CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761181Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

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Division/Office	Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Reviewer Name(s)	Laura Higginbotham, MD, MPH (adults) Eileen Craig, MD (pediatrics)
Review Completion Date	February 10, 2021
Established/Proper Name	evinacumab
(Proposed) Trade Name	Evkeeza
Applicant	Regeneron
Dosage Form(s)	intravenous (IV)
Applicant Proposed Dosing Regimen(s)	15 mg/kg every 4 weeks (Q4W)
Applicant Proposed Indication(s)/Population(s)	Homozygous familial hypercholesterolemia
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Adjunct to other LDL-C lowering therapies for the treatment of adult and pediatric patients, aged 12 years and older, with HoFH

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Glossary

AAA	abdominal aortic aneurysm
AC	advisory committee
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANGPTL3	angiopoietin-like 3
Apo A1	apolipoprotein A1
Apo B	apolipoprotein B
Apo CIII	apolipoprotein CIII
AR	adverse reaction
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CABG	coronary artery bypass graft surgery
CAD	coronary artery disease
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CEC	Clinical Events Committee
CETP	cholesterol ester transfer protein
CFR	Code of Federal Regulations
CHD	coronary heart disease
CK	creatine kinase
Cmax	maximum serum concentration
CMC	chemistry, manufacturing, and controls
CMQ	Custom MedDRA Query
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CPK	creatine phosphokinase
CPR	cardiopulmonary resuscitation
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CV	cardiovascular
CVA	cerebrovascular accident (stroke)

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DBP	diastolic blood pressure
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
EL	endothelial lipase
ETASU	elements to assure safe use
E.U.	European Union
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FH	familial hyperlipidemia
FMQ	FDA MedDRA Query
FPG	fasting plasma glucose
GCP	good clinical practice
GERD	gastroesophageal reflux disease
GRMP	good review management practice
HbA1c	hemoglobin A1c
HDL-C	high-density lipoprotein
HeFH	heterozygous familial hypercholesterolemia
HoFH	homozygous familial hypercholesterolemia
HR	heart rate
hsCRP	high-sensitivity C-reactive protein
ICH	International Council for Harmonization
IgG	immunoglobulin
IMP	investigational medical product
IND	Investigational New Drug Application
INR	international normalized ratio
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
kg	kilogram
LDL-C	low-density lipoprotein
LDLR	LDL-C receptor
LDLRAP1	low-density lipoprotein receptor adaptor protein 1
LFT	liver function test
LLT	lipid-lowering therapy
Lp(a)	lipoprotein A
LPL	lipoprotein lipase
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities

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mg	milligram
MI	myocardial infarction
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin kexin 9
PCSK9i	proprotein convertase subtilisin kexin 9 inhibitor
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	preferred term
QOL	quality of life
RD	risk difference
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SGE	special government employee
SMQ	Standard MedDRA Query
SOC	standard of care
s/p	status post
TC	total cholesterol
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
TG	triglycerides
Tmax	time to peak serum concentration
TSH	thyroid-stimulating hormone

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ULN	upper limit of normal
U.S.	United States
USUBJID	unique subject identification
VLDL-C	very-low-density lipoprotein
WBC	white blood cell count

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1. Executive Summary

1.1. Product Introduction

Evinacumab (Evkeeza) is a fully human recombinant monoclonal antibody (IgG4 isotype) that inhibits angiopoietin-like 3 (ANGPTL3), an enzyme involved in lipid metabolism. Inhibition of ANGPTL3 allows enhanced lipoprotein lipase (LPL) activity leading to increased VLDL processing and a reduction in LDL-C independent of the LDL-C receptor (LDLR).

The Applicant proposes the following indication:

> *EVKEEZA is indicated as an adjunct to diet and other LDL-C lowering therapies for the treatment of adult and adolescent patients aged 12 years and older with homozygous familial hypercholesterolemia (HoFH).*

Evinacumab is administered intravenously (IV) 15 mg/kg every 4 weeks. Evinacumab is a new biologic product and is not marketed or approved in the United States (U.S.) or worldwide.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided sufficient clinical data to demonstrate substantial evidence that evinacumab reduces LDL-C in individuals with HoFH, aged 12 years and older, when added to other lipid-lowering therapies (LLT).

In a single trial with 24 weeks of double-blinded, placebo-controlled data (trial 1629), evinacumab lowered LDL-C by 49% compared to placebo in patients with HoFH on maximally-tolerated LLT (defined as statin, ezetimibe, and PCSK9 inhibitor [PCSK9i]). Twenty-four (24) weeks of subsequent open-label treatment in the same trial demonstrated that the effect was sustained to at least 48 weeks.

Although two adequate and well-controlled trials are typically required to achieve the statutory definition of substantial evidence, a single trial was deemed acceptable by FDA given the rarity of HoFH in the U.S. and worldwide, the natural history of HoFH, and the magnitude of the observed treatment effect versus placebo. The typical clinical trajectory of HoFH is inconsistent with a 49% LDL-C decrease over 6 months without intervention. Additionally, other lipid-lowering therapies approved in this patient population achieve a smaller LDL-C reduction than that observed in the evinacumab trial. Thus, we conclude that the observed trial results are not solely due to chance.

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1.3. Benefit-Risk Assessment

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Benefit-Risk Integrated Assessment

HoFH is a rare genetic condition affecting an estimated 200-300 patients in the U.S. The disorder results from mutations to enzymes involved in LDL-C processing (most commonly the LDLR) with the consequence of ineffective plasma clearance of LDL-C. Patients with HoFH develop persistent, severe hyperlipidemia >400-500 mg/dL beginning in childhood. HoFH patients are susceptible to premature cardiovascular disease and death due to the early onset and prolonged duration of elevated lipid values.

Like patients with primary hyperlipidemia, patients with HoFH are treated with lipid-lowering therapies to reduce cardiovascular (CV) risk. However, despite the multitude of effective lipid-lowering treatment options available for primary hyperlipidemia, treatment options in HoFH are limited because of the lack of a functional LDLR (the primary target of the most effective lipid-lowering therapies, statins and PCSK9is). Patients with HoFH typically have severe hyperlipidemia (LDL-C ≥190 mg/dL) even after treatment with multiple lipid-lowering agents.

A single trial of evinacumab in patients with HoFH demonstrated a large LDL-C reduction treatment effect. In patients with HoFH who received evinacumab as add-on to other lipid-lowering therapies, evinacumab lowered LDL-C by an additional 49% at 24 weeks compared to placebo. Notably, evinacumab was effective even in patients with the most difficult-to-treat mutations. Additionally, its treatment effect was similar regardless of a patient's baseline LDL-C value, background lipid-lowering therapy (including use of apheresis), age, gender, race, or ethnicity.

Risks associated with evinacumab are typical of monoclonal antibodies and include anaphylaxis, mild-to-moderate infusion reactions, transient infusion-related changes to blood pressure and heart rate, upper respiratory and flu-like symptoms, nausea, weakness or decreased energy, and dizziness. Although interpretation of the safety results is limited by the small database, there were no apparent reactions associated with evinacumab's mechanism of action and no evidence of adverse consequences associated with LDL-C reduction itself. Of note, there was no evidence of myopathy/rhabdomyolysis or hepatic dysfunction as is commonly observed with other lipid-lowering therapies.

Approval of evinacumab in patients with HoFH would provide an additional therapeutic option for LDL-C reduction in a patient population with an unmet medical need. The treatment effect of evinacumab is substantially larger than that observed in other clinical trials of LDL-C reduction in HoFH and was evident even in patients with very low LDLR activity, consistent with evinacumab's mechanism of action independent of the LDLR. The risks associated with evinacumab generally occurred at low incidence, were clinically monitorable, were reversible, or were mild. Although no cardiovascular outcomes data is available to directly substantiate that LDL-C reduction with evinacumab will translate to CV risk reduction, most clinical and epidemiologic evidence supports the use of LDL-C as a surrogate for CV risk.

Overall, in this rare disease patient population of HoFH, it is reasonable to conclude that the presumed CV benefit of LDL-C reduction outweighs

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the known risks associated with evinacumab exposure. The benefit-risk assessment appears favorable for approval of evinacumab for treatment of patients aged 12 years and older with HoFH. The benefit-risk has not been established in other populations.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• HoFH o Rare genetic disorder (1 in 300,000 to 1 in 1,000,000); estimated 200-300 patients in the U.S. o Most common mutations: LDLR (90%), Apo B, PCSK9, LDLRAP1; mutations result in ineffective plasma clearance of LDL-C o Persistent hyperlipidemia >400-500 mg/dL beginning in childhood o Progressive and early heart disease ▪ Premature atherosclerosis, valvular stenosis, supravalvular stenosis ▪ Premature cardiovascular disease (CVD) and increased risk for CV events (myocardial infarction [MI] beginning 2nd decade) o Decreased life expectancy (mid-40s) without aggressive treatment • Patients with HoFH are treated with aggressive lipid-lowering therapies to reduce CV risk, primarily based on extrapolation of evidence from LDL-C reduction in primary hyperlipidemia • LDL-C reduction with statins and PCSK9 inhibitors is associated with improved CV outcomes in primary hyperlipidemia (heterozygous familial hypercholesterolemia [HeFH] and non-familial hyperlipidemia [FH])	HoFH is a rare genetic condition that results in persistent severe hyperlipidemia, premature cardiovascular disease, and premature death. Like patients with primary hyperlipidemia (HeFH or non-familial hyperlipidemia), patients with HoFH are treated with lipid-lowering therapies with the goal of reducing CV risk. However, many patients with HoFH respond poorly to traditional lipid-lowering therapies as these treatments typically require a functional LDLR. There is high unmet medical need in this population.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	o Meta-analysis of statin trials demonstrated that an absolute reduction of 38.7 mg/dL (1 mmol/L) with statins is associated with a 22% relative risk reduction in 5-year incidence of major coronary events, ischemic stroke, and revascularization o Outcomes trials of the two approved PCSK9 inhibitors demonstrated association between LDL-C lowering and reduced risk of CV events o A single outcomes trials with ezetimibe demonstrated incremental benefit (6% relative risk reduction) with moderate LDL-C lowering • LDL-C goals in HoFH vary by society but are typically: o LDL-C <100 mg/dL in patients without atherosclerotic cardiovascular disease (ASCVD) o LDL-C <70 mg/dL in patients with ASCVD o LDL-C reduction ≥50% from pretreatment values • Patients with HoFH are typically unable to achieve LDL-C goals and respond poorly to approved lipid-lowering therapies, since most therapies target the LDLR • Mutation type determines ability to respond to therapy; mutations resulting in limited LDLR activity are the most difficult to treat, and patients have the highest LDL-C values o Terminology and definitions of difficult-to-treat mutations are inconsistent in literature and in approved HoFH therapies; most common definition is <2% LDLR activity assessed by *in vitro* assays; difficult-to-treat mutations variably referred to as null, negative, or absent	

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	o Sponsor terminology and definitions ▪ Null/null mutations: mutations with <15% LDLR binding and uptake activity assessed by *in vitro* assays ▪ Negative/negative mutations: mutation genotype predicted to result in complete loss of function of both alleles (premature stop codons, splice site variations, frame shifts, insertions/deletions, and copy number variations)	
Current Treatment Options	• Treatment options (versus placebo, unless otherwise noted) o Statins (-14% to -30% LDL-C reduction in HoFH) o Ezetimibe (-21% to -27% LDL-C reduction in HoFH as add-on to statin) o Evolocumab (-31% LDL-C reduction in HoFH) o Lomitapide (-40% LDL-C reduction in HoFH): boxed warning for hepatotoxicity, not approved in pediatrics o Apheresis: high patient burden (requires access to specialized facility [lack of access or may require travel], time-consuming [2-5 hours every 1-2 weeks], expensive) • Poor response to traditional lipid-lowering therapies o Statins and PCSK9i lower LDL-C by increasing expression of LDLR on hepatocytes o Patients with HoFH lack fully functional LDLR o Statins and PCSK9i have smaller treatment effect or are not effective in patients with mutations resulting in little to no residual function	Currently approved lipid-lowering therapies, whether approved for HoFH or used off-label, do not adequately meet the need for LDL-C reduction in HoFH.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• In patients with HoFH who took evinacumab as add-on to background lipid-lowering therapy (typically high-intensity statin, ezetimibe, and PCSK9i +/- lomitapide and apheresis), evinacumab lowered LDL-C: o At 24 weeks, -49% reduction compared to placebo o At 48 weeks, -46% reduction (open-label) • Evinacumab's treatment effect was similar regardless of patients' baseline LDL-C values, number/type of background lipid-lowering therapies (including use of apheresis), and mutation genotype or phenotype • Patients with negative/negative or null/null mutations as defined by the Applicant responded to evinacumab treatment o At 24 weeks, -58% LDL-C reduction compared to placebo • Evinacumab also lowered Apo B, TG, non-HDL-C, and TC • The effect of evinacumab on cardiovascular morbidity and mortality has not been assessed	Evinacumab has a large LDL-C reduction treatment effect, particularly in comparison to currently available therapies for LDL-C reduction in HoFH. Evinacumab is effective in patients with the most difficult-to-treat mutations (negative/negative and null/null mutations per the Applicant's definitions) because of its mechanism of action that is independent of the LDLR. Despite the absence of cardiovascular outcomes data, most clinical and epidemiologic evidence (with the exception of CETP inhibitors) support that LDL-C reduction corresponds to CV risk reduction.
Risk and Risk Management	• In phase 2/3 trials, evinacumab was associated with hypersensitivity reactions, including anaphylaxis (0.9% evinacumab vs. 0% placebo) and infusion reactions (7.7% evinacumab vs. 3.7% placebo); in some cases, hypersensitivity reactions required treatment discontinuation • Transient blood pressure and heart rate changes were acutely observed during infusion administration but resolved afterwards • Evinacumab's safety profile was consistent with that expected of a monoclonal antibody (upper respiratory symptoms, influenza-like illness, infusion site pruritus, dizziness); these reactions occurred in 3-7% of patients • Other adverse reactions included gastrointestinal effects such as nausea, abdominal pain, constipation, and diarrhea; these reactions	Evinacumab's most concerning risk is hypersensitivity reactions, including anaphylaxis and infusion reactions. The most serious hypersensitivity reaction – anaphylaxis – occurred at low incidence (<1%). Evinacumab is administered in a healthcare setting, so this risk is clinically monitorable. Additionally, all hypersensitivity reactions were reversible upon drug discontinuation. Additional risks observed with evinacumab are mild, symptom-based, and clinically

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	occurred in 3-5% of patients • Evinacumab was not associated with other adverse reactions commonly associated with lipid-lowering therapy, including no signal of myopathy/rhabdomyolysis or liver enzyme abnormalities • No patients exposed to evinacumab developed anti-drug antibodies (ADA) • In animal reproduction studies, pregnant rabbits exposed to evinacumab during organogenesis experienced increases in fetal malformations at doses below human exposure, suggestive of teratogenicity	manageable. Based on animal data, evinacumab is likely teratogenic. However, this risk can be mitigated through patient selection, pregnancy testing, and use of contraception. In summary, all risks associated with evinacumab can be adequately addressed through labeling.

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1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☒	Clinical outcome assessment (COA) data, such as		
		☒	Patient reported outcome (PRO)	Section 6.1.1, Study Endpoints
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.			

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2. Therapeutic Context

2.1. Analysis of Condition

HoFH is a serious, life-threatening, rare, genetic disorder affecting an estimated 200-300 individuals in the U.S. (1 in 300,000 to 1 in 1,000,000). HoFH results from mutations to enzymes involved in lipid metabolism – most commonly from mutations to both alleles of the LDLR (90% of cases) but also from mutations to Apo B, PCSK9, or LDLRAP1 alleles. Patients with HoFH are unable to effectively clear plasma of LDL-C resulting in persistent hyperlipidemia beginning in childhood. Pediatric patients diagnosed with HoFH may have LDL-C values exceeding 400 to 500 mg/dL, while adult patients diagnosed with HoFH may have LDL-C values that exceed 650 to 1000 mg/dL.

Researchers and clinicians may characterize HoFH patients by the degree of residual LDLR activity from *in vitro* assays; however, the terminology and definitions used are inconsistent. In general, patients with 0% to <2% residual LDLR activity are considered the most difficult to treat and are variably described as having null, negative, or absent LDLR function. These patients typically have the highest LDL-C values and the worst prognosis.

In clinical practice, HoFH is suspected in patients with LDL-C >400 mg/dL; patients with xanthelasmas, xanthomas, or corneal arcus; or in patients with a family history of elevated LDL-C and early-onset cardiovascular disease. HoFH may be diagnosed by clinical criteria or confirmed via genetic testing.

Clinical manifestations of HoFH include progressive and early heart disease, including premature atherosclerosis, valvular or supravalvular stenosis, and increased risk for cardiovascular events, such as MI beginning in the 2nd decade of life. Without aggressive treatment to reduce LDL-C, patients with HoFH have decreased life expectancy to the mid-40s.

2.2. Analysis of Current Treatment Options

As with primary hyperlipidemia, the treatment goal in HoFH is the reduction of LDL-C to reduce the risk of ASCVD. Treatment guidelines vary, but most societies suggest an LDL-C <100 mg/dL in patients without ASCVD and an LDL-C <70 mg/dL in patients with ASCVD. The National Lipid Association (NLA) further recommends a reduction in LDL-C by ≥50% from pretreatment values. Most HoFH patients fail to achieve these goals, despite the use of multiple lipid-lowering therapies, since the most effective drugs target the LDLR.

Currently approved therapies include statins, ezetimibe, and PCSK9i. Additional therapies available in HoFH include lomitapide and apheresis. However, lomitapide use is often limited by its boxed warning for hepatotoxicity and its lack of approval in the pediatric population.

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Apheresis is successful at reducing LDL-C, but use is limited because of high patient burden – apheresis is timely, expensive, may require travel, and patients may lack access.

Approved lipid-lowering therapies, whether approved for HoFH or used off-label, do not adequately meet the need for LDL-C reduction in HoFH. For example, in a patient with a pretreatment LDL-C of 400 mg/dL, a reduction in LDL-C of 20-30% with a statin or PCSK9i results in an LDL-C value of 280 to 320 mg/dL. This patient would not be at goal by any society definition.

Table 1. Drugs Currently Approved in the U.S. for the Treatment of HoFH

Product Name	Mechanism of Action	Relevant Indication	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments for HoFH					
Simvastatin	HMG-CoA reductase inhibitor	Reduce total-C and LDL-C in patients with HoFH as an adjunct to other lipid-lowering therapies (e.g., LDL apheresis) or if such treatments are unavailable	5 to 40 mg PO daily	LDL-C reduction: -14% to -30% (N=12)	Contraindicated in active liver disease, pregnancy, and breastfeeding; myopathy/rhabdomyolysis; liver dysfunction; increases in HbA1c and FPG
Atorvastatin	HMG-CoA reductase inhibitor	To reduce total-C and LDL-C in patients with HoFH as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable	10 to 80 mg PO daily	LDL-C reduction: -18% (N=29)	Contraindicated in active liver disease, pregnancy, and breastfeeding; myopathy/rhabdomyolysis; liver dysfunction; increases in HbA1c and FPG
Rosuvastatin	HMG-CoA reductase inhibitor	As adjunctive therapy to other lipid-lowering treatments (e.g., LDL apheresis) or alone if such	5 to 40 mg PO daily	LDL-C reduction: -22% (N=40) Pediatrics: -22% (N=14)	Contraindicated in active liver disease, pregnancy, and breastfeeding; myopathy/rhabdomyolysis; liver enzyme abnormalities; increases in HbA1c and FPG

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		treatments are unavailable to reduce LDL-C, total-C, and ApoB in adult patients with HoFH			
Ezetimibe	Intestinal cholesterol and phytosterol absorption inhibitor	The combination of ZETIA and atorvastatin or simvastatin is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH, as an adjunct to other lipid-lowering therapies (e.g., LDL apheresis) or if such treatments are unavailable	10 mg PO daily	LDL-C reduction: -21% to -27% (N=50)	Contraindicated in active liver disease, pregnancy, and breastfeeding; myopathy/rhabdomyolysis; liver enzyme abnormalities
Evolocumab	PCSK9 inhibitor	As an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) for the treatment of patients with HoFH who require additional lowering of LDL-C	420 mg SC monthly	LDL-C reduction: -31% (N=49)	Hypersensitivity
Ezetimibe-simvastatin FCDP	HMG-CoA reductase inhibitor and intestinal cholesterol absorption inhibitor	For the reduction of elevated total-C and LDL-C in patients with HoFH, as an adjunct to other lipid-	10/40 mg PO daily	LDL-C reduction: -23% to -29% (N=14)	Contraindicated in active liver disease, pregnancy, and breastfeeding; myopathy/rhabdomyolysis; liver enzyme abnormalities; increases in HbA1c and FPG

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		lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable			
Lomitapide		As an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce LDL-C, TC, apo B, and non-HDL-C in patients with HoFH	5 to 60 mg PO daily	LDL-C reduction: -40% (N=29)	Only available through restricted program under REMS; boxed warning for hepatotoxicity, including hepatic steatosis; contraindicated in pregnancy and moderate-severe hepatic impairment or active liver disease; reduced absorption of fat-soluble vitamins; GI adverse reactions, including severe diarrhea and vomiting
LDL apheresis[1]		To acutely remove LDL-C from the plasma of the following high risk patient population for whom diet has been ineffective or not tolerated: Group A – functional hypercholesterolemic homozygotes with LDL-C >500 mg/dL	2-5 hours Q1-2W		Thrombocytopenia, infection/bacteremia, hypersensitivity, transient decrease in serum protein and albumin, hypotension, fainting, anemia, hemolysis
Other Treatments (Combined by Pharmacologic Class, where relevant)					
Statins[2]	HMG-CoA reductase inhibitor	Primary hyperlipidemia: reduction of total-C, LDL-C, Apo B, and TG, and to increase HDL-C in patients with primary hypercholeste	Varies	LDL-C reduction in primary hypercholesterolemia: -22% to -41%	Contraindicated in active liver disease, pregnancy, and breastfeeding; myopathy/rhabdomyolysis; liver enzyme abnormalities; increases in HbA1c and FPG

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		rolemia (HeFH and non-FH)			
Alirocumab	PCSK9 inhibitor	Primary hyperlipidemia (including HeFH): adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia to reduce LDL-C	75 mg SC Q2W or 300 mg SC monthly	LDL-C reduction in primary hyperlipidemia: -58%	Hypersensitivity
Bempedoic acid	ACL inhibitor	Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or established ASCVD who require additional lowering of LDL-C	180 mg PO daily	LDL-C reduction in HeFH and ASCVD: -17% to -18% (N=3009)	Hyperuricemia, tendon rupture
Bempedoic acid-ezetimibe FCDP	ACL inhibitor	Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or established ASCVD who require additional lowering of LDL-C	180/10 mg PO daily	LDL-C reduction in HeFH and ASCVD: -36% (N=301)	Hyperuricemia, tendon rupture
Fibrates[3]	PPAR-α activator	Primary hypercholeste	Varies	LDL-C reduction in primary	Contraindicated in severe renal impairment, active

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		rolemia: to reduce LDL-C, total-C, Apo B, and to increase HDL-C		hyperlipidemia: -21%	liver disease, patients with gallbladder disease, and breastfeeding; myopathy/rhabdomyolysis; liver dysfunction; increased creatinine; cholelithiasis; pancreatitis
Extended-release niacin	Niacin	Primary hyperlipidemia: to reduce elevated TC, LDL-C, Apo B, and TG levels, and to increase HDL-C	500 to 2000 mg PO QHS	LDL-C reduction in primary hyperlipidemia: -5% to -14%	Contraindicated in active liver disease and peptic ulcer disease; myopathy/rhabdomyolysis; liver dysfunction; increased FPG; increased uric acid; reduced platelets and increased PT
Bile acid sequestrants[4]	Bile acid sequestrant	Primary hypercholesterolemia: adjunctive therapy to diet for the reduction of elevated serum cholesterol	Varies	LDL-C reduction in primary hyperlipidemia: -10%	Contraindicated in complete biliary obstruction; increased bleeding

Source: Clinical reviewer.
Abbreviations: ACL, adenosine triphosphate-citrate lyase; Apo B, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; FDCP, fixed-dose combination product; FH, familial hyperlipidemia; FPG, fasting plasma glucose; GI, gastrointestinal; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein; N, number of patients in treatment group; PCSK9, proprotein convertase subtilisin kexin 9; PO, by mouth; PPAR-α, peroxisome proliferator-activated receptor alpha; PT, prothrombin time; QHS, every night at bedtime; QxW, every x week; SC, subcutaneous; TC, total cholesterol; TG, triglycerides; Total-C, total cholesterol.
1 Under CDRH regulation.
2 Includes lovastatin, pravastatin, fluvastatin, and pitavastatin.
3 Includes fenofibrate and fenofibric acid.
4 Includes colestipol hydrochloride, cholestyramine, and colesevelam hydrochloride.

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3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Evinacumab is a new biological product and is not currently marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

The evinacumab IND (IND 116398) was opened in November 2012 for the treatment of (b) (4) HoFH. An initial protocol in HoFH (trial 1331; Phase 2, proof-of-concept trial in planned 8 patients) was submitted in July 2014. In February 2016, evinacumab was granted Orphan Drug designation for the treatment of HoFH. In August 2016, the Applicant requested an end-of-phase 2 (EOP2) meeting, which was denied as the aforementioned Phase 2 trial was not complete.

A Type C guidance meeting was subsequently held in February 2017 to discuss the HoFH development program and its proposed pivotal trial (trial 1629). During that meeting, FDA advised that at least one year of safety data would be required prior to BLA submission, provided recommendations on adverse events of special interest (AESI), and agreed on the clinical criteria used to identify patients with HoFH. FDA also agreed that a thorough QT study was not required.

In March 2017, evinacumab was granted Breakthrough Therapy designation for the treatment of HoFH based on preliminary evidence from the completed Phase 2 trial 1331.

A pre-BLA meeting was held in October 2019. At that time, the clinical review team agreed on the appropriate size of the safety database and on the timeline for submission of the 120-Day Safety Update. FDA also requested submission of Data Monitoring Committee (DMC) meeting minutes with the final BLA submission.

