion in this study:

Clinically significant abno1mality in screening laboratol y results or electrocardiogram (see below for definition on the te1m "clinicall y significant " .

1. Uveitis that is so severe that, in the investigator's judgment, it is too Iisky to test an experimental drng.
2. Bilateral uveitis for which, in the opinion of the investigator, systemic immunosuppressive therapy is required to manage the inflammation in the fellow eye; **use of local therapy in the fellow eye is acceptable and not an explicit exclusion** (See Section 5.5.7 for acceptable concomitant treatments).
3. Histol y of retinal detachment
4. In the study eye, cataract expected to interfere with study conduct or require surgery during the study.
5. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the te1mination of gestation, confiimed by a positive hCG laboratory test (>5 mIU/ml).
6. Histmy of hypersensitivity to any monoclonal antibody (mAb).
7. Histol y of infectious uveitis or endophthalmitis in either eye
8. Anticipated need for intraocular surgel y during the study period
9. Pa1ticipation in another interventional clinical study within 12 weeks prior to the sta1t of study treatment.
10. Any medical, psychiatric, or substance-use condition likely to interfere with the patient's pa1ticipation in the study, or likely to cause se1ious adverse events during the study.
11. Uveitis with an underlying diagnosis that is uncertain and which would reasonably include a disease for which immunosuppression would be contraindicated (e.g., when the diagnosis of ocular lymphoma, histoplasmosis, toxoplasmosis, etc., are a reasonable possibility) or for which immunosuppression is not proven to be beneficial (e.g., acute zonal occult outer retinopathy, progressive outer retinal necrosis, acute retinal necrosis syndrome, etc.).
12. Fo1ms of uveitis that may spontaneously resolve such as multiple evanescent white dot syndrome (MEWDS).

13. Cunent use of or likely need for systemic medications known to be toxic to the lens, retina, or optic ne1ve (e.g., deferoxamine, chloroquine, ethambutol, etc.).
14. Change in low-molecular-weight immunosuppressive medications during the 3 weeks prior to baseline; this does not apply to co1ticosteroid doses.
15. Patient is taking co11icosteroids or another systemic immunosuppressive medication for any extraocular disease or concunent medical condition ***unrelated*** to uveiti s (e.g., multiple sclerosis, organ transplantation, moderate or severe asthma, autoimmune disease, etc.) and the tapering or discontinuation of the immunosuppression, including c011icosteroids would not be safe because of the risk of exacerbation of the extraocular condition; the patient would be excluded.
16. Any systemic immunosuppressive biologic agent given via intravitreal, intravenous or subcutaneous route such as:
    - Infliximab, daclizumab, etanercept, adalimumab, etc. **within 4** months prior to Day 1
    - Depleting antibodies, e.g., rituximab and alemtuzumab, are excluded for **12 months** prior to Day 1
17. Periocular or intra-vitrealm u gs (e.g., cmticosteroids) administered to the study eye within three months prior to Day 1.
18. Presence of ocular opacities that, in the opinion of the investigator, preclude imaging and/or reasonable vitreous haze scoring
19. Chronic hypotony (IOP < 6 mmHg) in either eye
20. Ozurdex® (dexame tha sone intra v itreal implant) administered in the study eye during the 6 months prior to Day 1
21. Retise1® (fluocinolone acetonide intravitreal implant) administered to the study eye within the 3 years prior to Day 1.
22. Topical ocular steroid therapy greater than the equivalent of prednisolone acetate 1% eve1y hour while awake within 1 week of Day 1.
23. Uncontrolled glaucoma or ocular hype11ension in either eye, defined as an intraocular pressure (IOP) >30 mmHg while on relevant therapy
24. Ocular surgery in the study eye within the last 4 months except for a diagnostic vitreous or aqueous tap with a small-gaugeneedle.
25. Laser photocoagulation in the study eye within 3 months prior to Day 1.

No additional exclusions may be applied by the investigator, in order to ensure that the sh1dy population will be representative of all eligible patients.

4.2.1 Interpretation of laboratory and electrocardiogram results

Any of the following results in isolation need not be considered clinically significant: low or moderately elevated sernm cholesterol or triglycerides; moderately low sernm creatinine; moderately elevated sernm glucose in a patient known to have diabetes mellitus; or urine white cells or positive leukocyte esterase in an patient without genitourinary symptoms. In the setting of a n01mal white blood count, mild anomalies in the leukocyte differential will not be considered clinically significant. On electrocardiogram, stable sinus bradycardia will not be considered clinically significant.

5 Treatment

5.1 Investigational treatment

The LFG3 l 6 solution for inject ion is a liquid solution at a concentration of Capon,,°''''''''''''''-
The vials contam CarparnCoaM. of active mgred1ent which conesponds to a volume of CmpamoCca5dcmtwI
The LFG316 solution for injection is also be manufactured and packaged by Nova1tis and supplied to the investigator in bulk in an open label fashion. Both f01mulations are cons idered equivalent.

Medications used as a part for IVT injection procedure need to be recorded in the appropriate concunent medication eCRF page.

5.1.1 Bio-batch Retention samples

Not applicable.

5.2 Treatment arms

Study patients will be randomized in 2:1 ratio to receive;

- LFG3l 6 (n=16) administered intravitreally or
  Corpora te Confidential Information

5.3 Treatment assignment

All study patients will be randomized to either receive c..,...,.~ of LFG316 administered intravitreally or coipora1e Confidential Information according to treatment assignment. The [redacted]numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from masked evaluator(s). A randomization list will be produced by, or under the responsibility of Nova1tis Drug Supply Management using a validated system that automates the random assignment of treatment aims to randomization numbers in the specified ratio. The randomization scheme for patients will be reviewed and approved by a member of the randomization office.

5.4 Treatment masking

The investigator, patients, and Nova1tis will not be masked to treatment condition. An evaluator at each site will be masked to treatment condition. The patient will be instructed not to divulge his or her treatment assignment to this evaluator.

