AMENDED CLINICAL TRIAL PROTOCOL 2

COMPOUND: alirocumab

Open-Label Extension Study of EFC12492, R727-CL-1112, EFC12732, & LTS11717 Studies to Assess the Long-Term Safety and Efficacy of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia

STUDY NUMBER: LTS13463

STUDY NAME: ODYSSEY OLE

VERSION DATE / STATUS: 10 July 2015 / Approved

CLINICAL STUDY DIRECTOR: [redacted]

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CLINICAL TRIAL SUMMARY

COMPOUND: alirocumab STUDY No: LTS13463 / ODYSSEY OLE

TITLE	Open-Label Extension Study of EFC12492, R727-CL-1112, EFC12732, & LTS11717 Studies to Assess the Long-Term Safety and Efficacy of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia
INVESTIGATOR/TRIAL LOCATION	Multinational - Multicenter
PHASE OF DEVELOPMENT	Phase 3
STUDY OBJECTIVES	**Primary objective** • To assess the long-term safety of alirocumab when added to currently available lipid-modifying drug therapy in patients with heterozygous familial hypercholesterolemia (heFH) who have completed one of the following studies: EFC12492, R727-CL-1112, EFC12732 & LTS11717. **Secondary objectives** • To evaluate the long-term efficacy of alirocumab on lipid parameters. • To evaluate the long term immunogenicity of alirocumab.
STUDY DESIGN	This is a Phase 3, open-label extension (OLE), uncontrolled study. Patients must have been diagnosed with heFH in the parent study and have completed one of the four randomized, double-blind, 18-month parent studies. Patients who missed the last injection or who performed the end of treatment visit outside the expected timelines can also be enrolled. The end of treatment visit of the Double-Blind Treatment Period of the parent study corresponds to the visit 1 (Day 1) of the OLE study, except for the patients having participated in the LTS11717. These latter patients will have the opportunity to enter the OLE study, after they have completed the parent study, including the 8 week follow-up period. Patients who meet eligibility criteria at the visit 1 (Day 1) will receive a first SC injection of alirocumab on that day. All patients will receive 75 mg Q2W at entry into the OLE, with the exception of patients from EFC12732 (ODYSSEY High-FH). These latter patients, who had a screening LDL-C ≥160 mg/dL in the parent study, will hence receive 150 mg Q2W at entry into the OLE, as in the parent study. At entry in the OLE (at visit 1 on Day 1): • All eligible patients from EFC12732 will get the alirocumab dose 150 mg at Day 1. • All eligible patients from EFC12492, R727-CL-1112 and LTS11717 will get 75 mg alirocumab. The first SC injection of alirocumab will be administered in the clinic (Day 1, Visit 1). Patients from the LTS11717 will have the possibility to perform a placebo self-injection training before the first alirocumab administration using an auto-injector on that same day (Day 1), as they used a different device (a prefilled syringe) in the parent study. From Visit 1, patients have the option to self-administer or have the study drug injection administered by another designated person (such as spouse,

	relative, etc.). From Day 1 (Visit 1) until Week 8 (first unblinded LDL-C value), neither the treatment received at the end of the double-blind treatment period in the parent study, nor the lipid parameters level, will be known by the Investigator, and by the patient, in order to prevent any potential blinding breaking of the parent clinical study. However, from Week 8 (Visit 3) in the OLE, the lipid values will be communicated to the investigator in real time. From Week 12 (Visit 4), the Investigator will be responsible, based on his/her own judgment and the patients' LDL levels, to manage alirocumab dose (up-titration from 75 to 150 mg every 2 weeks, down-titration from 150 to 75 mg every 2 weeks or maintenance of the dose, will be possible). Daily dose of statin or of other lipid-modifying therapy (LMT) (if applicable) can be modified based on the Investigator's judgment throughout the study. After Week 24 (visit 5), visits will be scheduled every 24 weeks (approximately 6 months) and a dispensation visit will be scheduled in between the 24 weeks visits interval. This dispensation visit will allow to supply IMP for the next 3 months, and will also allow to check the treatment compliance, the concomitant medications, and occurrence of any adverse event. Patients should be on a stable diet (NCEP-ATPIII TLC diet or equivalent) throughout the entire study duration from visit 1 (V1) to the end of OLE treatment period (OLETP) (V17).
STUDY POPULATION **Main selection criteria**	**Inclusion criteria** • Eligible patients for this OLE study will be men and women diagnosed with heFH in the parent study and who have completed one of the following studies, EFC12492, R727-CL-1112, EFC12732 or LTS11717. Patients who missed the last injection or who performed the end of treatment visit outside the expected timelines can also be enrolled. **Exclusion criteria** • Significant protocol deviation in the parent study based on the Investigator judgment, such as non-compliance by the patient. • Adverse event leading to permanent discontinuation from parent study. • Have any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study. • Positive pregnancy test at the end of treatment visit or end of study visit, according to the parent study the patient was originating from. • Women of childbearing potential not willing to continue highly-effective method of birth control and/or who are unwilling or unable to be tested for pregnancy.
Total expected number of patients	Up to approximately 1,200 patients may be enrolled in the study.
Expected number of sites	Approximately 200 sites worldwide

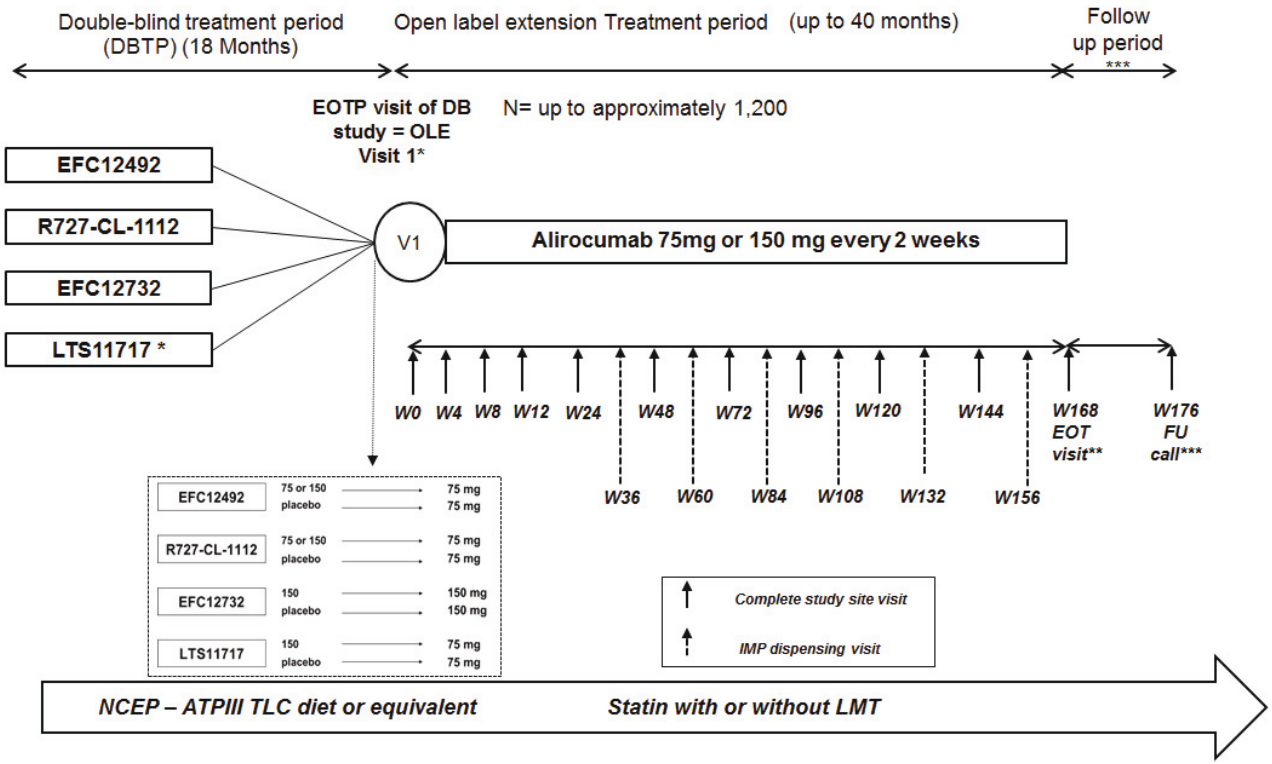
STUDY TREATMENT(s)	
Investigational medicinal product:	alirocumab
Formulation	Sterile alirocumab drug product supplied at a concentration of 75 mg/mL and 150 mg/mL in histidine, pH 6.0, polysorbate 20, and sucrose, both as 1 mL volume in an auto-injector.
Route of administration	Subcutaneous (SC) injections in the abdomen, thigh or outer area of upper arm.
Dose regimen	75 mg every 2 weeks OR 150 mg every 2 weeks
Injection for training:	Placebo
Formulation	Sterile solution consisting of histidine, pH 6.0, polysorbate 20, and sucrose, as 1 mL volume in an auto-injector.
Route of administration	Subcutaneous (SC) injections in the abdomen, thigh or outer area of upper arm
ENDPOINTS	**The primary endpoint of this study is safety.** **Safety Endpoints:** • Safety parameters (adverse events, laboratory data, vital signs) assessed throughout the OLE study. **Efficacy Endpoints of interest include:** • Calculated serum LDL-C values and percent changes from baseline of the parent study (EFC 12492, R727-CL-1112, EFC 12732 or LTS11717) over time in this study. • Proportion of patients achieving an LDL-C < 100 mg/dL (2.59 mmol/l) over time in this study. • Proportion of patients achieving an LDL-C < 70 mg/dL (1.81 mmol/L) over time in this study. • Proportion of patients with LDL-C <70 mg/dL (1.81 mmol/L) and/or ≥50% reduction from baseline of the parent study in LDL-C (if LDL-C ≥70 mg/dL [1.81 mmol/L]) over time in this study. • Values and percent changes from baseline of the parent study in other lipids and other lipoproteins, including total cholesterol, non-high-density lipoprotein cholesterol (non-HDL-C), HDL-C, triglycerides (TGs), apolipoprotein (Apo) B, ApoA-1, ApoB/ApoA-1 ratio and Lp(a) over time in this study. **Other Endpoints:** • Anti-alirocumab antibodies assessed throughout the study. • Proportion of patients who were up-titrated to 150 mg of alirocumab based on Investigator's judgment. • Proportion of patients who were down-titrated to 75 mg of alirocumab based on Investigator's judgment. • Reasons (ie, LDL-C threshold, AE) that trigger a down-titration or an up-titration of alirocumab. • EQ-5D summary scores.

ASSESSMENT SCHEDULE	**Patient assessments in the OLE period** • Day 1 / Week 0 (End of treatment visit of the parent double-blind study = OLE Visit 1, except for the patients having participated in the LTS11717). • Complete study visits: Patients will be assessed in the clinic at Weeks 4 (Visit 2), 8 (Visit 3), 12 (Visit 4), 24 (Visit 5), and then every 24 weeks until EOT Visit (Visit 17), or early termination. • IMP dispensing visits: From Week 24, until study completion IMP dispensing visits will be scheduled every 12 weeks, in-between the clinic visits in order to allow for dispensing IMP. **Patient assessments in the FU period** • A follow up call, Visit 18, will be planned 10 weeks after the last IMP injection, ie 8 weeks after the EOT visit, for the patients who will complete the study and for the patients who will early discontinue whatever the reason.
STATISTICAL CONSIDERATIONS	**Sample size determination:** As this study is an open-label extension planning to include patients from previous studies, no calculation for sample size was performed. It is expected to enroll up to 1,200 heFH patients based on the number of patients already enrolled in the parent studies. **Analysis Population:** Safety analyses will be performed on Safety population which consists of patients receiving at least one dose or partial dose of IMP in the current study. Efficacy analyses will be performed on patients receiving at least one dose or partial dose of IMP in the current study, with a baseline (from parent study) LDL-C available and with at least one LDL-C value available in the period from first IMP injection in the current study to last IMP injection + 21 days. **Analysis of safety endpoints:** Safety analysis (Adverse events, laboratory, vital signs) will be descriptive, based on the safety population. The safety analysis will focus on the Treatment Emergent Adverse Events (TEAE) period defined as the time from the first dose of the current study to the last dose of IMP + 70 days (10 weeks). For analyses of changes from baseline for laboratory and vital signs parameters, baseline of the parent study or of the current study may be considered. **Efficacy parameters:** As secondary objectives of the study, efficacy variables will be explored through descriptive statistics at each scheduled visit of the current study. Formal statistical testing is not planned and alpha adjustments not needed. 95% confidence intervals will be provided for percent changes from baseline and success rate to reach targets. In addition, percent changes from baseline of the parent study and success rate to reach targets from the week 8 time point will also be analyzed in all groups combined as the influence of treatment received during the parent study should be offset by the treatment received during the current study after 8 weeks of treatment.