Evinacumab was granted rolling review in February 2020, as a benefit of its Breakthrough Therapy designation. The BLA application was submitted in 3 segments, with the final segment submitted on June 11, 2020. The evinacumab BLA was granted Priority Review during filing on August 11, 2020.

3.3. Foreign Regulatory Actions and Marketing History

Evinacumab is a new biological product and is not marketed in the U.S. or elsewhere.

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4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An OSI audit was requested. Four sites (two foreign and two domestic) were selected based on high enrollment or on potential indicators of questionable data quality (low number of adverse events [AEs] reported or high site-specific efficacy). One foreign site was unable to be inspected because of the current COVID-19 pandemic. The second foreign site was inspected via remote assessment of source documents due to COVID-19 travel restrictions.

No data validity issues were identified during the domestic site inspections or the remote foreign inspection. See Dr. Kleppinger's review for a review of clinical site inspections (in DARRTS dated 01/07/2021; Reference ID: 4726712).

4.2. Product Quality

The drug product used in the clinical development program is the same as the to-be-marketed product.

This section is deferred pending the completed review of the chemistry, manufacturing, and controls data. See Dr. Chung's review for a review of product quality data.

4.3. Clinical Microbiology

This section is deferred pending the completed review of drug product and drug substance microbiology. See Dr. Jones' review for a review of microbiology data.

4.4. Nonclinical Pharmacology/Toxicology

Evinacumab is teratogenic based on results of nonclinical studies in pregnant rabbits. Evinacumab caused embryofetal deaths, abortion, and stillbirth as well as multiple external, visceral, and skeletal malformations to delivered neonates. Observed malformations included dilated central nervous system (CNS) ventricles with corresponding enlarged fontanelles and domed heads, cleft palate, abnormal skull ossification, and decreased ossification of paw metacarpal bones. Effects were observed at all but the lowest dose tested and at exposures below the maximum recommended human dose (MRHD).

Based on the severity of fetal findings and the occurrence at low exposure margins, a Warnings and Precaution for use of evinacumab in pregnancy is considered necessary. Refer to Section 10 for additional discussion.

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See Dr. Haile's review for a complete review of nonclinical data.

4.5. Clinical Pharmacology

Evinacumab is a fully human recombinant monoclonal antibody (IgG4 isotype) that inhibits ANGPTL3, an enzyme involved in lipid metabolism that inhibits LPL and endothelial lipase (EL). Inhibition of ANGPTL3 allows enhanced LPL activity leading to increased VLDL processing and a reduction in LDL-C independent of the LDLR. Evinacumab also increases EL activity, which may lead to reduced HDL-C plasma levels.

The pharmacokinetic (PK) and pharmacodynamic (PD) properties of evinacumab were assessed in three clinical pharmacology phase 1 studies conducted in healthy individuals (including Japanese individuals), two phase 2 trials (in patients with HoFH and in patients with HeFH or established ASCVD), and two phase 3 trials in HoFH (one 24-week randomized, placebo controlled trial with a 24-week open-label extension phase; and a single-arm, open-label, long-term extension study). A population PK study was conducted using data from pre-specified phase 1, 2, and 3 trials. The drug product used in the clinical development program is the same as the to-be-marketed product.

Evinacumab is administered as an IV infusion over 60 minutes. The peak concentration (Cmax) occurs at the end of drug infusion (Tmax = 1 hour). It is distributed primarily in the vascular compartment. Steady-state is achieved between 12 to 16 weeks of treatment, after 4 doses of evinacumab 15 mg/kg IV Q4W. As a large protein, evinacumab is eliminated via proteolytic catabolism; renal elimination or hepatic metabolism are not anticipated. After multiple doses of evinacumab 15 mg/kg IV Q4W, systemic elimination of evinacumab to undetectable levels occurs at 19 weeks.

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Table 2. Predicted Exposure in Patients with HoFH Using a Population PK Model

5 mg/kg IV Q4W N=95	AUC_{tau} (mg*day/L)		C_{max} (mg/L)		C_{trough} (mg/L)	
	1st dose	SS	1st dose	SS	1st dose	SS
Mean	1415	2405	170.7	194.1	15.74	43.27
SD	384	979	39.2	51.7	9.90	28.85
5%	906	1127	115.5	126.6	1.96	6.31
95%	2081	4384	230.2	292.5	35.63	102.10

15 mg/kg IV Q4W N=95	AUC_{tau} (mg*day/L)		C_{max} (mg/L)		C_{trough} (mg/L)	
	1st dose	SS	1st dose	SS	1st dose	SS
Mean	5114	10286	562	689	96.9	240.7
SD	1133	3138	118	157	29.7	96.5
5%	3634	6207	405	483	55.7	111.4
95%	7017	16209	739	970	151.2	438.4

SD: standard deviation; SS: steady-state; Steady-state AUC_{tau} is $AUC_{week\ 20\text{-}24}$; steady-state C_{max} is end of infusion concentration at week 20 and steady-state C_{trough} is pre-dose concentration at week 24.
Source: Module 5.3.3.5 R1500-PK-19139-SR-01V1 Table A

Source: Applicant, Summary of Clinical Pharmacology Studies, p. 48.

Body weight impacts evinacumab exposure, however, the weight-based administration of evinacumab rectifies this. Additionally, the impact of body weight on exposure was <30%. Importantly, evinacumab exposure does not vary based on patient age. In clinical trials, adolescent and adult patients achieved similar peak and trough evinacumab concentrations.

Dedicated studies in renal and hepatic impairment were not conducted based on evinacumab's lack of elimination by these systems. Clinical evidence in 24 patients with mild to moderate renal impairment demonstrated no difference in PK parameters compared to patients with normal renal function. No patients with hepatic impairment were included in the clinical development program. Dose adjustment is not expected in patients with renal or hepatic impairment.

No patients in the phase 3 development program developed ADA after evinacumab exposure.

Refer to Dr. Lau's review for a complete review of clinical pharmacology data (in DARRTS dated 12/03/2020; Reference ID: 4711454).

4.6. Devices and Companion Diagnostic Issues

Not applicable.

Reference ID: 4745518

4.7. Consumer Study Reviews

Not applicable.

Reference ID: 4745518

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

See Next Page.

Reference ID: 4745518

Table 3. Clinical Trials Submitted in Support of Efficacy and Safety Determinations

Trial Identified	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Patients Planned; Actual Randomized or Enrolled	No. of Centers and Countries
1331	Adult patients with HoFH (≥18 years), as defined by genotyping, and not on LDL apheresis therapy.	OL, MC, POC	Evinacumab Day 1: 250 mg SC, Day 15: 15 mg/kg IV, Day 85: 450 mg SC Q4W x 4 doses, Week 26: 300 mg SC QW x 4 doses, Week 38: 20 mg/kg IV x 1 dose, Week 58: 20 mg/kg IV Q12W (N=9), up to 4 years.	Primary: percent change in LDL-C from baseline to Week 4. Secondary: percent and absolute change in LDL-C from Week 2 to Week 4; percent and absolute change in LDL-C from baseline over time; percent and absolute change in Apo B, non-HDL-C, TC, and Lp(a) from baseline over time; proportion of patients who achieve LDL-C reduction of ≥25% or ≥50% from baseline; percent and absolute change in HDL-C, TG, and Apo A1 from baseline over time; percent and absolute change in Apo CIII from baseline over time.	8; 9	11 centers in 3 countries
1629	Adult and adolescent patients with HoFH (≥12 years) as defined by genotyping or clinical criteria, LDL-C ≥70 mg/dL, and on maximally-tolerated LLT.	Part 1: R, DB, PC, PG, MC Part 2: OL, MC	Part 1 (DBTP): Evinacumab 15 mg/kg IV Q4W (N=43), 24 weeks Placebo (N=22), 24 weeks Part 2 (OLTP): Evinacumab 15 mg/kg IV Q4W (N=64), 24 weeks	Primary: percent change in LDL-C from baseline to Week 24. Secondary: percent change in Apo B, non-HDL-C, TC, TG, Lp(a), and Apo CIII from baseline to Week 24; proportion of patients with ≥30% and ≥50% reduction in calculated LDL-C at Week 24; proportion of patients with LDL-C <100 mg/dL and <70 mg/dL at Week 24; proportion of patients who meet EU apheresis eligibility criteria; proportion of patients who meet US apheresis eligibility criteria.	57; 65	30 centers in 11 countries

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1719[1]	Adult and pediatric patients with HoFH (≥12 years) as defined by genotyping or clinical criteria, LDL-C ≥70 mg/dL, and on maximally-tolerated LLT. Patients were rolled over from trial 1331, trial 1629, or were treatment-naïve.	OL, MC, LTE	Evinacumab 15 mg/kg IV Q4W (N=64), up to 4 years	Primary: incidence and severity of TEAEs and safety variables. Secondary: percent and absolute change in LDL-C, Apo B, non-HDL-C, TC, and TG from baseline over time.	120; 64	25 centers in 10 countries
1643[2]	Adult patients (≥18 years) with HeFH or established ASCVD, LDL-C ≥70 mg/dL (patients with ASCVD) or ≥100 mg/dL (no ASCVD), and on maximally-tolerated LLT. HeFH diagnosis by genotyping or clinical criteria. ASCVD defined as history of ACS, MI, angina, arterial revascularization, stroke, TIA, or PAD.	Part 1: R, DB, PC, PG, MC Part 2: OL, MC	<u>Part 1 (DBTP):</u> Evinacumab 15 mg/kg IV Q4W (N=39), 24 weeks Evinacumab 5 mg/kg IV Q4W (N=36), 24 weeks Placebo (N=34), 24 weeks <u>Part 2 (OLTP):</u> Evinacumab 15 mg/kg IV Q4W (N=96), 24 weeks	Primary: percent change in LDL-C from baseline to Week 16. Secondary: percent change in Apo B, non-HDL-C, TC, TG, and Lp(a) from baseline to Week 16 and Week 24; proportion of patients with ≥30% and ≥50% reduction in LDL-C from baseline to Week 16; proportion of patients with LDL-C <100 mg/dL, <70 mg/dL, and <50 mg/dL at Week 16.	108; 109	40 centers in 15 countries

Source: Clinical reviewer.
Abbreviations: ACS, acute coronary syndrome; Apo A1, apolipoprotein A1; Apo B, apolipoprotein B; Apo CIII, apolipoprotein C3; ASCVD, atherosclerotic cardiovascular disease; DB, double-blind; DBTP, double-blind treatment period; HDL-C, high-density lipoprotein; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein; Lp(a), lipoprotein(a); LTE, long-term extension study; MC, multi-center; MI, myocardial infarction; non-HDL-C, non-high-density lipoprotein; OL, open-label; OLTP, open-label treatment period; PAD, peripheral arterial disease; PC, placebo-controlled; PG, parallel group; POC, proof-of-concept; R, randomized; TC, total cholesterol; TEAE, treatment-emergent adverse event; TG, triglycerides; TIA, transient ischemic attack.
1 Trial was ongoing at the time of BLA submission.
2 Only data from Part B (evinacumab IV infusions) was included in the BLA submission.

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Table 4. Clinical Trials that Enrolled Pediatric Patients

Trial Identified	Trial Type	Trial Design	No. of Pediatric Patients Randomized/Enrolled	No. of Centers[1]	Countries[1]
1629	Efficacy	Part 1: R, DB, PC, PG, MC Part 2: OL, MC	2	2 centers in 2 countries	France, Netherlands
1719[2]	Safety, efficacy	OL, MC, LTE	13	7 centers in 6 countries	Australia, France, Italy, Japan, Netherlands, and South Africa

Source: Clinical reviewer.
Abbreviations: ACS, acute coronary syndrome; Apo A1, apolipoprotein A1; Apo B, apolipoprotein B; Apo CIII, apolipoprotein C3; ASCVD, atherosclerotic cardiovascular disease; DB, double-blind; DBTP, double-blind treatment period; HDL-C, high-density lipoprotein; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein; Lp(a), lipoprotein(a); LTE, long-term extension study; MC, multi-center; MI, myocardial infarction; non-HDL-C, non-high-density lipoprotein; OL, open-label; OLTP, open-label treatment period; PAD, peripheral arterial disease; PC, placebo-controlled; PG, parallel group; POC, proof-of-concept; R, randomized; TC, total cholesterol; TEAE, treatment-emergent adverse event; TG, triglycerides; TIA, transient ischemic attack.
1 Only centers/countries that enrolled pediatric patients are displayed.
2 Trial was ongoing at the time of BLA submission.

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5.2. Review Strategy

The BLA submission included a single trial to support efficacy, trial 1629. Because the trial was conducted in two parts – a 24-week double-blind treatment period (DBTP) followed by a 24-week open-label treatment period (OLTP) – results of each part are discussed separately. Data from trial 1629 DBTP are considered as the primary demonstration of efficacy, while data from trial 1629 OLTP are considered as supportive evidence of long-term efficacy (to 48 weeks). Additional supportive evidence of long-term efficacy is obtained from the ongoing, long-term (up to 4 years), open-label extension trial 1719.

Dr. Laura Higginbotham reviewed evinacumab for efficacy, which included reviewing the lipid endpoints in the single phase 3 trial (1629 DBTP) and supportive evidence of long-term efficacy from open-label trials 1629 OLTP and 1719. Dr. Song from the Office of Biostatistics provided statistical support for this review (refer also to her review in DARRTS submitted 10/29/2020; Reference ID: 4694447).

Dr. Laura Higginbotham also reviewed evinacumab for safety, including adverse events, laboratory, vital sign, and electrocardiogram (ECG) parameters. Primary evidence of safety was obtained from placebo-controlled data in trial 1629 DBTP and from trial 1643 DBTP. Additional supportive safety information was obtained from open-label data (trials 1629 OLTP, 1643 OLTP, and 1719). Methods used in the safety review are detailed in Section 8.

Dr. Eileen Craig reviewed evinacumab for efficacy and safety in 13 pediatric patients.

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6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. R1500-CL-1629 DBTP

6.1.1. Study Design

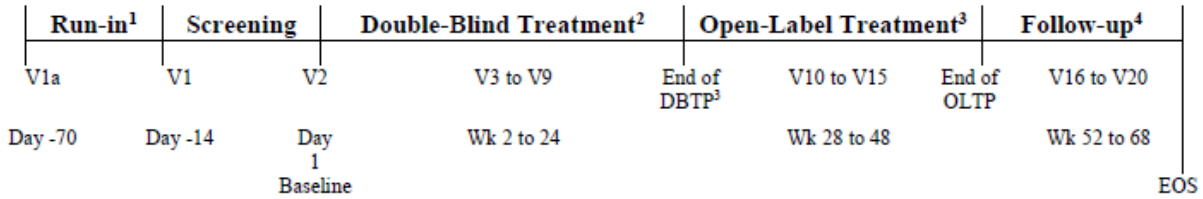
Overview and Objective

The primary objective of trial 1629 was to demonstrate the reduction of LDL-C by evinacumab 15 mg/kg IV in comparison to placebo after 24 weeks of treatment in patients with HoFH.

Trial Design

Basic Study Design:

Figure 1. Study Design of Trial 1629



Source: Applicant, 1629 CSR, p. 18.

Trial 1629 included an 8-week run-in period for genotyping and stabilization of background LLT. After successful completion of run-in and screening, patients were randomized 2:1 to receive evinacumab or placebo. Randomization was stratified by apheresis status and by geographical region (Japan vs. other). Patients then entered the DBTP – a 24-week, randomized, double-blinded, placebo-controlled treatment period in which they received evinacumab 15 mg/kg or placebo IV every 4 weeks for 24 weeks. During the subsequent OLTP, all patients received evinacumab 15 mg/kg IV every 4 weeks for 24 weeks. At the end of the OLTP, patients either entered into trial 1719 (an open-label, long-term extension trial) or entered into a 24-week follow-up period.

Trial Location: Trial 1629 was conducted at 30 sites in 11 countries, including the United States.

Choice of Control Group: LDL-lowering therapies are typically investigated against placebo as add-on therapy to a background of standard of care LLT. The primary reason for discouraging the use of an active control arm is ethical – approved therapies including statins and PCSK9i have proven CV risk reduction, and randomization to an arm without these therapies would be unethical. The Applicant's choice of matching placebo as the control group is acceptable and within Division expectations. This allows for a determination of any additional LDL-lowering

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effect of the investigational product on top of standard of care therapy.

Diagnostic Criteria: The Applicant's definition of HoFH, using genetic or clinical criteria, is reasonable. Clinical criteria for HoFH diagnosis varies within U.S.-based clinical practices but typically includes an untreated LDL-C >500 mg/dL or treated LDL-C >300 mg/dL. The presence of xanthomas before age 10 and elevated LDL-C in both parents further supports the diagnosis.

The Applicant's clinical criteria included an untreated TC >500 mg/dL rather than LDL-C. According to the Applicant during pre-submission discussions, this criterion is based on definitions used in European Union (E.U.)-based practices, and the Applicant provided evidence that the definition allows for increased sensitivity at identifying patients with HoFH. During the trial, all patients underwent genotyping to confirm their mutation status.

After enrollment, all patients were further characterized by HoFH genotype and phenotype in an attempt to identify those patients with the most difficult-to-treat mutations. Patients' HoFH genotype was described as negative/negative (mutation predicted to result in minimal to no LDLR function) or not negative/negative; mutations categorized as negative/negative included premature termination codons, splice site variations, frame shifts, insertions/deletions, and copy number variations. Patients' HoFH phenotype was described as null/null (LDLR activity <15% by *in vitro* assay) or not null/null. As previously stated, categorization of difficult-to-treat mutations is inconsistent in the literature and in current drug labeling. The most commonly used definition is LDLR activity <2% by *in vitro* assay, with these mutations variably referred to as null, negative, or absent. The Applicant's justification for additional genotype characterization – that given the large number of LDLR mutation variants, many mutations have not had LDLR function characterized by *in vitro* assay – is reasonable.

Key Eligibility Criteria: Trial 1629 was conducted in adult and adolescent patients ≥12 years with HoFH, whose LDL-C remained greater than 70 mg/dL despite the use of maximally-tolerated LLT, defined as daily statin, ezetimibe, PCSK9i, or other LLT including apheresis. Key inclusion and exclusion criteria are listed below. Criteria are consistent with those typically found in lipid-lowering development programs.

Inclusion

1. ≥12 years of age

2. HoFH

    a. Genetic confirmation of mutations in both *LDLR* alleles, both *APOB* alleles, both *PCSK9* alleles, or both *LDLRAP1* alleles, or double heterozygous mutations (mutations on different genes, such as *LDLR* + *PCSK9*)

        Reviewer comment: Inclusion of patients with double heterozygous mutations was encouraged by the Division given the phenotype consistent

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with HoFH.

b. Clinical criteria

- Untreated TC >500 mg/dL and TG <300 mg/dL AND
- Both parents with documented TC >250 mg/dL OR cutaneous/tendinous xanthoma before age 10 years

Exclusion

1. Tanner stage <2

2. LDL-C <70 mg/dL

3. Unstable apheresis schedule or background LLT

4. Presence of uncontrolled endocrine disease, use of any supplements / over-the-counter (OTC) drugs known to impact lipid levels, use of systemic steroids or estrogen/testosterone therapy

5. Unstable weight or initiation of new diet pre-screening

6. HbA1c >9% or newly-diagnosed (prior 3 months) type 2 diabetes mellitus (T2DM)

7. Recent (within 3 months) cardiovascular event or intervention

8. NYHA Class IV heart failure

9. Systolic blood pressure (SBP) >160 mmHg or diastolic blood pressure (DBP) >100 mmHg

10. Active malignancy within previous 5 years

11. Hypersensitivity to monoclonal antibodies

12. Abnormal lab values

- eGFR <30 mL/min/1.73 m^2
- ALT/AST >3x upper limit of normal (ULN)
- CPK >3x ULN
- TSH >1.5x ULN

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Dose Selection: The Applicant elected to investigate a single dose only of evinacumab (15 mg/kg IV Q4W) based on safety results from completed phase 1 and 2 studies and based on LDL-C reduction results from the initial phase 2, proof-of-concept trial 1331 in 9 patients with HoFH. Because evinacumab's target is saturated at 15 mg/kg, no additional efficacy was expected with the higher dose of 20 mg/kg. A lower dose of 5 mg/kg was also evaluated in early-stage trials but was less efficacious at LDL-C reduction.

Although evaluation of multiple doses was recommended for phase 3 trials, the Applicant's rationale for dose selection appears reasonable.

Study Treatments: Investigational medical product (IMP), either evinacumab or placebo, was administered as a weight-based infusion in 0.9% sodium chloride or 5% dextrose every 4 weeks: 15 mg/kg IV Q4W. The placebo infusion consisted of the same components as the evinacumab product, excluding the evinacumab purified protein (L-histidine, L-arginine-HCl, L-proline, and polysorbate 80).

Assignment to Treatment / Allocation Concealment: Patients were randomized 2:1 to evinacumab or placebo. Randomization was stratified by apheresis status and by region (Japan vs. other). Allocation concealment was appropriate; patients were randomized to evinacumab or placebo by trial staff using an interactive voice response system (IVRS).

Masking: Patients and investigators were masked to treatment assignment. Overall potential for unblinding during infusion administration is deemed low given the similar physical appearance of evinacumab and placebo. Hypersensitivity reactions, such as anaphylaxis or infusion reactions, could signal exposure to evinacumab with potential for unblinding; however, anaphylaxis occurred at low incidence, and infusion reactions also occurred in the placebo arm.

Endpoint assessment of primary and key secondary endpoints was objective – lab values were obtained by a central laboratory. Investigators were masked to lipid values throughout the trial.

Dose Modification or Discontinuation: No dose modification was permitted in the trial. Permanent drug discontinuation occurred if a patient withdrew consent, became pregnant, initiated a prohibited concomitant medication, developed an acute systemic infusion reaction, or by investigator recommendation. Patients who discontinued drug were requested to remain in the study and contribute data at all follow-up visits.

Administrative Structure: The trial included an independent DMC and an independent Clinical Events Committee (CEC). The DMC reviewed accumulated safety data throughout the trial period. The CEC included medical experts in cardiovascular disease and was responsible for adjudicating cardiovascular events and all-cause deaths. DMC and CEC meeting minutes were included in the BLA submission.

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Procedures and Schedule:

Tables 5-7. Schedule of Assessments, Trial 1629

Study Procedure	Double-Blind Treatment Period								Open-Label Treatment Period					
Visit	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 End DBTP[14]**	**10**	**11**	**12**	**13**	**14**	**15 End of OLTP**
Day	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**
Visit Window (Day)	**±1**	**±3**	**±3**	**±3**	**±3**	**±5**	**±5**	**±1**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
Week	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
Baseline:														
Informed Consent	X[1]													
Pharmacogenomics Consent	X[1]													
Treatment:														
Randomization	X[1]													
Administer IV Double-Blind Study Drug	X[1]		X	X	X	X	X							
Administer IV Open-Label Study Drug								X[10]	X	X	X	X	X	
Concomitant Medications (including LMT and apheresis)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Query LMT Compliance	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:														
Lipid Panel[2,3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Specialty Lipid Panel[3,4]	X		X	X	X	X		X		X		X		X
Safety:														
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination								X				X		X
Measured Height														X
Body Weight	X		X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs (pulse rate, BP)[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram[6]								X						X
Tanner stage[7]								X						X
Confirm contraception use and reminder of pregnancy reporting	X[1]		X	X	X	X	X	X	X	X	X	X	X	X
Remind male patients to use condoms	X		X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing[8]:														
Hematology	X		X	X	X	X		X		X		X		X

Study Procedure	Double-Blind Treatment Period								Open-Label Treatment Period					
Visit	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 End DBTP[14]**	**10**	**11**	**12**	**13**	**14**	**15 End of OLTP**
Day	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**
Visit Window (Day)	**±1**	**±3**	**±3**	**±3**	**±3**	**±5**	**±5**	**±1**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**
Week	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
Blood Chemistry	X		X	X	X	X		X		X		X		X
Creatine Phosphokinase	X		X	X	X	X		X		X		X		X
Serum Pregnancy Test[9]														X
Urine Pregnancy Test[9]	X		X	X	X	X	X	X	X	X	X	X	X	
Sex Hormones[7]								X						X
Urinalysis	X		X	X	X	X		X		X		X		X
hs-CRP	X							X						X
HbA1C	X[1]				X			X			X			X
LDLR function	X[1]													
Research Samples	X[1]		X	X		X		X	X					
PK and PD Samples														
ADA Sample[10]	X[1]		X		X			X						X
PK (evinacumab, alirocumab), ANGPTL3, PCSK9 Samples[11,12]	X[1]	X	X	X	X	X	X	X			X			X
PK of statin[11]	X[1]					X								
DNA sample for HoFH genotyping	X[1]													
Optional DNA Sample[13]	X[1]													
Other:														
EQ-5D	X							X						
HADS	X[1]							X				X[15]		X[15]
Review of diet	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X

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Study Procedure	Follow-up Period[5]				
Visit	16[5]	PV17[5,6]	18[5]	PV19[5,6]	EOS 20
Day	365	393	421	449	477
Visit Window (Day)	±5	±5	±5	±5	±5
Week	52	56	60	64	68
Treatment:					
Concomitant Medications (including LMT and apheresis)	X	X	X	X	X
Query LMT Compliance	X	X	X	X	X
Safety:					
Adverse Events	X	X	X	X	X
Physical Examination					X
Measured Height					
Body Weight					X
Vital Signs (pulse rate, BP)					X
Electrocardiogram[1]					X
Tanner stage[2]					X
Confirm contraception use and reminder of pregnancy reporting	X	X	X	X	X
Remind male patients to use condoms	X	X	X	X	
Laboratory Testing:					
Lipid Panel	X		X		X
Specialty Lipid Panel	X		X		X
Hematology	X		X		X
Blood Chemistry	X		X		X
Creatine Phosphokinase	X		X		X
Serum Pregnancy Test[3]					X
Urine Pregnancy Test[3]	X	X	X	X	
Sex Hormones[2]					X
Urinalysis					X
hs-CRP					X
HbA1C			X		X
PK and PD Samples					
ADA Sample					X
PK (evinacumab, alirocumab), ANGPTL3 Samples[4]					X
Other:					
Review of diet					X

Source: Applicant; 1629 Protocol, pp. 47-51.