5.5 Treating the patient

5.5.1 Patient numbering

Screening number

Eac h patient screened is assigned a unique screening number. The screening number is a combination of the center number that is provided by Novaliis and a three digit number sta1ting with 001 for each subject which is assigned by the Investigator. Therefore, if the center number is 1 (any leading O' s in the center number are dropped) the screening numbers

will be assigned such as 1001, 1002, 1003, etc. in ascending order. If the center number is 2 (or 0002), the screeningnumbers will be 2001, 2002, 2003, etc. in an ascending order.

Treatment number

If the patient is deemed eligible for emollment into the study and will commence the dosing period, site study personnel will contact Novaltis clinical trial leader or designee and a treatment number will be assigned for this patient.

Once assigned to a patient, a treatment number will not be reused.

There should be a source document maintained at the site which links the screening number to the treatment assignment number (once assigned).

Treatment numbers will be assigned in ascending, sequential order to eligible patients in accordance with entry into the study. The u-eatment number becomes the definitive patient number as soon as a patient receives the first dose of the respective study treatment.

The investigator will enter the u-eatment number on the eCRF.

Patients will be assigned a u-eatment number beginning with 5001 up to 5072. If a patient discontinues prior to completingthe trial, they may be replaced. The replacementpatient will be assigned a randomization number c01Tesponding to the original patient number and treatment (e.g., we will replace patient 5003 with 6003).

5.5.2 Dispensing the study treatment

Patients will receive active LFG316 or Coiporateconfidentialinformation according to their assigned treatment. LFG316 will be administered in the clinic according to the injection manual. Dispensing of Corporate ConfidentialInformation

5.5.3 Supply, storage and tracking of study treatment

LFG316 must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated staff have access. Upon receipt, the study drugs should be stored according to the instructions specified on the drng labels.

Storage conditions must be adequately monitored and appropriate temperature/humidity logs maintained as sourcedata. LFG316 solutionshouldbe storedin a refrigerator at 2 to 8°C.

LFG316 Solution for Injectionshouldbe **administered immediately and should not be used after 4 hours of initial opening at room temperature.**

Any waste material (such as syringes and needles) should be disposed of in accordance with local requiremenst. The Investigator must maintain an accurate record of the shipment, expiration date, and dispensing of study mug in a mug accountability ledger. Drug accountability will be noted by the Monitor during site visits and/or at the completion of the trial.

The following investigation site-provided products should be stored according to the manufacturers' package inse1ts:

- ProparacaineHCl 0.5% ophthalmic solution
- Lidocaine2% solution
- Povidone-iodine5% solution
- Approved ophthalmic topical fluoroquinolone

To the extent possible, same batches/lots of the above mentioned investigation site-provided products should be used in the cmTent study. Batch numbers and/or lot numbers should also be recorded in a dtug accountability ledger. *Note: site standard of care may require use of other products than those listed above-in this case the same requirements for storage and accountability apply.*

All dmg supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed by Novaitis, the Investigator must not destr·oy any dtug labels, or any pa1tly used or unused dt11g supply.

At the conclusion of the study, and during the course of the study, the Investigator will provide a copy of the dtug accountability ledgerto the Monitor.

Only after receiving a written authorization by Nova1its, the Investigator/designee will send all the unused and pa1tly used dtug supplies as well as the empty containers to the address provided at the time of authorization for destruction.

5.5.4 Instructions for prescribing and taking of study treatment

Please refer to the manual provided separately, for detailed instru ction on the use of LFG316. Procedures and required material related to IVT injection and preparation ai·e detailed in a separate manual.

For the usage of each vial of LFG316 the study personnel should record in the somce document the time when the solution is withdrawn in to the injection syringe.

For each patient the total dose injected (in mg), volume injected and the injection time need to be recorded in the somce document and on the Dosage Administr·ation Record eCRF page.

LFG316 may be prepared by qualified site personnel but the inu-avitreal injection must be administered by a qualifiedophthalmologist

5.5.5 Permitted dose adjustment

No dose adjustment is pe1mitted.

5.5.6 Rescue

5.5.6.1 Rescue of study eye

For any patients who meet the following criteria in the study eye, the study mug will be discontinued, and conventional therapy instituted:

- Loss of >10 letters in best conected visual acuity (BCVA) at any visit, as compared to baseline that in the opinion of the investigator is due to worsening of uveitis.
- Active vitritis, anterior chamber inflammation, or chorioretinitis 28 ± 3 days after their last dose that, in the opinion of the investigator, is significantly worse as compared to the previous visit and requires alternate therapy
- Unilateral flare in fellow / non-study eye which does not respond to local treatment (including ozurdex® implant) or bilateral flare in both eyes which require the intensification of systemic immunosuppressive therapy.

Patients who are rescued will be asked to attend the per protocol visit schedule for the remainder of the trial in order to be followed up for safety.

5.5.6.2 Rescue of fellow eye

The investigator will care for the fellow eye at his or her discretion. There are no restrictions on topical, periocular, or intravitreal therapy in the fellow eye other than those noted in Section 5.5.7; Table 5-1.

NOTE: If during the trial, a patient requires systemic immunosuppressive therapy for the fellow eye, investigational therapy for the study eye should be stopped and conventional therapy instituted. The patient should continue in the study for assessment purposes. Patients who require systemic immunosuppressive therapy may be replaced to maintain adequate study power if the treatment was implemented for the sole purpose of treating the fellow eye.

5.5.6.3 Recommended treatment of adverse events

Ocular adverse events should be treated according to the type of adverse event. For clinically significant acute elevation of intraocular pressure (IOP) following LFG316injection, anterior chamber paracentesis should be perfo1med and normalization of IOP verified. For sub-acute or persistent elevation in IOP, aqueous suppressants may be indicated. Iritis or vitritis should be treated in accordance with pe1mitted medications (see below). Endophthalmitis should be treated with vitreous paracentesis and culture and/or vitrectomy, as indicated, plus appropriate IVT antibiotics per local practice.

NOTE: In case of an adverse event attributed to IVT LFG316, the investigatormay wish to remove the LFG316 by pars plana vitrectomy.

With any biologic treatment, systemic hypersensitivity reactions are theoretically possible. These can manifest with itching, flushing, headache, nausea/voiniting, hypotension, urticaria, bronchospasm, or angioedema. Assess and treat for anaphylaxis if indicated, and initiate suppmtive care. Fluids, vasopressors, cmticoste roids, antihistamines, bronchodilators, and oxygen should be on hand.