DURATION OF STUDY PERIOD (per patient)	Study will end in second quarter 2017 or until the drug is commercially available for the patient in the respective country, whatever comes first. The study duration includes up to 168 weeks of treatment, ie approximately 3.5 years, for the first patients enrolled, and an additional 8 week follow up safety period for the patients who will complete the study and for the patients who will early discontinue whatever the reason. For patients in the UK, the study will last a maximum of 176 weeks.
STUDY COMMITTEES	**Data Monitoring Committee:** ☒ Yes ☐ No The independent Data Monitoring Committee (DMC) is implemented in order to monitor patient safety by conducting formal reviews of accumulated safety data. The DMC will provide the Sponsor with appropriate recommendations on the conduct of the clinical trial to ensure the protection and the safety of the enrolled patients in the study.

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



* The end of treatment period visit of the Double-Blind parent study corresponds at the V1visit (Day 1) of the OLE study, except for patient having participated in the LTS11717. These latter patients will have the opportunity to enter in the OLE study, after they have completed the parent study, including the 8-week follow-up period. For these patients, the visit V1 (Day 1) of the OLE study can occur at the time of the end of study visit, after the 8-week follow-up period.

** EOT visit = to be performed 2 weeks after the last injection for the patients who complete the study or within 5 days of treatment discontinuation for the patients who early discontinue.

*** FU call= to be performed 10 weeks after the last injection for the patients who complete the study and for the patients who early discontinue.

1.2 STUDY FLOW CHART

Day (D)/Week (W)/ Month (M)	W0 (End of DB treatment visit parent study)[c] (D1)	W 4	W 8	W 12	W 24	W 36	W 48	W 60	W 72 M18	W 84	W 96 M24	W 108	W 120 M30	W 132	W 144 M36	W 156	W 168 EOT 2Q 2017 M40	W176 EOS Call***
Visit Number	1	2	3	4	5	*6**	7	*8**	9	*10**	11	*12**	13	*14**	15	*16**	17	18
Visit Window (days)		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Design																		
Informed consent	X[a]																	
Patient demography	X																	
Inclusion/Exclusion Criteria	X[a]																	
Physical examination	X	X		X	X		X		X		X		X		X		X	
Body weight	X	X		X	X		X		X		X		X		X		X	
IVRS/IWRS contact	X[a]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment																		
Injection at site	X[a]																	
Review of diet	X						X				X				X		X	
Investigational Medicinal Product (IMP) kit dispensation	X[a]			X	X	X	X	X	X	X	X	X	X	X	X	X		
Compliance check of IMP (review patient diary [e] and treatment kit) and data collection on IMP administration	X (diary [a])	X (diary only)	X (diary only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Day (D)/Week (W)/ Month (M)	W0 (End of DB treatment visit parent study)[c] (D1)	W 4	W 8	W 12	W 24	W 36	W 48	W 60	W 72 M18	W 84	W 96 M24	W 108	W 120 M30	W 132	W 144 M36	W 156	W 168 EOT 2Q 2017 M40	W176 EOS Call***
Visit Number	1	2	3	4	5	*6**	7	*8**	9	*10**	11	*12**	13	*14**	15	*16**	17	18
Visit Window (days)		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Vital signs																		
Heart rate, blood pressure	X	X	X	X	X		X		X		X		X		X		X	
Safety																		
AE / SAE recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Central Laboratory Testing – Efficacy																		
Total-C, calculated LDL-C, HDL-C, TG, non-HDL-C	X		X		X		X		X		X		X		X		X	
Apo B, Apo A-1, ratio Apo B / Apo A-1, and Lp (a)	X						X				X		~~X~~		X		X	
Laboratory Testing – Safety																		
Central Hematology and chemistry	X		X		X		X		X		X		X		X		X	
Central Creatine phosphokinase (CPK)	X		X		X		X		X		X		X		X		X	
Central Liver panel	X	X	X	X	X		X		X		X		X		X		X	
Local Urine pregnancy test	X[b]	X	X	X	X		X		X		X		X		X		X	

Day (D)/Week (W)/ Month (M)	W0 (End of DB treatment visit parent study)[c] (D1)	W 4	W 8	W 12	W 24	W 36	W 48	W 60	W 72 M18	W 84	W 96 M24	W 108	W 120 M30	W 132	W 144 M36	W 156	W 168 EOT 2Q 2017 M40	W176 EOS Call***
Visit Number	1	2	3	4	5	6*	7	8*	9	10*	11	12*	13	14*	15	16*	17	18
Visit Window (days)		±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Laboratory Testing – Other																		
Central Anti-alirocumab antibodies**	X				X		X		X		X		X		X		X	
[redacted]	X				X						X						X	
Quality of Life Variables																		
EQ-5D patient questionnaire	X[a]			X	X		X										X	

a. Investigations to be performed specifically for the entry in OLE at Day 1 (Visit 1) in addition to all investigations planned to be performed during the End of Double-Blind treatment visit of the parent study or for patients from the LTS11717, the visit V1 (Day 1) of the OLE study can occur at the time of the end of study visit, after the 8-week follow-up period.

b. Pregnancy status should be checked by urine pregnancy testing on the Day 1 at visit 1 and during the OLE period.

c. The end of treatment period visit of the Double-Blind parent study corresponds to the visit V1 (Day 1) of the OLE study, except for patient having participated in the LTS11717. These latter patients will have the opportunity to enter in the OLE study, after they have completed the parent study, including the 8-week follow-up period. For these patients, the visit V1 (Day 1) of the OLE study can occur at the time of the end of study visit, after the 8-week follow-up period.

d. [redacted]

e. It is recommended a new diary to be dispensed to the patient at each visit starting from week 24, so that the compliance could be effectively checked at each visit

* These visits are mainly dispensing visits

** Anti-alirocumab antibodies collections are to be done prior to the IMP injection, except for the EOT visit where no IMP injection is done.

*** A follow-up safety call will be done 10 weeks after the last injection of alirocumab in case of premature discontinuation and for the patients who complete the study (see section 10.3.4).

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AI	auto-injector
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
Apo	apolipoprotein
ARF	acute renal failure
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
CBC	complete blood count
CHD	coronary heart disease
CI	confidence interval
CIB	clinical Investigator's brochure
CPK	creatine phosphokinase
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CVD	cardiovascular disease
DBTP	double blind treatment period
DM	diabetes mellitus
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DRF	discrepancy resolution form
ECG	electrocardiogram
eg	exempli gratia = for example
e-SMS	emergency scientific & medical services
e-CRF	electronic case report form
eGFR	estimated glomerular filtration rate
EDTA	ethylene diamine tetra-acetic acid
ELISA	enzyme linked immuno-sorbent assay
EOS	end of Study
EOT	end of Treatment
FH	familial hypercholesterolemia
FPI	first patient in
FU	follow-up
GCP	good clinical practice
γGT	gamma-glutamyl transferase
Hb	hemoglobin
HDL-C	high density lipoprotein cholesterol
heFH	heterozygous familial hypercholesterolemia

HLGT	high level group term
HLT	high level term
HR	heart rate
HRQoL	health-related quality of life
hs-CRP	high-sensitivity C-reactive protein
ICF	informed consent form
ICH	International Conference on Harmonization
ie	id est = that is
IEC	independent ethics committee
INN	international nonproprietary name
IMP	investigational medicinal product
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
Kg	kilogram
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
LDL-R	low-density lipoprotein receptor
LLN	lower limit of normal range
LLT	lowest Level Term
LMT	lipid-modifying therapy
LPI	last patient in
LOCF	last-observation-carried-forward
Lp(a)	lipoprotein a
MDRD	modification of diet in renal disease
MedDRA	medical dictionary for regulatory activities
µg	microgram
mITT	modified intent-to-treat
mmHg	millimeter of mercury
MTD	maximally tolerated dose
NCEP-ATPIII	National Cholesterol Education Program Adult Treatment Panel III
NIMP	non investigational medicinal product
OLE	open label extension
OLETP	open label extension treatment period
PAD	peripheral arterial disease
PCSA	potentially clinically significant abnormality
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamics
PDM	project demand manager
PT	preferred term
PTC	product technical complaint
Q2W	every 2 weeks
RDW	red blood cell distribution width
SAE	serious adverse event

SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SMQ	standardized MedDRA query
SNP	single nucleotide polymorphisms
SOC	system-organ-class
SUSAR	suspected unexpected serious adverse reaction
TOTAL-C	total cholesterol
TEAE	treatment emergent adverse event
TG	triglycerides
ULN	upper limit of normal range
WBC	white blood cell
WHO-DD	World Health Organization-Drug Dictionary
WOCBP	women of childbearing potential

4 INTRODUCTION AND RATIONALE

SAR236553 is a fully human monoclonal antibody that binds with high affinity to PCSK9. Its International Nonproprietary Name (INN) is alirocumab. Alirocumab was previously referred as SAR236553 or REGN727. All relevant information concerning the compound is available in the latest version of the Clinical Investigator's Brochure (CIB).

Background on patient populations:

This open-label extension study will include patients diagnosed with heterozygous familial hypercholesterolemia (heFH) who have completed EFC12492, R727-CL-1112, EFC12732 or LTS11717.

Familial hypercholesterolemia (FH) is an inherited disorder of lipid metabolism that predisposes a person to premature severe cardiovascular disease (CVD). Familial hypercholesterolemia has a high prevalence in Caucasian populations, where an estimated 1 in 500 individuals are affected. Defects in at least 3 different genes that code for proteins involved in hepatic clearance of low density lipoprotein-cholesterol (LDL-C) can cause FH. These include mutations in the gene coding for the LDL receptor (LDL-R) that removes LDL-C from the circulation, and less commonly, in the gene for Apo B, which is the major protein of the LDL particle. In rare cases, the gene coding for proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme involved in degrading the LDL-R (gain of function mutation), is mutated. In all cases, this results in an accumulation of LDL-C in the plasma from birth, and subsequent development of tendon xanthomas, xanthelasmas, atheromata, and premature CVD.

In the heterozygous form of FH (heFH), the cumulative risk of experiencing a coronary event by the age of 60 years without effective treatment is at least 50% in men and approximately 30% in women (coronary disease occurs approximately 10 years later in women than in men, with a marked increase in post-menopausal women). Before effective treatment with 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (commonly referred to as statins) became available, mortality from coronary disease was increased by nearly 100 fold in young FH adults aged 20 to 39 years, and approximately 4 fold for FH patients aged 40 to 59 years (1).

In the real world, a large proportion of patients with FH do not reach treatment goals and, by consequence, remain at increased risk of CVD (2). In a recent large cross-sectional study conducted in the Netherlands, nearly all heterozygous FH patients (96%) were on statin treatment. Only 21% of patients achieved the LDL-C goal of less than 100 mg/dL (less than 2.59 mmol/L) and about 5% of patients still had an LDL-C concentration greater than 200 mg/dL. Among those not at goal, 27% were on combination therapy of maximum statin dose and ezetimibe (3). These data emphasize the need for new LDL-lowering therapies.

Introduction to proprotein convertase subtilisin kexin type 9 (PCSK9) and alirocumab:

Proprotein convertase subtilisin kexin type 9 (PCSK9) belongs to the subtilisin family of serine proteases and is highly expressed in the liver. PCSK9 is involved in regulating the levels of the low-density lipoprotein receptor (LDL-R) protein (4) (5). Once PCSK9 is secreted into plasma, it directly binds to the LDL-R and promotes its degradation. The increased degradation of LDL-Rs leads to a reduced removal of LDL particles -C and therefore, higher circulating levels of LDL-C.Experiments with mice have shown that increasing PCSK9 protein levels decreases levels of LDL-R protein in the liver while PCSK9 knockout mice have increased levels of LDL-R in the liver (6), (7). In humans, PCSK9 mutations have been identified: the gain-of-function mutations are rare and cause an autosomal dominant form of severe hypercholesterolemia and premature coronary heart disease (CHD), whereas loss-of-function mutations are more common and are associated with reduced plasma levels of LDL-C and protection from CHD (8) (9).

Therefore, blocking PCSK9 from binding to the LDL-R can potentially benefit patients with hypercholesterolemia by decreasing their plasma LDL-C levels. In addition, PCSK9 messenger ribonucleic acid (mRNA) and protein levels are increased in response to statins, potentially attenuating their cholesterol-lowering effect (10).

Rationale for study design:

The objective of the present study is to provide additional long term safety and efficacy experience with alirocumab in a closer to real life setting than a double-blind design study, in patients with heFH receiving lipid-modifying drug therapy including statins.