Dietary Restrictions: Patients were instructed to follow a low-fat or heart-healthy diet. This approach is consistent with dietary recommendations in U.S. clinical practice.

Concurrent Medications: Evinacumab or placebo was administered as add-on therapy to a background of maximally-tolerated LLT, defined in the protocol as daily statin, ezetimibe, and a PCSK9i. Additional LLTs, such as apheresis or lomitapide were also allowed. Patients were required to be on stable doses prior to randomization, which could be achieved during the 8-week run-in period. Patients who were not taking statin, ezetimibe, or PCSK9i were required to have a documented history of intolerability or lack of efficacy. Dose adjustments to background LLT or addition of new LLT were not permitted during the trial. Administration of IMP on a background of LLT is consistent with standard clinical practice in the U.S.

Prohibited medications included non-LLTs that could impact lipid levels, such as steroids or hormone replacement therapy.

Treatment Compliance: IMP was administered by clinical staff at the trial site.

Subject Discontinuation or Withdrawal: Patients who withdrew from the trial were asked to attend an unscheduled visit within 5 days for safety and pregnancy assessment and a final end-

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of-study visit for collection of efficacy and safety data. Additionally, patients were requested to participate in follow-up for at least 24 weeks after the last dose of IMP.

Patients who withdrew were not replaced.

Study Endpoints

Primary Endpoint: Trial 1629's primary endpoint was the percent reduction from baseline to Week 24 in calculated LDL-C. LDL-C lowering is considered a surrogate for CV risk reduction and has been used as the basis for full approval of lipid-lowering drugs. The timing of primary endpoint assessment is consistent with the observation period used in other lipid-lowering programs.

At all timepoints, LDL-C was calculated using the Friedewald equation, generally considered reliable within 0.5 mg/dL of directly-measured LDL, with reflexive assessment via direct measurement (beta quantification) in instances of TG >400 mg/dL or LDL-C <25 mg/dL because of loss of accuracy at these lipid extremes. This approach is consistent with other lipid-lowering development programs. In patients meeting criteria for direct LDL-C assessment (extreme TG or LDL-C), where direct LDL-C was missing, the Friedewald value was used.

No adjustment to background LLT or apheresis schedule was permitted during the trial.

Key Secondary Endpoints: Key secondary endpoints in trial 1629 included percent reduction in other lipid parameters from baseline to Week 24, categorical changes in LDL-C, and patient requirement for apheresis.

- % change from baseline to Week 24 in Apo B
- % change from baseline to Week 24 in non-HDL-C
- % change from baseline to Week 24 in TC
- Patients with ≥30% reduction in LDL-C
- Patients with ≥50% reduction in LDL-C
- Absolute change from baseline in LDL-C
- Required apheresis (U.S. criteria)
- Patients with LDL-C <100 mg/dL
- Required apheresis (E.U. criteria)

The Applicant's inclusion of Apo B, non-HDL-C, and TC as secondary endpoints is reasonable. While LDL-C is the major atherogenic cholesterol, VLDL-C (the carrier of TG) is also atherogenic and Apo B is the primary protein contained in both LDL-C and VLDL-C. Thus, increased Apo B is presumed to represent increased risk for atherogenicity. Recent reports suggest that Apo B may be more clinically meaningful than LDL-C; however, widespread adoption in standard lipid panels has not yet occurred. Thus, its position as a secondary endpoint is appropriate.

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Non-HDL-C refers to the combination of LDL-C plus VLDL-C (TG carrier). As such, increased non-HDL-C is also presumed to represent increased atherogenic risk. However, review of changes to the individual components of non-HDL-C is considered more clinically meaningful.

In clinical practice, TC may be considered in treatment decisions regarding CV risk optimization, but because TC includes several lipid parameters of less relevance (e.g., HDL-C), it is the least relevant of the three secondary endpoint lipid parameters. Its positioning in the statistical hierarchy after Apo B and non-HDL-C is reasonable.

The Division previously advised the Applicant that absolute change and categorical changes (patients with 50% reduction or patients reaching various targets) in LDL-C or apheresis status would not be considered for labeling inclusion. The magnitude of absolute change in LDL-C with lipid lowering therapy is dependent on the baseline value and thus less generalizable to individual patients than percent change from baseline. Categorical description of a continuous variable (i.e. proportion of patient with ≥50% reduction) does not additionally inform median change from baseline, and categorical description of various targets is dependent on the mean or median value at baseline. Furthermore, a clinician's decision to initiate or modify LLT is based on the individual patient's LDL-C value, not on the ability of a therapy to achieve an LDL-C cutoff in a population.

Other Clinically Relevant Endpoints: Although not formally included as primary or secondary endpoints, change in HDL-C and TG were also assessed from baseline to Week 24. These endpoints are considered clinically relevant by practicing clinicians and would be reviewed during treatment decisions. TG ≥175 mg/dL and HDL-C <40 to 50 mg/dL are considered risk enhancers for ASCVD, although it is unclear if these risks are modifiable with pharmacotherapy (i.e., it is unclear that lowering TG or increasing HDL with pharmacotherapy has a meaningful impact on CV risk).

Exploratory Endpoints: The Applicant also included exploratory endpoints to assess the effect of evinacumab on quality of life (QOL) using EuroQol-5 (EQ-5D) and Patient-Assessed Hospital Anxiety and Depression Scale (HADS) questionnaires. The EQ-5D assesses 5 QOL domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The HADS is primarily used for screening of anxiety and depression in nonpsychiatric populations. The Applicant provided no evidence to support the validity, reliability, and ability to detect change of either instrument for LDL-C reduction in patients with HoFH. The endpoints were added during the first protocol amendment, 7 months after trial initiation. Because they are exploratory, and given the lack of validation, results will not be included in labeling.

Statistical Analysis Plan

Efficacy analyses were performed on the intent-to-treat (ITT) population, defined as all randomized patients according to the randomized treatment group and regardless of treatment

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adherence. Missing data was imputed using mixed-model repeated measures (MMRM). The primary and nine key secondary endpoints were tested using a stepdown hierarchy for multiplicity control. Endpoints were assessed in the following fixed sequence:

- % change from baseline to Week 24 in LDL-C
- % change from baseline to Week 24 in Apo B
- % change from baseline to Week 24 in non-HDL-C
- % change from baseline to Week 24 in TC
- Patients with ≥30% reduction in LDL-C
- Patients with ≥50% reduction in LDL-C
- Absolute change from baseline in LDL-C
- Required apheresis (U.S. criteria)
- Patients with LDL-C <100 mg/dL
- Required apheresis (E.U. criteria)

The statistical reviewer did not agree with the Applicant's imputation strategy, which assumes that data is missing at random (MAR). Refer to Dr. Song's statistical review for complete details of the Applicant's Statistical Analysis Plan (SAP).

Protocol Amendments

The protocol for trial 1629 was amended 3 times. Notable amendments include:

- Requirement for sexually active males to consistently use condoms, based on nonclinical data suggesting presence of evinacumab in sperm
- Addition of QOL questionnaires to study assessments
- Clarification that patients should be on maximally-tolerated LLT at enrollment
- Exclusion of patients with LDL-C <70 mg/dL

Amendments are not expected to impact trial integrity or interpretation of efficacy results.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant attested that studies were conducted in accordance with good clinical practice (GCP).

Financial Disclosure

The Applicant adequately disclosed financial interests and arrangements with investigators. Disclosed interests in a single sub-investigator, whose site contributed 1 patient, do not raise questions about data integrity based on the trial design (randomized treatment allocation via IVRS, double-blind masking, use of objective endpoints, and independent DMC) and the

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minimal contribution to trial data. The disclosed interest does not impact the approvability of the application.

Patient Disposition

The majority (87%) of patients screened were enrolled into trial 1629. Reasons for screen failure included failure to meet eligibility criteria (n=8) and withdrawal of consent (n=2). Sixty-five patients were randomized into the trial. One placebo patient withdrew consent after one dose. No patients discontinued study drug.

Table 8. Patient Disposition, Trial 1629, DBTP[1]

Patients screened		**75**
Screen failures		10 (13.3%)
Randomized		65 (86.7%)
	Evinacumab N=43 n(%)	**Placebo N=22 n(%)**
Patients randomized	**43 (100%)**	**22 (100%)**
ITT population[2]	43 (100%)	22 (100%)
Safety population[3]	44 (102%)	21 (95.5%)
Discontinued study	**0 (0.0%)**	**1 (4.5%)**
Withdrawal by patient	0 (0.0%)	1 (4.5%)
Discontinued study drug	**0 (0.0%)**	**0 (0.0%)**

Source: adsl.xpt; Software: JMP.
Abbreviations: DBTP, double-blind treatment period; ITT, intent to treat; N, number of patients in treatment group; n, number of patients in specified population or group.
1 Duration = 24 weeks.
2 Defined as all randomized patients, analyzed per randomized arm.
3 Defined as all patients who received at least one dose of study drug, analyzed per protocol. One placebo patient received evinacumab erroneously and is counted in the evinacumab arm.

Protocol Violations/Deviations

A substantial number of protocol deviations occurred during the trial; however, most were minor and not anticipated to impact data integrity or the interpretation of trial results.

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Table 9. Protocol Deviations, Trial 1629, DBTP and OLTP

	Evinacumab N=43 n(%)	Placebo N=22 n(%)
Any protocol deviation	41 (95.3%)	19 (86.4%)
Important	22 (51.2%)	10 (45.5%)
Minor	40 (93.0%)	16 (72.7%)
Important deviations		
Procedure performed outside window	10 (23.3%)	8 (36.4%)
WOCBP not receiving monthly pregnancy testing	8 (18.6%)	2 (9.1%)
Enrollment of patients with unstable medication use	6 (14.0%)	2 (9.1%)
Drug allocation error	1 (2.3%)	0 (0.0%)
Inadequate informed consent	1 (2.3%)	0 (0.0%)

Source: addv.xpt; Software: JMP.
Abbreviations: DBTP, double-blind treatment period; N, number of patients in treatment group; n, number of patients in specified population of group; OLTP, open-label treatment period; WOCBP, women of child-bearing potential.

Amongst important protocol deviations, the primary reasons for deviation were procedural irregularities or enrollment of patients with unstable background LLT, systemic steroids, or thyroid replacement therapy during the screening period. Procedural irregularities included alterations to a patient's apheresis schedule (which was supposed to remain stable throughout the trial) or LDL-C assessment after receipt of apheresis (lipid panels were to be drawn prior to apheresis). Changes to the apheresis schedule could impact interpretation of the primary LDL-C endpoint; however, the anticipated effect is narrowing of the treatment effect since the irregularity occurred at higher incidence in the placebo arm. Enrollment of patients with unstable background LLT should also not impact the 24-week primary efficacy endpoint, since by 24 weeks, background LLT would have stabilized.

Baseline Demographic and Clinical Characteristics

Enrolled patients were predominantly white (74%) and non-Hispanic (89%), with a mean age of 42 years. Two pediatric patients were included in the trial. Most patients were enrolled outside of the U.S. (85%). Demographics were generally well-balanced between the treatment arms, although the evinacumab arm included more patients over the age of 65 years (19% vs. 0% placebo).

Enrolled patients were diagnosed with HoFH for an average of 14 years at trial entry. Fifty-one percent (51%) of patients had negative/negative or null/null mutations as defined by the Applicant. Although more placebo patients had negative/negative or null/null mutations (59%) compared to evinacumab (47%), the overall mean LDL-C was similar between treatment arms.

Over half of patients had a baseline LDL-C value ≥190 mg/dL (severe hyperlipidemia), and nearly

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20% had a baseline ≥400 mg/dL. Most patients were taking 3 LLTs at baseline. Most patients were on a high-intensity statin (77%) or other intensity (17%), PCKS9i (77%), and ezetimibe (75%). Additionally, most patients (69%) had established or risk-equivalent coronary heart disease (CHD).

The enrolled trial population was consistent with the HoFH population encountered in clinical practice – patients on maximal LLT who still require additional LDL-C reduction. Baseline clinical characteristics were generally well-balanced between the treatment arms, within reasonable expectations given the small sample size.

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Table 10. Baseline Demographic and Clinical Characteristics, Trial 1629, DBTP[1]

Characteristic	Evinacumab N=43 n(%)	Placebo N=22 n(%)	Total Population N=65 n(%)
Age, years	43	22	65
Mean (SD)	44.3 (16.8)	36.7 (11.5)	41.7 (15.5)
Median (min, max)	41.0 (15, 75)	39.5 (30, 44)	41.0 (12, 75)
Age groups (years), n(%)	43	22	65
≥12 to <18	1 (2.3%)	1 (4.5%)	2 (3.1%)
≥18 to <65	34 (79.1%)	21 (95.5%)	55 (84.6%)
≥65 to <75	7 (16.3%)	0 (0.0%)	7 (10.8%)
≥75	1 (2.3%)	0 (0.0%)	1 (1.5%)
Sex, n(%)	43	22	65
Male	19 (44.2%)	11 (50.0%)	30 (46.2%)
Female	24 (55.8%)	11 (50.0%)	35 (53.8%)
Race, n(%)	43	22	65
White	31 (72.1%)	17 (77.3%)	48 (73.8%)
Black	2 (4.7%)	0 (0.0%)	2 (3.1%)
Asian	6 (14.0%)	4 (18.2%)	10 (15.4%)
Other	2 (4.7%)	1 (4.5%)	3 (4.6%)
Unknown	2 (4.7%)	0 (0.0%)	2 (3.1%)
Ethnicity, n(%)	43	22	65
Hispanic	1 (2.3%)	1 (4.5%)	2 (3.1%)
Non-Hispanic	38 (88.4%)	20 (90.9%)	58 (89.2%)
Unknown	4 (9.3%)	1 (4.5%)	5 (7.7%)
Country/region of participation, n(%)	43	22	65
United States	8 (18.6%)	2 (9.1%)	10 (15.4%)
Canada	3 (7.0%)	0 (0.0%)	3 (4.6%)
Australia	2 (4.7%)	2 (9.1%)	4 (6.2%)
New Zealand	1 (2.3%)	1 (4.5%)	2 (3.1%)
European Union	12 (27.9%)	8 (36.4%)	20 (30.8%)
Ukraine	6 (14.0%)	2 (9.1%)	8 (12.3%)
South Africa	6 (14.0%)	2 (9.1%)	8 (12.3%)
Japan	6 (14.0%)	4 (18.2%)	10 (15.4%)
HoFH diagnosis method[2], n(%)	43	22	65
Genotyping	29 (67.4%)	15 (68.2%)	44 (67.7%)
Clinical criteria	14 (32.6%)	7 (31.8%)	21 (32.3%)
Duration of HoFH diagnosis (years)	43	22	65
Mean (SD)	16.2 (14.6)	10.7 (12.5)	14.3 (14.1)
Median (min, max)	15.4 (0.0, 47.6)	5.5 (0.1, 38.0)	9.2 (0.0, 47.6)
HoFH genotype[3,4], n(%)			
Homozygous	22 (51.2%)	8 (36.4%)	30 (46.2%)
Compound heterozygous	12 (27.9%)	8 (36.4%)	20 (30.8%)
Double heterozygous	2 (4.7%)	1 (4.5%)	3 (4.6%)
Other	7 (16.3%)	5 (22.7%)	12 (18.5%)
HoFH phenotype[5], n(%)	43	22	65
Negative/negative	5 (11.6%)	7 (31.2%)	12 (18.5%)

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Null/null	15 (34.9%)	6 (27.3%)	21 (32.3%)
Neither	16 (37.2%)	4 (18.2%)	20 (30.8%)
Other	7 (16.3%)	5 (22.7%)	12 (18.5%)
LDL-C (mg/dL)	43	22	65
Mean (SD)	259.5 (172.4)	246.5 (153.7)	255.1 (165.2)
Median (min, max)	208.0 (46, 907)	198.5 (39, 605)	202.0 (39, 907)
LDL-C groups (mg/dL), n(%)	43	22	65
<70	1 (2.3%)	1 (4.5%)	2 (3.1%)
≥70 to <100	4 (9.3%)	0 (0.0%)	4 (6.2%)
≥100 to <130	4 (9.3%)	4 (18.2%)	8 (12.3%)
≥130 to <160	3 (7.0%)	3 (13.6%)	6 (9.2%)
≥160 to <190	7 (16.3%)	2 (9.1%)	9 (13.8%)
≥190 to <300	9 (20.9%)	5 (22.7%)	14 (21.5%)
≥300 to <400	7 (16.3%)	3 (13.6%)	10 (15.4%)
≥400 to <500	4 (9.3%)	1 (4.5%)	5 (7.7%)
≥500	4 (9.3%)	3 (13.6%)	7 (10.8%)
TG (mg/dL)	43	22	65
Mean (SD)	113.1 (68.4)	144.1 (144.5)	123.6 (100.7)
Median (min, max)	91 (37, 348)	103.5 (41, 723)	96.0 (37, 723)
HDL (mg/dL)	43	22	65
Mean (SD)	43.9 (14.8)	45.6 (16.4)	44.4 (15.2)
Median (min, max)	41.5 (17, 90)	43.0 (20, 72)	42.0 (17, 90)
Apo B (mg/dL)	43	22	65
Mean (SD)	169.1 (82.8)	175.9 (98.8)	171.4 (87.8)
Median (min, max)	149 (55, 472)	134.0 (49, 455)	147.0 (49, 472)
Lp(a) (mmol/L)	43	22	65
Mean (SD)	111.3 (114.4)	103.4 (109.4)	108.7 (112.0)
Median (min, max)	59 (5, 462)	53.0 (2, 472)	57.0 (2, 472)
TC (mg/dL)	43	22	65
Mean (SD)	325.6 (170.8)	315.9 (150.4)	322.3 (163.1)
Median (min, max)	262 (110, 971)	254.4 (130, 691)	255.0 (110, 971)
Number of baseline LLT medications	43	22	65
Mean (SD)	2.8 (0.7)	2.5 (1.0)	2.7 (0.8)
Median (min, max)	3 (1, 4)	3 (0, 4)	3 (0, 4)
Statin use, n(%)	43	22	65
Yes	41 (95.3%)	20 (90.9%)	61 (93.8%)
No	2 (4.7%)	2 (9.1%)	4 (6.2%)
Statin category, n(%)	43	22	65
High-intensity	34 (79.1%)	16 (72.7%)	50 (76.9%)
Moderate-intensity	1 (2.3%)	0 (0.0%)	1 (1.5%)
Low-intensity	1 (2.3%)	2 (9.1%)	3 (4.6%)
None	2 (4.7%)	2 (9.1%)	4 (6.2%)
Unknown	5 (11.6%)	2 (9.1%)	7 (10.8%)
PCSK9i use, n(%)	43	22	65
Yes	34 (79.1%)	16 (72.7%)	50 (76.9%)
No	9 (20.9%)	6 (27.3%)	15 (23.1%)
Ezetimibe use, n(%)	43	22	65
Yes	33 (76.7%)	16 (72.7%)	49 (75.4%)

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No	10 (23.3%)	6 (27.3%)	16 (24.6%)
Lomitapide use, n(%)	43	22	65
Yes	11 (25.6%)	3 (13.6%)	14 (21.5%)
No	32 (74.4%)	19 (86.4%)	51 (78.5%)
Apheresis[6], n(%)	43	22	65
Yes	14 (32.6%)	8 (36.4%)	22 (33.8%)
No	29 (67.4%)	14 (63.6%)	43 (66.2%)
CV history[7], n(%)	43	22	65
Established CHD	22 (51.2%)	12 (54.5%)	34 (52.3%)
CHD risk equivalent	10 (23.3%)	1 (4.5%)	11 (16.9%)
Neither	11 (25.6%)	9 (40.9%)	20 (30.8%)

Source: adsl.xpt; Software: JMP.
Abbreviations: Apo B, apolipoprotein B; CHD, coronary heart disease; CV, cardiovascular; HDL, high-density lipoprotein; LDL-C, low-density lipoprotein; Lp(a), lipoprotein A; N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation; TC, total cholesterol; TG, triglycerides.
1 Randomized population.
2 At screening.
3 All patients underwent genotyping post-randomization.
4 Homozygous, same mutation in both alleles. Compound heterozygous, different mutations in both alleles. Double heterozygous, mutations in different genes. Other, undetermined or no mutation.
5 Negative/negative, LDLR or LDLRAP1 mutation predicted to result in complete loss of function (premature stop codon, splice site variation, frame shift, insertion, deletion, or copy number variation). Null/null, LDLR or LDLRAP1 mutation resulting in <15% LDLR activity by *in vitro* assay. Neither, mutation not predicted to result in loss of function or minimal LDLR activity. Other, undetermined or no mutation.
6 Randomization stratified by apheresis status.
7 Established CHD = acute myocardial infarction, silent myocardial infarction, angina, or coronary revascularization. CHD risk equivalent = peripheral arterial disease, ischemic stroke, chronic kidney disease, or diabetes mellitus plus 2 additional risk factors.

Treatment Compliance, Concomitant Medications

All patients who remained in the trial complied with treatment.

One patient, a 31-year-old male randomized to evinacumab with baseline LDL-C 325 mg/dL, initiated high-intensity atorvastatin and alirocumab during the course of the trial (on days 70 and 73, respectively). This occurred prior to assessment of the primary endpoint.

The patient's LDL-C values are displayed below.

Table 11. LDL-C Values for Patient with Change to Background LLT

Study Visit	LDL-C (mg/dL)
Baseline	325
Week 2	213
Week 4	171
Week 8[1]	167
Week 12[1]	109
Week 16	116
Week 20	98
Week 24	116

Source: adcm.xpt and adlbeff.xpt; Software: JMP.
Abbreviations: LDL-C, low-density lipoprotein; LLT, lipid-lowering therapy.
1 Atorvastatin and alirocumab were initiated between Weeks 8 and 12 of trial.

In this single patient, it appears the addition of high-intensity statin and a PCSK9i resulted in

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further LDL-C lowering than was achieved by evinacumab use alone. However, the results of this single patient (representing 2% of the evinacumab arm data) are not expected to impact interpretation of the overall efficacy results given the minor data contribution. Additionally, the majority of patients enrolled in trial 1629 were already taking statin, ezetimibe, and PCSK9i at baseline, and the anticipated real-world use of evinacumab is as add-on to these approved lipid-lowering therapies.

Efficacy Results – Primary Endpoint

Patients treated with evinacumab for 24 weeks experienced an LDL-C reduction of 47% compared to patients treated with placebo whose LDL-C values increased by 2%. The placebo-adjusted treatment effect of -49% is clinically and statistically significant.

Table 12. LDL-C Percent Change from Baseline to Week 24[1]

	LS Mean (95% CI)	Diff (95% CI); p value
Evinacumab (n=43)	-47.1 (-56.3, -37.9)	
Placebo (n=22)	1.9 (-11.0, 14.9)	
		-49.0 (-65.0, -33.1); <0.0001

Source: Statistical reviewer.
Abbreviations: CI, confidence interval; LDL-C, low-density lipoprotein; LS, least squares.
1 MMRM model with treatment, stratification factor, time, treatment by time, strata by time, baseline LDL-C, and baseline LDL-C by time.

Only 1 patient was missing 24-week data (a placebo patient who discontinued the trial). The statistical reviewer performed several sensitivity analyses using various imputation strategies (MMRM and pattern mixture modeling). Primary endpoint results were consistent regardless of the imputation strategy used. A sensitivity analysis to address the patient with modified background LLT was not performed; however, as previously described, minimal impact on the overall result is expected. Please refer to Dr. Song's review for additional details.

LDL-C reduction with evinacumab treatment was evident as early as Week 4 and persisted through Week 24. Persistence of effect beyond 24 weeks of treatment will be discussed under Sections 6.2 and 6.3.

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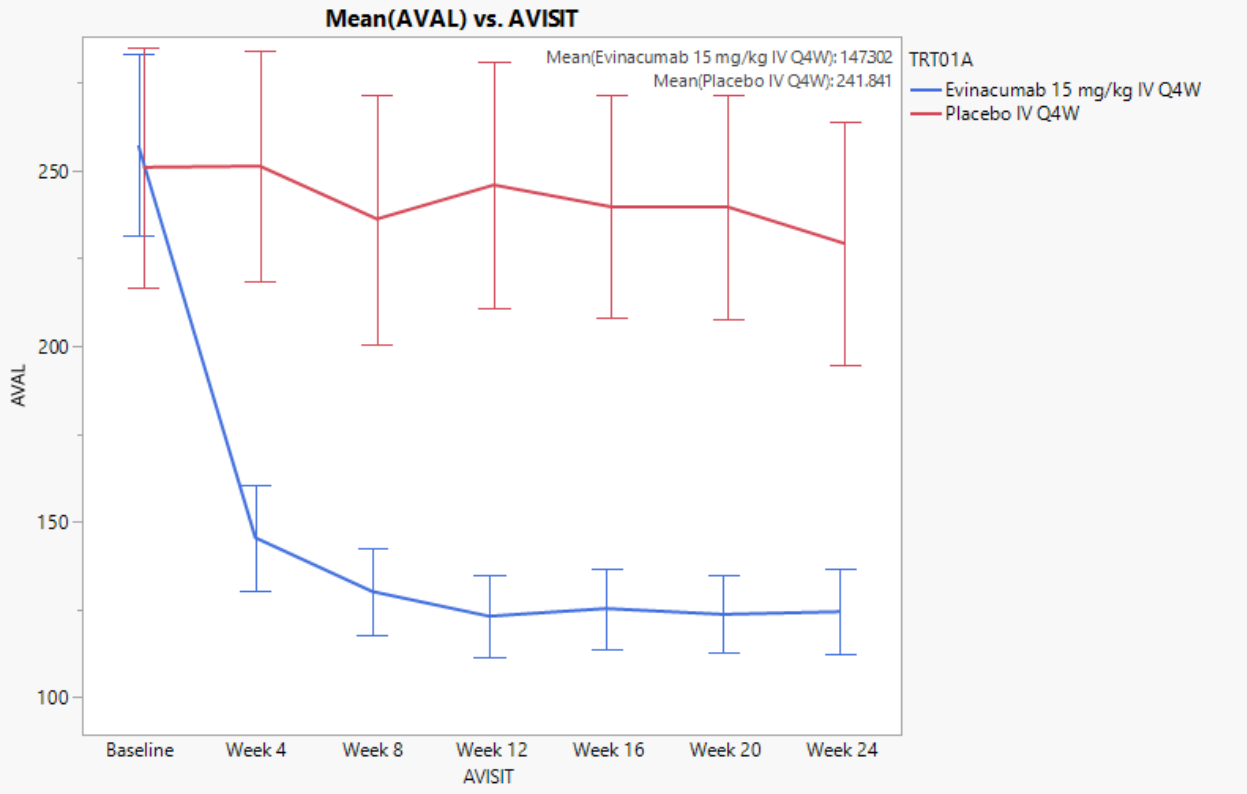
Figure 2. LDL-C Reduction Over Time



Source: adlbeff.xpt; Software: JMP.
Abbreviations: aval, analysis value; avisit, study visit; trt01a, actual treatment.
Error bars = SE.