Patients may remain in the study even after receiving treatment for adverse events.

Medication used to treat AEs must be recorded on the Concoinitant medications/Significant non-drng therapies eCRF page after the sta1t of study drng.

5.5.7 Concomitant, permitted, and prohibited treatments

Pe1mitted and concomitant therapies are listed in Table 5-1. Concomitant therapies should be entered on the appropriated CRF.

Table 5-1 **Permitted and concomitant therapies** Corporate Confidential Information

Arm:	**LFG316 treatment arm**	
Eye:	**Study eye**	**Fellow eye**
Complement inhibitor (other than LFG316)	**Prohibited**	**Prohibited**
Antibody (other than LFG316)	**Prohibited**	**Prohibited**
Intraocular surgery	**Prohibited**	**Prohibit ed**
Ocular laser	**Prohibited**	**Prohibit ed**
Systemic steroid or IMT already in use at screening	Pe rmitted up to base line Will be titrated / stopped per protocol May **not** be increased in dose or frequency	
New systemic steroids or IMT	**Prohibited**	
Intravitreal medication (other than LFG316)	**Prohibited**	Permitted
Periocular/intravitreal steroids	**Prohibited**	Permitted
New topical steroid or anti-inflammatory	**Prohibited**	Permitted
Cycoplegic or !OP-lowering eyedrops	Permitted	Permitted
Topical/local anesthetics and antibiotics used for intravitreal administration	Permitted	Permitted
Incidental medications not prohibited above	Permitted	Permitted

IMT = Immuno-Modulatory Therapy

5.5.8 Prohibited treatment

Prohibited treatments are listed above in Table 5-1. If a patient 1s deemed to reqmre a prohibited treatment, he or she should be withdrawn from the study.

5.5.9 Tapering schedule for oral corticosteroids

If a patient is receiving oral corticosteroids, one of the following schedules will be used for tapering the dose. The selection of the reduction schedule will be based on the prednisone dose the patient was receiving during the week prior to baseline.

1. For patients on up to 100 mg of prednisone-equivalent during the week prior to Day 1, the cmticosteroid dose should be tapered according to the following scheme (with the exact doses detennined by rounding to the nearest 5 mg): week 1, 85% of the baseline dose; week 2, 67%; week 3; 50%, week 4, 33%; week 5, 17%; week 6, 8%; weeks 7, 0%. Examples of tapering schemes in Table 5-2 are provided for baseline prednisone doses in the range 10 to 100 mg/day. During this schedule, when the patient' s prednisone equivalent is 20 mg/day or below, the dose should be taken in the morning after waking up to reduce suppression of the pituita1y and adrenal glands.
2. For patients who previously had uveitis that was controlled with a systemic immuno-suppressive drng or regimen that was discontinued and whose uveitis has flared and in whom the resumption of prednisone is not considered the appropriate systemic immunosuppressive therapy by the investigator, no prednisone will be given.

Table 5-2 Prednisone tapering schedule (100 to 10 mg/day prior to Day 1 of study)

Dose (mg/day) prior to Day 1		100	90	80	70	60	50	40	30	20	15	10
Week	**Approx. % of baseline**	Actual Daily Doses (mg)										
1	83%	85	75	65	60	50	40	35	25	15	15	10
2	67 %	65	60	50	45	40	35	25	20	15	10	5
3	50%	50	45	40	35	30	25	20	15	10	5	5
4	33	30	30	25	20	20	15	15	10	5	5	5
5	17%	20	15	10	10	10	10	5	5	5	0	0
6	8%	10	5	5	5	5	5	5	0	0	0	0
7	0%	0	0	0	0	0	0	0	0	0	0	0

The oral prednisone dose may be tapered more rapidly than specified by the appropriate schedule above in the following situations:

- the patient's uveitis is subsiding rapidly and the investigator feels it is safe to accelerate the reduction in prednisone or prednisolone dose or
- the investigator feels the prednisone or prednisolone must be tapered more rapidly because of corticosteroid-related side effects.

If a patient 's uveitis is not, in the investigator's opinion, improving rapidly enough to safely continue the steroid taper, the investigator may maintain the steroid dose for 1-2 additional weeks, after which the patient will resume tapering as per the weekly schedules above. This is not considered a rescue.

5.5.10 Discontinuation of study treatment and premature subject withdrawal

Study stopping criteria

If any of the following criteria is met, study enrollment and drug administration will stop:

- Two or more incidents of Serious Adverse Events that are, in the opinion of the investigator, related to LFG316 treatment *and not to the injection procedure.*
- The aggregate frequency, severity, and/or drug relatedness of adverse events merit such.
- The Sponsor requests it.

If drug administration is stopped, subjects already enrolled may remain in the study for observation only.

Individual patient withdrawal

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature withdrawal occurs for any reason, the investigator must make eve1y eff01i to dete1mine the prima1y reason for a subject's premature withdrawal from the study and record this info1mation on the Study Completion eCRF.

The subject should be withdrawn from the trial under the following circumstances (but not limited to):

- Withdrawalof info1med consent
- New on setof healthy issues
- Pregnancy
- Any other protocol deviation that results in a significant risk to the subject's safety

For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should document the steps taken to contact the subject, e.g., dates of telephone calls, registered letters.

5.5.11 Emergency unblinding of treatment assignment

Not applicable. Both patient and investigator are aware of treatment assignment.

5.5.12 Study completion and post-study treatment

Eac h patient will be required to complete the study in its entirety, and thereafter no further study treatment will be made available to them. The study will complete when the last subject completes his/her Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately bythe fuvestigator.

5.5.12.1 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessa1y, study patients should be seen as soon as possible and treated as described in Section 5.5.10 for a prematurely withdrawn subject. The investigator may be info1med of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for info1ming IRBs and/or ECs of the early te1mination of the trial.

6 Visit schedule and assessments

The timing of assessments required during the study is delineated in the Assessment schedule. All data obtained from these assessments must be suppo1ted in the subject' s source documentation. Source documentation must be available for all data collected during the study and a source documentation verification list provided.