Patients with heFH who cannot attain LDL-C goal despite lipid-modifying therapy, including a statin at maximally tolerated dose, present a high unmet need regarding their life-long increased cardiovascular risk. This study gives these heFH patients, who already participated in one of the double-blind 18-month ODYSSEY Phase 3 studies, the possibility to start or continue treatment with alirocumab after the end of the parent study. All patients will receive alirocumab at entry in the open-label extension study regardless of the study treatment they received during the 18-month double-blind treatment period of the parent study, provided they fulfill the eligibility criteria of the open-label extension study.

Description of the parent studies:

The study design of the four concerned parent studies was similar: Phase 3, 18-month treatment duration, randomized, double-blind, placebo controlled, parallel-group, multi-national, multi-center study.

They are briefly described in the table below.

Studies	EFC12492 ODYSSEY FH I	R727-CL-1112 ODYSSEY FH II	EFC12732 ODYSSEY High FH	LTS11717 ODYSSEY Long Term
Patient population enrolled	Patients diagnosed with heFH, not adequately controlled with a maximally tolerated daily dose (MTD) of statin, stable for at least 4 weeks prior to the screening visit, with or without other lipid modifying therapy (LMT)			
Screening LDL-C at entry (mg/dL)	≥ 70 with a history of documented cardiovascular disease ≥ 100 without history of documented cardiovascular disease		≥ 160	≥ 100 (then ≥ 70, as per amendment 3, for about 10% of the heFH enrolled patients) With or without documented cardiovascular disease
Sample size (heFH patients actually randomized in the parent study)	486	249	107	385 *(about 20% of all enrolled patients)*
Placebo or alirocumab dose at entry in parent study Q2W	75 mg		150 mg	
Double-blind treatment period duration	18 months			
Background LMT	MTD* statin (atorvastatin, rosuvastatin, simvastatin) +/- other LMT			

* Definition of Maximally Tolerated Dose (any of the following are acceptable):
- Rosuvastatin 20 mg or 40 mg daily
- Atorvastatin 40 mg or 80 mg daily
- Simvastatin 80 mg daily (if already on this dose for >1 year)
- Patients not able to be on any of the above statin doses should be treated with the daily dose of atorvastatin, rosuvastatin or simvastatin which is considered appropriate for the patient as per the investigator's judgment or concerns. Some examples of acceptable reasons for a patient taking a lower statin dose include, but are not limited to: adverse effects on higher doses, advanced age, low body mass index, regional practices, local prescribing information, concomitant medications, co-morbid conditions such as impaired glucose tolerance/impaired fasting glucose. The reason(s) will need to be documented in the case report form.

Rationale for dose selection:

Two doses of alirocumab are currently being evaluated in the ODYSSEY Phase 3 program: 75 mg and 150 mg, to be administered subcutaneously every 2 weeks (Q2W), based on data from the Phase 1 and 2 programs. However, for many patients, the magnitude of effect observed with the

150 mg Q2W dose may not be needed to achieve the target LDL-C goal, and starting with a lower dose may be undertaken.

From the range of Q2W doses tested in the alirocumab Phase 2 program, 75 mg Q2W has been selected to be investigated in the Phase 3 program by employing the use of a dose response model. Most patients participating in the double-blind Phase 3 trials have initially been treated with 75 mg Q2W and only those patients whose LDL-C levels remain above goal after 8 weeks of treatment are up-titrated to 150 mg Q2W (at week 12) in this initial double-blind treatment period.

Only patients who are participating in two studies, LTS11717 and EFC12732 were initiated with 150 mg Q2W. In the LTS11717 study, the aim was to provide the highest systemic exposure to alirocumab, in order to gather adequate safety and tolerability information at this dose; EFC12732 only included patients with a LDL-C level above 160 mg/dL (4.14 mmol/L) while receiving maximal tolerated statin: the aim was to assess the benefit from starting directly at the most effective dose in this specific population of patients who need large LDL-C decrease.

In the OLE study, patients will start treatment with 75 mg Q2W, regardless of the treatment / dose they received at the end of the parent study, except patients from EFC12732. These latter patients, who had a screening LDL-C $\geq$ 160 mg/dL in the parent study, will receive 150 mg Q2W at entry into the OLE. Based on LDL-C value that will be unblinded from Week 8, the treatment dose can be up-titrated to 150 mg Q2W for patients receiving 75 mg Q2W or down-titrated to 75 mg Q2W for patients receiving 150 mg Q2W from Week 12 as needed. In order to maintain the blind in the parent study, which will still be ongoing at the time the first patients are included in the OLE, no information will be available on the treatment / dose received at the end of the parent study, nor on LDL-C level at the end of the parent study / baseline of the OLE.

Brief description of the OLE study:

Depending on the parent study the patient participated in, either 75 mg or 150 mg every 2 weeks will be administered at the entry in the OLE study.

From Week 12 (Visit 4), based on the Investigator judgment and the LDL-C level unblinded from Week 8, dose adjustment, such as up-titration to 150 mg Q2W or down-titration to 75 mg Q2W of alirocumab, will be possible. It is anticipated that in real life, after initial up-titration, subsequent dose adjustment over time may include down-titration. This will be allowed in this study, and the Investigator will be asked to report the reason for down-titration from 150 to 75 mg Q2W and for up-titration from 75 mg to 150 mg Q2W.

Taking into consideration the current number of patients enrolled in the four parent studies, it is estimated that up to approximately 1,200 patients could be enrolled.

This open-label extension study will be conducted for approximately three additional years or more, depending on the inclusion date in the current study, after the 18-month double-blind treatment period of the parent studies.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of this study is to assess the long-term safety of alirocumab when added to currently available lipid-modifying drug therapy, in patients diagnosed with heterozygous Familial Hypercholesterolemia who have completed one of the four parent studies.

5.2 SECONDARY

The secondary objectives of this study are

- To evaluate the long-term efficacy of alirocumab on lipid parameters
- To evaluate the long-term immunogenicity of alirocumab

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This is a multicenter, multinational, Phase 3, open-label extension, uncontrolled study to assess the long-term safety and efficacy of alirocumab, when added to currently available LMT, in heFH patients previously participating in the ODYSSEY FH I, ODYSSEY FH II, ODYSSEY High FH or ODYSSEY Long Term studies.

Patients must have been diagnosed with heFH in the parent study, have completed one of the above parent studies, and be willing to participate in the ODYSSEY OLE study. Patients who missed the last injection or who performed the end of treatment visit outside the expected timelines can also be enrolled.

The visit 1 (Day 1) of the ODYSSEY OLE study corresponds to:

- the end of treatment visit of the Double-Blind Treatment Period for the patients enrolled in one of the three following parent studies ODYSSEY FH I, ODYSSEY FH II, ODYSSEY High FH.
- the end of study visit, after the 8 week follow-up period, for the patients having participated in the ODYSSEY Long Term study.

Patients who meet eligibility criteria at the visit 1 (Day 1) will receive the first SC injection of alirocumab in the clinic on the same day.

In addition, patients from the ODYSSEY Long Term study will have the possibility to perform a placebo, self-injection training, before the first alirocumab administration using an auto-injector on that same day (Day 1), as they used a different device (a prefilled syringe) in the parent study.

At entry in the ODYSSEY OLE study, visit 1 on Day 1:

- All eligible patients from ODYSSEY High FH will get the alirocumab 150 mg dose.
- All eligible patients from ODYSSEY FH I, ODYSSEY FH II and ODYSSEY Long Term will get alirocumab 75 mg.

From Week 12 (Visit 4), the Investigator will manage, based on his/her own judgment and LDL-C values, adjustment of alirocumab doses (either up-titration from 75 to 150 mg every 2 weeks or down-titration from 150 to 75 mg every 2 weeks, or maintenance of the dose, will be possible).

The study consists of:

- An open-label treatment period with alirocumab of up to 168 weeks, ie approximately 3.5 years, for the first patients enrolled, or until the product becomes commercially available for the patient in the country, whatever comes first.
- A post-treatment safety follow up period of 10 week-duration after last IMP injection for all the patients, the patients who will complete the study and the patients who will early discontinue whatever the reason.

Although the background therapies, statin at MTD or other LMT (if applicable), should be maintained stable if possible, they might be adjusted based on Investigator judgment, in particular in case of tolerability issue. The reasons of any adjustment should be documented and recorded in the e-CRF.

For adjustments based on LDL-C values, simultaneous adjustments in alirocumab dose and any LMT should be avoided.

Patients will be asked to continue to follow a stable diet (equivalent to the National Cholesterol Education Program Adult Treatment Panel III Therapeutic Lifestyle Changes (NCEP ATP III TLC) during the study.

Patients will return for regular on site visits according to the flow chart for additional laboratory testing, questionnaires, clinical examination and IMP dispensation.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The OLE study is planned to be completed in second quarter 2017 which corresponds to a study duration of approximately 168 weeks for the first patients enrolled or until the drug is commercially available for the patient in the respective country, whatever comes first. For patients in the UK, the study will last a maximum of 176 weeks.

The study duration includes up to approximately 3.5 years of treatment for the first patients enrolled, and 10 weeks of follow up after the last IMP injection for all the patients, those who will complete the study and those who will early discontinue whatever the reason.

The study will be considered as completed for a patient in the following situations:

- When the alirocumab is commercially available in the patient’s country
- In second quarter 2017, if alirocumab is not yet commercially available in the patient’s country

An EOT visit will be done 2 weeks after the last IMP injection and a safety follow up call 10 weeks after the last IMP injection.

The following situations will be considered as premature discontinuation of the patient from the study:

- Any withdrawal from the study to switch to an anti-PCSK9 inhibitor different from commercial alirocumab
- Any other reason

An unscheduled visit should take place within 5 days after the last IMP administration if possible, with assessments normally planned at the EOT visit, and a safety follow up call performed 10 weeks after the last IMP injection (see section 10.3.4).

The end of study per patient is the last protocol planned call. Patients with a Serious Adverse Events (SAEs) or an Adverse Event of Special Interest (AESI) should be followed until resolution, stabilization, or death.

6.2.2 Determination of end of clinical trial (all patients)

The end of the study is scheduled to be in second quarter 2017, including in the UK, which corresponds to the last protocol planned call of the last patient.

6.3 INTERIM ANALYSIS

Interim analyses might be performed if requested by Health Authorities or if needed for the purpose of scientific communication.

6.4 STUDY COMMITTEE

Data Monitoring Committee:

An independent Data Monitoring Committee (DMC), composed of members who are independent from the Sponsor and the study Investigators, is implemented in order to monitor patient safety by conducting formal reviews of accumulated safety data. The DMC will provide the Sponsor with appropriate recommendations on the conduct of the clinical trial to ensure the protection and safety of the patients enrolled in the study.

All activities and responsibilities of the DMC are described in the DMC charter.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Eligible patients for this OLE study will be patients diagnosed with heFH in the parent study and who have completed one of them: ODYSSEY FH I, ODYSSEY FH II, ODYSSEY High FH or ODYSSEY Long Term studies. Patients who missed the last injection or who performed the end of treatment visit outside the expected timelines can also be enrolled.

I 02. Signed written informed consent

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are sorted into the following 3 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. Significant protocol deviation in the parent study based on the Investigator judgment, such as non-compliance by the patient

E 02. Any patient who experienced an adverse event leading to permanent discontinuation from parent study

E 03. Patients having any new condition or worsening of existing condition which in the opinion of the Investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study

E 04. Patients who will be prescribed fibrates, other than fenofibrate

7.2.2 Exclusion criteria related to the background therapies

E 05. All contraindications to the background therapies or warnings/precautions of use (when appropriate) as displayed in the respective National Product Labeling

7.2.3 Exclusion criteria related to the current knowledge of alirocumab

E 06. Known hypersensitivity to monoclonal antibody or any component of the drug product

E 07. Positive pregnancy test at last visit of the parent double-blind study (Day 1, Visit 1)

E 08. Women of childbearing potential not willing to continue highly-effective method(s) of birth control (as defined in the informed consent form and/or in a local protocol addendum) and/or who are unwilling or unable to be tested for pregnancy

Note: Women of childbearing potential must have a confirmed negative pregnancy test at Visit 1 at entry in the OLE. They must use an effective contraceptive method throughout the entire duration of the study treatment, and for 10 weeks after the last injection of IMP, and agree to repeat urine pregnancy test at designated visits. The applied methods of contraception have to meet the criteria for a highly effective method of birth control according to the "Note for guidance on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals (CPMP/ICH/286/95)" (11).

Postmenopausal women must be amenorrheic for at least 12 months.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT

Sterile alirocumab drug product will be supplied at a concentration of 75 mg/mL and 150 mg/mL in histidine, pH 6.0, polysorbate 20, and sucrose, both as 1 mL volume in an auto-injector (AI).