The treatment effect of evinacumab at LDL-C reduction was similar regardless of a patient's HoFH mutation status, baseline LDL-C, or the number/type of background lipid-lowering therapy (Table 13).

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Table 13. Subgroup Analyses for Primary Endpoint, LDL-C Reduction at 24 Weeks

	Evinacumab (N=43)		Placebo (N=22)		Interaction Term p value
	n	LSM (SE)	n	LSM (SE)	
Age[1]					
<65	35	-51.4 (5.1)	22	2.2 (6.4)	-
≥65	8	-28.9 (11.1)	0	-	
Gender					
Male	19	-48.5 (7.0)	11	-6.0 (9.1)	0.40
Female	24	-46.0 (6.3)	11	10.1 (9.3)	
Race[1]					
White	31	-46.2	17	2.2	-
Black	2	-	0	-	
Asian	6	-42.0	4	-8.9	
Other	2	-61.3	1	43.6	
Unknown	2	-	0	-	
Ethnicity					
Hispanic	1	-63.1 (31.9)	1	28.1 (30.3)	0.48
Non-Hispanic	38	-44.2 (5.1)	20	3.1 (6.8)	
Unknown	4	-70.9 (18.6)	1	-47.6 (31.9)	
Baseline LDL-C					
<130 mg/dL	9	-27.3 (10.2)	5	-4.6 (13.4)	0.08
≥130 mg/dL	34	-52.5 (5.2)	17	4.8 (7.4)	
Baseline LDL-C					
<190 mg/dL	19	-42.8 (7.0)	10	13.5 (9.6)	0.44
≥190 mg/dL	24	-50.8 (6.2)	12	-6.9 (9.0)	
Neg/neg or Null/null Mutation[2]					
Yes	17	-42.8 (7.5)	9	15.4 (10.2)	0.32
No	26	-50.0 (6.0)	13	-7.7 (8.5)	
Number of Baseline LLT Drugs					
0, 1, or 2	13	-32.6 (8.1)	11	9.8 (9.2)	0.73
3 or 4	30	-53.5 (5.4)	11	-5.5 (8.9)	
Baseline Lomitapide Use					
Yes	11	-52.2 (9.8)	3	-21.6 (17.6)	0.37
No	32	-45.3 (5.5)	19	5.7 (7.0)	
Baseline Apheresis					
Yes	14	-46.5 (8.8)	8	-8.3 (11.6)	0.31
No	29	-47.3 (5.9)	14	7.9 (8.4)	

Source: Statistical reviewer.
Abbreviations: LDL-C, low-density lipoprotein; LLT, lipid-lowering therapy; LSM, least squares mean; SE, standard error.
1 Interaction term p values were unable to be calculated in cases where strata contained 0 data.
2 Negative/negative, LDLR or LDLRAP1 mutation predicted to result in complete loss of function (premature stop codon, splice site variation, frame shift, insertion, deletion, or copy number variation). Null/null, LDLR or LDLRAP1 mutation resulting in <15% LDLR activity by *in vitro* assay.

The Applicant also investigated LDL-C reduction by several categorical endpoints (Table 14). More patients treated with evinacumab achieved ≥50% reduction in baseline LDL-C or a 24-week LDL-C <70 mg/dL. However, all measurements were imprecise as evidenced by the wide confidence intervals. Additionally, as previously discussed, the Division does not typically

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consider categorical changes in LDL-C for labeling inclusion based on limited clinical applicability.

Table 14. Additional Endpoints Related to LDL-C Reduction

Week 24	Evinacumab vs. Placebo: LSM Diff (95% CI) or OR (%)	p value or 95% CI	Multiplicity Control?
Absolute change from baseline in LDL-C	-132.1 (-175.3, -88.9)	<0.0001	Yes
Patients with ≥30% reduction in LDL-C	OR 25.2 83.7% vs. 18.2%	5.7, 110.5	Yes
Patients with ≥50% reduction in LDL-C	OR 24.2 55.8% vs. 4.5%	3.0, 195.6	Yes
Patients with LDL-C <100 mg/dL	OR 5.7 46.5% vs. 22.7%	1.3, 24.9	No
Patients with LDL-C <70 mg/dL	OR 20.9 27.9% vs. 4.5%	1.6, 276.8	No
Required apheresis by U.S. criteria	OR 0.1 7.0% vs. 22.7%	0.0, 1.3	Yes
Required apheresis by E.U. criteria	OR 0.1 32.6% v. 77.3%	0.0, 0.3	No

Source: Statistical and clinical reviewer, adlbeff.xpt; Software: JMP.
Abbreviations: CI, confidence interval; EU, European Union; LDL-C, low-density lipoprotein; LSM, least squares mean; OR, odds ratio; US, United States; vs., versus.

Efficacy Results – Secondary and Other Relevant Endpoints

In addition to LDL-C reduction, evinacumab also reduced TG, HDL-C, Apo B, non-HDL-C, and TC at 24 weeks (Table 15). The degree of reduction in TG, Apo B, non-HDL-C, and TC is considered clinically meaningful.

Evinacumab lowered HDL-C by 30% compared to placebo after 24 weeks of treatment. The exact nature of the association between HDL-C and CV risk remains unclear, with recent studies suggesting a U-shaped association, where extreme low and extreme high levels are adverse.[1,2,3,4] Clinical trials of CETP inhibitors have failed to demonstrate that increased HDL-C is associated with CV risk reduction; one trial (torcetrapib) demonstrated increased CV risk, and two trials demonstrated no effect. Additionally, while epidemiologic evidence suggests that

[1] Li, X., Guan, B., Wang, Y. et al. Association between high-density lipoprotein cholesterol and all-cause mortality in the general population of northern China. Nature Sci Rep 2019; 9:14426.
[2] Madsen, C., Varbo, A., Nordestgaard, B. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies. Eur Heart J 2017; 38(32): 2478-2486.
[3] Singh, K., Rohatgi, A. Examining the paradox of high high-density lipoprotein and elevated cardiovascular risk. J Thorac Dis 2018; 10(1): 109-112.
[4] Yu, Y., Minghui, L., Huang, X., et al. A U-shaped association between the LDL-cholesterol to HDL-cholesterol ratio and all-cause mortality in elderly hypertensive patients: a prospective cohort study. Lipids Health Dis 2020; 19(1):238.

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patients with low HDL-C are at increased CV risk, this may be due to an unmeasured confounder; i.e., no data suggests that a further reduction in HDL-C leads to increased CV risk.

Nevertheless, patients treated with evinacumab had a mean (SD) HDL-C of 30.9 (11.8) mg/dL at 24 weeks, compared to 45.4 (17.9) in placebo patients. HDL-C values <40 mg/dL in men and <50 mg/dL in women are considered low. However, for this high-risk patient population where more than half of patients have severe hypercholesterolemia lasting decades because of childhood onset, the CV benefit of LDL-C reduction likely outweighs any theoretical risk associated with HDL-C reduction.

Table 15. Reduction in Additional Lipid Endpoints[1] from Baseline to Week 24

Week 24	Evinacumab vs. Placebo: LSM Diff (95% CI)	p value or 95% CI	Multiplicity Control?
% change from baseline in TG[2]	-50.4 (-65.6, -35.2)	<0.0001	No
% change from baseline in HDL-C[2]	-29.6 (-33.6, -25.6))	<0.001	No
% change from baseline in Apo B[3]	-36.9 (-48.6, -25.2)	<0.0001	Yes
% change from baseline in non-HDL-C[2]	-51.7 (-64.8, -38.5)	<0.0001	Yes
% change from baseline in TC[2]	-48.4 (-58.7, -38.1)	<0.0001	Yes
% change from baseline in Lp(a)[3]	-1.9 (-15.7, 12.0)	0.79	No
% change from baseline in Apo CIII[3]	-90.0 (-103.5, -76.5)	<0.0001	No
% change from baseline in Apo A1[3]	-31.3 (-35.5, -27.1)	<0.001	No

Source: Statistical and clinical reviewer, adlbeff.xpt; Software: JMP.
Abbreviations: Apo A1, apolipoprotein A1; Apo B, apolipoprotein B; Apo CIII, apolipoprotein CIII; CI, confidence interval; HDL-C, high-density lipoprotein; Lp(a), lipoprotein a; LSM, least squares mean; TC, total cholesterol; TG, triglycerides.
1 Assessed on the ITT population.
2 Missing data imputed using MMRM.
3 Missing data not imputed.

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6.2. R1500-CL-1629 OLTP

6.2.1. Study Design

The study design of 1629 OLTP is described under 1629 DBTP. Refer to Section 6.1.1. Lipid endpoints in the OLTP were summarized descriptively without formal statistical testing or control for multiplicity.

6.2.2. Study Results

Compliance with Good Clinical Practices

Refer to the discussion of GCP compliance for trial 1629 under Section 6.1.2.

Financial Disclosure

Refer to the discussion of financial disclosure in trial 1629 under Section 6.1.2.

Patient Disposition

After completion of the DBTP in trial 1629, 64 of the original 65 randomized patients entered into the OLTP. Two patients discontinued the OLTP early – one due to pregnancy and one due to protocol noncompliance. Amongst the 62 patients who remained in the trial, no patients discontinued study drug.

Table 16. Patient Disposition, Trial 1629, OLTP[1]

	DB Evinacumab[2] N=44 n(%)	DB Placebo[3] N=20 n(%)	Total Evinacumab[4] N=64 n(%)
Patients treated	**44 (100%)**	**20 (100%)**	**64 (100%)**
ITT population[5]	44 (100%)	20 (100%)	64 (100%)
Safety population[6]	44 (100%)	20 (100%)	64 (100%)
Discontinued study	**1 (2.3%)**	**1 (5.0%)**	**2 (3.1%)**
Pregnancy	1 (2.3%)	0 (0.0%)	1 (1.6%)
Protocol noncompliance	0 (0.0%)	1 (5.0%)	1 (1.6%)
Discontinued study drug	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**

Source: adsl.xpt; Software: JMP.
Abbreviations: DB, double-blind; ITT, intent to treat; N, number of patients in treatment group; n, number of patients in specified population or group; OLTP, open-label treatment period.
1 Duration = 24 weeks.
2 DB evinacumab = patients enrolled in the evinacumab arm during the DBTP. One former placebo patient received evinacumab erroneously during the DBTP and is counted in the evinacumab arm.
3 DB placebo = patients enrolled in the placebo arm during the DBTP. One former placebo patient discontinued the trial during the DBPT, and one former placebo patient received evinacumab erroneously during the DBTP and is counted in the evinacumab arm.
4 All patients received evinacumab during the OLTP.
5 Defined as all randomized patients, analyzed per randomized arm.
6 Defined as all patients who received at least one dose of study drug, analyzed per protocol. One placebo patient received evinacumab erroneously and is counted in the evinacumab arm.

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Protocol Violations/Deviations

Refer to the discussion of protocol deviations in trial 1629 under Section 6.1.2.

Baseline Demographic and Clinical Characteristics

Refer to the discussion of baseline demographic and clinical characteristics in trial 1629 under Section 6.1.2.

Treatment Compliance, Concomitant Medications

All patients who remained in the OLTP portion of trial 1629 complied with treatment.

Two patients modified background LLT during the OLTP prior to assessment of Week 48 LDL-C. Both patients were assigned to evinacumab during the DBTP. The first patient was a 49-year-old female who experienced a 41% reduction in LDL-C at the end of the DBTP. She initiated evolocumab on day 253, most likely because of continued LDL-C values >200 mg/dL. The second patient was a 23-year-old female, on high-intensity rosuvastatin, ezetimibe, alirocumab, lomitapide, and fish oil at baseline, who experienced a 50% reduction in LDL-C at the end of the DBTP. On day 211, the patient discontinued high-intensity rosuvastatin, most likely because of a decrease in LDL-C to 41 mg/dL.

Table 17. LDL-C Values in Patients with Changes to Background LLT

Study Visit	LDL-C (mg/dL)
49-year-old F (USUBJID (b) (6))	
Baseline	414
Week 24 (DBTP)[1]	243
Week 28 (OLTP Week 4)	231
Week 32 (OLTP Week 8)	239
Week 36 (OLTP Week 12)[2]	238
Week 40 (OLTP Week 16)[2]	218
Week 44 (OLTP Week 20)	226
Week 48 (OLTP Week 24)	237
23-year-old F (USUBJID (b) (6))	
Baseline	149
Week 24 (DBTP)[1]	75
Week 28 (OLTP Week 4)[3]	41
Week 32 (OLTP Week 8)[3]	143
Week 36 (OLTP Week 12)	103
Week 40 (OLTP Week 16)	72
Week 44 (OLTP Week 20)	66
Week 48 (OLTP Week 24)	55

Source: adcm.xpt and adlbeff.xpt; Software: JMP.
Abbreviations: DBTP, double-blind treatment period; LDL-C, low-density lipoprotein; LLT, lipid-lowering therapy; OLTP, open-label treatment period; USUBJID, unique subject identification.
1 Primary endpoint assessment in trial 1629 DBTP.
2 Treatment with evolocumab was initiated between OLTP Weeks 12 and 16.
3 Treatment with rosuvastatin was discontinued.

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Overall, the modification to concomitant medications is not expected to impact interpretation of the Week 48 LDL-C values given the minor contribution to data from two patients (representing 3% of the enrolled OLTP population). Additionally, the modifications were in opposite directions – one patient started additional LLT due to elevated LDL-C, and one patient discontinued background LLT due to decreased LDL-C. Use of multiple agents with occasional modification is not unexpected in an HoFH population and is consistent with the anticipated real-world use of the study drug.

Efficacy Results

Patients treated with evinacumab during the OLTP experienced a reduction in LDL-C of 46% from baseline after 24 (DB placebo) to 48 weeks (DB evinacumab) of treatment (Table 19).

Amongst previously-treated evinacumab patients (randomized to evinacumab during the DBTP [DB evinacumab]), efficacy was maintained from 24 weeks to 48 weeks. The absolute mean change in LDL-C from Week 0 to Week 24 was -134.7 mg/dl and from Week 24 to Week 48 was 3.5 mg/dL.

Amongst patients who switched from placebo to evinacumab at 24 weeks (DB placebo), the degree of LDL-C reduction, -55%, was consistent with that observed in the primary endpoint of trial 1629 DBTP (Table 18 and Figure 3). All but one DB placebo patient experienced a reduction in LDL-C upon initiation of evinacumab at Week 24. The percent LDL-C reduction in these patients ranged from -19% to -94% (Figure 4), and the absolute mean change was -129.6 mg/dL (compared to -2.6 mg/dL reduction during the DBTP). Additionally, 95% (18 of 19) DB placebo patients experienced a reduced LDL-C during the OLTP compared to only 33% during the DBTP.

In addition to LDL-C reduction, reductions were observed for all other lipid parameters and were similar to results observed during the DBTP.

Overall, the results of trial 1629 OLTP substantiate the primary endpoint findings in the DBTP and demonstrate the durability of LDL-C reduction with continued evinacumab treatment.

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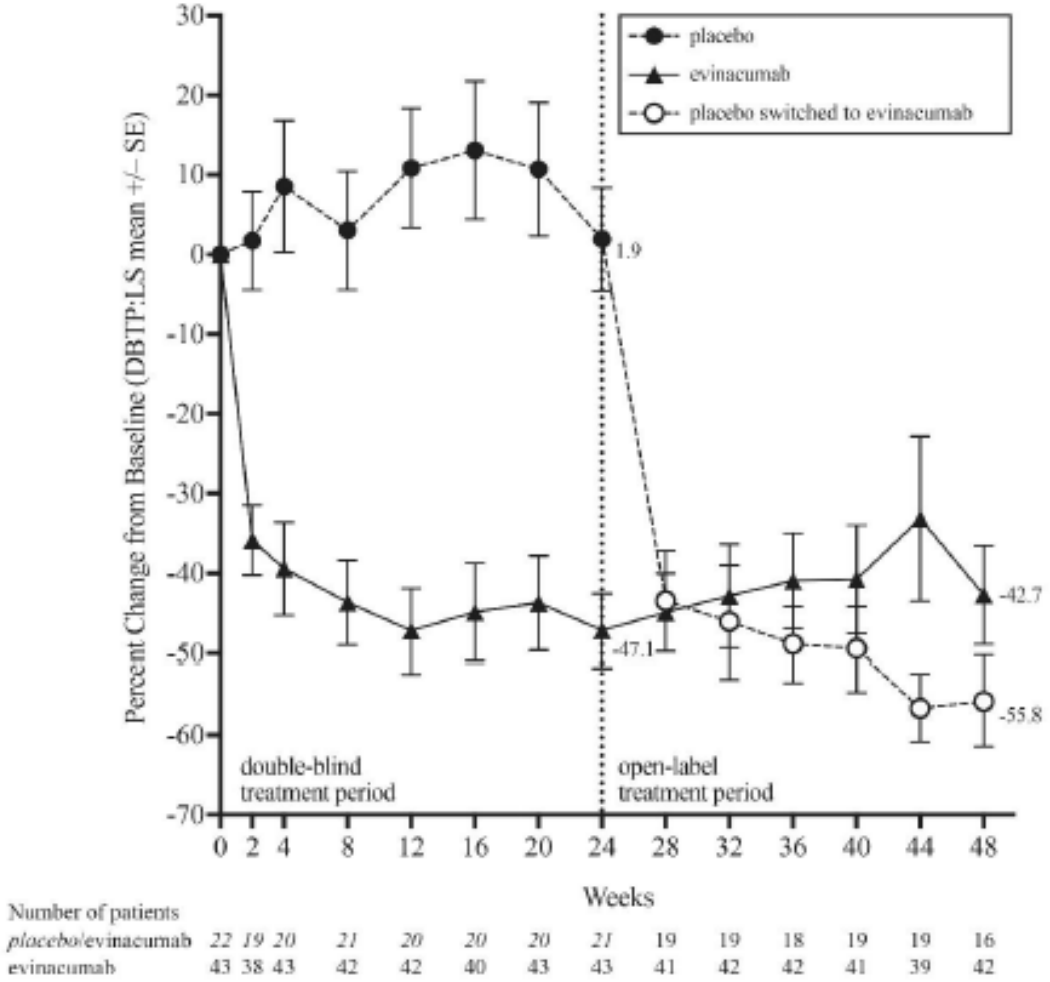
Table 18. Percent Change in Calculated LDL-C[1], OLTP

	LS Mean (SD)
Week 0 to Week 48	
DB Evinacumab[2] (n=42)	-42.7 (40.0)
DB Placebo[3] (n=16)	-55.8 (22.5)
Week 24 to Week 48	
DB Evinacumab[2] (n=42)	14.8 (83.2)
DB Placebo[3] (n=16)	-54.5 (26.5)

Source: Statistical reviewer, adlbeff.xpt; Software: JMP.
Abbreviations: DB, double blind; LDL-C, low-density lipoprotein; LS, least squares; n, number of patients with analysis value; SD, standard deviation.
1 No formal testing was performed for lipid endpoints in the OLTP. The primary and key secondary endpoints for trial 1629 were obtained at Week 24 of the DBTP.
2 Treated with evinacumab 15 mg/kg IV Q4W from Weeks 0-48. N=44. Only observed data displayed.
3 Treated with evinacumab 15 mg/kg IV Q4W from Weeks 24-48. N=20. Only observed data displayed.

Figure 3. Change in LDL-C Over Time, Trial 1629, OLTP



Source: Applicant; Trial 1629 OLTP CSR.
Double-blind treatment period = missing data imputed using MMRM. Open-label treatment period = observed data only.

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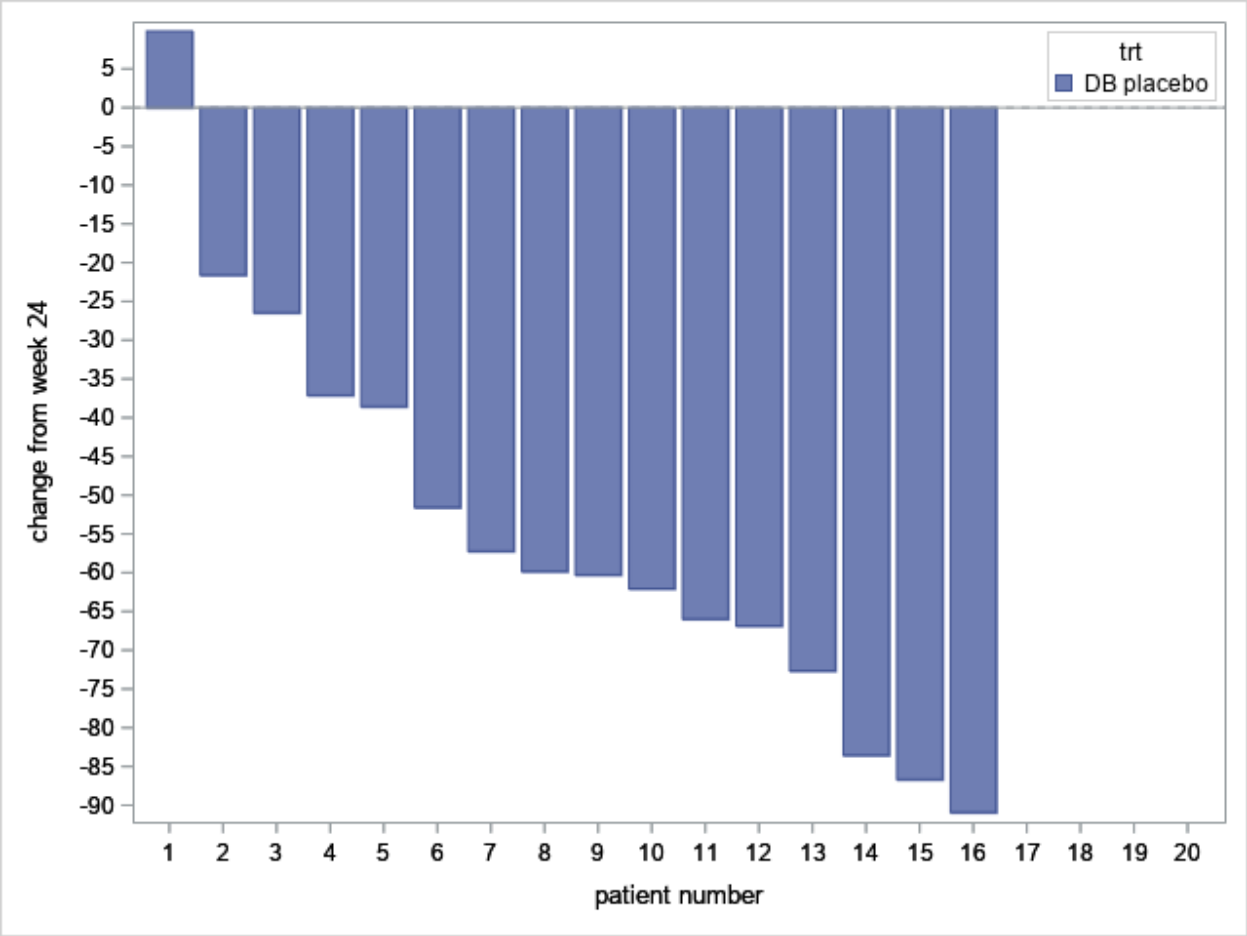
Figure 4. Waterfall Plot of Individual Patient Changes in LDL-C Percent Reduction from Week 24 to Week 48, Trial 1629 OLTP, DB Placebo Arm[1]



Source: Statistical reviewer, adlbeff.xpt; Software: JMP.
Abbreviations: DB, double blind; DBTP, double-blind treatment period; LDL-C, low-density lipoprotein cholesterol; OLTP, open-label treatment period; trt, treatment.
1 Includes patients who were randomized to placebo during the DBTP. Patients with missing data at Week 48 not shown.

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Table 19. Percent Reduction in Lipid Parameters[1] from Baseline to Week 48

	DB Evinacumab[2] N=44 Mean (SD)	DB Placebo[3] N=20 Mean (SD)	All OLTP N=64 Mean (SD)
LDL-C	-42.7 (40.0)	-55.8 (22.5)	-46.3 (36.3)
HDL-C	-32.0 (13.1)	-26.1 (20.5)	-30.4 (15.6)
TG	-47.7 (18.7)	-56.9 (20.1)	-50.3 (19.4)
non-HDL-C	-45.8 (30.6)	-57.1 (19.7)	-48.9 (28.3)
TC	-44.9 (21.0)	-52.6 (17.1)	-47.0 (20.2)
Apo B	-37.1 (27.7)	-49.9 (19.8)	-40.8 (26.2)
Lp(a)	-10.3 (38.4)	-14.0 (35.0)	-11.4 (37.2)
Apo CIII	-81.2 (14.8)	-78.6 (15.0)	-80.5 (14.8)
Apo A1	-32.4 (11.4)	-29.9 (15.1)	-31.7 (12.5)

Source: Statistical and clinical reviewer, adlbeff.xpt; Software: JMP.
Abbreviations: Apo A1, apolipoprotein A1; Apo B, apolipoprotein B; Apo CIII, apolipoprotein CIII; DB, double blind; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; Lp(a), lipoprotein a; OLTP, open-label treatment period; SD, standard deviation; TC, total cholesterol; TG, triglycerides.
1 No formal testing was performed for lipid endpoints in the OLTP. The primary and key secondary endpoints for trial 1629 were obtained at Week 24 of the DBTP. Observed data only.
2 Treated with evinacumab 15 mg/kg IV Q4W from Weeks 0-48.
3 Treated with evinacumab 15 mg/kg IV Q4W from Weeks 24-48.