Should it become necessaiy to repeat an evaluation, the results of the repeat evaluation should be captured.

Patients should be seen for all visits on the designated day with an allowed "visit window" as indicated in the Assessment schedule, or as close to it as possible.

Patients emolledCdj)Oea(6 ufitlentiallnfonnationwho discontinue LFG31 6 treatment prior to Day 85 should attend all remaining study visits in accordance with the protocol

Corporate Confidential Information

All baseline assessments must be completed prior to LFG316 administration.

Minor deviations for the following post-dose assessment times (~10-15 minutes) during baseline/Day 1 visit ai·e acceptable based on logistical and operational considerations:

- Vitals signs and body measurements during Baseline/Day 1 visit
- Ocular assessments during Baseline/Day1 visit
- 4 hours Post-injection PK/PD blood collection (if applicable)

There is no strict requirement on the time of day when patients need to return for their outpatient follow up visits.

6.1 Dietary, fluid and other restrictions

None.

6.2 Patient demographics/other baseline characteristics

Demographics

Date of birth, sex, race, and predominant ethnicity will be collected.

Relevant medical history/ Current medical conditions

Relevant medical histo1y and cmTent med ica l condit ions will be recorded on the in the eCRF until the sta1t of the study drng.

Histo1y of surgical sterilization and postmenopausal status needs to be captured under relevant medical histo1y page in the eCRF. Any event or change in the subject's condition or health status occmTing ***prior to*** the initial study drng administration will be reported in the Relevant medical hist01y/Cun ent med ical cond itions sect ion of the eCRF.

Ocular and uveitis history

Past or concmTent ocular histo1y and histo1y of uveitis diagnosis, progression, and treatments will be captured in the eCRF.

Smoking history

Smoking histo1ywill be recorded in the eCRF.

6.3 Treatment exposure and compliance

Patient compliance, based on the completion of the IVT injection, will be evaluated by the study investigator.

Drug administration record

All doses prescribed and dispensed to the subject must be recorded on the Dosage Administration Record.

Date and time of dose administration, including the staii time of the IVT injection, will be recorded in the Dosage administration record section of the eCRFs.

Study completion information

Infmmation on the date the subject last received the study drug, the subject completion or discontinuation of the study and the reason for discontinuation of the study will be recorded on the Study Completion eCRF page.

Study Completion evaluations must also be perfo1med when a subject prematmely withdraws from the study for whatever reason.

Comments

All comments related to study conduct will be added to the eCRF.

6.4 Efficacy / Pharmacodynamic assessment

6.4.1 Vitreous haze

Vitreous haze in the study eye will be measmed by the Nussenblatt scale, as described below.

Table 6-1 Vitreous haze scoring

Grade O	No haze
Trace	Slight blurring of optic disc margin
Grade 1+	Slightly blurred optic nerve and vessels
Grade 2+	Moderately blurred optic nerve and vessels
Grade 3+	Optic nerve head border blurry but visible
Grade 4+	Optic nerve head obscured

6.4.2 Anterior Chamber cells

Anter ior chamber cells will be scored as per SUN cliteria (Jabs et al 2005) described below:

Table 6-2 Anterior chamber cell grading

Grade Description	Aqueous Cells
0	1 cell
0.5	1-5 cells
1	6-15 cells
2	16-25 cells
3	26-50 cells
4	> 50 cells

6.4.3 Chorioretinal lesions

Chorioretinal lesions will be assessed as present or absent by the investigator

6.4.6 Visual acuity

Visual acuity in the study eye will be measured as described in Section 6.5.9.2 this protocol.

6.4.7 Optical coherence tomography(sd-OCT)

Spectral domain optical coherence tomography will be performed on both eyes for each patient according to the Assessment schedule. sd-OCT images will be transferred according to the imaging manual or as directed by thesponsor.

6.4.8 Total CS

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6.4.8.1 Total CS sample collection and processing

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6.4.8.2 Total CS analytical method

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6.5 Safety

6.5.1 Physical examination

Physical examination may be perfo1med by the investigatoror by the patient' s prima1y care provider, if properly source-documented. A physical exam perfo1med within 4 weeks of the appointeddate will suffice, unless the patient' s medical histo1y has changed in the interim.

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, hea1,t abdomen, back, lymph nodes, extremities, vascular system and neurological system. If indicated based on medical hist01y and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be perfo1med.

lnfo1mation for all physical examinations must be included in the source documentaiton at the study site and will not be recorded the eCRF. Significant findings that are present prior

to the sta1tof study drng must be included in the Relevant Medical Hist01y /Cun-ent Medical Conditions screen on the subject's eCRF. Significant findings made after the start of study diug which meet the definition of an Adverse Event must be recorded on the Adverse Event screen of thesubject's eCRF.

6.5.2 Vital signs

For the pmpose of this study, vital signs will include blood pressure and pulse measurements, and otic or oral body temperature. Systolic and diastolic blood pressure and pulse rate will be assessed after the subjecthas rested quietly in the sitting position for at least 3 minutes.

6.5.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

6.5.4 Laboratory evaluations

In the case where a laborat01y assessment that is listed in the inclusion/exclusion criteria is considered a clinically significant abnormality at screening, the assessment may be repeated once (for the pmpose of inclusion), and in any case, prior to emollment, to rnle out laborat01y en-or. If the repeat value is still a clinically significant abno1mality, the subject should be excluded from the study.

In the case where a laborat01y range is **not specified by the protocol,** but is outside the reference range for the center at screening, a decision regarding whether the result is of clinical significanceor not shall be made by the Investigator and shall be based, in pa1,t upon the nature and degree of the obse1ved abn01mality. The assessment may be repeated once (for the purpose of inclusion) and in any case, prior to emollment/randomization,to rnle out laboratoryen-or.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the subjectto continue in the study.

Clinically relevant deviations of laborato1ytest results occun-ing during or at completion of the study must be repo1ted and discussed with Novalt is personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandat01y until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

6.5.4.1 Hematology

Hemoglobin, hematocrit, RBC, WBC count with differential (monocytes, eosinophils, basophils, neutrophisl, lymphocytes) as percentage or as absolute value (depending on the standard rep01ting procedure of the central or local lab), and platelet count.