Unlike the patients from the other studies, the patients from the ODYSSEY Long Term study used a different device (a prefilled syringe) in the parent study, and thus will have the possibility to perform on Visit 1 (Day 1) a placebo, self-injection training, using an auto-injector, before the first alirocumab administration.

Injection for training: Sterile placebo for alirocumab will be prepared in the same formulation as alirocumab without the addition of protein as 1 mL volume in an auto-injector, for those patients willing to perform injection training.

Note: Only in the event the manufacturer faces any performance or supply issues of the auto-injector, contingency alternatives are the following ones, in order to ensure the continuity of the study treatment without interruption:

- In case of disruption of the 150 mg auto-injector, and the use of 75 mg auto-injectors is maintained:
  - patients receiving the 150 mg dose will need to administer 2 injections of 75 mg as 1 mL each in an auto-injector,

  OR

  - patients will be switched to the use of prefilled syringes of 150 mg, with one injection of 1 mL.
- In case of disruption of either 75 mg or both auto-injectors, patients will be switched to the use of prefilled syringes of 75 mg and 150 mg, with one injection of 1 mL for each of these doses.

Should this occur, the alternative investigational medicinal product will be maintained until the end of the study.

8.1.1 Route and method of administration

A manual for IMP administration (injection instruction manual) will be provided to patients containing detailed instructions on use, in particular for the patients having participated in the ODYSSEY Long Term study, for which the device was a prefilled syringe. Also, an administration package containing gauzes, alcohol swabs, band aids, etc. will be provided to the patients.

The IMP could be administered by self-injection or by another designated person (such as a spouse, relative, etc…). The used auto-injector will be discarded in a sharps container which will be provided to patients. It is recommended that the subcutaneous IMP injections be rotated within an anatomical area (eg, right thigh then left thigh or right abdomen then left abdomen). Patients also have the option to inject in a different anatomical area (eg, thigh then abdomen) during the study.

If another concomitant drug is being injected at the same site planned for the IMP injection, then the patient should be advised to use an alternate location for administration of the IMP.

Patients will be asked to store the IMP in a refrigerator. Prior to administration, the IMP should be set outside in a safe location at room temperature for about 30 to 40 minutes. Thereafter, the IMP should be administered as soon as possible.

Instructions as outlined above should be provided to the patient (or another designated person [such as spouse, relative, etc...] that will administer the injections) at training and as needed during the course of the study. Close supervision and feedback should be given at the first visit, and other visits as needed. Anyone that plans to administer the IMP must be trained by the study staff.

8.1.2 Timing of administration

On Day 1, visit 1, patients from the ODYSSEY Long Term study will have the possibility to perform a placebo, self-injection training using an auto-injector, before the first alirocumab injection.

On the same day, the first alirocumab injection will be done at the site by the patient or another designated person (such as spouse, relative, etc) under direct site staff supervision. Patients will be monitored at the investigational site for at least 30 minutes after this first injection in this study.

Alirocumab subcutaneous injections will then be performed outside of the clinic, every two weeks up to the last injection planned in the protocol. If the injection is scheduled to take place on the same date as the site visit, then the IMP should be administered after the blood sampling has been completed.

Alirocumab should ideally be administered subcutaneously every two weeks at approximately the same time of the day. The time of the day is based upon patient’s preference; however it is acceptable to have a window period of ± 3 days.

If by mistake or due to other circumstances an injection is delayed:

- by more than 7 days or completely missed, then the patient should return to the original schedule of study treatment administration without administering delayed injections.
- by less than or equal to 7 days from the missed date, then the patient should administer the delayed injection and then resume the original schedule of study treatment administration.

8.2 NON-INVESTIGATIONAL MEDICINAL PRODUCTS

The following classes of drugs are identified as non-IMP because the medication is either a background therapy or a potential rescue medication:

- Statins
- Cholesterol absorption inhibitors (ezetimibe)
- Bile acid-binding sequestrants (such as cholestyramine, colestipol, colesevelam)
- Nicotinic acid
- Fenofibrate
- Omega-3 fatty acids (≥1000 mg daily)

Please see Section 8.8 for further information.

8.3 BLINDING PROCEDURES

From Day 1 (visit 1) until Week 8 (first unblinded LDL-C value),

- neither the treatment received during the double-blind treatment period of the parent study,
- nor the lipid parameters levels,

will be known by the Investigator and by the patient, in order to prevent any potential to jeopardize the blinding of the parent clinical study.

From Week 8 (visit 3), the lipid parameters values will be communicated to the Investigator in real time.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

This is an open-label study and every patient will receive alirocumab. Treatment kit numbers will be allocated via interactive voice/web response system (IVRS/IWRS). Patients will keep the same identification number that they were allocated in the parent study.

From Week 12 (Visit 4), the Investigator will manage, based on his/her own judgment and LDL-C value from sample obtained at the previous scheduled visit, adjustment of alirocumab doses (either up-titration from 75 mg to 150 mg every 2 weeks or down-titration from 150 mg to 75 mg every 2 weeks, or maintenance of the dose, will be possible). For adjustments based on LDL-C values, simultaneous adjustments in alirocumab dose and any LMT should be avoided.

8.5 PACKAGING AND LABELING

Each alirocumab treatment kit will be prepared to contain 6 auto-injectors in a child-resistant package.

In addition to the alirocumab treatment kits, a training kit containing 1 placebo auto-injector will be prepared for the purpose of instructing patients on injection administration, in particular for patients originating from the ODYSSEY Long Term study.

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

8.6 STORAGE CONDITIONS AND SHELF LIFE

The IMP will be stored in a refrigerator between +2°C and + 8°C (36°F to 46° F) by the site. The temperature of the site refrigerator should be checked daily and recorded on a log sheet.

The IMP that will be stored at the investigational site should be kept in an appropriate locked room, under the responsibility of the Investigator or designee or other authorized person in accordance with the storage conditions indicated on the label.

After the supply of IMP kits to patients at the study site visits, appropriate provisions will be in place for transportation of the IMP kits from the study site to the patient’s refrigerator.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMP will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.7.1 Treatment accountability and compliance

IMP administration data will be recorded by the patients onto a patient’s diary.

Measures taken to ensure and document IMP compliance and accountability are described below:

- The Investigator or designee will obtain via IVRS/IWRS the treatment kit number(s) and he/she will dispense the treatment kit(s) to the patient.
- The accountability is to be performed at IMP kit re-supply visits only (see Section 10.1.1). The used kit(s) and unused auto-injector(s) should be brought back to such visits for accountability purposes.
- The Investigator or designee will complete the corresponding treatment log form from patient's diary.
- The Investigator/study coordinator will enter data in the appropriate e-CRF pages, according to data recorded in the treatment log form.
- The monitor will check the data consistency between e-CRF pages, treatment log forms using patient's diary, and returned unused auto-injectors of a corresponding kit.

8.7.2 Return and/or destruction of treatments

A detailed treatment log of the destroyed IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team. The Investigator will not destroy the unused IMP unless the Sponsor provides written authorization.

If the site is not able to destroy or destruction of IMPs are not allowed in the country, all treatments kits will be retrieved by the Sponsor. A detailed treatment log of the returned IMP will be established with the Investigator or designee and countersigned by the Investigator and the Monitoring Team.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to the study drug until the end of the patient's participation in the study.

Concomitant medications should be kept to a minimum during the study. However, if these are considered necessary for the patient's welfare and are unlikely to interfere with the IMP, they may be given at the discretion of the Investigator, with a stable dose (when possible). Besides the specific information related to concomitant medications provided in this section, any other concomitant medication(s) will be allowed and will have to be recorded in the e-CRF and source data.

8.8.1 Management of background lipid-modifying therapy

Throughout the whole treatment period, the patients should stay, as far as possible, on the stable maximally tolerated registered daily dose of statins, with or without other LMT, that was received during the parent study.

Background LMT may be adjusted as per the Investigator's judgment, for example in case of tolerability issue. Any adjustment will be documented in the e-CRF. For adjustments based on LDL-C values, simultaneous adjustments in alirocumab dose and any LMT should be avoided.

For background LMT, including statins, sites must follow the national product label for the safety monitoring and management of patients.

Lipid profile values from samples obtained after inclusion will be blinded until week 8.

8.8.2 Contraception

Women of childbearing potential must use an effective contraceptive method throughout the study treatment, and for 10 weeks after the last IMP injection for those patients who discontinue prematurely.

8.8.3 Prohibited concomitant medications

Forbidden concomitant medications from the initial visit until the last visit include the following:

- Fibrates, other than fenofibrate.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY SAFETY ENDPOINTS

The safety parameters (adverse events, laboratory data, vital signs) will be assessed throughout the study.

The definition and reporting procedures of Adverse Events (AE), Adverse Events of Special Interest (AESI) and Serious Adverse Events (SAE) and management of specific laboratory abnormalities are described in sections 10.4 to 10.6.

Adverse event observation period:

The observation of safety data will be as follows:

- Pre-treatment observation period is defined as the time from signing the informed consent to the time of first dose of alirocumab in the current study. The adverse events occurring during this period will be reported and recorded in the parent study data base.
- TEAE period: the TEAE (Treatment Emergent Adverse Event) observation period is defined as the time from first dose of alirocumab in the OLE up to 70 days (10 weeks) after the last dose of alirocumab received in the OLE study for the patients who will either complete the study or who will prematurely discontinue, as residual effect of treatment is expected until 10 weeks after the stop of alirocumab.
- Post-treatment period: the post-treatment observation period is defined as the time starting the day after the end of the TEAE period up to the end of the study (see definition in section 6.2.1).

Death observation period:

The death observations are per the observation period defined above. In addition, “post-study” death includes all deaths reported after the end of the study (see definition of end of study period per patient in Section 6.2.1).

9.1.1 Adverse events

All adverse events diagnosed by the investigator will be reported and described.

All AEs will be coded to a “Lowest Level Term (LLT)”, “Preferred Term (PT)”, “High Level Term (HLT)”, “High Level Group Term (HLGT)” and associated primary “System Organ Class (SOC)” using the version of MedDRA (Medical Dictionary for Regulatory Activities) currently in effect at Sanofi at the time of the considered database lock.

9.1.2 Safety laboratory

The clinical laboratory data consist of hematology (red blood cell count, hemoglobin, red blood cell distribution width (RDW), reticulocyte count, hematocrit, platelets, white blood cell count with differential blood count), standard chemistry (glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, total protein, LDH, albumin, γ Glutamyl Transferase [γGT]), liver panel (ALT, AST, ALP, and total bilirubin), and CPK.

Some additional safety laboratory parameters may be reflexively measured based on actual data (see Section 10.4.5.1).

Clinical laboratory values will be analyzed after conversion into standard international units. Standard international units will be used in all listings and tables.

9.1.3 Vital signs measurement

Vital signs include: heart rate, systolic and diastolic blood pressure in sitting position.

The study-specific and general safety criteria are developed in Section 10.4.

9.2 SECONDARY ENDPOINTS

9.2.1 Efficacy endpoints

Efficacy will be assessed on the following parameters during the efficacy period. The efficacy period is defined as the time from the first alirocumab dose in the current study up to 21 days after the last dose of alirocumab.

- Percent change in calculated LDL-C from baseline of the parent study over time in this study

  Percent change at Week X is defined as: 100 x (calculated LDL-C value at Week X - calculated LDL-C value at baseline) / calculated LDL-C value at baseline
- The absolute change in calculated LDL-C (mg/dL and mmol/L) from baseline of the parent study over time in this study
- Proportion of patients achieving an LDL-C<100 mg/dL (2.59 mmol/L) over time in this study
- Proportion of patients achieving an LDL-C<70 mg/dL (1.81 mmol/L) over time in this study
- Proportion of patients with calculated LDL-C<70 mg/dL (1.81 mmol/L) and/or ≥50% reduction in calculated LDL-C from baseline of the parent study (if LDL-C ≥70 mg/dL) over time in this study
- Values and percent changes from baseline of the parent study over time in this study for the following parameters:
  - total cholesterol,

- non-high-density lipoprotein cholesterol (non-HDL-C),
- HDL-C,
- Fasting triglycerides (TGs),
- lipoproteins: apolipoprotein (Apo) B, ApoA-1, ApoB/ApoA-1 ratio (for this parameter only absolute changes) and Lp(a)

The analysis windows used to allocate a time point to a measurement will be defined in the Statistical Analysis Plan (SAP).

9.2.2 Efficacy assessment method

Total-C, HDL-C, TG, Apo B, Apo A-1, and Lp (a) will be directly measured by the Central Laboratory as per the schedule in Section 1.2. LDL-C will be calculated using the Friedewald formula (12) at all visits. If TG values exceed 400 mg/dL (4.52 mmol/L) then the central lab will reflexively measure (via the beta quantification method) the LDL-C rather than calculating it. Non-HDL-C will be calculated by subtracting HDL-C from the total-C. Ratio Apo B/Apo A-1 will be calculated. Detailed procedures of sample preparation, storage and shipment will be described in the specific laboratory manual which will be provided to sites. Information on the processing, methodology and other relevant information will be available upon request, in The Medpace Reference Laboratory Manual.