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6.3. R1500-CL-1719

6.3.1. Study Design

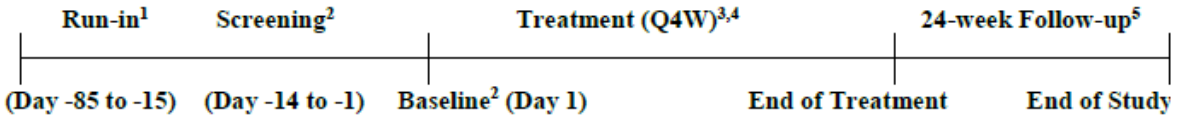
Overview and Objective

Trial 1719 is an ongoing, open-label, long-term extension (up to 4 years) trial designed to evaluate the long-term safety, tolerability, and efficacy of evinacumab in adult and adolescent patients with HoFH.

Trial Design

Basic Study Design:

Figure 5. Study Design, Trial 1719



Source: Applicant, 1719 CSR, p. 16.

After a ten-week run-in period for genotyping and stabilization of background LLT, all enrolled patients will receive evinacumab 15 mg/kg IV every 4 weeks for up to 4 years.

Trial Location: Trial 1719 is being conducted at 25 sites in 10 countries, including the United States.

Choice of Control Group: In this open-label trial, no control arm was included. While lack of a control arm makes interpretation of efficacy and safety data difficult, the placebo arm in trial 1629 showed no LDL-C reduction after 24 weeks. Thus, lipid endpoint results obtained during the trial can be compared to baseline values with reasonable certainty that any observed reduction is attributable to evinacumab. Use of concomitant medications will be assessed throughout the trial; patients were instructed to maintain stable background LLT through at least Week 24 and longer as feasible.

Diagnostic Criteria: The Applicant used the same HoFH diagnostic criteria as that used in trial 1629 DBTP. Refer to Section 6.1.1 for further discussion.

Key Eligibility Criteria: The target population for trial 1719 was identical to trial 1629 and included patients with HoFH, 12 years of age or older, with an LDL-C ≥70 mg/dL on stable maximally-tolerated statin, ezetimibe, and PCSK9i. Enrolled patients were rolled over from trial 1629 or trial 1331 or were treatment-naïve. Refer to Section 6.1.1 for specific inclusion and

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exclusion criteria.

Notable differences in eligibility criteria from trial 1629 include:

- Exclusion of patients with LDL-C <40 mg/dL at baseline (<70 mg/dL in trial 1629)
- Exclusion of patients with a significant protocol deviation in a prior evinacumab trial
- Exclusion of patients who experienced an adverse event leading to permanent discontinuation in a prior evinacumab trial

Dose Selection: Based on favorable efficacy and safety results obtained from trial 1629, the Applicant chose a single dose regimen of evinacumab 15 mg/kg IV Q4W for investigation in trial 1719. The Applicant's intention is to gain additional safety and long-term efficacy insight into the 15 mg/kg IV Q4W regimen.

Study Treatment: All patients will receive open-label evinacumab as a weight-based infusion every 4 weeks: 15 mg/kg IV Q4W. The dose will be calculated based on the patient's most recent weight. Dosing is allowed within a window of +/- 7 days. Patients who miss a dose >14 days will skip that dose.

Assignment to Treatment / Allocation Concealment: Not applicable in this open-label trial.

Masking: Not applicable in this open-label trial.

Dose Modification or Discontinuation: No dose modification is permitted in the trial. Permanent drug discontinuation occurs if a patient withdraws consent, becomes pregnant, develops an acute systemic infusion reaction, develops a serious or severe allergic reaction deemed related to evinacumab by the investigator, or by investigator recommendation. Patients who discontinue drug will be requested to remain in the study and contribute data at all follow-up visits.

Administrative Structure: The trial includes an independent DMC and an independent CEC. The DMC will review accumulated safety data throughout the trial period and advise the Applicant on whether trial modification is necessary for safety assurance. The CEC is responsible for adjudicating cardiovascular events and all-cause deaths. The committee includes medical experts in cardiovascular disease.

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Procedures and Schedule:

Tables 20-23. Schedule of Assessments, Trial 1719

Study Procedure	Baseline[1]	Open-Label Treatment Period						Q4-Week Visit Sequence[13]	
Visit	1	2	3	4	5	6	7	A	B
Day	1	29	57	85	113	141	169	±7 days	±7 days
Visit Window (Day)		±7	±7	±7	±7	±7	±7		
Week	0	4	8	12	16	20	24		
Baseline:									
Informed Consent	X								
Treatment:									
Administer IV Open-Label Study Drug[3,4]	X	X	X	X	X	X	X	X	X
Concomitant Medications and Procedures (including LMT and apheresis)[3]	X	X	X	X	X	X	X	X	X
Efficacy:									
Lipid Panel[3,5]	X		X	X	X		X		X
Specialty Lipid Panel[3,5]	X		X		X		X		X
Safety:									
Adverse Events	X	X	X	X	X	X	X	X	X
Physical Examination	X								
Measured Height[6]	X						X		
Body Weight	X	X	X	X	X	X	X	X	X
Vital Signs[4]	X	X	X	X	X	X	X	X	X
Electrocardiogram[7]	X						X		
Tanner Stage[8]							X		
Contraception Use Reminder	X	X	X	X	X	X	X	X	X
Remind male patients to use condoms	X	X	X	X	X	X	X	X	X
Laboratory Testing[2]:									
Hematology	X		X		X		X		X

Study Procedure	Baseline[1]	Open-Label Treatment Period						Q4-Week Visit Sequence[13]	
Visit	1	2	3	4	5	6	7	A	B
Day	1	29	57	85	113	141	169	±7 days	±7 days
Visit Window (Day)		±7	±7	±7	±7	±7	±7		
Week	0	4	8	12	16	20	24		
Blood Chemistry	X		X		X		X		X
Sex Hormones[6,8]							X		
Serum Pregnancy Test[9]									
Urine Pregnancy Test[9]	X	X	X	X	X	X	X	X	X
Urinalysis	X		X		X		X		X
hs-CRP	X		X		X		X		X
HbA1C	X			X			X		
Research Samples	X		X				X		X
ADA Samples[10]	X		-				X		
Pharmacokinetics (PK) of Evinacumab[11]	X[12]	X[17]	X[17]	X[12]	X[17]	X[17]	X[12]	X[17]	
Optional DNA sample[16]									
Other:									
Review of Diet	X	X	X	X	X	X	X	X	X
Reminder of LMT Compliance	X	X	X	X	X	X	X	X	X

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Study Procedure	Q4-Week Visit Sequence[10]				End of Treatment (4 weeks post last dose)/ Early Termination Visit[14]	24-Week Follow-up Period				
Visit	C	D	E	F		PV 8 weeks post last dose[15]	12 weeks post last dose	PV 16 weeks post last dose[15]	20 weeks post last dose	24 weeks post last dose/ End of Study Visit
Visit Window (Day)	±7	±7	±7	±7		F/U ±5	F/U ±5	F/U ±5	F/U ±5	F/U ±5
Treatment:										
Administer IV Open-Label Study Drug[3]	X	X	X	X						
Concomitant Medications and Procedures including LMT and apheresis)[3]	X	X	X	X	X	X	X	X	X	X
Efficacy:										
Lipid Panel[3,5]	X	X		X	X		X			X
Specialty Lipid Panel[3,5]		X		X	X		X			X
Safety:										
Adverse Events	X	X	X	X	X	X	X	X	X	X
Physical Examination										X
Measured Height[6]				X	X					X
Body Weight	X	X	X	X	X					X
Vital Signs[4]	X	X	X	X	X		X		X	X
Electrocardiogram[7]				X	X					X
Tanner Stage[6,8]				X	X					X
Contraception Use Reminder	X	X	X	X	X	X	X	X	X	X
Remind male patients to use condoms	X	X	X	X	X	X	X	X	X	X

Study Procedure	Q4-Week Visit Sequence[10]				End of Treatment (4 weeks post last dose)/ Early Termination Visit[14]	24-Week Follow-up Period				
Visit	C	D	E	F		PV 8 weeks post last dose[15]	12 weeks post last dose	PV 16 weeks post last dose[15]	20 weeks post last dose	24 weeks post last dose/ End of Study Visit
Visit Window (Day)	±7	±7	±7	±7		F/U ±5	F/U ±5	F/U ±5	F/U ±5	F/U ±5
Laboratory Testing[2]:										
Hematology		X		X	X		X		X	X
Blood Chemistry		X		X	X		X		X	X
Serum Pregnancy Test[9]					X					X
Urine Pregnancy Test[9]	X	X	X	X		X	X	X	X	X
Urinalysis		X		X	X					X
hs-CRP		X		X	X					X
HbA1C	X			X	X		X			X
Research Samples				X	X					X
ADA Samples[10]				X	X					X
Pharmacokinetics (PK) of Evinacumab[11]	X[12]			X[12]	X[12]					X[12]
Optional DNA Sample[16]	X									
Other:										
Review of Diet	X	X	X	X	X	X	X	X	X	X
Reminder of LMT Compliance	X	X	X	X	X	X	X	X	X	X

Source: Applicant; 1719 Protocol, pp. 48-54.

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Dietary Restrictions: Patients are instructed to follow a heart-healthy diet throughout the trial. This recommendation is consistent with U.S. clinical practice.

Concurrent Medications: Evinacumab will be administered as add-on therapy to background LLT. Allowable LLT in trial 1719 includes maximally-tolerated statin, ezetimibe, PCSK9i, lomitapide, and apheresis. Patients are required to be on stable doses prior to randomization; this can be achieved during the 10-week run-in period as needed. Patients taking LLT with demonstrated CV risk reduction (statins, ezetimibe, or PCSK9i) are instructed to maintain the regimen throughout the trial as feasible. Patients taking other LLT (lomitapide or apheresis) are instructed to maintain stable background LLT through at least Week 24; adjustments are allowed thereafter.

Trial 1629 (discussed in Section 6.1) aimed to ensure that enrolled patients were on appropriate background LLT at baseline, consistent with current U.S. recommendations, by requiring that patients not taking maximally-tolerated statin, ezetimibe, or PCSK9i have a documented history of intolerability or lack of efficacy. This requirement ensures the ethical enrollment of patients (given known CV risk reduction with these products) and allows for a more conservative interpretation of the IMP's treatment effect.

In contrast, trial 1719 eliminated this requirement. Although FDA would prefer to see all patients on optimized LLT prior to trial enrollment, the language used in trial 1719's protocol likely better reflects standard U.S. practice and may give a sense of real-world use of evinacumab. Nevertheless, efficacy results should be interpreted with caution in comparison to those observed in trial 1629.

Prohibited medications in trial 1719 include non-LLTs that could impact lipid levels, such as steroids or hormone replacement therapy.

Treatment Compliance: IMP will be administered by clinical staff at the trial site.

Subject Discontinuation or Withdrawal: Patients who withdraw from the trial are asked to attend an unscheduled visit within 5 days for safety and pregnancy assessment and an additional follow-up visit at least 24 weeks after the last dose of IMP.

Patients who withdraw will not be replaced.

Study Endpoints

Primary Endpoint: Trial 1719's primary endpoint is the incidence and severity of treatment-emergent adverse events (TEAEs).

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Secondary Endpoints: Efficacy endpoints, including LDL-C, are included as secondary endpoints in trial 1719.

- % and absolute change in LDL-C over time
- % and absolute change in Apo B over time
- % and absolute change in non-HDL-C over time
- % and absolute change in TC over time
- % and absolute change in TG over time
- ADA status and titers

LDL-C will be calculated using the Friedewald equation, considered reliable within 0.5 mg/dL of directly-measured LDL. Patients with TG >400 mg/dL or LDL-C <25 mg/dL will be assessed via direct measurement because of loss of accuracy at these lipid extremes. TG and TC will be directly measured. Non-HDL-C will be calculated (TC minus HDL-C).

For rollover patients from trial 1629, baseline lipid values are the last value taken before the first evinacumab dose in trial 1629. For rollover patients from trial 1331 and for treatment-naïve patients, baseline lipid values are the last value taken before the first evinacumab dose in trial 1719.

No adjustment to background LLT or apheresis schedule is permitted until 24 weeks. After 24 weeks, lomitapide or apheresis may be adjusted; however, adjustment of statins, ezetimibe, or PCSK9i is discouraged.

Other Clinically Relevant Endpoints: Although not included as a secondary endpoint by the Applicant, change in HDL-C from baseline will also be assessed by the review team.

Statistical Analysis Plan

No formal statistical testing is planned for this open-label trial. According to the protocol, efficacy analyses will be performed on the safety population, defined as all patients who receive at least 1 dose or part of a dose of open-label evinacumab. The Applicant does not plan to impute missing data or control for multiplicity. Efficacy endpoints (positioned as secondary in the SAP) will be summarized descriptively for each study timepoint.

Use of the ITT population, imputation, and multiplicity control ensure a conservative estimate of evinacumab's treatment effect and was performed in trial 1629. For this open-label trial, lack of imputation or multiplicity control is not ideal but acceptable since results are intended as supportive only. Efficacy results from trial 1719 will be more reflective of evinacumab's anticipated real-world use.

Efficacy results should be interpreted with caution when attempting to directly compare results

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to those observed in trial 1629 given the SAP differences.

Protocol Amendments

The protocol for trial 1719 was amended 4 times. Notable amendments include:

- Increase in anticipated sample size for the enrollment of additional evinacumab-naïve adolescent patients
- Addition of adolescent efficacy and safety endpoints
- Revision to apheresis criteria to allow study drug administration prior to apheresis based on data showing apheresis has a minor effect on drug concentration
- Allowance of plasma exchange in order to assess the impact of plasma exchange on evinacumab PK
- Revision to eligibility criteria to allow enrollment of treatment-naïve patients
- Exclusion of patients with Tanner stage <2

Amendments are not expected to impact trial integrity or interpretation of efficacy results.

6.3.2. Study Results

Compliance with Good Clinical Practices

The Applicant attested that studies were conducted in accordance with GCP.

Financial Disclosure

The Applicant adequately disclosed financial interests and arrangements with investigators. No interests or arrangements pertained to trial 1719.

Patient Disposition

As of the initial BLA submission on June 11, 2020, 64 of an anticipated 120 patients were enrolled into trial 1719. The majority (83%) of screened patients were enrolled. Reasons for screen failure were failure to meet eligibility criteria. As of the data cutoff date of September 24, 2019, all patients remain ongoing with no treatment or study discontinuations. At the time of submission, the mean treatment exposure was 22 weeks. Thirty patients (47%) have reached ≥12 weeks of exposure, 19 patients (30%) have reached ≥24 weeks of exposure, and 8 patients (13%) have reached ≥1 year of exposure.

> *Reviewer comment: On September 22, 2020, the Applicant submitted a 120-Day Safety Update, which included updated safety data on enrolled patients in trial 1719 (data cutoff date 06/12/2020). The submission indicated that 40 additional patients have since enrolled into the trial; however, updated disposition and efficacy data were not submitted. Results of the updated safety data are discussed under Section 8.7.*

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Table 24. Patient Disposition, Trial 1719[1]

Patients screened	**77**		
Enrolled	**64 (83.1%)**		
Screen failures	**2 (2.6%)**		
In screening	**11 (14.3%)**		
	Treatment-Naïve N=22 n(%)	**Rollovers[2] N=42 n(%)**	**Total Evinacumab N=64 n (%)**
Patients treated	**22 (100%)**	**42 (100%)**	**64 (100%)**
Safety population[3]	22 (100%)	42 (100%)	64 (100%)
Anti-evinacumab antibody population[4]	13 (59.1%)	13 (31.0%)	26 (40.6%)
Discontinued study	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**
Discontinued study drug	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**

Source: adsl.xpt; Software: JMP.
Abbreviations: N, number of patients in treatment group; n, number of patients in specified population or group.
1 Trial ongoing; duration = up to 4 years. Data cutoff date: 09/24/2019.
2 Includes 33 patients from Trial 1629 and 9 patients from Trial 1331.
3 Defined as patients who received at least one dose (or partial dose) of study drug.
4 Defined as patients who received at least one dose of study drug and had at least one ADA result.

Protocol Violations/Deviations

Protocol deviations occurred during the trial; however, most were minor and are not expected to impact data integrity or interpretation of the trial's results.

Table 25. Protocol Deviations, Trial 1719

	Treatment-Naïve N=22 n(%)	**Rollovers[1] N=42 n(%)**	**Total N=64 n(%)**
Any protocol deviation	13 (59.1%)	19 (45.2%)	32 (50.0%)
Important	7 (31.8%)	12 (28.6%)	19 (29.7%)
Minor	9 (40.9%)	14 (33.3%)	23 (35.9%)
Important deviations			
Procedural irregularities	7 (31.8%)	9 (21.4%)	16 (25.0%)
Received prohibited medications	2 (9.1%)	4 (9.5%)	6 (9.4%)
Other	0 (0.0%)	1 (2.4%)	1 (1.6%)

Source: addv.xpt; Software: JMP.
Abbreviations: N, number of patients in treatment group; n, number of patients in specified population or group.
1 Includes 33 patients from Trial 1629 and 9 patients from Trial 1331.

Amongst important deviations, the primary reasons were procedural irregularities and receipt of prohibited medications. Procedural irregularities included alterations to a patient's apheresis schedule (n=8) or failure to collect protocol-specified assessments (PK, lipid panel, or high-sensitivity C-reactive protein [hsCRP]). Receipt of prohibited medications included modifications to background LLT (n=4), enrollment of patients with unstable background LLT (n=2), and enrollment of a patient with unstable thyroid replacement therapy (n=1).

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Changes to the apheresis schedule or modification of background LLT in 12 patients (19% of data) could impact interpretation of lipid endpoints.

Baseline Demographic and Clinical Characteristics

Enrolled patients were predominantly white (78%) and non-Hispanic (80%), with a mean age of 41 years. One pediatric patient was included in the trial. Most patients were enrolled outside of the U.S. (78%).

> *Reviewer comment: A large proportion (nearly 25%) of treatment-naïve patients were missing baseline demographic data for race and ethnicity. This underscores the limitations of reviewing data from an ongoing trial. Efficacy results should be interpreted with caution given potential questions about data capture and quality and the limited sample size.*

Enrolled patients were diagnosed with HoFH for an average of 15.5 years at trial entry. Fifty-two percent (52%) of patients had negative/negative or null/null mutations per the Applicant's definitions. Over half of patients had a baseline LDL-C value ≥190 mg/dL, and 20% had a baseline ≥400 mg/dL. Most patients were taking 3 LLTs at baseline, including high-intensity statin (94%), PCKS9i (67%), and ezetimibe (86%). Amongst the treatment-naïve enrollees, all patients were taking statin (96% high-intensity) and 91% were taking ezetimibe. Fewer treatment-naïve patients were taking PCSK9i at baseline. This may be due to differences in the concomitant medication requirements, as described in Section 6.3.1. Most patients (75%) had established or risk-equivalent CHD.

Newly-enrolled, treatment-naïve patients were slightly higher risk than patients who rolled over from trials 1331 or 1629. Treatment-naïve patients had higher baseline LDL-C values, longer duration of HoFH diagnosis, increased prevalence of negative/negative or null/null mutations per the Applicant's definitions, and increased prevalence of established or risk-equivalent CHD.

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Table 26. Baseline Demographic and Clinical Characteristics, Trial 1719[1]

Characteristic	Treatment-Naive N=22 n(%)	Rollovers N=42 n(%)	Total Population N=64 n(%)
Age, years	22 (100%)	42 (100%)	64 (100%)
Mean (SD)	39.1 (12.7)	41.5 (12.1)	40.7 (12.3)
Median (min, max)	40.0 (12, 60)	41.5 (20, 72)	40.5 (12, 72)
Age groups (years), n(%)	22 (100%)	42 (100%)	64 (100%)
≥12 to <18	1 (4.5%)	0 (0.0%)	1 (1.6%)
≥18 to <65	21 (95.5%)	40 (95.2%)	61 (95.3%)
≥65 to <75	0 (0.0%)	2 (4.8%)	2 (3.1%)
≥75	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sex, n(%)	22 (100%)	42 (100%)	64 (100%)
Male	13 (59.1%)	22 (52.4%)	35 (54.7%)
Female	9 (40.9%)	20 (47.6%)	29 (45.3%)
Race, n(%)	22 (100%)	42 (100%)	64 (100%)
White	14 (63.6%)	36 (85.7%)	50 (78.1%)
Black	1 (4.5%)	0 (0.0%)	1 (1.6%)
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	2 (9.1%)	4 (9.5%)	6 (9.4%)
Unknown	5 (22.7%)	2 (4.8%)	7 (10.9%)
Ethnicity, n(%)	22 (100%)	42 (100%)	64 (100%)
Hispanic	2 (9.1%)	4 (9.5%)	6 (9.4%)
Non-Hispanic	15 (68.2%)	36 (85.7%)	51 (79.7%)
Unknown	5 (22.7%)	2 (4.8%)	7 (10.9%)
Country/region of participation, n(%)	22 (100%)	42 (100%)	64 (100%)
United States	5 (22.7%)	9 (21.4%)	14 (21.9%)
Canada	5 (22.7%)	6 (14.3%)	11 (17.2%)
Australia	0 (0.0%)	3 (7.1%)	3 (4.7%)
New Zealand	0 (0.0%)	1 (2.4%)	1 (1.6%)
European Union	10 (45.5%)	9 (21.4%)	19 (30.0%)
Ukraine	0 (0.0%)	6 (14.3%)	6 (9.4%)
South Africa	2 (9.1%)	8 (19.0%)	10 (15.6%)
HoFH diagnosis method[2], n(%)	22 (100%)	42 (100%)	64 (100%)
Genotyping	17 (77.3%)	31 (73.8%)	48 (75.0%)
Clinical criteria	5 (22.7%)	11 (26.2%)	16 (25.0%)
Duration of HoFH diagnosis (years)	22 (100%)	42 (100%)	64 (100%)
Mean (SD)	17.5 (13.8)	14.5 (13.4)	15.5 (13.5)
Median (min, max)	19.4 (0.5, 48.0)	7.7 (0.8, 44.0)	10.5 (0.5, 48.0)
HoFH genotype[3,4], n(%)	22 (100%)	42 (100%)	64 (100%)
Homozygous	11 (50.0%)	17 (40.5%)	28 (43.8%)
Compound heterozygous	8 (36.4%)	14 (33.3%)	22 (34.4%)
Double heterozygous	0 (0.0%)	1 (2.4%)	1 (1.6%)
Other	3 (13.6%)	10 (23.8%)	13 (20.3%)
HoFH phenotype[5], n(%)	22 (100%)	42 (100%)	64 (100%)
Negative/negative	6 (27.3%)	5 (11.9%)	11 (17.2%)
Null/null	8 (36.4%)	14 (33.3%)	22 (34.4%)

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Neither	5 (22.7%)	13 (31.0%)	18 (28.1%)
Other	3 (13.6%)	10 (23.8%)	13 (20.3%)
LDL-C (mg/dL)	22 (100%)	42 (100%)	64 (100%)
Mean (SD)	271.1 (134.1)	262.6 (216.2)	265.5 (190.8)
Median (min, max)	267.5 (92, 559)	179.5 (39, 907)	207 (39, 907)
LDL-C groups (mg/dL), n(%)	22 (100%)	42 (100%)	64 (100%)
<70	0 (0.0%)	4 (9.5%)	4 (6.3%)
≥70 to <100	1 (4.5%)	5 (11.9%)	6 (9.4%)
≥100 to <130	2 (9.1%)	5 (11.9%)	7 (10.9%)
≥130 to <160	1 (4.5%)	2 (4.8%)	3 (4.7%)
≥160 to <190	4 (18.2%)	6 (14.3%)	10 (15.6%)
≥190 to <300	6 (27.3%)	8 (19.0%)	14 (21.9%)
≥300 to <400	4 (18.2%)	3 (7.1%)	7 (10.9%)
≥400 to <500	2 (9.1%)	1 (2.4%)	3 (4.7%)
≥500	2 (9.1%)	8 (19.0%)	10 (15.6%)
TG (mg/dL)	22 (100%)	42 (100%)	64 (100%)
Mean (SD)	120.9 (109.3)	113.9 (78.4)	116.3 (89.6)
Median (min, max)	85.0 (27, 540)	90.0 (20, 348)	90.0 (20, 540)
HDL (mg/dL)	22 (100%)	42 (100%)	64 (100%)
Mean (SD)	42.6 (19.4)	42.7 (15.5)	42.7 (16.8)
Median (min, max)	40.5 (21, 115)	39.5 (20, 90)	40.0 (20, 115)
Apo B (mg/dL)	22 (100%)	42 (100%)	64 (100%)
Mean (SD)	183.9 (72.3)	170.8 (111.4)	175.3 (99.3)
Median (min, max)	174.0 (64, 346)	135.5 (37, 518)	152.0 (37, 518)
Lp(a) (mmol/L)	22 (100%)	42 (100%)	64 (100%)
Mean (SD)	108.0 (97.6)	132.9 (110.6)	124.3 (106.2)
Median (min, max)	73.0 (12, 418)	109.5 (2, 472)	102.0 (2, 472)
TC (mg/dL)	22 (100%)	42 (100%)	64 (100%)
Mean (SD)	337.4 (128.4)	328.2 (216.8)	331.4 (190.0)
Median (min, max)	327.5 (136, 599)	249.5 (81, 971)	292.0 (81, 971)
Number of baseline LLT medications	22 (100%)	42 (100%)	64 (100%)
Mean (SD)	2.5 (0.7)	2.7 (0.8)	2.6 (0.7)
Median (min, max)	3 (1, 4)	3 (0, 4)	3 (0, 4)
Statin use, n(%)	22 (100%)	42 (100%)	64 (100%)
Yes	22 (100%)	38 (90.5%)	60 (93.8%)
No	0 (0.0%)	4 (9.5%)	4 (6.3%)
Statin category, n(%)	22 (100%)	42 (100%)	64 (100%)
High-intensity	21 (95.5%)	36 (85.7%)	57 (89.1%)
Moderate-intensity	1 (4.5%)	2 (4.8%)	3 (4.7%)
Low-intensity	0 (0.0%)	0 (0.0%)	0 (0.0%)
None	0 (0.0%)	4 (9.5%)	4 (6.3%)
PCSK9i use, n(%)	22 (100%)	42 (100%)	64 (100%)
Yes	9 (40.9%)	34 (81.0%)	43 (67.2%)
No	13 (59.1%)	8 (19.0%)	21 (32.8%)
Ezetimibe use, n(%)	22 (100%)	42 (100%)	64 (100%)
Yes	20 (90.9%)	35 (83.3%)	55 (85.9%)
No	2 (9.1%)	7 (16.7%)	9 (14.1%)
Lomitapide use, n(%)	22 (100%)	42 (100%)	64 (100%)

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Yes	5 (22.7%)	5 (11.9%)	10 (15.6%)
No	17 (77.3%)	37 (88.1%)	54 (84.4%)
Apheresis[6], n(%)	22 (100%)	42 (100%)	64 (100%)
Yes	7 (31.8%)	7 (16.7%)	14 (21.9%)
No	15 (68.2%)	35 (83.3%)	50 (78.1%)
CV history[7], n(%)	22 (100%)	42 (100%)	64 (100%)
Established CHD	15 (68.2%)	24 (57.1%)	39 (60.9%)
CHD risk equivalent	3 (13.6%)	6 (14.3%)	9 (14.1%)
Neither	4 (18.2%)	12 (28.6%)	16 (25.0%)

Source: adsl.xpt; Software: JMP.
Abbreviations: Apo B, apolipoprotein B; CHD, coronary heart disease; CV, cardiovascular; HDL, high-density lipoprotein; LDL-C, low-density lipoprotein; Lp(a), lipoprotein A; N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation; TC, total cholesterol; TG, triglycerides.
1 Randomized population.
2 At screening.
3 All patients underwent genotyping post-randomization.
4 Homozygous, same mutation in both alleles. Compound heterozygous, different mutations in both alleles. Double heterozygous, mutations in different genes. Other, undetermined or no mutation.
5 Negative/negative, LDLR or LDLRAP1 mutation predicted to result in complete loss of function (premature stop codon, splice site variation, frame shift, insertion, deletion, or copy number variation). Null/null, LDLR or LDLRAP1 mutation resulting in <15% LDLR activity by *in vitro* assay. Neither, mutation not predicted to result in loss of function or minimal LDLR activity. Other, undetermined or no mutation.
6 Stratified randomization by apheresis status.
7 Established CHD = acute myocardial infarction, silent myocardial infarction, angina, or coronary revascularization. CHD risk equivalent = peripheral arterial disease, ischemic stroke, chronic kidney disease, or diabetes mellitus plus 2 additional risk factors.