6.5.4.2 Clinical chemistry

Albumin, alkaline phosphatase, total bilirnbin, bicarbonate/CO_2, calcium, cholesterol, chloride, creatinine, CK, y-GT, glucose, LDH, inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, sodium, triglycerides,BUN and uric acid.

If the total bilirnbin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirnbin should be differenitated.

6.5.4.3 Urinalysis

A midstrean1 urine san1ple (approximately 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

A semi-quantitative "dipstick" evaluation for the following parameters will be performed: specific gravity, pH, glucose, protein, bilirnbin, ketones, leukocytes and blood.

If the dipstick result is positive for protein leucocytes and/or blood, the sample will be sent for microscopic analysis of WBC, RBC and casts.

6.5.5 Electrocardiogram (ECG)

ECGs will be collected at the pre-specified times. Standard 12-lead ECGs will be perfonned. Data will include the following: time of ECG, heart rate, PR interval, RR interval, QT interv al (unconected)and QRS duration. OriginalECG tracings, appropriatelysigned, will be archived at study site. This assessment will be evaluated by a central laboratory , but the investigator will be responsible for determ ining eligibility based on the ECG.

6.5.6 Pregnancy

Pregnancy tests are required of all female patients regardless of reported reproducitve/menopausal status.

Sernm pregnancy tests will be perfo1med at screening; at all other times urine pregnancy tests may be used. A female patient in this study may not receive LFG316 until the screening pregnancy test is dete1mined to be negative.

If a urine pregnancy test is performed and is found to be positive, se1um -hCG will be perf01med. If serum -hCG is positive, the patient must be discontinued from the trial.

6.5.7 Meal Record

Not applicable.

6.5.8 Chest X-ray

Not applicable.

6.5.9 Ocular assessments

6.5.9.1 Post-injection safety assessment

Following IVT injection of LFG316, perfusion of the central retinal artery should be verified by indirect ophthalmoscopy; in case of non-perfusion, treat with anterior chamber paracentesis. Normalization of intraocular pressure should be verified within 30 minutes of the injection. Intraocular pressure should be re-measured again at 60 minutes post-injection if the pressure is elevated > 10 mmHg above baseline or above 30 mmHg when measured at 30 minutes post-injection.

6.5.9.2 Best corrected visual acuity

ETDRS best-corrected visual acuity will be obtained in each eye separately under certified ETDRS conditions. This assessment is to be performed prior to pupil dilation. The number of letters read correctly (for each eye) will be recorded in the appropriate eCRF page.

6.5.9.3 Slit lamp biomicroscopy

Slit lamp exam of the adnexae, conjunctiva/sclera, cornea, anterior chamber, iris, and lens will be obtained on both eye for each patient according to the Assessment schedule. Attention should be directed to the presence of any anterior chamber cell or flare. Results from the slit lamp biomicroscopy exam (for each eye) will be recorded in the appropriate eCRF page.

6.5.9.4 Anterior Chamber cells assessment

Anterior chamber cell score will be evaluated by slit lamp biomicroscopy. The anterior chamber cells score will be determined according to the SUN criteria (Jabb et al 2005) as described in Table 6-1.

6.5.9.5 Dilated ophthalmoscopy

Dilated exam of the vitreous, optic disc, retinal vessels, macula, and retinal periphery will be obtained on both eye for each patient according to the Assessment schedule. Dilated ophthalmoscopy should be performed right after LFG316 IVT injection. Immediate anterior chamber paracentesis should be performed if central retinal artery is not perfused.

6.5.9.6 Vitreous haze assessment

Vitreous haze will be evaluated with an indirect ophthalmoscope and a hand-held 20-diopter lens. Haze is defined as a reduction in the clarity of fundus details seen through the vitreous; the degree of haze will be quantified by the examiner comparing the view to standard NEI photographs (Nussenblatt et al 1985). The standard photographs provide a grading scale with photographs of fundi with vitreous haze grades "0" (zero), "trace" (which counts as 0.5+), 1+, 2+, 3+, and 4+. If the amount of vitreous haze appears to fall between two integer grades, the value would be recorded as halfway between the grades. For example, if the haze was intermediate between that in the photographs of grades 1+ and 2+ the value would be recorded as 1.5+. The "trace" photographs correspond to 0.5+, so there is no intermediate value allowed between the grade 0 and trace, nor between trace and grade 1+. In this protocol, the words "step" and "grade" are used synonymously. One step or grade means a change of

one full unit except for the "trace" grade. For example, a change from grade 2+ to grade 1+ would count as an improvementof one grade (one step), as would a change from grade 2.5+ to grade 1.5+. However, a change from grade 1+ to O wo uld count as two grades or two steps, since it would include the "trace" grade. A change from 1.5+ to "trace" would count as a change of one grade.

Color fundus photography

Color fundus photography will be perfo1med on the designated eye(s) for each patient according to the Assessment schedule and the imaging manual. Color fundus photos will be evaluated according to AREDS scale. Color funduspho tos will be transfened according to the imaging manual provided.

6.6 Pharmacokinetics

6.6.1 PK Blood Collection and Processing

All blood samples will be taken by either direct venipuncture or an indwelling cannula. For a detailed sampling schedule please refer to the Assessment schedule and Section 13-Appendix 1.

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For all pa1ticipating patients, the date and exact time of each blood draw must be recorded on the PK Blood Collection page in the eCRF. Sampling problems will be noted in the Comments section of the PK Blood Collection page eCRF page.

6.6.2 Urine Collection and processing

Not applicable.

6.6.3 Pharmacokinetic analytical method(s)

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6.7 Other assessments

6.7.1 Health-related quality of Life

Not applicable.

7 Safety monitoring

7.1 Adverse events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occm1ing after starting the study drng even if the event is not considered to be related to study mug. Study mug includes the investigational drng under evaluation and the comparator drng or placebo that is given dming any phase of the study. Medical conditions/diseases present before starting study drng are only considered adverse events if they worsen after starting studym ug. Abnmmal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, or ar·e cons idered clinically significant, or require therapy.