Efficacy endpoints will not be considered as Adverse Events, such as those involving abnormalities in lipid levels, unless meeting the criteria in Section 10.4.2.

9.3 OTHER ENDPOINTS

9.3.1 Anti-alirocumab antibody assessment

9.3.1.1 Sampling time

Serum samples for anti-alirocumab antibody determination will be drawn periodically throughout the study as per schedule noted in the study flowchart of Section 1.2. All scheduled samples will be obtained before IMP injection (predose).

9.3.1.2 Sampling procedure

Detailed procedure of sample preparation, storage and shipment will be described in the specific laboratory manual which will be provided to sites. Five (5) ml blood volume is to be collected for each anti-alirocumab antibody sample.

9.3.1.3 Bioanalytical method

[redacted]

[redacted]

9.3.2 EQ-5D patient questionnaire

EQ-5D™ (13) is a standardized and generic instrument for measuring patient's health status and health-related quality of life (HRQoL) for clinical and economic assessments (See Appendix E).

EQ-5D™ instrument includes 5 items corresponding to the following domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Each item can take one of three responses: (1) "no problems", (2) "some problems", and (3) "severe problems".

Response to items can be converted to a standard utility score ranging between -0.594 representing "severe problems" and 1 representing "no problem".

EQ-5D endpoints include:

- Change in proportion of patients within each domain and response categories from baseline to Weeks 12, 24, 48, and End of OLETP.
- Change in mean EQ-5D utility scores from baseline to Weeks 12, 24, 48, and End of OLETP.

9.3.3 Other exploratory endpoints

9.3.3.1 Up-titration assessment

- Proportion of patients who were up-titrated to 150 mg of alirocumab based on Investigator's judgment.
- Reasons that trigger an up-titration of alirocumab will be documented in the e-CRF.

9.3.3.2 Down-titration assessment

- Proportion of patients who were down-titrated to 75 mg of alirocumab based on Investigator's judgment.
- Reasons that trigger a down-titration of alirocumab will be documented in the e-CRF.

10 STUDY PROCEDURES

For all visits after Day 1/Week 0 (first visit), a time window of ± 7 days during the whole treatment period, including the follow-up call as applicable) will be allowed.

For all visits after Day 1/first visit, if one visit date is changed, then the next visit should take place according to the original schedule as outlined Section 1.2.

Blood samplings:

The blood sampling for determination of lipid parameters (ie, total-C, LDL-C, HDL-C, TG, non-HDL-C, Apo B, Apo A-1, ratio Apo B/Apo A-1, Lp [a]) should be performed in the morning, in fasting condition (ie overnight, at least 10-12 hours fast and refrain from smoking) for all site visits requiring blood sampling throughout the study. Alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the blood sampling are discouraged.

Note: if the patient is not in fasting conditions, the blood sample will not be collected and a new appointment will be given the closest as possible to the date of this visit) to the patient with instruction to be fasted (see above conditions).

Laboratory tests:

The laboratory data are collected in accordance with the study schedule in Section 1.2 and forwarded to the central laboratory:

- Hematology: blood cell count including hematocrit, hemoglobin, red blood cell count, red blood cell distribution width, reticulocyte count, white blood cell count with differential count and platelets
- Chemistry: glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, total protein, LDH, albumin, and γGT
- Liver panel: ALT, AST, ALP, and total bilirubin; in case of total bilirubin values above the normal range, differentiation into conjugated and non-conjugated bilirubin will occur automatically.
- Creatine Phosphokinase (CPK).
- Local urine pregnancy test.

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix C and Appendix D.

Anti-alirocumab antibody samples: see section 9.3.1.

[redacted]

Physical examination:

A general physical examination should be performed at the time points indicated in the study schedule flowchart in Section 1.2. If a new clinically significant abnormality or worsening from baseline is detected after informed consent signed, then an AE should be reported and the patient should be considered for further clinical investigations and/or specialist consultation as per the Investigator's medical judgment.

Blood pressure (BP)/heart rate:

BP should be measured in sitting position under standardized conditions, approximately at the same time of the day, on the same arm, with the same apparatus (after the patient has rested comfortably in sitting position for at least five minutes). Values are to be recorded in the e-CRF; both systolic blood pressure and diastolic blood pressure should be recorded.

Throughout the OLE study, blood pressure should be measured on the same arm as the one used in the parent study.

Heart rate will be measured at the time of the measurement of blood pressure.

Notes: in case of high BP values at first visit the Investigator is responsible for the optimization of the patient's treatment to achieve BP targets as defined by local guidelines or the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) (14).

Body weight:

Body weight should be obtained with the patient wearing undergarments or very light clothing and no shoes, and with an empty bladder. The same scale should be used throughout the study.

Calibrated balance scales should be used to guarantee accuracy of patients' weight. Self-reported weights are not acceptable; patients must not read the scales themselves.

10.1 VISIT SCHEDULE

10.1.1 Open-label Treatment Period

10.1.1.1 Initial Visit: Visit 1 (Visit 1/Week 0/Day 1)

Only patients who meet the inclusion criteria as noted in Section 7.1 should be asked for participation of this extension study.

The first visit will take place:

- At the end of treatment (EOT) visit of the double-blind treatment period for the patients enrolled in the following parent studies: ODYSSEY FH I, ODYSSEY FH II and ODYSSEY High FH. A minimal interval of 11 days between the last injection of IMP in the parent study and the parent EOT visit/OLE first visit should be kept in order to avoid any possible overdose.
- At the end of study (EOS) visit, after the 8-week follow up period, for the patients enrolled in the ODYSSEY Long Term study.

For the patients having participated to one of these studies: ODYSSEY FH I, ODYSSEY FH II and ODYSSEY High FH.

Perform the investigations already planned in the EOT visit of the parent study:

Only the investigations scheduled in the EOT of the parent studies and which are necessary at the inclusion in OLE are listed below:

- Collect adverse events
- Record concomitant medication
- Get body weight measurement
- Take vital signs including heart rate and blood pressure
- Perform physical examination
- Review patient's diet. Patient should be on a NCEP-ATPIII TLC diet or equivalent.
- Completion of EQ-5D questionnaire by patient
- Urine pregnancy test (females of childbearing potential only)
- Obtain fasting blood sample for:
  - Lipid parameters: measure and/or calculation
  - [redacted]

- Hematology
- Chemistry
- Liver panel
- CPK
- Anti-alirocumab antibodies

In addition, perform the investigations scheduled for the current OLE study:

- Complete informed consent - the patient will receive complete information about the study both verbally and in writing. Written informed consent for the study must be obtained prior to any study-related investigations.
- Assess inclusion/exclusion criteria
- If the patient is confirmed eligible, the Investigator will start the next study procedures:
  - IVRS/IWRS contact for allocation of a 7-digit treatment kit number according to the list. Investigators should never allocate a treatment kit number to a patient without contacting IVRS/IWRS.
- IMP kit dispensation as per treatment kit number provided by IVRS along with schedule reminder. The patient injection instruction manual and treatment administration package should be provided. The patient diary should be given and instructions on its completion should be reviewed.
- The first IMP injection will take place at the study site, but only after the collection of the fasting blood samples and after the assessment of all evaluations planned at that visit. Close supervision, feedback and further training, if necessary, to be provided for IMP administration. The patient should be observed for at least 30 minutes after the injection.
- Collect adverse events from this point onward:
  - All adverse events and serious adverse events will be collected from the time of informed consent signature and throughout the study until the last planned protocol visit.
- Reminders
  - An appointment will be given for the next visit.
  - Patient to bring the diary at the next visit.

For the patients having participated to the ODYSSEY Long Term study

Perform the investigations already planned in the EOS visit of the parent study:

Only the investigations scheduled in the EOS of the parent study and which are necessary at the inclusion in OLE are listed below:

- Collect adverse events
- Record concomitant medication

- Get body weight measurement
- Take vital signs including heart rate and blood pressure.
- Perform physical examination (including neurological exam)
- Urine pregnancy test (females of childbearing potential only)
- Obtain fasting blood sample for:
  - Anti-alirocumab antibodies.
  - In case of clinically relevant abnormal values of the following parameters at the EOT visit, fasting blood sample will be obtained at this EOS visit for:
    - Hematology
    - Chemistry
    - Liver panel
    - CPK.

Note: if the patient is not in fasting conditions, the blood sample will not be collected and a new appointment will be given the day after (or as close as possible to this date) to the patient with instruction to be fasted (at least 10 to 12 hours fasting). Alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the blood sampling are discouraged.

<u>In addition, perform the investigations scheduled for the current OLE study:</u>

- Complete informed consent - the patient will receive complete information about the study both verbally and in writing. Written informed consent for the study must be obtained prior to any study-related investigations.
- Assess inclusion/exclusion criteria
- Completion of EQ-5D questionnaire by patient
- Obtain fasting blood sample for:
  - Lipid parameters
  - [redacted]
  - If not done at the EOS visit:
    - Hematology
    - Chemistry
    - Liver panel
    - CPK.

If the patient is confirmed eligible, the Investigator will start the next study procedures:

- A training placebo injection with an auto-injector will be proposed:
  - IVRS/IWRS contact for allocation of a batch number for training kit

- Record batch number allocated in e-CRF.
- Injection training should be provided as outlined in Section 8.1.1
- The placebo should be administered by the patient or another designated person (such as spouse, relative, etc...) at the study site under supervision of site staff with appropriate feedback.
- IVRS/IWRS contact for allocation of a 7-digit treatment kit number according to the list. Investigators should never allocate a treatment kit number to a patient without contacting IVRS/IWRS.
- IMP kit dispensation as per treatment kit number provided by IVRS along with schedule reminder. The patient injection instruction manual and treatment administration package should be provided. The patient diary should be given and instructions on its completion should be reviewed.
- The first IMP injection will take place at the study site, but only after the collection of the fasting blood samples and after the assessment of all evaluations planned at that visit. Close supervision, feedback and further training to be provided for IMP administration. The patient should be observed for at least 30 minutes after the injection.

- Collect adverse events from this point onward: All adverse events and serious adverse events will be collected from the time of informed consent signature and throughout the study until the last planned protocol visit.
- Reminders
  - An appointment will be given for the next visit.
  - Patient to bring the diary at the next visit.

10.1.1.2 Visit 2/ Week 4 (Day 29 ± 7)

- Collect adverse events
- Record concomitant medication
- Take vital signs including heart rate and blood pressure
- Get body weight measurement
- Physical examination
- Data collection on IMP administration and IMP compliance check by review of diary
- Obtain blood sample for:
  - Liver panel
- Local urine pregnancy test (females of childbearing potential only).
- Reminders
  - An appointment will be given for the next visit.

- Patient to bring the diary at the next visit.
- Remind patient to be in fasting conditions (ie overnight, at least 10-12 hours fast and refrain from smoking) for next study site visit. Also, alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next visit are discouraged.

10.1.1.3 Visit 3/ Week 8 (Day 57 ± 7)

- Collect adverse events
- Record concomitant medication
- Take vital signs including heart rate and blood pressure
- Data collection on IMP administration and IMP compliance check by review of diary
- Obtain fasting blood sample for:
  - Lipids: measure or calculation of total-C, LDL-C, HDL-C, TG, non-HDL-C
  - Hematology
  - Chemistry
  - CPK
  - Liver panel
- From week 8 onwards, lipid parameters will be unblinded and communicated to the investigator in real time.
- Local urine pregnancy test (females of childbearing potential only).
- Reminders
  - An appointment will be given for the next visit.
  - Patient to bring the diary and used kits and unused auto-injectors at the next visit.
  - Remind patient to be in fasting conditions (ie, overnight, at least 10-12 hours fast and refrain from smoking) for next visit. Also, alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next visit are discouraged.

10.1.1.4 Visit 4/ Week 12 (Day 85 ± 7)

- Collect adverse events
- Record concomitant medication
- Take vital signs including heart rate and blood pressure
- Get body weight measurement
- Physical examination
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit

- Obtain blood sample for:
  - Liver panel
- Local urine pregnancy test (females of childbearing potential only).
- Completion of EQ-5D questionnaire by patient
- IVRS/IWRS contact for allocation of a batch number for treatment kit, in accordance with dosage adjustment decided by the investigator
- IMP kit dispensation and treatment administration package should be provided. The patient injection instruction manual and diary may be given, as needed. From week 12 onwards, the Investigator will have the possibility to up or down-titrate the alirocumab dosage according to the lipid values and his/her clinical judgment.
- Reminders
  - An appointment will be given for the next visit.
  - Patient to bring the diary and used kits and unused auto-injectors at the next visit
  - Remind patient to be in fasting conditions (ie overnight, at least 10-12 hours fast and refrain from smoking) for next visit. Also, alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next visit are discouraged.