Treatment Compliance, Concomitant Medications

All patients who remain in the trial complied with treatment.

Five (11.9%) rollover patients and 1 (4.5%) treatment-naïve patient modified their baseline LLT during the course of trial 1719. Changes are summarized below.

Table 27. Patients with On-Treatment Changes to Background LLT, Trial 1719

USUBJID	Trial Status	New LLT	Study Day
(b) (6)	Rollover (trial 1331)	Ezetimibe, high-intensity atorvastatin	28
	Rollover (trial 1629)	Evolocumab	57
	Treatment-naïve	Ezetimibe	59
	Rollover (trial 1629)	Evolocumab	85
	Rollover (trial 1331)	Ezetimibe, high-intensity rosuvastatin	258
	Rollover (trial 1331)	Evolocumab	305

Source: adcm.xpt; Software: JMP.
Abbreviations: LLT, lipid-lowering therapy; USUBJID, unique subject identification.

As of the data cutoff date of September 24, 2019, 6 patients (representing 9% of the data) modified background LLT. Modifications may impact interpretability of the trial's lipid endpoints. Results should be interpreted with caution.

Reference ID: 4745518

Efficacy Results

Efficacy data for trial 1719 included in the BLA submission is limited given the ongoing nature of the trial and the significant proportion of patients who modified background LLT or apheresis prior to Week 24. Efficacy results are intended as supportive only and should be interpreted with caution.

Although designed to demonstrate long-term efficacy and safety of evinacumab, 24-week data is only available on 19 patients, and 48-week data is only available for 8 patients.

Table 28. Percent Reduction in Lipid Endpoints, Baseline to Week 24 and Week 48, Trial 1719

	% Reduction Baseline to Week 24 (95% CI)			% Reduction Baseline to Week 48 (95% CI)		
	Treatment-Naïve N=7	Rollovers N=12	All Patients N=19	Treatment-Naïve N=0	Rollovers N=8	All Patients N=8
% reduction in LDL-C	-41.8 (-63.6, -20.0)	-47.0 (-59.4, -34.7)	-45.1 (-55.0, -35.2)	-	-40.3 (-85.1, 4.5)	-40.3 (-85.1, 4.5)
% reduction in HDL-C	-25.1 (-44.2, -6.0)	-28.1 (-39.6, -16.6)	-27.0 (-35.9, -18.0)	-	-18.1 (-44.9, 8.7)	-18.1 (-44.9, 8.7)
% reduction in TG	-44.6 (-75.6, -13.7)	-37.9 (-54.0, -21.7)	-40.5 (-54.1, -26.9)	-	-23.0 (-40.9, -5.2)	-23.0 (-40.9, -5.2)
% reduction in TC	-40.9 (-61.9, -19.9)	-43.0 (-54.5, -31.4)	-42.2 (-51.5, -32.8)	-	-36.4 (-74.6, 1.9)	-36.4 (-74.6, 1.9)

Source: Statistical and clinical reviewer, adlbeff.xpt; Software: JMP.
Abbreviations: CI, confidence interval; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; TC, total cholesterol; TG, triglycerides.

Based on observed data, evinacumab lowered LDL-C by 45% at 24 weeks and by 40% at 48 weeks. Other lipid parameters, including TG and TC, were also reduced with evinacumab treatment.

6.3.3. Pediatric Update

In the initial BLA submission, the Applicant provided an interim Clinical Study Report (CSR) that summarized the safety and efficacy results of 63 adults and 1 adolescent participant as of the data cutoff date of September 24, 2019. A summary of additional data in the subgroup of 13 pediatric participants (12 to <18 years of age) in R1500-CL-1719 as of the data cutoff date of August 28, 2020 (database lock on October 6, 2020) is provided below.

Trial Location

The 13 pediatric participants came from 7 sites across 6 countries: Australia, France, Italy, Japan, Netherlands, and South Africa.

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Patient Disposition

As of the interim analysis cutoff date of August 28, 2020, a total of 13 pediatric participants were enrolled and treated (11 in the Treatment-Naïve/New Evinacumab group and 2 in the Rollover/Continue Evinacumab group). For the 2 patients previously receiving evinacumab, both were treated in the R1500-CL-1629 study.

All 13 participants are ongoing in study 1719, and no participants have discontinued the study treatment early.

Patient Exposure

As of the cutoff date, the median duration of evinacumab treatment for the pediatric subpopulation was 32.8 weeks (mean 34.5 weeks), ranging from 4 to 61 weeks. Eleven patients had ≥32 weeks and 3 patients had greater than 48 weeks of treatment exposure.

> *Reviewer Comment: The number of subjects exposed and the duration of exposure to evinacumab in pediatric participants with HoFH is significantly less than what is typically requested and expected in double-blind, placebo-controlled trials to support a pediatric indication for the treatment of HoFH. However, the number of patients exposed and the duration of exposure to evinacumab in the open-label trial, supported by the efficacy and safety data in the adult population, is adequate to make a determination of safety and effectiveness for evinacumab in light of the large treatment effect of this therapy in patients with HoFH, particularly those with <15% LDLR function.*

Baseline Demographic and Clinical Characteristics

Enrolled patients were predominantly white (46%) and non-Hispanic (85%), with a mean age of 14 years (range 12 to 17 years). Sixty-two percent were male. All patients were enrolled outside of the U.S. Two patients (15%) were missing baseline demographic data for race and ethnicity.

Enrolled patients were diagnosed with HoFH for an average of 9 years at trial entry. Eight (61.6%) patients were considered to be null/null or negative/negative for LDLR mutations per the Applicant's definitions, with 4 patients in each mutation category. The mean (SD) baseline LDL-C in these pediatric patients was 300 (101) mg/dL. Eleven patients (85%) had a baseline LDL-C value ≥190 mg/dL and 4 patients (33%) had a baseline ≥400 mg/dL. All patients were on statin at baseline, of which 77% were on high-intensity statin therapy; 46% were on PCKS9i (evolocumab); 69% were on ezetimibe; and 62% were receiving lipid apheresis, either weekly or bi-weekly. Three patients (23%) had established CHD.

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Table 29. Baseline Demographic and Clinical Characteristics, Study 1719, Safety Analysis Set-Pediatrics

Characteristic	Treatment-Naive N=11 n (%)	Rollovers N=2 n (%)	Total Population N=13 n (%)
Age, years	11 (100%)	2 (100%)	13 (100%)
Mean (SD)	14.3 (1.7)	13.5 (2.1)	14.2 (1.7)
Median (min, max)	15.0 (12, 17)	13.5 (12, 15)	15.0 (12, 17)
Sex, n(%)	11 (100%)	2 (100%)	13 (100%)
Male	7 (63.6%)	1 (50.0%)	8 (61.5%)
Female	4 (36.4%)	1 (50.0%)	5 (38.5%)
Race, n(%)	11 (100%)	2 (100%)	13 (100%)
White	5 (45.5%)	1 (50.0%)	6 (46.2%)
Black or African American	1 (9.1%)	0	1 (7.7%)
Asian	2 (18.2%)	0	2(15.4%)
Other	2 (18.2%)	0	2 (15.4%)
Unknown	1 (9.1%)	1 (50.0%)	2 (15.4%)
Ethnicity, n(%)	11 (100%)	2 (100%)	13 (100%)
Hispanic	0	0	0
Non-Hispanic	10 (90.9%)	1 (50.0%)	11 (84.6%)
Unknown	1 (9.1%)	1 (50.0%)	2 (15.4%)
Country/region of participation, n(%)	11 (100%)	2 (100%)	13 (100%)
Australia	2 (18.2%)	0	2 (15.4%)
France	2 (18.2%)	1 (50.0%)	3 (23.1%)
Italy	1 (9.1%)	0	1 (7.7%)
Japan	1 (9.1%)	0	1 (7.7%)
Netherlands	1 (9.1%)	1 (50.0%)	2 (15.4%)
South Africa	4 (36.4%)	0	4 (30.8%)
Weight (kg)	11 (100%)	2 (100%)	13 (100%)
Median (min, max)	54.8 (45, 94)	57.2 (48, 67)	54.8 (45, 94)
BMI (kg/m^2)	11 (100%)	2 (100%)	13 (100%)
Median (min, max)	20.3 (17, 29)	18.5 (16, 21)	20.3 (16, 29)
HoFH diagnosis method, n(%)	11 (100%)	2 (100%)	13 (100%)
Genotyping	10 (90.9%)	1 (50.0%)	11 (84.6%)
Clinical criteria	1 (9.1%)	1 (50.0%)	2 (15.4%)
Duration of HoFH diagnosis (years)	11 (100%)	2 (100%)	13 (100%)
Mean (SD)	8.6 (3.9)	12.8 (5.0)	9.3 (4.2)
Median (min, max)	11.0 (2.9, 13.6)	12.8 (9.2, 16.3)	11.0 (2.9, 16.3)
HoFH genotype[1], n(%)	11 (100%)	2 (100%)	13 (100%)
Homozygous	5 (45.5%)	1 (50.0%)	6 (46.2%)
Compound heterozygous	5 (45.5%)	1 (50.0%)	6 (46.2%)
Other (Heterozygous, undetermined, or no mutation)	1 (9.1%)	0	1 (7.7%)
Negative/negative status[2], n(%)	11 (100%)	2 (100%)	13 (100%)
Defective/defective	6 (54.5%)	0	6 (46.2%)
Defective/negative	1 (9.1%)	1 (50.0%)	2 (15.4%)
Negative/negative	3 (27.3%)	1 (50.0%)	4 (30.8%)

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Unknown or not reported	1 (9.1%)	0	1 (7.7%)
Null/null status[3], n(%)	11 (100%)	2 (100%)	13 (100%)
Null/null	3 (27.3%)	1 (50.0%)	4 (30.8%)
Not null/null	7 (63.6%)	1 (50.0%)	8 (61.5%)
Unknown or not reported	1 (9.1%)	0	1 (7.7%)
LDL-C (mg/dL)	11 (100%)	2 (100%)	13 (100%)
Mean (SD)	317.5 (87.0)	270.5 (184.6)	310.3 (97.3)
Median (min, max)	320.0 (179, 428)	270.5 (140, 401)	320.0 (140, 428)
LDL-C groups (mg/dL), n(%)	11 (100%)	2 (100%)	13 (100%)
≥130 to <160	0	1 (50.0%)	1 (7.7%)
≥160 to <190	1 (9.1%)	0	1 (7.7%)
≥190 to <300	4 (36.4%)	0	4 (33.3%)
≥300 to <400	3 (27.3%)	0	3 (23.1%)
≥400 to <500	3 (27.3%)	1 (50.0%)	4 (33.3%)
TG (mg/dL)	11 (100%)	2 (100%)	13 (100%)
Mean (SD)	78.9 (29.9)	154.0 (100.4)	90.5(48.8)
Median (min, max)	65.0 (49, 124)	154.0 (83, 225)	66.0 (49, 225)
HDL (mg/dL)	11 (100%)	2 (100%)	13 (100%)
Mean (SD)	38.3 (13.1)	47.0 (5.7)	39.6 (12.5)
Median (min, max)	34.0 (23, 67)	47.0 (43, 51)	36.0 (23, 67)
Apo B (mg/dL)	11 (100%)	2 (100%)	13 (100%)
Mean (SD)	197.0 (48.3)	187.5 (78.5)	195.5 (49.7)
Median (min, max)	190.0 (110, 255)	187.5 (132, 243)	190.0 (110, 255)
Lp(a) (mmol/L)	11 (100%)	2 (100%)	13 (100%)
Mean (SD)	65.7 (62.5)	153.5 (171.8)	79.2 (82.5)
Median (min, max)	30.0 (9, 168)	153.5 (32, 275)	32.0 (9, 275)
TC (mg/dL)	11 (100%)	2 (100%)	13 (100%)
Mean (SD)	371.5 (81.5)	348.5 (170.4)	368.0 (89.6)
Median (min, max)	375.0 (231, 481)	348.5 (228, 469)	375.0 (228, 481)
Statin use, n(%)	11 (100%)	2 (100%)	13 (100%)
Yes	11 (100%)	2 (100%)	13 (100%)
High-intensity	8 (72.7%)	2 (100%)	10 (76.9%)
PCSK9i use, n(%)	5 (45.5%)	1 (50.0%)	6 (46.2%)
Ezetimibe use, n(%)	7 (63.6%)	2 (100%)	9 (69.2%)
Lomitapide use, n(%)	0	0	0
Apheresis, n(%)	6 (54.5%)	2 (100%)	8 (61.5%)
CV history[4], n(%)	11 (100%)	2 (100%)	13 (100%)
Established CHD	3 (27.3%)	0	3 (23.1%)
CHD risk equivalent	0	0	0
Neither	8 (72.7%)	2 (100%)	10 (76.9%)

Source: adsl.xpt; Software: JMP and Applicant 1719 CSR Tables 14.4.1A, 14.4.2A, 14.4.4A, 14.4.9A, 14.4.29A, 14.4.32A, 14.4.34A.
Abbreviations: Apo B, Apolipoprotein B; CHD, coronary heart disease; CV, cardiovascular; HDL, high-density lipoprotein; LDL-C, low-density lipoprotein; Lp(a), lipoprotein A; N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation; TC, total cholesterol; TG, triglycerides.
1 Homozygous, same mutation in both alleles. Compound heterozygous, different mutations in both alleles. Double heterozygous, mutations in different genes. Other, undetermined or no mutation.
2 Negative/negative, LDLR or LDLRAP1 mutation predicted to result in complete loss of function (premature stop codon, splice site variation, frame shift, insertion, deletion, or copy number variation).
3 Null/null, LDLR or LDLRAP1 mutation resulting in <15% LDLR activity by *in vitro* assay.
4 Established CHD = acute myocardial infarction, silent myocardial infarction, angina, or coronary revascularization. CHD risk equivalent = peripheral arterial disease, ischemic stroke, chronic kidney disease, or diabetes mellitus plus 2 additional risk factors.

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Treatment Compliance, Concomitant Medications

In R1500-CL-1719, patients were required to be on stable background LLT, including medications and apheresis, at study entry and to maintain this for at least the first 24 week of treatment. Patients receiving apheresis were required to have initiated apheresis at least 3 months prior to screening and to be on a stable schedule for at least 8 weeks prior to screening. After the first 24 weeks of treatment, patients were encouraged to make their best effort to maintain stable LLT, but it could be adjusted after week 24, based on their LDL-C levels and judgment of the investigator.

As of the data cutoff date of August 28, 2020, no adolescent patients modified their baseline lipid-lowering medications during the course of study R1500-CL-1719.

Eight patients deviated from their baseline apheresis schedule. Two patients had adjustments after the week 24 visit and 6 patients had deviations during the first 24 weeks of treatment.

Table 30. Pediatric Patients with On-Treatment Changes to Background LLT, Trial 1719

Patient ID	Apheresis Schedule at Baseline	Number of Days Prior to the Study Visit of the Most Recent Apheresis Treatment
(b) (6)	Every 2 weeks	28 days before Week 12
		27 days before Week 16
		29 days before Week 20
		28 days before Week 24
	Every week	14 days before Week 12
		11 days before Week 20
		28 days before Week 24
	Every 2 weeks	8 days before Week 12
		19 days before Week 16
	Every 2 weeks	9 days before Week 8
	Every week	4 days before Week 4
		14 days before Week 12
		12 days before Week 16
		14 days before Week 20
		20 days before Week 24
	Every 2 weeks	9 days before Week 4
		6 days before Week 8
		10 days before Week 12
		9 days before Week 24

Source: Applicant's response to FDA IR, 12/4/2020
Abbreviations: LLT, lipid-lowering therapy.

Apheresis schedule modifications may impact some of the trial's lipid endpoints; results should be interpreted with caution.

Reference ID: 4745518

Efficacy Results

Table 32 summarizes the lipid endpoint results at Week 16 and Week 24 for the pediatric subpopulation in the safety analysis set. Two of the thirteen pediatric patients had not made it to Week 12 assessments by the time of the data cut-off. Two of the 11 pediatric patients who completed 24 weeks of treatment were missing the lipid assessment at Week 24, including one patient who missed the Week 24 study visit because of COVID-19-related issues and another patient who attended the Week 24 study visit but the lipid tests were collected after the apheresis procedure started and the lipid results were excluded from the Applicant's analysis.

As per the SAP for study R1500-CL-1719, any lipid values collected after apheresis for the respective visit were excluded from the efficacy analyses. This was meant to avoid the potential confounding effect of apheresis on the LDL-C effect of evinacumab, if the lipid sample is collected after the apheresis procedure has started. For patient (b) (6), the Week 24 blood collection time for the lipid panel was reported to have occurred at 9:20. The apheresis procedure was reported to have started at 9:00 and was completed at 11:00. The Applicant states that because the blood sample collection occurred after the apheresis had started, the Week 24 lipid data from patient (b) (6) was removed from the efficacy analysis. This patient's LDL-C results through Week 24 are provided below, with the times of lipid apheresis initiation and lipid sample collection. The results from Visit 7 (in bold text) were removed from the analysis but were consistent with previous results for this patient.

Table 31. Patient (b) (6): LDL-C results through Week 24 in Study 1719

Visit label	Week	Visit date	Sampling time	Apheresis start time	LDL-C result (mg/dL)
Visit 1a	Screening	7Jan2020	9:30	9:35	165
Visit 1	Baseline	14Jan2020	10:00	10:05	179
Visit 3	Week 8	10Mar2020	9:15	9:20	96
Visit 4	Week 12	7Apr2020	10:30	10:35	148
Visit 5	Week 16	4May2020	11:20	11:25	171
Visit 7	**Week 24**	**30Jun2020**	**9:20**	**9:00**	**143**
Source: Applicant's response to FDA IR, 12/4/2020					

The observed data in the table below represent the actual (raw) data provided by the central lab. Trial 1719 is ongoing; efficacy results are intended as supportive and should be interpreted with caution. Although designed to demonstrate long-term efficacy and safety of evinacumab, 16-week data is only available on 11 pediatric patients, and 24-week data is only available for 9 pediatric patients.

Reference ID: 4745518

Table 32. Percent Reduction in Lipid Endpoints, Baseline to Week 16 and Week 24, Study 1719: Pediatrics-Safety Analysis Set

	Mean % Change Baseline to Week 16 (Min: Max)			Mean % Change Baseline to Week 24 (Min: Max)		
	Treatment-Naïve N=11 (n=9)	Rollovers[1] N=2 (n=2)	All Patients N=13 (n=11)	Treatment-Naïve N=11 (n=7)	Rollovers[1] N=2 (n=2)	All Patients N=13 (n=9)
Mean % change in LDL-C (SD); Min: Max	-51.4 (21.3) -77.5: -4.5	-50.5 (34.0) -74.6: -26.4	-51.2 (21.9) -77.5: -4.5	-58.7 (12.9) -76.8: -39.4	-30.6 (65.4) -76.8: 15.7	-52.4 (28.5) -76.8: 15.7
Mean % change in Apo B (SD); Min: Max	-42.9 (21.1) -72.3: 3.3	-43.2 (33.2) -66.7: -19.7	-43.0 (21.7) -72.3: 3.3	-51.6 (12.4) -71.8: -38.4	-40.8 (40.6) -69.5: -12.1	-49.2 (18.6) -71.8: -12.1
Mean % change in HDL-C (SD); Min: Max	-35.9 (17.5) -57.1: -4.3	-61.5 (14.9) -72.1: -51.0	-40.6 (19.3) -72.1: -4.3	-38.7 (11.1) -53.6: -25.0	-46.8 (0.4) -47.1: -46.5	-40.5 (10.3) -53.6: -25.0
Mean % change in TG (SD); Min: Max	-34.1 (17.0) -54.5: -12.7	-61.8 (5.6) -65.8: -57.8	-39.2 (19.0) -65.8: -12.7	-46.0 (14.9) -66.1: -21.3	-74.4 (14.9) -84.9: -63.9	-52.3 (18.8) -84.9: -21.3
Mean % change in TC (SD); Min: Max	-50.03(17.3) -73.5: -14.3	-57.2 (20.1) -71.4: -43.0	-51.3 (17.0) -73.5: -14.3	-56.4 (11.3) -73.0: -40.6	-44.5 (40.5) -73.1: -15.8	-53.7 (18.1) -73.1: -15.8

Source: adlbeff.xpt; Software: JMP. Applicant's response to FDA IR 12/4/2020 (Post-text Table 14.9.3.10A), and Applicant 1719 CSR Post-text Tables 14.6.1.1A, 14.6.1.4A, 14.6.1.10A, 14.6.1.13A.
Abbreviations: Apo B, apolipoprotein B; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; N, number of patients in treatment group; n, number of patients contributing data at that timepoint; SD, standard deviation; TC, total cholesterol; TG, triglycerides.
1 For calculations requiring baseline, the Continue Evinacumab (Rollovers) group uses the baseline from R1500-CL-1629 (study R1500-CL-1629 consisted of a 24-week DBTP followed by a 24-week OLTP).

Based on observed data, evinacumab lowered LDL-C by 51% at 16 weeks and by 52% at 24 weeks. Other lipid parameters, including HDL-C, TG and TC, were also reduced with evinacumab treatment.

Data for LDL-C throughout the study are shown in the figure below. These results should be interpreted with caution as the sample size is small, particularly at later study visits. The Applicant states that reasons include visits at later timepoints had not occurred or, in some cases, were missed entirely, primarily because of COVID-19-related issues. However, this data does support that evinacumab provides clinically meaningful reductions in LDL-C in adolescent patients with HoFH, although it is difficult to quantify the treatment effect.

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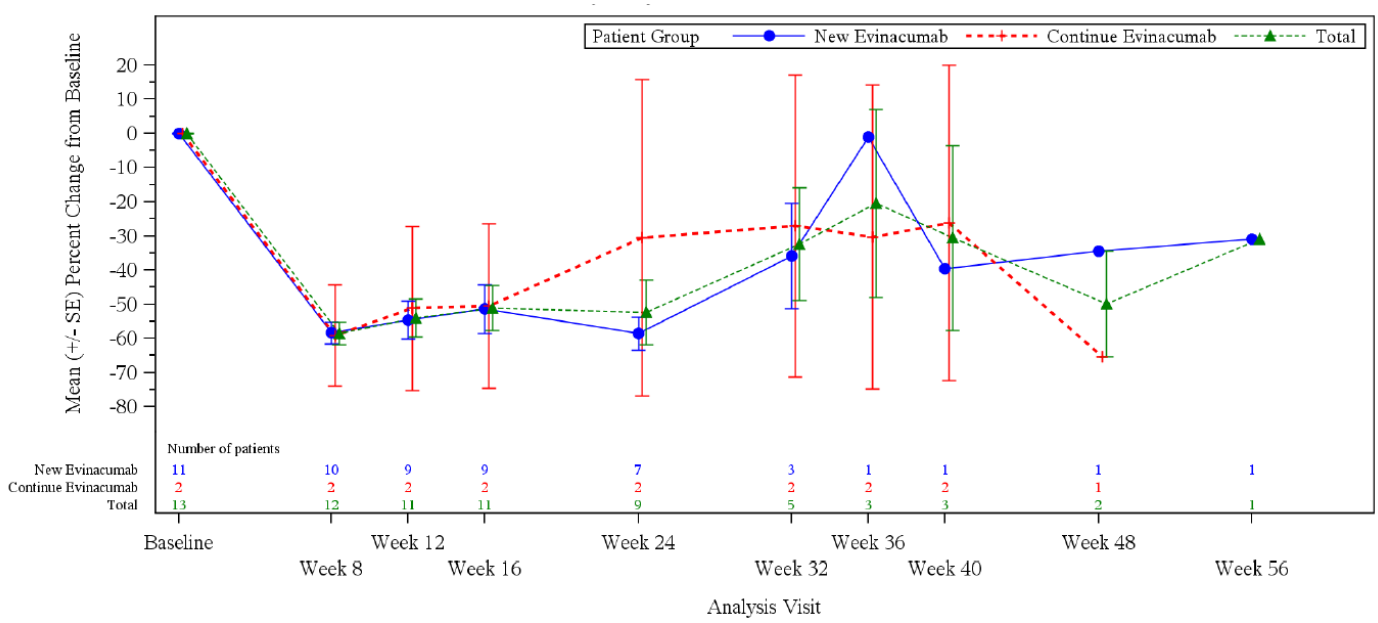
Figure 6. Calculated LDL-C B Mean (+/- SE) Percent Change from Baseline Over Time - Raw Data Description –Study 1719 Safety Analysis Set – Adolescents



Source: Applicant's Figure 14.6.1.3A, Clinical Study Report, submitted 11/06/2020.