The occunence of adverse events should be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detectedwhen they are volunteered by the subject during or between visits or through physical examination, laborato1ytest, or

other assessments. All adverse events must be recorded on the Adverse Events eCRF with the following info1mation:

1. the severity grade (mild, moderate, or severe)
2. its relationshipto the study drng(s) (suspected/not suspected)
3. its duration(sta1t and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

An SAE is defined as an event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birthdefect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatmentor monitoring of the studied indication,not associatedwith any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the sta1t of study drng
  - treatment on an emergencyoutpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomeslisted above

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.

If an adverse event involves an eye, the affected eye(s) must be specified.

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e., fu1ther obse1vation only); study drng dosage adjusted/temporarily intenupted; study drng perm anen tly discontinued due to this adverse event; conc01nitant medication given; non-mug therapy given; patient hospitalized/patient' s hospitalization prolonged.The action taken to treat the adverse event should be recorded on the Adverse Event eCRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be pe1manent, and assessment should be made at each visit (or more frequently, if necessa1y)of any changes in severity, the suspected relationship to the study drng, the inte1ventions required to treat it, and the outcome.

Information about common side effects already known about the investigational mug can be found in the Investigator Brochure (IB) or will be communicated between 1B updates in the fmm of Investigator Notifications. This inf01mation will be included in the patient infmmed consent and should be discussed with the patient during the study as needed.

7.2 Serious adverse event reporting

To ensure subject safety, eve1y SAE, regardless of suspected causality, occmTing after the subject has provided info1med consent and until 30 days after the subject has stopped study pa1ticipation (defined as time of last dose of study mug taken or last visit whichever is later) must be repmted to Novartis within 24 hours of learning of its occunence.

Any SAEs experienced after this 30-day period should only be reported to Novaitis if the investigator suspects a causal relationship to the study mug. RecmTent episo des, complications, or progression of the initial SAE must be repmted as follow-upto the original episode, regai·dless of when the event occurs. This repo1tmust be submittedwithin 24 hours of the investigator receiving the follow-up info1mation. An SAE that is considered completdy umelatedto a previously reported one should be repo1ted separately as a new event.

Info1mation about all SAEs is collected and recorded on the Serious Adverse Event Report Fmm. The investigator must assess the relationship of any SAE to study mug, complete the SAE Report Form in English, and send the completed, signed fo1m by fax within 24 hours to the local Novaitis Drug Safety and Epidemiology Depa1tment. The telephone and telecopy number of the contact persons in the local depaitment of Clinical Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Repo1t Fo1m and the fax confirmation sheet must be kept with the case repo1t fo1m documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Repmt Form was sent, using a new SAE Report Fo1m stating that this is a follow-up to the previously repo1ted SAE and giving the date of the original repo1t. The follow -up info1mation should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the subjectcontinued or withdrew from study pa1itcipation.

If the SAE is not previously documented in the Investigator's Brochure or Package Inse1t (new occun ence) and is thought to be related to the Novaitis study drug, a Drug Safety and Epidemiology Depa1tment associate may urgently require fu11her info1m ation from the investigator for Health Authority repo1ting. Nova1t is may need to issue an Investigator Notification(IN) to info1m all investigators invo lved in any study with the same mug that this SAE has been repmted. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and repo1ted to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulato1y requirements in pa1itcipatingcountries.

7.3 Pregnancies

To ensure subject safety, each pregnancy in a subject on study drug must be repo1ted to Novaitis within 24 hours of leaining of its occmTence. The pregnancy should be followed up to dete1mine outcome, including spontaneous or volunta1yte1mination, details of the birth, and the presence or absence of any bilt h defects, congenital abno1malities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and repmted by the investigator to the local Novaitis Thug Safety and EpidemiologyDepartment. Pregnancy follow-up should be recorded on the san1e fo1m and should include an assessment of the possible

relationship to the Novartis study drng of any pregnancyoutcome. Any SAE experienced during pregnancy must be repo1ted on the SAE Rep01t Fo1m.

Pre gnancy outcomes are not required for the female partners of the male patients who took study drng in this study.

7.4 Data Monitoring Committee

Not applicable.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator' s meeting, a Novartis representative will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entri es on the eCRFs, the adherence to the protocol and to Good Clinical Practice, the progress of emollment, and to ensure that study mug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical inf01mation, laborat01y data , elecu·ocardiog rams, and the results of any other tests or assessments. All information on eCRFs must be u·aceable to these source document s in the subject' s file. The investigator must also keep the original informed consent fo1m signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confilm their consistency with the eCRF enu·ies. Nova1tis monitoring standards require full verification for the presence of inf01med consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the eCRFs are perf01med accord ing to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated inve stigator staff will enter the data required by the protocol into the Electronic Case Report Fo1ms using fully validated software that confo1ms to 21 CFR Pait 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate e1Tor me ssages , allo w the data to be confirmed or co1Tected before u·ansfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report F01ms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the subject data for archiving at the investigational site.

8.3 Database management and quality control

The data management vendor and Novartis staff will review the data entered into the eCRFs by investigational staff for completeness and accmacy and instruct the site personnel to make any required con ections or additions. Obvious enors are conected by Cmed data manager. Queriesare sent to the investigational site using an electJ.·onic data que1y. Designated investigator site staff is required to respond to the que1y and confiim or conect the data. If the electronic que1ysystem is not used, a paper Data Que1yF01m will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novaitis staff who will make the c01Tection to the database. The signed copy of the Data Que1y F01m is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drng Reference List, which employs the Anatomical TherapeuticChemical classification system.

Medical hist01y/cmTent medical conditions and adverse events will be coded using the Medical dictiona1yfor regulatoryactivities (MedDRA) tenninology.

Throughout the study, the occmTence of any protocol deviations will be detennined. After these actions have been completed and the database has been declared to be complete and accmate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Global Head of Clinical Info1mation Sciences and the Clinical Franchise Head.

9 Data analysis

9.1 Analysis sets

All patients who received study dmg will be included in the safety analysis set.

All patients in the safety analysis set with evaluable PK data and with no major protocol deviations that have an impact on PK data will be included in the PK analysis set.