10.1.1.5 Visit 5/ Week 24 (Day 169 ± 7)

- Collect adverse events
- Record concomitant medication
- Take vital signs including heart rate and blood pressure
- Get body weight measurement
- Physical examination
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit
- Obtain fasting blood sample for:
  - Lipids: measure or calculation of total-C, LDL-C, HDL-C, TG, non-HDL-C
  - Hematology
  - Chemistry
  - CPK
  - Liver panel
  - Anti-alirocumab antibodies
  - [redacted]
- Local urine pregnancy test (females of childbearing potential only).

- Completion of EQ-5D questionnaire by patient
- IVRS/IWRS contact for allocation of a batch number for treatment kit
- IMP kit dispensation and treatment administration package should be provided. The patient injection instruction manual and diary may be given, as needed.
- Reminders
  - An appointment will be given for the next visit.
  - Patient to bring the diary and used kits and unused auto-injectors at the next visit.

10.1.1.6 Visit 6/ Week 36 (Day 253 ± 7)

- Collect adverse events
- Record concomitant medication
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit.
- IVRS/IWRS contact for allocation of a batch number for treatment kit
- IMP kit dispensation and treatment administration package should be provided. The patient injection instruction manual and diary may be given, as needed.
- Reminders
  - An appointment will be given for the next visit.
  - Patient to bring the diary and used kits and unused auto-injectors at the next visit
  - Remind patient to be in fasting conditions (ie, overnight, at least 10-12 hours fast and refrain from smoking) for next visit. Alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next visit are discouraged.

10.1.1.7 Visit 7/ Week 48 (Day 337 ± 7)

- Collect adverse events
- Record concomitant medication
- Take vital signs including heart rate and blood pressure
- Get body weight measurement
- Physical examination
- Review patient's diet. Patient should be on a NCEP-ATPIII TLC diet or equivalent.
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit
- Obtain fasting blood sample for:
  - Lipids: measure and/or calculation of total-C, LDL-C, HDL-C, TG, non-HDL-C, Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp (a)

- Hematology
- Chemistry
- CPK
- Liver panel
- Anti-alirocumab antibodies

- Local urine pregnancy test (females of childbearing potential only).
- Completion of EQ-5D questionnaire by patient
- IVRS/IWRS contact for allocation of a batch number for treatment kit
- IMP kit dispensation and treatment administration package should be provided. The patient injection instruction manual and diary may be given, as needed.
- Reminders
  - An appointment will be given for the next visit.
  - Patient to bring the diary and used kits and unused auto-injectors at the next visit.

10.1.1.8 Visit 8/ Week 60 (Day 421 ± 7)

- Collect adverse events
- Record concomitant medication
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit.
- IVRS/IWRS contact for allocation of a batch number for treatment kit
- IMP kit dispensation and treatment administration package should be provided. The patient injection instruction manual and diary may be given, as needed.
- Reminders
  - An appointment will be given for the next visit.
  - Patient to bring the diary and used kits and unused auto-injectors at the next visit
  - Remind patient to be in fasting conditions (ie overnight, at least 10-12 hours fast and refrain from smoking) for next visit. Alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next visit are discouraged.

10.1.1.9 Visit 9/ Week 72/ Month 18 (Day 505 ± 7)

- Collect adverse events
- Record concomitant medication
- Take vital signs including heart rate and blood pressure
- Get body weight measurement

- Physical examination
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit
- Obtain fasting blood sample for:
  - Lipids: measure or calculation of total-C, LDL-C, HDL-C, TG, non-HDL-C
  - Hematology
  - Chemistry
  - CPK
  - Liver panel
  - Anti-alirocumab antibodies
- Local urine pregnancy test (females of childbearing potential only).
- IVRS/IWRS contact for allocation of a batch number for treatment kit
- IMP kit dispensation and treatment administration package should be provided. The patient injection instruction manual and diary may be given, as needed.
- Reminders
  - An appointment will be given for the next visit.
  - Patient to bring the diary and used kits and unused auto-injectors at the next visit.

10.1.1.10 Visit 10/ Week 84 (Day 589 ± 7)

- Collect adverse events
- Record concomitant medication
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit.
- IVRS/IWRS contact for allocation of a batch number for treatment kit
- IMP kit dispensation and treatment administration package should be provided. The patient injection instruction manual and diary may be given, as needed.
- Reminders
  - An appointment will be given for the next visit.
  - Patient to bring the diary and used kits and unused auto-injectors at the next visit
  - Remind patient to be in fasting conditions (ie, overnight, at least 10-12 hours fast and refrain from smoking) for next visit. Alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next visit are discouraged.

10.1.1.11 Visit 11/ Week 96 / Month 24 (Day 673 ± 7)

- Collect adverse events
- Record concomitant medication
- Take vital signs including heart rate and blood pressure
- Get body weight measurement
- Physical examination
- Review patient's diet. Patient should be on a NCEP-ATPIII TLC diet or equivalent.
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit
- Obtain fasting blood sample for:
  - Lipids: measure and/or calculation of total-C, LDL-C, HDL-C, TG, non-HDL-C, Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp (a)
  - Hematology
  - Chemistry
  - CPK
  - Liver panel
  - Anti-alirocumab antibodies
  - [redacted]
- Local urine pregnancy test (females of childbearing potential only).
- IVRS/IWRS contact for allocation of a batch number for treatment kit
- IMP kit dispensation and treatment administration package should be provided. The patient injection instruction manual and diary may be given, as needed.
- Reminders
  - An appointment will be given for the next visit.
  - Patient to bring the diary and used kits and unused auto-injectors at the next visit.

10.1.1.12 Visit 12/ Week 108 (Day 757 ± 7)

- Collect adverse events
- Record concomitant medication
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit.
- IVRS/IWRS contact for allocation of a batch number for treatment kit

- IMP kit dispensation and treatment administration package should be provided. The patient injection instruction manual and diary may be given, as needed.
- Reminders
  - An appointment will be given for the next visit.
  - Patient to bring the diary and used kits and unused auto-injectors at the next visit
  - Remind patient to be in fasting conditions (ie, overnight, at least 10-12 hours fast and refrain from smoking) for next visit. Alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next visit are discouraged.

10.1.1.13 Visit 13/ Week 120/ Month 30 (Day 841 ± 7)

- Collect adverse events
- Record concomitant medication
- Take vital signs including heart rate and blood pressure
- Get body weight measurement
- Physical examination
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit
- Obtain fasting blood sample for:
  - Lipids: measure and/or calculation of total-C, LDL-C, HDL-C, TG, non-HDL-C
  - Hematology
  - Chemistry
  - CPK
  - Liver panel
  - Anti-alirocumab antibodies
- Local urine pregnancy test (females of childbearing potential only).
- IVRS/IWRS contact for allocation of a batch number for treatment kit
- IMP kit dispensation and treatment administration package should be provided. The patient injection instruction manual and diary may be given, as needed.
- Reminders
  - An appointment will be given for the next visit.
  - Patient to bring the diary and used kits and unused auto-injectors at the next visit.

10.1.1.14 Visit 14/ Week 132 (Day 925 ± 7)

- Collect adverse events

- Record concomitant medication
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit.
- IVRS/IWRS contact for allocation of a batch number for treatment kit
- IMP kit dispensation and treatment administration package should be provided. The patient injection instruction manual and diary may be given, as needed.
- Reminders
  - An appointment will be given for the next visit.
  - Patient to bring the diary and used kits and unused auto-injectors at the next visit
  - Remind patient to be in fasting conditions (ie, overnight, at least 10-12 hours fast and refrain from smoking) for next visit. Alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next visit are discouraged.

10.1.1.15 Visit 15/ Week 144/ Month 36 (Day 1009 ± 7)

- Collect adverse events
- Record concomitant medication
- Take vital signs including heart rate and blood pressure
- Get body weight measurement
- Physical examination
- Review patient's diet. Patient should be on a NCEP-ATPIII TLC diet or equivalent.
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit
- Obtain fasting blood sample for:
  - Lipids: measure and/or calculation of total-C, LDL-C, HDL-C, TG, non-HDL-C, Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp (a)
  - Hematology
  - Chemistry
  - CPK
  - Liver panel
  - Anti-alirocumab antibodies
- Local urine pregnancy test (females of childbearing potential only).
- IVRS/IWRS contact for allocation of a batch number for treatment kit
- IMP kit dispensation and treatment administration package should be provided. The patient injection instruction manual and diary may be given, as needed.
- Reminders

- An appointment will be given for the next visit.
- Patient to bring the diary and used kits and unused auto-injectors at the next visit.

10.1.1.16 Visit 16/ Week 156 (Day 1093 ± 7)

- Collect adverse events
- Record concomitant medication
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit.
- IVRS/IWRS contact for allocation of a batch number for treatment kit
- IMP kit dispensation and treatment administration package should be provided. The patient injection instruction manual and diary may be given, as needed.
- Reminders
  - An appointment will be given for the next visit.
  - Patient to bring the diary and used kits and unused auto-injectors at the next visit
  - Remind patient to be in fasting conditions (ie, overnight, at least 10-12 hours fast and refrain from smoking) for next visit. Alcohol consumption within 48 hours and intense physical exercise within 24 hours preceding the next visit are discouraged.

10.1.1.17 End-of-treatment visit: Visit 17/ Week 168/ Month 40 (Day 1177± 7)

The end of study is scheduled to be in second quarter 2017 or when the drug will become commercially available for the patient in the respective country whatever comes first. Thus, the End-of-treatment visit might be performed earlier than on Week 168 according to the date of inclusion of each patient in the OLE study, or if the patient early discontinues the study.

- Collect adverse events
- Record concomitant medication
- Take vital signs including heart rate and blood pressure
- Get body weight measurement
- Physical examination
- Review patient's diet. Patient should be on a NCEP-ATPIII TLC diet or equivalent.
- Data collection on IMP administration and IMP compliance check by review of diary and treatment kit
- IVRS/IWRS contact to document the end of treatment
- Obtain fasting blood sample for:
  - Lipids: measure and/or calculation of total-C, LDL-C, HDL-C, TG, non-HDL-C, Apo B, Apo A-1, ratio Apo B/Apo A-1, and Lp (a)

- Hematology
- Chemistry
- CPK
- Liver panel
- Anti-alirocumab antibodies
- [redacted]

- Local urine pregnancy test (females of childbearing potential only).
- Completion of EQ-5D questionnaire by patient.
- Reminders
  - For all the patients, those who prematurely discontinue the treatment irrespective of the reason and those who will complete the study, an appointment will be given for the Follow up call. This phone call will have to be scheduled 10 weeks after last injection (+/- 7 days).

10.1.2 Post-treatment Follow up period

End of Study Phone call: Visit 18/ Week 176 (± 7 days)

This phone call is to be done for all the patients, those who discontinue the treatment prematurely, whatever the reason, and those who will complete the study, and will take place approximately 10 weeks after the last injection of alirocumab.

- Collect adverse events
- Record concomitant medication, including any commercially available PCSK9 inhibitor different from alirocumab
- IVRS/IWRS contact to document the end of study

10.2 DEFINITION OF SOURCE DATA

Evaluations that are reported in the e-CRF must be supported by appropriately signed identified source documentation related but not limited to the following:

- Agreement, date, and signature of informed consent mentioning the study identification.
- Patient identification, last participation in a clinical trial, medical history, associated diseases, and data related to the studied pathology.
- Contraception methods for women of childbearing potential.
- Previous and concomitant medication (including the lipid modifying therapy).
- Study identification.
- Treatment number, dates of administration.

- Dates of visits and assessments including the examination report.
- Vital signs, height, body weight.
- Faxed central lab reports (dated and signed by the Principal Investigator or Sub-Investigator).
- IVRS/IWRS confirmation fax (training kit allocation, treatment reallocation, discontinuation, end of open label extension period, end of study).
- Adverse events and follow-up:
  - In case of SAE, the site should file in the source document at least copies of the hospitalization reports and any relevant examination reports documenting the follow-up of the SAE.
- Date of premature study discontinuation (if any) and reason.

Source documentation may be found in the following:

- Patient's identity.
- Medical history.
- Hospital records.
- Nursing notes.
- Physician's notes.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily or permanently according to the context. Any IMP discontinuation should be fully documented in the e-CRF and source notes.

Pregnancy will lead to definitive treatment discontinuation in all cases.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation (also referred to as treatment interruption) may be considered by the Investigator because of suspected AEs. Reinitiating of treatment with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 7.1 and Section 7.2).