In the figure above, the 'New Evinacumab' patient (patient [redacted] (b) (6)) had a percent change in LDL-C from baseline of -1% at Week 36. This patient missed the previous 3 visits (Weeks 24, 28, 32), reportedly because of travel restrictions and limited site personnel availability as a result of COVID-19. The last dose of evinacumab prior to Week 36 was administered at Week 20 (i.e. the patient missed 3 doses prior to this visit). This may partly explain why the patient's LDL-C value had basically returned to the patient's baseline value by Week 36. The patient re-started evinacumab treatment at Week 36, after which an LDL-C reduction of -40% was observed at Week 40.

In the figure above, the confidence intervals in red are quite wide from Weeks 24 to 40. This is due to the LDL results for the 'Continue Evinacumab' patient (subject # [redacted] (b) (6); ID [redacted] (b) (6) [redacted]). This patient had a >20% decrease from baseline at Week 16 but had an increase in LDL-C ranging from 14 to 20% from baseline at Week 24 until Week 40. The Applicant was asked to provide additional information on this patient to understand this change in LDL response. The Applicant responded that this 12-year-old patient was on a background LLT of rosuvastatin 20 mg daily, ezetimibe 10 mg daily, and weekly apheresis. The patient was randomized to placebo in Study CL-1629. A review of the LDL-C results at screening (LDL=208 mg/dL), baseline (LDL=140 mg/dL), and during the 24 week, double-blind placebo-controlled phase of CL-1629 (LDL ranges from 208 to 316 mg/dL) indicates the baseline LDL-C of 140 mg/dL was lower than and not representative of the patient's typical pre-apheresis LDL-C result, which were generally in the 200's mg/dL. After starting evinacumab during the open-label portion of CL-1629 (first dose given at Visit 9/Week 24), the patient's LDL-C was reduced

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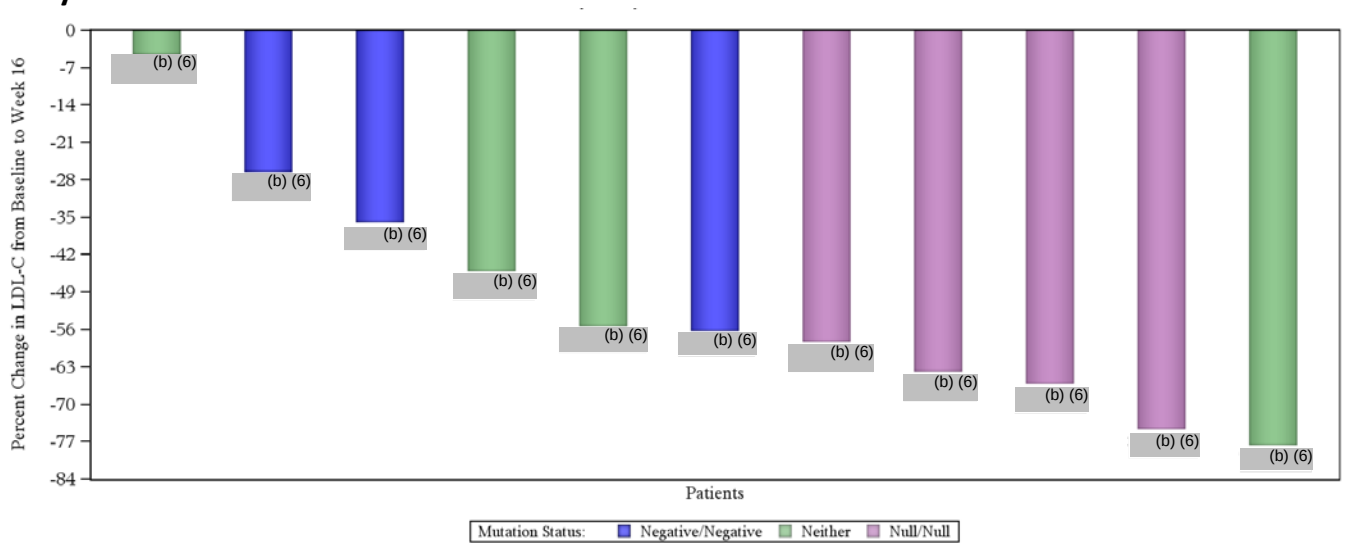
to around 100 mg/dL and generally remained around that level for the duration of the open-label phase in CL-1629. The patient reported remaining compliant with her rosuvastatin and ezetimibe and was generally consistent with her weekly apheresis schedule during CL-1629. The patient entered the open-label study CL-1719 with an LDL-C of 90 mg/dL. The LDL-C continued to remain around 100 mg/dL until the Week 24 visit in CL-1719, where it was around the 160's mg/dL for the subsequent few months. The patient reported remaining compliant with her rosuvastatin and ezetimibe, but her weekly apheresis schedule was reduced to a monthly regimen. This change was allowed per protocol; beginning at Week 24 of CL-1719, patients were permitted to adjust their background lipid lowering therapies. Thus, the LDL-C increase is more likely due to this change in the patient's apheresis frequency from a weekly to a monthly schedule than because of loss of efficacy with evinacumab.

In general, administration of evinacumab provided large decreases in LDL-C in almost all pediatric patients, regardless of genotype state (homozygous, compound heterozygous, other [heterozygous, undetermined, or no mutation]), genotype group (defective/defective vs defective/negative vs negative/negative[6]) or mutation status (null/null[5] vs. negative/negative vs. neither). A Waterfall Plot of the pediatric patients for percent change from baseline in LDL-C at Week 16 by mutation status (null/null[5] vs negative/negative[6] vs neither) is shown below.

Figure 7. Waterfall Plot of Calculated LDL-C Percent Change from Baseline at Week 16 by Mutation Status (null/null vs negative/negative vs neither) –Study 1719 Safety Analysis Set-Pediatric Patients



Source: Applicant's response to FDA IR submitted 12/04/2020 (Figure 14.9.3.56A).

[5] Null/Null is defined as LDLR activity <15%
[6] Receptor-negative defined as a mutation resulting in termination codons, splice site mutations, frame shifts and large insertion/deletions.

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Conclusion

Overall, the effect of evinacumab on lipid parameters in pediatric patients with HoFH was generally similar to that seen in adults with HoFH.

- LDL-C: In the phase 3 study, R1500-CL-1629, the mean percent change from baseline in LDL-C at Week 24 was -47% in the evinacumab group. In the pediatric population in R1500-CL-1719, the mean percent change from baseline in LDL-C at Week 24 was -52%.

- Apo B: In the phase 3 study, R1500-CL-1629, the mean percent change from baseline in Apo B at Week 24 was -41% in the evinacumab group. In the pediatric population in R1500-CL-1719, the mean percent change from baseline in Apo B at Week 24 was -49%.

- TG: In the phase 3 study, R1500-CL-1629, the mean percent change from baseline in TG at week 24 was -55% in the evinacumab group. In the pediatric population in R1500-CL-1719, the mean percent change from baseline in TG at Week 24 was -52%.

- HDL-C: In the phase 3 study, R1500-CL-1629, the mean percent change from baseline in HDL-C at Week 24 was -30% in the evinacumab group. In the pediatric population in R1500-CL-1719, the mean percent change from baseline in HDL-C at Week 24 was -41%.

As was commented on earlier for Study R1500-CL-1629, the reduction of HDL-C by evinacumab is of unknown significance in this population. Drug-induced increases in HDL-C by CETP inhibitors have not demonstrated that increased HDL-C is associated with CV risk reduction. For this very high CV-risk patient population, the CV benefit of LDL-C reduction likely outweighs any theoretical risk associated with HDL-C reduction.

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7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Primary demonstration of evinacumab's efficacy on LDL-C reduction was demonstrated by a single trial, 1629 DBTP. Refer to Section 6.1 for discussion of the primary endpoint, secondary endpoints, subpopulations, and durability of efficacy effects.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

In the postmarket setting, evinacumab is anticipated to have a similar treatment effect on LDL-C reduction to that observed within the context of clinical trials.

The enrolled trial population was generally reflective of the HoFH population encountered in clinical practice. Enrolled patients represented a range of HoFH disease severity as evidenced by the various HoFH genotypes and phenotypes enrolled, range of HoFH disease duration, range of baseline LDL-C values, and presence or absence of established ASCVD. Enrolled patients were also taking a variety of background LLT. Nearly all patients were taking statins, and most patients were taking ezetimibe and PCSK9i as expected in this serious and life-threatening disease. In the postmarket setting, fewer patients may take PCSK9i because of lack of insurance coverage (although HoFH is an FDA-approved indication for one PCSK9i). However, results from trial 1629 DBTP demonstrated a similar LDL-C reduction effect regardless of background LLT.

The clinical diagnostic criteria used for enrollment in the clinical trials was broader than that typically used in U.S.-based clinical practices (TC >500 mg/dL vs. LDL-C >500 mg/dL, respectively). Thus, the pivotal trial likely included patients with less severe disease than would typically be encountered in clinical practice. Again, however, results from trial 1629 DBTP demonstrated a similar LDL-C reduction effect regardless of baseline LDL-C value.

Elderly patients (≥65 years) were not well-represented in the trials, however, this is likely due to HoFH's decreased life expectancy rather than to selection bias in trial enrollment. Pediatric patients were not well-represented in the controlled trials, but an additional 11 pediatric participants were enrolled in the open-label study 1719. While the number of pediatric patients treated (N=13) and the duration of exposure (median=33 weeks) to evinacumab in the open-label trial was less than ideal, it was nonetheless sufficient to make a determination of benefit for evinacumab in light of the large treatment effect of this therapy in patients with HoFH, particularly those with <15% LDLR function, that cannot be attributed to chance or other factors.

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The majority of efficacy data was contributed from sites outside of the U.S. However, no exposure or PK differences were observed based on race/ethnicity, and HoFH treatment is generally consistent worldwide given its rare disease nature. Thus, it is reasonable to expect that efficacy results will be similar in a U.S.-based postmarket setting.

Off-label use, in patients with HeFH or established ASCVD who require additional LDL-C lowering, may be anticipated in the postmarket setting. The labeled indication should include a statement that benefit in these patient populations has not been demonstrated, primarily because of different benefit-risk considerations.

7.2.2. Other Relevant Benefits

Monthly IV administration may improve patient compliance, since a healthcare encounter is required rather than reliance on a patient's ability to remember a particular dosing schedule (e.g., Q2-4W SC administration with PCSK9i). Additionally, the monthly frequency and 1-hour duration offers an improvement to patients on apheresis, who typically require a healthcare encounter every 1-2 weeks for 2-5 hours.

7.3. Integrated Assessment of Effectiveness

The Applicant provided sufficient clinical data to demonstrate substantial evidence that evinacumab reduces LDL-C in adults and pediatric patients, 12 years and older, with HoFH when added to other lipid-lowering therapies. In a single trial with 24 weeks of double-blinded, placebo-controlled data (trial 1629 DBTP, Section 6.1), evinacumab lowered LDL-C by 49% compared to placebo in patients with HoFH on maximally-tolerated LLT (defined as statin, ezetimibe, and PCSK9i). The primary endpoint, LDL-C, is an accepted surrogate endpoint used as the basis for full approval in other lipid-lowering programs, and the result was statistically significant. Although two adequate and well-controlled trials are typically required to achieve the statutory definition of substantial evidence, a single trial was deemed acceptable by FDA given the rarity of HoFH in the U.S. and worldwide. The single trial was of high quality, robust, and statistically sound. Supportive evidence from open-label trials substantiates evinacumab's LDL-lowering ability. Evidence from the open-label trial supports expanding the indication to pediatric patients aged 12 and older.

The evidence provided from trial 1629 supports the Applicant's proposed indication with a modification – the indication should include a Limitation of Use statement to acknowledge that the effect on CV morbidity and mortality is unknown. Refer to Section 10 for additional discussion of labeling.

A reduction in baseline LDL-C of nearly 50% is clinically meaningful, particularly in patients with HoFH. While HoFH treatment guidelines generally recommend a reduction in LDL-C to <70-100 mg/dL or ≥50% reduction, HoFH patients are notoriously difficult to treat with conventional LLT

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given the lack of a functional LDLR (the target of most approved LLTs). Statins, ezetimibe, and PCSK9i approved for use in HoFH lower LDL-C by -14% to -30% only. This is substantially lower than the LDL-C reduction observed in non-HoFH patients, which exceeds 50% with high-intensity statin use and 60-70% with PCSK9i use. Lomitapide lowers LDL-C by 40% in HoFH but use is limited by hepatotoxicity. Furthermore, more than half of enrolled patients were taking statin, ezetimibe, and PCSK9i at baseline yet had LDL-C values greater than 190 mg/dL (severe hyperlipidemia). Additional LDL-C reduction is clearly needed, but no additional treatment options exist at present.

Also noteworthy is evinacumab's ability to lower LDL-C to a substantial degree in patients with difficult-to-treat mutations, defined by the Applicant as either resulting or predicted to result in zero to minimal LDLR activity (<15%). Clinical trials of evolocumab and statins in HoFH attempted to identify a similar subpopulation (<2% residual LDLR function) and demonstrated no or blunted LDL-C reduction ability in these patients. However, a direct comparison between evinacumab and other LLT for patients with difficult-to-treat mutations is not possible due to the different definitions used.

Supportive, open-label data demonstrates the durability of evinacumab's LDL-C lowering effect with continued treatment to at least 48 weeks. Evinacumab is also effective as add-on to commonly used LLT, including apheresis, and also lowers Apo B, non-HDL-C, TG, and TC.

Approval of evinacumab for LDL-C reduction would represent a substantial improvement in available therapies for this rare disease population.

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8. Review of Safety

8.1. Safety Review Approach

For the primary demonstration of safety, placebo-controlled data from the 24-week DBTP of trial 1629 was pooled with placebo-controlled data from the 24-week DBTP of trial 1643 in order to increase the total number of patient exposures with placebo-controlled data. The safety profile of evinacumab was anticipated to be similar in both trial populations (HoFH in trial 1629 and HeFH or established ASCVD in trial 1643). Sixty-five patients contributed to the pool from trial 1629, and 106 contributed from trial 1643. Only patients from trial 1643 who were randomized to evinacumab 5 mg/kg IV Q4W, 15 mg/kg IV Q4W, or placebo were included in the pool. In this review, the pool is referred to as "placebo-controlled pool". Results are described in Sections 8.2-8.6.

Supportive safety data was obtained from three single-arm, open-label trials of evinacumab – the 24-week OLTP of trial 1629, the 48-week OLTP of trial 1643, and the long-term safety trial 1719. Trial 1643 OLTP and trial 1719 remain ongoing. The Applicant presented data from the open-label trials in a pooled analysis submitted in the 120-Day Safety Update on September 22, 2020. However, because of differences in trial duration, this review will present results separately for each trial to avoid Simpson's paradox and underestimation of any evinacumab-associated risk. Results of open-label data will be discussed under Section 8.7.

In this review, the safety population is defined as randomized patients who received at least one dose of study drug. Only adverse events that occurred in the safety population and were treatment-emergent (occurring after the first dose of study drug) were analyzed. Patients were analyzed according to the actual treatment received. Serious adverse events (SAEs), AEs leading to drug discontinuation, severe AEs, and selected AESIs underwent narrative review for determination of drug relatedness.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Across relevant phase 2 and 3 trials, a total of 216 patients were exposed to evinacumab 15 mg/kg IV Q4W (Table 33). The mean exposure duration was 55 weeks. Of these, 194 patients were treated with evinacumab for six months or longer, and 108 were treated for 1 year or longer.

At the time of BLA submission, exposure to evinacumab is ongoing in trials 1719 and 1643. Enrollment remains open in trial 1719 (planned 120 patients on open-label evinacumab, current enrollment 104) with treatment planned for up to 4 years. Trial 1643 is fully enrolled (96 patients on open-label evinacumab) with treatment ongoing for up to 72 weeks.

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Table 33. Duration of Exposure[1], Safety Population, Pooled Analysis[2]

Parameter	Evinacumab 5 mg/kg IV N=36	Evinacumab 15 mg/kg IV N=216	Placebo N=55
Duration of treatment, weeks			
Mean (SD)	22.4 (5.8)	54.7 (22.5)	23.1 (4.4)
Median (min, max)	24.0 (0.0, 26.0)	50.0 (0.0, 118.9)	24.0 (4.0, 26.7)
Interquartile range (25%, 75%)	0.2 (24.0, 24.2)	25.8 (42.5, 68.3)	0.1 (23.9, 24.0)
Total exposure (person years)	15.5	226.3	24.3
Patients treated, by duration[3], n(%)			
Any duration (at least 1 dose)	35 (97.2%)	215 (99.5%)	55 (100%)
<1 month	2 (5.6%)	5 (2.3%)	2 (3.6%)
≥1 month	34 (94.4%)	211 (97.7%)	53 (96.4%)
≥3 months	33 (91.7%)	209 (96.8%)	52 (94.5%)
≥6 months	2 (5.6%)	194 (89.8%)	2 (3.6%)
≥12 months	0 (0.0%)	108 (50.0%)	0 (0.0%)

Source: adsl.xpt; Software: JMP.
Abbreviations: N, number of patients in treatment arm; n, number of patients with given treatment duration; SD, standard deviation.
1 Data cutoff date 06/12/2020.
2 Includes patients from trials 1331, 1629, 1719, and 1643. Trials 1719 and 1643 are ongoing.
3 1 month = 30 days, 3 months = 90 days, 6 months = 180 days, 12 months = 360 days.

8.2.2. Relevant Characteristics of the Safety Population

The Applicant defined the safety population as randomized patients who received at least one dose of study drug. Patients were analyzed according to the actual treatment received.

Patients in the placebo-controlled pool were predominantly white (83%) and non-Hispanic (89%), with a mean age of 50 years (Table 34). Demographics were generally well-balanced between the treatment arms, although the placebo arm included fewer patients over the age of 65 years than the evinacumab arms.

Nearly 40% of enrolled patients were diagnosed with HoFH, and 50% were diagnosed with HeFH. The mean baseline LDL-C was 186.5 mg/dL. One-third of patients had a baseline LDL-C value ≥190 mg/dL. Baseline LDL-C was slightly higher amongst patients in the evinacumab 15 mg/kg IV arm compared to the placebo arm (205.5 mg/dL vs. 185.9 mg/dL). Less than half of patients were taking high-intensity statin at baseline (40.9%); however, 83% were on a PCSK9i, and 88% were taking ezetimibe. Most patients in the placebo-controlled pool were non-diabetics (90.1%), and over half were non-smokers (58.5%).

Baseline clinical characteristics were generally well-balanced between the treatment arms. Clinical differences between the evinacumab 5 mg/kg IV and 15 mg/kg IV arms (such as higher

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baseline LDL-C and use of concomitant LLT) can be explained by differences in the enrolled populations – 5 mg/kg IV was only administered in trial 1643 (patients with HeFH or established ASCVD), while over half of patients in the 15 mg/kg IV arm have HoFH. There were no clinically significant differences between the evinacumab 15 mg/kg IV and placebo arms – the primary comparison for this pool.

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Table 34. Baseline Demographic and Clinical Characteristics, Safety Population, Placebo-Controlled Pool[1]

Characteristic	Evinacumab 5 mg/kg N=36 n(%)	Evinacumab 15 mg/kg N=81 n(%)	Evinacumab All[2] N=117 n(%)	Placebo N=54 n(%)	Total Population N=171 n(%)
Age, years	36 (100%)	81 (100%)	117 (100%)	54 (100%)	171 (100%)
Mean (SD)	56.1 (9.7)	47.8 (15.1)	50.3 (14.1)	48.3 (14.8)	49.7 (14.3)
Median (min, max)	55.5 (36.0, 74.0)	49.0 (15.0, 75.0)	53.0 (15.0, 75.0)	50.0 (12.0, 76.0)	52.0 (12.0, 76.0)
Age groups (years), n(%)	36 (100%)	81 (100%)	117 (100%)	54 (100%)	171 (100%)
≥12 to <18	0 (0.0%)	1 (1.2%)	1 (0.9%)	1 (1.9%)	2 (1.2%)
≥18 to <65	28 (77.8%)	68 (84.0%)	96 (82.1%)	46 (85.2%)	142 (83.0%)
≥65 to <75	8 (22.2%)	11 (13.6%)	19 (16.2%)	5 (9.3%)	24 (14.0%)
≥75	0 (0.0%)	1 (1.2%)	1 (0.9%)	2 (3.7%)	3 (1.8%)
Sex, n(%)	36 (100%)	81 (100%)	117 (100%)	54 (100%)	171 (100%)
Male	13 (36.1%)	39 (48.1%)	52 (44.4%)	25 (46.3%)	77 (45.0%)
Female	23 (63.9%)	42 (51.9%)	65 (55.6%)	29 (53.7%)	94 (55.0%)
Race, n(%)	36 (100%)	81 (100%)	117 (100%)	54 (100%)	171 (100%)
White	33 (91.7%)	66 (81.5%)	99 (84.6%)	43 (79.6%)	142 (83.0%)
Black	0 (0.0%)	2 (2.5%)	2 (1.7%)	2 (3.7%)	4 (2.3%)
Asian	1 (2.8%)	6 (7.4%)	7 (6.0%)	5 (9.3%)	12 (7.0%)
Other	2 (5.6%)	5 (6.2%)	7 (6.0%)	4 (7.4%)	11 (6.4%)
Unknown	0 (0.0%)	2 (2.5%)	2 (1.7%)	0 (0.0%)	2 (1.2%)
Ethnicity, n(%)	36 (100%)	81 (100%)	117 (100%)	54 (100%)	171 (100%)
Hispanic	7 (19.4%)	4 (4.9%)	11 (9.4%)	3 (5.6%)	14 (8.2%)
Non-Hispanic	29 (80.6%)	73 (90.1%)	102 (87.2%)	50 (92.6%)	152 (88.9%)
Unknown	0 (0.0%)	4 (4.9%)	4 (3.4%)	1 (1.9%)	5 (2.9%)
Diagnosis	36 (100%)	81 (100%)	117 (100%)	54 (100%)	171 (100%)
HoFH	0 (0.0%)	44 (54.3%)	44 (37.6%)	21 (38.9%)	65 (38.0%)
HeFH	29 (80.6%)	31 (38.3%)	60 (51.3%)	26 (48.1%)	86 (50.3%)
Non-FH + ASCVD	7 (19.4%)	6 (7.4%)	13 (11.1%)	7 (13.0%)	20 (11.7%)
LDL-C (mg/dL)	36 (100%)	81 (100%)	117 (100%)	54 (100%)	171 (100%)
Mean (SD)	144.9 (60.5)	205.5 (142.5)	186.9 (126.1)	185.9 (115.1)	186.5 (122.4)
Median (min, max)	130.0 (30.0, 311.0)	167.0 (39.0, 907.0)	150.0 (30.0, 907.0)	150.0 (39.0, 605.0)	150.0 (30.0, 907.0)
LDL-C groups (mg/dL), n(%)	36 (100%)	81 (100%)	117 (100%)	54 (100%)	171 (100%)
<70	2 (5.6%)	3 (3.7%)	5 (4.3%)	2 (3.7%)	7 (4.1%)
≥70 to <100	6 (16.7%)	10 (12.3%)	16 (13.7%)	3 (5.6%)	19 (11.1%)
≥100 to <130	10 (27.8%)	14 (17.3%)	24 (20.5%)	15 (27.8%)	39 (22.8%)
≥130 to <160	6 (16.7%)	12 (14.8%)	18 (15.4%)	9 (16.7%)	27 (15.8%)
≥160 to <190	5 (13.9%)	11 (13.6%)	16 (13.7%)	6 (11.1%)	22 (12.9%)
≥190 to <300	6 (16.7%)	16 (19.8%)	22 (18.8%)	12 (22.2%)	34 (19.9%)
≥300 to <400	1 (2.8%)	7 (8.6%)	8 (6.8%)	3 (5.6%)	11 (6.4%)
≥400 to <500	0 (0.0%)	4 (4.9%)	4 (3.4%)	1 (1.9%)	5 (2.9%)
≥500	0 (0.0%)	4 (4.9%)	4 (3.4%)	3 (5.6%)	7 (4.1%)

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High-intensity statin use, n(%)	36 (100%)	81 (100%)	117 (100%)	54 (100%)	171 (100%)
Yes	24 (66.7%)	24 (29.6%)	48 (41.0%)	22 (40.7%)	70 (40.9%)
No	12 (33.3%)	13 (16.0%)	25 (21.4%)	11 (20.4%)	36 (21.1%)
PCSK9i use, n(%)	36 (100%)	81 (100%)	117 (100%)	54 (100%)	171 (100%)
Yes	35 (97.2%)	71 (87.7%)	106 (90.6%)	47 (87.0%)	142 (83.0%)
No	1 (2.8%)	10 (12.3%)	11 (9.4%)	7 (13.0%)	29 (17.0%)
Ezetimibe use, n(%)	36 (100%)	81 (100%)	117 (100%)	54 (100%)	171 (100%)
Yes	15 (41.7%)	46 (56.8%)	61 (52.1%)	28 (51.9%)	150 (87.7%)
No	21 (58.3%)	35 (43.2%)	56 (47.9%)	26 (48.1%)	21 (12.3%)
Lomitapide use, n(%)	36 (100%)	81 (100%)	117 (100%)	54 (100%)	171 (100%)
Yes	0 (0.0%)	11 (13.6%)	11 (9.4%)	3 (5.6%)	25 (14.6%)
No	36 (100.0%)	70 (86.4%)	106 (90.6%)	51 (94.4%)	146 (85.4%)
Apheresis, n(%)	36 (100%)	81 (100%)	117 (100%)	54 (100%)	171 (100%)
Yes	0 (0.0%)	14 (17.3%)	14 (12.0%)	8 (14.8%)	22 (12.9%)
No	36 (100.0%)	67 (82.7%)	103 (88.0%)	46 (85.2%)	149 (87.1%)
BMI (kg/m^2)	36 (100%)	81 (100%)	117 (100%)	54 (100%)	171 (100%)
Mean (SD)	28.8 (4.5)	27.6 (5.7)	27.9 (5.3)	27.2 (5.8)	27.7 (5.5)
Median (min, max)	28.4 (19.4, 40.0)	27.2 (17.7, 46.4)	27.4 (17.7, 46.4)	25.7 (16.3, 39.8)	27.1 (16.3, 46.4)
BMI category (kg/m^2), n(%)	36 (100%)	81 (100%)	117 (100%)	54 (100%)	171 (100%)
<30	23 (63.9%)	56 (69.1%)	79 (67.5%)	39 (72.2%)	118 (69.0%)
≥30	13 (36.1%)	25 (30.9%)	38 (32.5%)	15 (27.8%)	53 (31.0%)
Baseline T2DM, n(%)	36 (100%)	81 (100%)	117 (100%)	54 (100%)	171 (100%)
Yes	3 (8.3%)	7 (8.6%)	10 (8.5%)	7 (13.0%)	17 (9.9%)
No	33 (91.7%)	74 (91.4%)	107 (91.5%)	47 (87.0%)	154 (90.1%)
Tobacco use, n(%)	36 (100%)	81 (100%)	117 (100%)	54 (100%)	171 (100%)
Current/former	17 (47.2%)	31 (38.3%)	48 (41.0%)	23 (42.6%)	71 (41.5%)
Never	19 (52.8%)	50 (61.7%)	69 (59.0%)	31 (57.4%)	100 (58.5%)

Source: adsl.xpt, adcm.xpt; Software: JMP.
Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; LDL-C, low-density lipoprotein; N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation.
1 Includes trial 1629 DBTP and trial 1643 DBTP; duration = 24 weeks. Patients enrolled in ongoing open-label trials, submitted in the 120-Day Safety Update, are described in Section 8.7.
2 Includes evinacumab 5 mg/kg IV Q4W and 15 mg/kg IV Q4W.