9.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and patients. For these parameters summary statistics will be provided by treatment group (i.e., each LFG316 treatment group). Corporate Confidential Information

Relevant medical hist01y, cmTent medical conditions, results of laboratory screens, drug tests and any other relevant information will be listedby treatment group andpatients.

9.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Study drug administration (including date, time of injection) will be listed by treatment and patients.

9.4 Analysis of the primary variable(s)

The primary objective of the study is to assess the effect of IVT LFG316 on Day 85 response rate in patients with active NIU requiring intensification of systemic immunosuppressive therapy. The analysis of safety data is described in Section 9.5.2. Additionalanalysis of ocular safety is described in Section 9.5.8.

9.4.1 Response rate

The primary endpoint is the response rate (proportion of patients that respond in the study eye) and the remission (complete response)rate at Day 85. The analysis of responserate at Day 85 will be caITied out on the PD analysis set. Patients will be analyzed as treated. The 90% confidence interv als for the proportion of responders in the LFG316 CorporateC onfidential Information as well as the 90% confidence interval for the difference in response rates will be reported. T he response rates at other time points (e.g., at Days 15, 29, 57) will be analyzed similarly.

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9.5 Analysis of secondary variables

9.5.1 Efficacy / Pharmacodynamics

Summary statistics for the secondary endpoints and their changes from baseline will be provided by treatment group and visit/time. Corporate Confidential Information

A longitudinal analysis of the secondary PD endpoints may be performed if deemed relevant. Graphical displays of mean time profiles may be constructed as appropriate.

9.5.2 Safety

Adverse events

All infmm ation obtained on adverse events will be listed by treatment group and subject. Time since stait of IVT injection will be indicated in the listing.

The number and percentage of subjectswith adverse events will be listed by treatment group, body system and prefen ed term. Ocular adverse events will be tabulated and summarized by study eye vs. fellow (non-study) eye. A subject with multiple adverse events within a body system or prefened term is only counted once towards the total of this body system or prefened term Corpora te Co nfidential Information

Concomitant medications / Significant non-drug therapies

All concomitant therapies will be listed by treatment group and patients.

9.5.3 Health-related quality of Life

Not applicable.

9.5.4 Pharmacokinetics

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9.5.5 Pharmacogenetics / pharmacogenomics

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9.5.6 Other assessments

Corporate Confidential Information

Corporate Confidential Information

9.5.7 PK/PD

Not applicable.

9.5.8 Ocular assessments

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Ocular assessments will be listed by treatment group and patients.

Summa1y statistics of ocular assessments will be provided by treatment group and visit/time point.

9.7 Power for analysis of key secondary variables

Not applicable .

9.8 Interim analyses

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10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and repo1ted in accordance with the ICH Haimonized Tripaltite Guidelines for Good Clinical Practice, with applicable local regulations(including EuropeanDirective 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation),IRB/IEC-approvedinfo1med consent , or, if incapable of doing so, after such consent has been provided by a legallyacceptable representative of the patient. In cases where the patient' s representative gives consent, the subject should be info1med about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicateassent by personally signing and dating the written info1med consent document or a separate assent f01m. Info1med consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Nova1tis will provide to investigators in a separate document a proposed info1medconsent fo1m that complies with the ICH GCP guideline and regulato1y requirements and is considered appropriate for this study. Any changes to the proposed consent f01m suggestedby the investigator must be agreed to by Novaitis before sublnission to the IRB/IEC, and a copy of the approved version must be provided to the Novaitis monitor after IRB/IEC approval.

In the event that Novalt is wants to perforn1 testing on the samples that ai·e not described in this protocol, additional Institutional Review Board and/or ethics comlnittee approval will be obtained.

10.3 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed info1med consent fo1m must be reviewed and approved by a properly constituted Institutional Review Board (IRB) before study stait. A signed and dated statement that the protocol and info1med consent have been approved by the IRB must be given to Novartis before study initiation. Prior to study stait, the investigator is required to sign a protocol signature page confiiming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this

protocol and to give access to all relevant data and records to Novaltis monitors, auditors, Novaltis Clinical QualityAssmance representatives, designatedagents of Novaltis, IRBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigatormust inform Novaltis immediately that this request has been made.

10.4 Publication of study protocol and results

Upon study completion and finalization of the study repolt the results of this trial may be submittedfor publication and/or posted in a publicly accessible database of clinical trial results.

11 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novaltis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are pennitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novaltis, Health Authorities where required, and the IRB. Only amendments that are required for subject safety may be implemented prior to IRB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB at the study site should be informed within 10 working days.

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Ava ilable upon request.

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13 Appendix 1: Blood collection log: blood sampling schedule for safety, PG, PK, PD, and immunogenicity

StudyPhase	Visit No	Visit Window (Days)	Time point	Safety; Biochem and hematology	PK Blood Sample	PK Col no.	PK Sample no.	Immunogenicity;Anti-l FG316	Immunogenicity Anti-l FG316 sample #	PD Blood Sample Total CS	PD Blood Total CS Sample #	Pham,acogene ic Sample #	Pharmacogenetic Sample
				ml	ml			ml		ml		ml	
Screening (Day-14 to -1)	1			15								10	9999
Day1	2		pre-dose		5	1	10	5	101	5	201		
Day2	3				5	1	11			5	202		
Day8	4												
Day15	5	+/- 1			5	1	12			5	203		
Day29	6	+/-3	pre-dose		5	2	13	5	102	5	204		
Day43	7	+/-3			5	2	14			5	205		
Day57	8	+/- 3	pre-dose		5	3	15			5	206		
Day85/EOS	9/777	+/- 3	pre-dose	15	5	4	16	5	103	5	207		
PRN		+/- 5	pre-dose		5	5	17	5	104	5	208		
Day169	10	+/- 5	pre-dose		5	6	18	5	105	5	209		
PRN		+/- 5	pre-dose		5	7	19	5	106	5	210		
Day253)	11	+/- 5	pre-dose		5	8	20	5	107	5	211		
Day281/ EOES	778	+/- 5		15	5	8	21	5	108	5	212		
Total ml				45	60			40		60		10	
Consolidated(approximate) total m l :	215												

14 Appendix 2: Sample labeling and shipping information

14.1 Sample labeling

The Samp le Numbers are reported in Section 13-Appendix 1.