All treatment interruption duration should be recorded by the Investigator in the appropriate e-CRF screens when considered as confirmed.

Treatment interruption is defined as one or more scheduled injections that are not administered to the patient as decided by the Investigator.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation (also referred to as treatment discontinuation) is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time.

Patient withdrawal from the study treatment or study should be avoided as much as possible.

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the e-CRF.

Patients should discontinue the IMP for the following reasons:

- Pregnancy, intention for pregnancy, or no longer with effective contraceptive method of birth control (females only).
- Acute injection reaction of clinical concern.
- Serious adverse event (or non-serious but severe in intensity) of hypersensitivity reaction considered related to IMP.
- At patient request.
- If, in the Investigator's opinion, continuation with the administration of the IMP would be detrimental to the patient's well-being.
- Intercurrent condition that requires discontinuation of the IMP (eg, laboratory abnormalities, please refer to decision tree Appendix C).
- Any abnormal laboratory value will be immediately rechecked for confirmation before making a decision of permanent discontinuation of the IMP for the concerned patient
- At the specific request of the Sponsor.

10.3.4 Handling of patients after permanent treatment discontinuation

Patients who prematurely discontinue study treatment (regardless of the reason) should undergo an unscheduled visit with assessments normally planned at the end of treatment visit (it should take place within 5 days of treatment discontinuation, if possible).

The patient, at a minimum, should then be followed up for at least 10 weeks from last study treatment administration or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

A final End of Study phone call will take place with assessments at 10 weeks after the premature treatment discontinuation.

All definitive discontinuation of study treatment should be recorded by the Investigator in the appropriate screens of the e-CRF and in the patient's medical records when considered as confirmed. IVRS/IWRS should be notified when a patient prematurely discontinues study treatment.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason. If possible, the patients should be assessed using the procedure defined above.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the e-CRF and in the patient's medical records (with, in this medical records, at least date of withdrawal and reason for) when considered as confirmed.

For patients who fail to return to the site, the Investigator should make the best effort to re-contact the patient (eg, contacting patient's family or private physician, reviewing available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter)

Patients who have withdrawn from the study cannot be included in the study again. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

Please refer to Appendix B for Adverse Event (AE) reporting requirements.

10.4.1.1 Adverse event

An **adverse event (**AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.1.2 Serious adverse event

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

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

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event
  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

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

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependency or drug abuse
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study or aggravated during the study
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study.

10.4.1.3 Adverse event of special interest

Adverse events of special interest (AESI) are AEs (serious or non-serious) that need to be monitored, documented, and managed in a pre-specified manner described in the protocol. Please see Section 10.4.4 for additional information.

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP, spanning from the signature of the informed consent form of the current study until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding screen(s) of the e-CRF.

- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP.
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI

See Appendix B for a summary of AE reporting guidelines.

10.4.3 Instructions for reporting serious adverse events

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

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

- A back-up plan (using paper flow) is available and should be used when the e-CRF system does not work.

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

10.4.4 Guidelines for reporting adverse events of special interest

10.4.4.1 AESI with immediate notification:

For these AEs, the Sponsor will be informed immediately (ie, within 24 hours), as per SAEs notification described in Section 10.4.3, even if not fulfilling a seriousness criterion, using the corresponding screens in the e-CRF.

- ALT≥3 ULN (if baseline ALT<ULN) Or ALT≥2 times the baseline value (if baseline ALT≥ULN) (Please refer to related flowchart in Appendix C). Baseline to be considered is the baseline of the current study.
- Allergic events
  - Allergic drug reactions and/or local injection site reactions deemed to be allergic (or have an allergic component) that require consultation with another physician for further evaluation of hypersensitivity/allergy, as per the investigator's medical judgment or as per Section 10.6.2, should be reported as an AESI with immediate notification.
  - All allergic events, and all injection site reactions having an allergic component or deemed to be allergic, require completion of the specific e-CRF screen (see Section 10.6.2), regardless of requirements for immediate reporting.
- Hemolytic anemia (See Section 10.4.5.1 and Appendix D)
  - If there is a decrease in hemoglobin and reflexive testing as per Appendix D suggesting hemolysis, then report this as an AESI with immediate notification. Special e-CRF screen will need to be completed.
- Pregnancy
  - Pregnancy occurring in a female patient included in the clinical trial.
    - Pregnancy will be recorded as a pre-specified AE with immediate notification in all cases. It will be qualified as an SAE only if it fulfills the SAE criteria.
    - IMP should be discontinued.
    - The follow-up of the pregnancy will be mandatory until the outcome has been determined.
  - Pregnancy occurring in the partner of a male patient included in the clinical trial. If permitted by the female partner and by local regulatory policies,

- Pregnancy will be recorded as a pre-specified AE with immediate notification in all cases. It will be qualified as an SAE only if it fulfills the SAE criteria.
- The follow-up of the pregnancy will be mandatory until the outcome has been determined.

- Symptomatic Overdose with IMP
  - An overdose (accidental or intentional) is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic injection counts) and defined as at least twice of the intended dose within the intended therapeutic interval (ie, 2 or more injections from the treatment kit are administered in <7 calendar days); to be reported using the corresponding screens in the e-CRF using the Term 'Symptomatic OVERDOSE (accidental [or intentional])'. The patient should be monitored and appropriate symptomatic treatment instituted.
  - The circumstances of the overdose should be clearly specified in the verbatim.
- Neurologic Events
  - Neurologic Events that require additional examinations/procedures and/or referral to a specialist should be reported immediately (ie, within 24 hours), as per SAEs notification described in Section 10.4.1.3, even if not fulfilling a seriousness criterion.
- Ophthalmologic Events
  - Ophthalmologic Events that require additional examinations/procedures and/or referral to a specialist should be reported immediately (ie, within 24 hours), as per SAEs notification described in Section 10.4.1.3, even if not fulfilling a seriousness criterion.

10.4.4.2 AESI without immediate notification:

- Asymptomatic Overdose with IMP

An overdose is defined in the above section.

In case of an asymptomatic overdose with IMP, the event should be reported using the corresponding screens in the e-CRF using the Term "Asymptomatic OVERDOSE (accidental [or intentional])". The patient should be monitored for any adverse events and treated, as needed

- Local injection site reactions (see section 10.6.1)

Local injection site reactions that are considered as non-allergic events and that are related to the IMP injection, as opposed to another injectable agent, should be further characterized by evaluating the related symptoms that comprise an injection site reaction such as but not limited to redness, pain, etc (See Appendix F). Special e-CRF screens will need to be completed. If such an AE were to occur, then do not report the individual components of the reaction but rather the term "local injection site reaction", with the individual components being described in the specific e-CRF screen.

- Allergic events not referred for consultation with another physician (see above section)

- All allergic events will need to have allergy specific e-CRF screens completed (see Section 10.6.2), regardless of requirements for immediate reporting.

- Neurologic Events
  - Any AEs related to neurologic abnormalities with the exception of those requiring additional examinations/procedures and/or referral to a specialist should be reported.
- Ophthalmologic Events
  - Any AEs related to ophthalmologic abnormalities with the exception of those requiring additional examinations/procedures and/or referral to a specialist should be reported.

10.4.5 Guidelines for management of specific laboratory abnormalities

Laboratory abnormalities with pre-specified monitoring should be monitored, documented, and managed according to the related flowchart in protocol Appendix C and Appendix D.

Where it is applicable in the flowchart, baseline is defined as baseline in the current study.

- Neutropenia
- Thrombocytopenia
- Increase in ALT
- Acute renal insufficiency
- Decrease in hemoglobin (defined as ≥1.5 g/dL)
- Increase in CPK and suspicion of rhabdomyolysis.

10.4.5.1 Hemoglobin decrease

At the first post-inclusion occurrence of a hemoglobin (Hb) measurement decrease by ≥1.5 g/dL as compared to the first visit (in the current study) hemoglobin measurement, then the Central Lab will reflexively measure haptoglobin using specimens already obtained at the same time point for which the hemoglobin decrease was detected. The Central Lab will provide the results of the reticulocyte count, haptoglobin, LDH and indirect bilirubin [reflexively measured only if the total bilirubin >ULN] to the investigator (see Appendix D).

- If the following pattern of abnormalities is noted:
  - Reticulocyte count >Central Lab's upper limit of the reference range (also referred to as ULN) AND
  - Haptoglobin <Central Lab's lower limit of the reference range (also referred to as LLN) AND
  - LDH>ULN AND
  - Indirect bilirubin >ULN (only if the total bilirubin >ULN),

- The patient should be referred to a hematologist. The hematologist should obtain a peripheral blood smear and anti-erythrocyte antibodies (direct and indirect) by Coombs test. Further investigations are at the discretion of the hematologist.

- If the results are normal or the pattern of abnormality is something other than that described above, then the Investigator should exercise his/her medical judgment in the interpretation of the results, necessity for workup of the decrease in hemoglobin or referral to a hematologist.

If a second hemoglobin measurement demonstrating a further decrease of ≥1 g/dL from the last available value is observed, even if the previous work-up was negative, the same investigations can be repeated and a hematology consultation can be requested at the discretion of the Investigator or at the Sponsor's request.

10.5 OBLIGATIONS OF THE SPONSOR

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

- all SAEs that are both unexpected and at least reasonably related to the IMP (Suspected Unexpected Serious Adverse Reaction; SUSAR), to the Health Authorities, IECs/IRBs as appropriate and to the Investigators.
- all SAEs that are expected and at least reasonably related to the IMPs to the Health Authorities, according to local regulations.

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected, as given in the Investigator's Brochure.

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

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

10.6 SAFETY INSTRUCTIONS

10.6.1 Local tolerability (Local Injection Site Reactions)

In case the Investigator or the patient recognizes any signs of local intolerability, then this should be treated and followed up as per the investigator's medical judgment. See Appendix F for further information.

10.6.2 Allergic adverse events

Specific e-CRF screens are to be filled in to assess allergic reactions or allergic-like reactions that may occur during the clinical studies conducted with alirocumab.

Sometimes transient injection site reactions, irritant in nature, may occur, requiring no intervention and being of dubious significance. These reactions would not be considered to be allergic reactions.

Adverse events that may constitute an allergic reaction (eg, generalized itch, nasal itch, swelling at injection site, flushing, hives, swelling at lips, eyes, face, tongue, hands, feet, lump in throat, difficulty to swallow, hoarseness, change in pitch of voice, incapacity to speak, wheezing, chest tightness, stridor, etc) should be considered to be reported on the General Allergic Reaction and/or Local Injection Site Reaction Complementary Form (see Section 10.4.4).

Adverse events that are obviously not of allergic origin (eg, local injection site reactions) should only be recorded on the Local Injection Site Reaction Complementary Form. However, injection site reactions which progress/expand/worsen/etc should be evaluated as recommended in 10.6.2.1 and General Allergic Reaction Complementary form should be completed. (See Sections 10.4.4)

The IMP should be immediately interrupted (temporarily discontinued) if there is a suspicion of an allergic event related to IMP. See Section 10.3.1 for further information on treatment interruption and Section 10.3.3 for criteria for permanent treatment discontinuation.

10.6.2.1 Allergic events with cutaneous involvement

Adverse events with cutaneous involvement which are obviously of allergic origin or injection site reactions which progress/expand/worsen/etc should be evaluated by a dermatologist as soon as possible, and preferably within one week of the site first becoming aware of the event.

The investigator should evaluate the patient for possible etiologies (new medications, etc) and extra-cutaneous symptoms and signs. An unscheduled Central Laboratory assessment for hematology, chemistry, liver panel and ADA should be obtained. If it is possible, the site will take pictures of the skin lesions in order to provide the patient with them for the dermatologist's visit.

If the photos are obtained, then copies should be kept as source documents which may later be collected by the sponsor. The investigator will provide a summary of the patient's case, reason for consultation, and information being requested to the consulting dermatologist.

A full consultation report should be sent by the dermatologist to the investigator. The full report should contain, at a minimum, the following information; a detailed description of the rash (such as the morphology [lesion type], shape of individual lesions, arrangement of multiple lesions [eg, scattered, grouped, linear, etc.], distribution, color, consistency, presence of pruritus or pain, and other clinical signs) and in case a skin biopsy (including histopathology and immunofluorescence) was done (if it was deemed necessary as per the dermatologist's or investigator's medical judgment), the results of this investigation with, if applicable, a specific diagnosis of the AE. The investigator will fax the full report and the corrected AE form if necessary, to the Monitoring Team Representative within 24 hours.

10.6.2.2 Acute allergic Injection Reactions

Acute allergic injection reaction (which are considered under the category of general allergic reactions) is defined as any AE that occurs during or shortly after injection of the IMP (characterized by but not limited to hypotension, bronchoconstriction, urticaria, edema, angioedema, nausea, vomiting). Emergency equipment and medication for the treatment of these potential adverse effects (eg, antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and epinephrine) must be available for immediate use for the injections at the training, and randomization visits. (See Section 10.4.2)

Patients will be observed at the investigational site for at least 30 minutes following the injection that takes place at the randomization visit. Patients should be treated symptomatically if any AEs are observed. Patients are to remain at the site until any acute injection reaction is assessed as stable, per the Investigator's discretion. General Allergic Reaction and/or Local Injection Site Reaction Complementary Form will have to be completed.

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

Taking into consideration the current number of patients enrolled in the four parent studies, it is estimated that up to approximately 1,200 patients could be enrolled.

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who originally met the inclusion criteria and signed the informed consent form.

Enrolled patients consist of all screened patients, with a treatment kit number allocated and recorded in the IVRS/IWRS database, regardless of whether treatment kit was used or not.

11.3 ANALYSIS POPULATIONS

11.3.1 Safety population

The Safety population considered for safety analyses will be the population who did actually receive at least one dose or partial dose of IMP in the current study.

11.3.2 Efficacy population

11.3.2.1 Modified Intent–to-treat population

The efficacy population considered for efficacy analyses will be the population of patients who received at least one dose or partial dose of IMP in the current study, with a baseline (from parent study) LDL-C available and with at least one LDL-C value available in the period from first IMP injection in the current study to last IMP injection + 21 days.

11.3.3 Other analysis population

The anti-alirocumab antibody analysis will be performed on all treated patients (safety population) with a blood sample on Week 0 (baseline from parent study) and at least one evaluable blood sample for antibodies post IMP injection in the current study.

11.4 STATISTICAL METHODS

11.4.1 Extent of alirocumab exposure and compliance

The alirocumab extent exposure and compliance will be assessed and summarized within the safety population.

In order to ensure the continuity of the investigational treatment for the patients without interruption (only in the event the manufacturer faces any performance or supply issues of the auto-injector), back-up plans may be implemented as described in Section 8.1. In that case, exposure to initial device and back-up device will be summarized and impact on study results will be assessed. More details will be provided in the SAP, if applicable.

11.4.1.1 Extent of investigational medicinal product exposure

The total exposure will be assessed by:

- Duration of alirocumab exposure in weeks defined as: (last alirocumab injection date + 14 -first alirocumab injection date) / 7, regardless of unplanned intermittent discontinuations.
- The total number of injections by patient.

11.4.1.2 Compliance

Compliance will be assessed using the following parameters:

- The mean injection frequency will be defined for each patient as the average number of days between 2 consecutive injections, that is: (last dose date – first dose date)/(number of injections -1).

This parameter will be summarized descriptively (N, Mean, SD, Median, Min and Max).

- The overall compliance will be defined for each patient as: 100 - (% days with under-planned dosing + % days with above-planned dosing). Under-planned and above-planned dosing will be defined as follows, considering that injections should be performed every 2 weeks (+ - 3 days):

    - The %days with under-planned dosing will be defined for each patient as the number of days with no injection administered within the previous 17 days divided by the duration of IMP injection exposure in days. For example, if a patient takes a dose 18 days after his/her previous injection, then 1 day is counted as a day under-planned dosing.

    - The %days with above-planned dosing will be defined for each patient as the number of days with more than one injection administered within the 11 days before divided by the duration of IMP injection exposure in days. For example, if a patient takes a dose 9 days after his/her previous injection, then 2 days are counted as a days above-planned dosing.

11.4.2 Analyses of safety endpoints

All safety analyses will be performed on the Safety population using the following common rule:

The baseline value is defined generally as the last available value before first injection. For analyses of changes from baseline for laboratory and vital signs parameters, baseline of the parent study or of the current study (ie value at visit 1 before the first injection) may be considered.

The safety analysis will focus on the Treatment Emergent Adverse Events (TEAE) period defined as the time from the first dose of the current study to the last dose of IMP + 70 days (10 weeks).

The following definitions will be applied to laboratory parameters and vital signs.

The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests and vital signs.

PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the PCSA percentage.

Treatment period: the treatment period used for quantitative analysis is defined as the time from first dose of IMP injection to the last dose of IMP injection + 21 days.

AE definition:

- Pre-treatment AEs are AEs that developed or worsened or became serious during the PRE-TREATMENT period;
- Treatment-emergent AEs (TEAEs) are AEs that developed or worsened or became serious during the TEAE period;
- Post-treatment AEs are AEs that developed or worsened or became serious during the POST-TREATMENT period.

Drug-induced liver injury:

Liver function tests, namely ALT, AST, alkaline phosphatase and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any post-baseline visit by baseline status will be displayed by treatment group for each parameter. A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented. Note that the ALT and total bilirubin values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

The incidence of liver-related AEs will be summarized by treatment group. The selection of preferred terms will be based on standardized MedDRA query (SMQ) Hepatic disorder. Time to liver-related treatment discontinuation and time to liver death may also be provided based on hepatic disorder SMQ.

11.4.2.1 Adverse events

Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order, the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population.

Adverse event incidence table will be provided for all types of TEAEs: all TEAEs, all treatment emergent AESI, all treatment emergent SAEs and all TEAEs leading to permanent treatment discontinuation.

If any clinically significant signal is detected and need further characterization or for adverse event of clinical interest, exploration of time to onset could be performed for these selected TEAEs as described below to account for the differential exposure time in all patients.
Selected TEAEs will be also analyzed using time-to-event approach (Kaplan-Meier methodology). Time from the first dose of IMP injection to the first occurrence of the event will be calculated (only the first event will be counted). Patients without any event will be censored at the end of the TEAE period. Incidence rates at different time points of exposure will be presented and Kaplan-Meier curves will be provided.

Death:

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study, post-study) summarized on the safety population
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC , HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

11.4.2.2 Laboratory data and vital signs

The summary statistics (including mean, median, Q1, Q3, standard error, minimum and maximum) of all laboratory variables, all vital signs parameters (raw data and changes from baseline) will be calculated for each visit, last and worst value assessed during the treatment period. For selected parameters, mean changes from baseline with the corresponding standard error will be plotted over time (at same time points).

The incidence of PCSAs at any time during the TEAE period (on-treatment PCSAs) will be summarized whatever the baseline level and/or according to the following baseline categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

For laboratory parameters for which PCSA criterion is not defined, similar table(s) using the normal range could be provided.

11.4.3 Analyses of efficacy data

Efficacy variables will be explored through descriptive statistics at each scheduled visit of the current study.

Percent changes from baseline of the parent study and success rate to reach targets from week 8 time point will be analyzed all groups combined as influence of treatment received during the parent study should be offset by the treatment received during the current study after 8 weeks of treatment.

Percent changes, and when appropriate absolute change, from baseline of the parent study in calculated LDL-C, total-C, HDL-C, TG, and non-HDL-C will be summarized at each time point in the efficacy population using number of available data, mean, SD, median, minimum, and maximum. For percent change, 95% confidence intervals of the mean will also be provided. All measurements, scheduled or unscheduled, collected from week 8 up to 21days after the last IMP injection, will be assigned to analysis windows defined in the SAP in order to provide an assessment for these time points. Laboratory assessments other than the ones provided by the central laboratory will be excluded. For TG, measurements on not fasting patients will be excluded.

Same kind of tables (with either percent change from baseline or absolute change from baseline) will be provided for other efficacy parameters: Apo B, Apo A-1, ratio Apo B/Apo A-1, Lp(a).

For TG and Lp(a), summary statistics will include Q1 and Q3.

Success rate to reach the different targets defined for LDL-C in Section 9.2.1 will be provided with corresponding 95% confidence intervals.

11.4.4 Analyses of other endpoints

The antibody status (positive/negative) and antibody titers will be summarized by visit using descriptive statistics. If appropriate, correlations between antibody titers, safety and/or efficacy endpoints will be provided by graphical methods.

The number (n) and percentage (%) of patients with an up-titration to 150 mg of alirocumab will be described as well as the detailed reasons that trigger the up-titration for patients for whom the parent study was not ODYSSEY High FH.

The number (n) and percentage (%) of patients with a down-titration to 75 mg of alirocumab will be described as well as the detailed reasons that trigger the down-titration.

Further details will be provided in SAP.

11.4.4.1 Analyses of quality of life/health economics variables

The analysis of data from EQ-5D instrument will be performed on efficacy population.

Descriptive summaries for individual EQ-5D items.

- Frequency and proportion of patients within each EQ-5D domain and response categories will be summarized by visits on which EQ-5D is assessed (Weeks 0,12, 24, 48, and End of OLETP)

Descriptive summaries for EQ-5D utility scores.

- Response from individual items will be converted into a single EQ-5D utility score by means of a standard regression model. Summary statistics for the utility score (number, mean, median, Q1, Q3, standard deviation, minimum and maximum) will be calculated by visits on which EQ-5D is assessed (Weeks 0, 12, 24, 48, and End of OLETP). Change in mean EQ-5D utility scores from baseline (Week 0) to Weeks 12, 24, 48, and End of OLETP, will be calculated.

Further details will be provided in SAP.

11.5 INTERIM ANALYSIS

Interim analyses might be performed if requested by Health Authorities or if needed for the purpose of scientific communication.

12 ETHICAL AND REGULATORY STANDARDS

12.1 ETHICAL PRINCIPLES

This clinical trial will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for good clinical practice (GCP).

In compliance with Sanofi public disclosure commitments, this clinical trial will be recorded in the public registry website clinicaltrials.gov before the enrollment of the first patient. The registry will contain basic information about the trial sufficient to inform interested patients (and their healthcare practitioners) how to enroll in the trial.

12.2 LAWS AND REGULATIONS

This clinical trial will be conducted in compliance with all international guidelines, and national laws and regulations of the country(ies) in which the clinical trial is performed, as well as any applicable guidelines (see Section 13.1).

12.3 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient’s participation in the clinical trial, the written informed consent form should be signed, name filled in and personally dated by the patient or by the patient’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

The informed consent form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

12.4 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the appropriate Ethics Committee (IRB/IEC), and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with Ethics Committee (IRB/IEC) composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator's Brochure, Investigator's curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the Ethics Committee (IRB/IEC) before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the Ethics Committee (IRB/IEC).

A progress report is sent to the Ethics Committee (IRB/IEC) at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator(s) and delegated Investigator staff undertake(s) to perform the clinical trial in accordance with this clinical trial protocol, ICH guidelines for Good Clinical Practice and the applicable regulatory requirements.

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to health authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial protocol as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH guidelines for Good Clinical Practice, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor when available in the eCRF may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

13.5 USE OF COMPUTERIZED SYSTEMS

Computerized systems used during the different steps of the study are:

- For data management activities, Inform 4.6
- For statistical activities, SAS
- For pharmacovigilance activities, AWARE, Business Object XI
- For monitoring activities, MedPace Clintrack and IMPACT (SANOFI)
- For medical writing activities, DOMASYS.

External data loading is planned for this clinical trial.

14 ADMINISTRATIVE EXPECTATIONS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Subinvestigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, the CRFs, the Investigator's Brochure and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the Ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

Furthermore, the Investigator and the Sponsor agree to adhere to the principles of personal data confidentiality in relation to the patients, Investigator and its collaborators involved in the study.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor’s databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.
- Subject race will be collected in this study in the Covance laboratory requisition form, for clearance creatinine calculation purpose.
- The data will not be captured in the eCRF, however it is part of data transfer between the Sponsor and the Central Lab Covance.
- The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/ risk ratio, efficacy and safety of the product(s). They may be further processed if they have been anonymized.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from maintaining their own liability insurance policy. An insurance certificate will be provided to the Ethics Committees (IECs/IRBs) or health authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 Decided by the Sponsor

Decided by the Sponsor in the following cases

- If the information on the product leads to doubt as to the benefit/risk ratio;
- If the Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon;

- In the event of breach by the Investigator of a fundamental obligation under this agreement, including but not limited to breach of the clinical trial protocol, breach of the applicable laws and regulations or breach of the ICH guidelines on Good Clinical Practice;

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 Decided by the Investigator

The Investigator must notify (30 days' prior notice) the Sponsor of his/her decision and give the reason in writing.

In all cases (decided by the Sponsor or by the Investigator), the appropriate Ethics Committee(s) (IRB/IEC) and Health Authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor’s written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, first presentation or publication of the results of the study shall be made only as part of a publication of the results obtained by all sites performing the protocol. However, if no multicenter publication has occurred within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study to the review procedure set forth herein. The Investigator shall provide the Sponsor with a copy of any such presentation or publication derived from the study for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial Patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the Ethics Committee (IRB/IEC) prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

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