The subject ID, exact clock time of dosing, as well as actual sample collection date and time will be recorded using a 24-hour clock on the appropriate blood collection summa1ypage of the eCRFs. Sampling problems will be noted in the Notes field of the eCRFs.

Examples of sample labels for different sample types are presented below.

Sample labeling for serum PK sample

The sample label is to include the following info1mation:

Study Code:	LFG3l 6A2204
Subject Number:	5101
Sample Number:	Sample 1 XX (sernm) (ex. 110 (se1um))
Vial indicator:	A or B (because resulted selum is to be split into 2 vials)
Required Timepoint:	ex. Pre-injection (or other predete lmined timepoints)
And/ Or Study Day:	ex. Day 1
Time:	hh:mm (24 hours fo1mat)
Date:	dd-Mmm-YY (ex. 18-Aug-l l)

Sample labeling for serum PD samples (total CS assay)

The sample label is to include the following info1mation:

Study Code:	LFG3l 6A2204
Subject Number:	5101
Sample Number:	Sample 2XX (sernm) (ex. 201 (se1um))
Vial indicator:	A or B (because resulted sernm is to be split into 2 vials)
Required Timepoint:	ex. Pre-injection (or other predete1mined timepoints)
And/ Or Study Day:	ex. Day 1
Time:	hh:mm (24 hours format)
Date:	dd-Mmm-YY (ex. 18-Aug-11)

Sample labeling for serum immunogenicity samples

The sample label is to include the following info1mation:

Study Code:	LFG316A2204
Subject Number:	5101
Sample Number:	Sample 1:XX (eg 101 serum)
Vial indicator:	A or B (because resulted setllllll is to be split into 2 vials)
Required Timepoint:	ex. Pre-injection (or other predete1mined timepoints)
And/ Or Study Day:	ex. Day 1
Time:	hh:mm (24 hours fo1mat)
Date:	dd-Mmm-YY (ex. 01-Oct-11)

14.2 Sample shipment instructions

For each shipment, an invent01y of the samples should accompany the shipment. This invent01y should include the study ID, subject ID, sample number, visit number, and scheduled time of collection.

Clearly indicate any missing specimens. The original inventoy will be retained at the site in the Investigator's file.

All samples will be kept at the temperature specified up to and during the shipment. Unless instructed othe1wise, the samples will be packed carefully with suitable packing material and dlyice to keep them frozen.

All shipments should be sent (Monday through Wednesday **only)** by a canier guaranteeing overnight delivery. The following items should be considered:

- Advise the ca1Tier of the type of service desired, need for personalized door-to-door pickup, and delivey guaranteed within 24 hours.
- Advise the canier of the nature of the shipment's contents (human biological specimens) and label the package accordingly.
- Indicate Novaitis drug code and Study No. on the face of the parcel to be shipped. The parcel also must cany a "dangerous goods" label because of the dty ice (labels supplied by the courier).
- The canier must be asked to store the parcel(s) in a freezer if shipment is delayed and to replaceexhausted dty ice before transpo1tation continues.
- Shipping reservations should be made to allow delive1y to Novartis before 16:00 (4 pm) local time Monday to Thursday and before 11:00 (11 am) local time on Friday. Shipmentsshouldnot be sent between Thursday and Sunday, to prevent aITival over the weekend.

14.2.1 Instructions for shipment of PK, PD, PG, and immunogenicity samples to the central lab

All study samples (PK, PD, PG, and immunogenicity) will be first sent from the study clinics to the central lab for initial storage pending scheduled batch shipments to the appropriate analytical lab. Samples should be sent to the following address-unless othe1wise directed by

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For each shipment, an invento1y of the samples should accompany the shipment. This invento1yshould include the study ID, subject ID, sample number, visit number, scheduled time ofcollection.

Additional inf01mation will be provided by the central lab manual.

Clearly indicate any Inissing specimens. The original invento1y will be retained at the site in the Investigator's file.

All samples will be kept at the temperature specified up to and during the shipment. Samples have to be packed according to the ICAO/IATA-Packing-Instrnctionsin an insulated box. To guarantee that the samples remain deep frozen during transport, use about **10 kg of dry ice** per box which will keep the samples frozen during the whole duration of the transp01t (air freight). One aliquot of samples will be shipped to the designated Laboratory. The remaining aliquots will be shipped to the same address after assurance that the first aliquots aITived in good condition.

Please notif y the addressee above *in advance* of the shipment and indicate:

- The time and date of shipping and approximate time of aITiva l,
- To whom the shipment is addressed, the study number, the name of the caITier and the shipping fo1m number(or equivalentairbill number),
- The sender's name, telephone number and alternative contact personnel,
- The total number of samples, numberof matrices if applicable, and number of ca1tons and unit weight of each ca1ton.

Also notify the Clinical Trial Leader at Novaltis when a shipment has been scheduled.

14.2.2 Instructions for shipment of PK, PD, and immunogenicity samples from central lab to the bioanalyticallab

All PK, PD, and immunogenicity specimens will be kept at the temperature specified in the PK, PD, and immunogenicity sample collection and processing sections untilshipment.

Samples have to be packed according to the ICAO/IATA-Packing-Instrnctions in an insulated box. To guarantee that the samples remain deep frozen during transport, use about **10 kg of dry ice** per box which will keep the samples frozen during the whole duration of the transpo1t (air freight).

Please notify the analytical lab contact person *in advance* of the shipment.

A shipping log must be included with the shipment. Samples should be shipped with d1y ice (use about 10 kg of diy ice per box).

Selection of the bioanalytical lab is ongoing and will be communicated to the central lab once it is finalized.

Please notify the addressee *in advance* of the shipment and indicate:

- Number of the airbill,
- The time and date of shipping and approximate time of an ival,
- Flight Number,
- To whom the shipmentis addressed, the study number, canier and the shippingform number (or equivalent airbill number),
- The sender's name, telephone number and alternative contact personnel,
- The total number of ca1tons and unit weight of each ca1ton.

Also notify the Clinical Trial Leader at Nova1tis when a shipmenthas been scheduled.

The samples should be sent at the beginning of a week in order to anive not later than Thursday.