8.2.3. Adequacy of the Safety Database

The total number of patient exposures are acceptable and align with previous Division agreements for this drug intended to treat a rare disease population (estimated 200-300 U.S. patients with HoFH). The Division also agreed to a smaller safety database based on the large treatment effect observed in early phase trials. A total of 215 patients have been exposed to the to-be-marketed dose of evinacumab 15 mg/kg IV Q4W; 194 patients have been exposed for at least 6 months, and 108 patients have been exposed for at least 1 year. Most of the evinacumab exposure occurred during open-label treatment.

Assessment of safety is challenging in rare disease populations given limited trial enrollment numbers and open-label trial designs. The safety of evinacumab within the first 6 months of

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therapy can be reasonably characterized from double-blinded, placebo-controlled data in 171 patients (117 on drug). The long-term safety of evinacumab, beyond 6 months of treatment, is less certain but can be ascertained from continued exposures in ongoing open-label trials (up to 4 years in duration).

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

In general, the submission was high-quality, complete, and well-organized. Because of the high degree of overlap in trial participation for this rare disease population, it was occasionally difficult to determine which patients were included in a particular dataset, during which trial an AE occurred, an individual patient's total treatment duration, or the amount of drug exposure prior to a given adverse event. For example, patients enrolled into trial 1719 may contain data in datasets for 1629 DBTP, 1629 OLTP, and 1719. However, the submitted Reviewer's Guides were useful, and additional information from the Applicant was generally not required.

8.3.2. Categorization of Adverse Events

The Division agreed with the Applicant's definition of TEAEs, defined in all trials as AEs that developed or worsened after the first dose of study drug. For the placebo-controlled pool, TEAEs were included from the first dose of study drug through 168 days after the last dose of study drug for patients not entering the OLTP. For patients who did enter the OLTP, AEs were only captured until the last day of the DBTP (and then recorded under the OLTP datasets). Adverse events were coded using MedDRA version 22.0.

Adverse events were graded as mild, moderate, or severe according to the following criteria:

- Mild: does not interfere in a significant manner with the patient's normal functioning level; may be an annoyance; prescription drugs not ordinarily needed for relief of symptoms
- Moderate: produces some impairment of functioning but is not hazardous to health; uncomfortable or embarrassing; treatment may be needed
- Severe: produces significant impairment of functioning or incapacitation, definite hazard to patient's health; treatment may be given and/or patient hospitalized

The translation of investigator-reported verbatim terms to preferred terms was examined by this reviewer. Overall, few errors in translation were identified, although several adverse events were reclassified (Appendix 13.3). In general, reclassification decisions were meant to capture an adverse event's underlying etiology or to improve specificity. Reclassification decisions did not significantly impact AE incidence.

The Applicant prespecified several AESI. AESI were identified by the Applicant using the

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following definitions:

Anaphylactic reactions
- Investigator report

Infusion reactions
- Investigator report

Allergic reactions
- Hypersensitivity standard MedDRA query (SMQ) (broad + narrow)
    - Excluding preferred terms (PTs) associated with local injection site reactions
    - Adding idiopathic angioedema

Immune complex diseases
- Systemic lupus erythematous SMQ (narrow)
- Vasculitis SMQ (narrow)
- Guillain-Barre syndrome (narrow)

Pregnancy
- Investigator report

Hepatic disorders
- Drug-related hepatic disorder SMQ
- Clinically significant lab values: ALT/AST >2x ULN, AP >1.5x ULN, TB >1.5x ULN (when baseline normal)
- Hy's law plot

Muscle events/CK elevation
- Clinically significant lab values: CPK >3x ULN (when baseline normal)
- AEs reported under musculoskeletal and connective tissue disorders System Organ Classes (SOC)
- Rhabdomyolysis/myopathy SMQ (narrow)

Neurocognitive events
- Custom MedDRA query (CMQ) (see Appendix)

Neurologic events
- Investigator report

New-onset diabetes
- No baseline history of diabetes PLUS
- Any of the following
    - HbA1c ≥6.5% on two or more occasions
    - Fasting glucose ≥126 mg/dL on two or more occasions
    - AE occurring under high level term (HLT) diabetes mellitus
    - Initiation of any new concomitant medication for hyperglycemia

Worsening diabetes
- AE occurring under high level group term (HLGT) diabetes complications
- AE occurring under HLT diabetes mellitus or carbohydrate tolerance analyses (including diabetes)

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    - Excluding PTs for blood glucose decreased, glycosylated hemoglobin decreased
    - Adding PTs for hyperglycemia, hyperglycemia unconsciousness, and hyperglycemic seizure
- Increased dosage of diabetic medication
- Initiation of additional diabetic medication

Cataracts
- AE occurring under HTL cataract conditions

Pancreatitis
- Investigator report

Drug overdose
- Investigator report

Infusion reactions were graded as mild, moderate, or severe using the following criteria:
- Mild: mild transient reaction; infusion interruption or intervention not indicated
- Moderate: therapy or infusion interruption initiated but responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, IV fluids); prophylactic medications indicated for <24 hours
- Severe: prolonged (e.g., not rapidly responsive to symptomatic medication or infusion interruption); recurrence of symptoms following initial improvement; hospitalization indicated; life-threatening; urgent intervention indicated; death

An independent CEC adjudicated cardiovascular events and all-cause deaths. The CEC members included medical experts in the field of cardiovascular disease. Events that were positively adjudicated were classified as CHD death, non-fatal MI, fatal or non-fatal ischemic stroke, unstable angina requiring hospitalization, congestive heart failure (CHF) requiring hospitalization, or ischemia-driven coronary revascularization procedure. CEC meeting minutes were provided by the Applicant.

8.3.3. Routine Clinical Tests

The timing and components of the Applicant's safety monitoring plan in the placebo-controlled pool were generally adequate. The Applicant regularly monitored vital signs, physical exam (including Tanner stage for adolescent patients), ECG, lab tests, and ADA. Vital signs were assessed pre-infusion, 30 minutes post-infusion, and 60 minutes post-infusion, which is reasonable given the potential for infusion reaction with evinacumab, a monoclonal antibody, administration. Physical exam and ECG were performed at baseline and at the end of the DBTP (24 weeks). ADA were assessed at Weeks 4, 12, and 24.

All safety labs were analyzed by a central laboratory. The timing of lab assessments was acceptable. Coagulation parameters were not assessed but would have been useful. The following table summarizes the timing and components of laboratory testing in the placebo-controlled pool.

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Table 35. Components of Safety Laboratory Tests, Placebo-Controlled Pool[1]

Laboratory Test	Components	Timing of Assessment
Chemistry	Sodium Potassium Chloride Carbon dioxide (trial 1629 only) Bicarbonate (trial 1643 only) Calcium Glucose Albumin Total protein, serum Creatinine BUN AST ALT Alkaline phosphatase LDH Total bilirubin Uric acid CPK	1629 DBTP: Screening Week 0 Week 4 Week 8 Week 12 Week 16 Week 24 1643 DBTP: Screening Week 0 Week 2 Week 4 Week 8 Week 12 Week 16 Week 20 Week 24
Hematology	Hemoglobin Hematocrit RBC WBC Red cell indices Platelet count Differential	1629 DBTP: Screening Week 0 Week 4 Week 8 Week 12 Week 16 Week 24 1643 DBTP: Screening Week 0 Week 2 Week 4 Week 8 Week 12 Week 16 Week 20 Week 24
Urinalysis	Color Clarity pH Specific gravity Ketones Protein Glucose Blood Bilirubin	1629 DBTP: Screening Week 0 Week 4 Week 8 Week 12 Week 16 Week 24

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	Leukocyte esterase Nitrite WBC RBC Hyaline and other casts Bacteria Epithelial cells Crystals Yeast	1643 DBTP: Screening Week 0 Week 2 Week 4 Week 8 Week 12 Week 16 Week 20 Week 24
Other	FSH	1629 DBTP: Screening 1643 DBTP: Screening
	TSH	1629 DBTP: Screening 1643 DBTP: Screening
	hsCRP	1629 DBTP: Week 0 Week 24 1643 DBTP: Week 0 Week 12 Week 24
	HbA1c	1629 DBTP: Week 0 Week 12 Week 24 1643 DBTP: Screening Week 12 Week 24
	Serum pregnancy	1629 DBTP: Screening 1643 DBTP: Screening
	Urine pregnancy	1629 DBTP: Week 0 Week 4 Week 8 Week 12 Week 16 Week 20 Week 24

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		1643 DBTP: Screening Week 0 Week 4 Week 8 Week 12 Week 16 Week 20 Week 24
	LH, FSH, estradiol, total testosterone[2]	1629 DBTP: Screening Week 24

Source: Clinical reviewer.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CPK, creatine phosphokinase; DBTP, double-blind treatment period; FSH, follicle-stimulating hormone; HbA1c, hemoglobin A1c; hsCRP, high-sensitivity C-reactive protein; LDH, lactic acid dehydrogenase; RBC, red blood cell; TSH, thyroid-stimulating hormone; WBC, white blood cell.
1 Includes trials 1629 DBTP and 1643 DBTP.
2 Adolescents in trial 1629 only.

8.4. Safety Results

In general, there were no differences in the incidence of overall or mild adverse events between evinacumab and placebo. Patients treated with evinacumab experienced more moderate to severe AEs, more SAEs, and more AEs leading to drug discontinuation, although these events occurred in only a handful of patients. Additional discussion is provided in the subsequent sections below.

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Table 36. Overview of Treatment-Emergent Adverse Events[1], Evinacumab 15 mg/kg versus Placebo, Safety Population, Placebo-Controlled Pool[2]

Event	Evinacumab 5 mg/kg IV N=36	Evinacumab 15 mg/kg N=81 n(%)	Evinacumab All[3] N=117 n(%)	Placebo N=54 n(%)	Absolute Risk Difference (95% CI)[4]
Any AE	27 (75.0%)	60 (74.1%)	87 (74.4%)	40 (74.1%)	0.0 (-15.1, 15.1)
Mild	22 (61.1%)	47 (58.0%)	69 (59.0%)	33 (61.1%)	-3.1 (-20.0, 13.8)
Moderate	15 (41.7%)	26 (32.1%)	41 (35.0%)	14 (25.9%)	6.2 (-9.3, 21.7)
Severe	1 (2.8%)	4 (4.9%)	5 (4.3%)	1 (1.9%)	3.1 (-2.8, 9.0)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0 (0.0, 0.0)
SAE	2 (5.6%)	8 (9.9%)	10 (8.5%)	1 (1.9%)	8.0 (0.6, 15.5)
AE leading to permanent drug discontinuation	2 (5.6%)	2 (2.5%)	4 (3.4%)	1 (1.9%)	0.6 (-4.3, 5.6)
AE leading to dose interruption	1 (2.8%)	4 (4.9%)	5 (4.3%)	2 (3.7%)	1.2 (-5.7, 8.1)

Source: adae.xpt; Software: JMP.
Abbreviations: AE, adverse event; SAE, serious adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event.
1 Treatment-emergent AE defined as an AE that developed or worsened during the DBTP. MedDRA version 22.0.
2 Includes trials 1629 and 1643, DBTP only. Duration = 24 weeks.
3 Includes evinacumab 5 mg/kg IV Q4W and 15 mg/kg IV Q4W.
4 Difference is shown between evinacumab 15 mg/kg and placebo.

8.4.1. Deaths

No deaths occurred during the DBTP of trials 1629 or 1643.

8.4.2. Serious Adverse Events

More SAEs were experienced by patients exposed to evinacumab 15 mg/kg compared to placebo (9.9% vs. 1.9%, RD 8.0% [0.6%, 15.5%]). Although there appears to be a dose-dependent relationship of SAEs with increasing evinacumab exposure, review of patient narratives indicated that most SAEs were likely unrelated to study drug and were consistent with the patient's baseline medical history. Additionally, there was no discernible pattern amongst SAEs as all were experienced by single patients only. Consistent with the enrolled population, in which 70% had pre-existing or risk-equivalent CHD at baseline, the most frequent organ system involved was cardiac and included events of unstable angina, atrial fibrillation, and coronary artery disease (CAD).

Only 1 SAE, anaphylactic reaction, was determined to be clearly drug-related by this reviewer. The reaction occurred in a 53-year-old Hispanic female with a history notable for atopy (asthma and allergic rhinitis). During the 2nd infusion of evinacumab 15 mg/kg IV, on day 28, the patient developed symptoms and physical exam findings consistent with anaphylaxis (symptoms: dizzy, racing heart, chest pressure, tingling, shortness of breath, itchy, warm, lethargic; physical exam:

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flushed face and chest, hypotensive to 78/57). Symptom onset began within 5 minutes of infusion initiation. The infusion was discontinued, and oral diphenhydramine was administered. The patient's symptoms and blood pressure resolved within 11 minutes of infusion discontinuation. The patient was monitored for two hours at the trial site, required no further intervention, and was discharged to home.

Table 37. Overview of Serious Adverse Events[1], Evinacumab 15 mg/kg versus Placebo, Safety Population, Placebo-Controlled Pool[2]

Event	Evinacumab 5 mg/kg N=36 n(%)	Evinacumab 15 mg/kg N=81 n(%)	Evinacumab All[3] N=117 n(%)	Placebo N=54 n(%)	Absolute Risk Difference (95% CI)[4]
SAE	**2 (5.6%)**	**8 (9.9%)**	**10 (8.5%)**	**1 (1.9%)**	**8.0 (0.6, 15.5)**
Fatal outcome	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0 (0.0, 0.0)
Life-threatening	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2 (-1.2, 3.6)
Requiring hospitalization	2 (5.6%)	5 (6.2%)	7 (6.0%)	1 (1.9%)	4.3 (-2.0, 10.7)
Resulting in substantial disruption of normal life functions	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0 (0.0, 0.0)
Congenital anomaly or birth defect	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0 (0.0, 0.0)
Other	0 (0.0%)	3 (3.7%)	3 (2.6%)	0 (0.0%)	3.7 (-0.4, 7.8)

Source: adae.xpt; Software: JMP.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event.
1 Defined as any untoward medical occurrence at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
2 Includes trial 1629 DBTP and trial 1643 DBTP. Duration = 24 weeks.
3 Includes evinacumab 5 mg/kg IV Q4W and 15 mg/kg IV Q4W.
4 Difference is shown between evinacumab 15 mg/kg and placebo.

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Table 38. Patients with Serious Adverse Events[1] by System Organ Class and Preferred Term, Evinacumab 15 mg/kg versus Placebo, Safety Population, Placebo-Controlled Pool[2]

System Organ Class *Preferred Term*	Evinacumab 5 mg/kg N=36 n(%)	Evinacumab 15 mg/kg N=81 n(%)	Evinacumab All[3] N=117 n(%)	Placebo N=54 n(%)	Absolute Risk Difference (95% CI)[4]
Proportion of patients with SAE	**2 (5.6%)**	**8 (9.9%)**	**10 (8.5%)**	**1 (1.9%)**	**8.0 (0.6, 15.5)**
Number of events	**4**	**10**	**14**	**1**	**-**
Cardiac disorders	**1 (2.8%)**	**2 (2.5%)**	**3 (2.6%)**	**0 (0.0%)**	**2.5% (-0.9%, 5.8%)**
Angina unstable	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
Atrial fibrillation	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
Coronary artery disease	1 (2.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Immune system disorders	**0 (0.0%)**	**1 (1.2%)**	**1 (0.9%)**	**0 (0.0%)**	**1.2% (-1.2%, 3.6%)**
Anaphylactic reaction	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
Infections and infestations	**0 (0.0%)**	**1 (1.2%)**	**1 (0.9%)**	**0 (0.0%)**	**1.2% (-1.2%, 3.6%)**
Urosepsis	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
Injury, poisoning, and procedural complications	**1 (2.8%)**	**1 (1.2%)**	**2 (1.7%)**	**0 (0.0%)**	**1.2% (-1.2%, 3.6%)**
Tibia fracture	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
Tendon rupture	1 (2.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Investigations	**0 (0.0%)**	**1 (1.2%)**	**1 (0.9%)**	**0 (0.0%)**	**1.2% (-1.2%, 3.6%)**
ALT increased	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
Neoplasms benign, malignant, and unspecified	**0 (0.0%)**	**1 (1.2%)**	**1 (0.9%)**	**0 (0.0%)**	**1.2% (-1.2%, 3.6%)**
Glioblastoma	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
Nervous system disorders	**2 (5.6%)**	**0 (0.0%)**	**2 (1.7%)**	**0 (0.0%)**	**0.0% (0.0%, 0.0%)**
Hypertensive encephalopathy	1 (2.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Syncope	1 (2.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Psychiatric disorders	**0 (0.0%)**	**1 (1.2%)**	**1 (0.9%)**	**0 (0.0%)**	**1.2% (-1.2%, 3.6%)**
Suicide attempt	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
Respiratory, thoracic, and mediastinal disorders	**0 (0.0%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (1.9%)**	**-1.9% (-5.4%, 1.7%)**

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Dyspnea exertional	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	-1.9% (-5.4%, 1.7%)
Vascular disorders	**0 (0.0%)**	**1 (1.2%)**	**1 (0.9%)**	**0 (0.0%)**	**1.2% (-1.2%, 3.6%)**
Peripheral arterial occlusive disease	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)

Source: adae.xpt; Software: JMP.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event.
1 Defined as any untoward medical occurrence at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
2 Includes trial 1629 DBTP and trial 1643 DBTP. Duration = 24 weeks.
3 Includes evinacumab 5 mg/kg IV Q4W and 15 mg/kg IV Q4W.
4 Difference is shown between evinacumab 15 mg/kg and placebo.

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Table 39. List of All Individual Patients with Serious Adverse Events in Safety Population, Placebo-Controlled Pool[1]

Study Arm	Subject ID	Age Gender	Study Day	MedDRA PT	Severity	Action Taken	Outcome
Evinacumab 5 mg/kg	(b) (6)	68 F	50	Coronary artery disease	Moderate	Dose not changed	Not recovered
		74 F	66	Syncope	Severe	Dose not changed	Recovered
		74 F	88	Tendon rupture	Severe	Dose not changed	Recovered
		74 F	111	Hypertensive encephalopathy	Severe	Dose not changed	Recovered
Evinacumab 15 mg/kg		36 F	145	Suicide attempt	Severe	Dose not changed	Recovered
		30 F	112	Urosepsis	Severe	Drug interrupted	Recovered
		46 F	28	Peripheral arterial occlusive disease	Moderate	Dose not changed	Recovered
		51 F	125	Tibia fracture	Moderate	Dose not changed	Recovering
		59 F	141	ALT increased	Moderate	N/A	Recovered
		59 F	167	Atrial fibrillation	Moderate	N/A	Recovered
		59 M	144	Glioblastoma	Severe	Drug withdrawn	Not recovered
		53 F	28	Anaphylactic reaction	Moderate	Drug withdrawn	Recovered
		68 M	42	Angina unstable	Severe	Drug interrupted	Recovered
Placebo		69 M	116	Dyspnoea exertional	Severe	Dose not changed	Recovered

Source: adae.xpt; Software: JMP.
Abbreviations: F, female; M, male.
1 Includes trial 1629 DBTP and trial 1643 DBTP. Duration = 24 weeks.

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8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Five patients experienced nine adverse events leading to permanent drug discontinuation. Slightly more evinacumab-treated patients (15 mg/kg and 5 mg/kg doses) discontinued (3.4%) than placebo-treated patients (1.9%). Notably all discontinuations were in trial 1643 (HeFH or established ASCVD); no patients in trial 1629 (HoFH) discontinued drug due to an AE. Discontinuations were determined to be drug-related in 3 patients (representing <3% of evinacumab-exposed patients). Drug-related reasons for discontinuation included anaphylactic reaction, headache, and rash.

Table 40. Patients with Adverse Events[1] Leading to Drug Discontinuation, Evinacumab 15 mg/kg versus Placebo, Safety Population, Placebo-Controlled Pool[2]

Adverse Event	Evinacumab 5 mg/kg N=36 n(%)	Evinacumab 15 mg/kg N=81 n(%)	Evinacumab All[3] N=117 n(%)	Placebo N=54 n(%)	Absolute Risk Difference (95% CI)[4]
Patients with at least 1 AE leading to discontinuation	**2 (5.6%)**	**2 (2.5%)**	**4 (3.4%)**	**1 (1.9%)**	**0.6% (-4.3%, 5.6%)**
Number of events	**2**	**2**	**4**	**5**	**-**
Glioblastoma	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
Anaphylactic reaction	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
Rash	1 (2.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Headache	1 (2.8%)	0 (0.0%)	1 (0.9%)	1 (1.9%)	-1.9% (-5.4%, 1.7%)
Arthralgia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	-1.9% (-5.4%, 1.7%)
Calcium deficiency	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	-1.9% (-5.4%, 1.7%)
Myalgia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	-1.9% (-5.4%, 1.7%)
Pruritus	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	-1.9% (-5.4%, 1.7%)

Source: adae.xpt; Software: JMP.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; AE, adverse event.
1 Treatment-emergent AE defined as AE that developed or worsened during DBTP. MedDRA version 22.0.
2 Includes trial 1629 DBTP and trial 1643 DBTP. Duration = 24 weeks.
3 Includes evinacumab 5 mg/kg IV Q4W and 15 mg/kg IV Q4W.
4 Difference is shown between evinacumab 15 mg/kg and placebo.

Reference ID: 4745518

Table 41. List of All Individual Patients with Adverse Events Leading to Drug Discontinuation in Safety Population, Placebo-Controlled Pool[1]

Study Arm	Subject ID	Age/Gender	Study Day	MedDRA PT	Severity
Evinacumab 5 mg/kg	(b) (6)	55 F	30	Headache	Mild
		50 F	11	Rash	Moderate
Evinacumab 15 mg/kg		59 M	144	Glioblastoma	Severe
		53 F	28	Anaphylactic reaction	Moderate
Placebo		53 M	1	Headache	Moderate
			1	Myalgia	Moderate
			1	Pruritus	Mild
			2	Arthralgia	Moderate
			14	Calcium deficiency	Mild

Source: adae.xpt; Softwar
Abbreviations: F, female; M, male; PT, preferred term.
1 Includes trial 1629 DBTP and trial 1643 DBTP. Duration = 24 weeks.

8.4.4. Significant Adverse Events

Eleven severe adverse events were experienced by 6 patients in the placebo-controlled pool. More events were experienced by patients exposed to evinacumab (4.3% vs. 1.9% placebo). Upon narrative review, only 1 severe AE was deemed as possibly related to drug by this reviewer, an event of myalgia (see narrative below). Other AEs were determined to be unrelated to drug based on consistency with patients' medical history or biologic implausibility.

<u>Narrative:</u>

- Patient (b) (6) was a 74-year-old female with an extensive past medical history including cardiovascular disease (CAD s/p MI, CABG, and PCI; carotid artery occlusion s/p CVA, endarterectomy, and carotid stent placement; AAA s/p repair; peripheral vascular disease s/p bypass, stent insertion, and angioplasty; renal artery stenosis s/p revascularization), sinus node dysfunction s/p pacemaker insertion, atrial fibrillation, dizziness, syncope, pulmonary hypertension, hypertension on metoprolol, and chronic kidney disease (eGFR 30). The patient's background LLT consisted of only alirocumab; the patient reported a history of statin intolerance at trial enrollment. During trial 1643, the patient experienced a severe event of myalgia on day 41. No additional details were provided. Myalgia is associated with alirocumab; however, the patient had taken alirocumab since 2018 without myalgia. Therefore, an association with evinacumab cannot be ruled out.

  The patient also experienced a severe event of syncope on day 66 (8 days after the last evinacumab infusion; treated for dehydration and vertigo with fludrocortisone, meclizine, and IV fluids); a severe event of left hip tendon rupture on day 88 (unknown

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etiology, diagnosed on imaging); and a severe event of hypertensive encephalopathy on day 111 requiring IV diltiazem and metoprolol (25 days after the last evinacumab infusion). These events were consistent with her underlying medical history and determined to be unlikely related to evinacumab by this reviewer.

Table 42. Patients with Severe[1] Adverse Events, Evinacumab 15 mg/kg versus Placebo, Safety Population, Placebo-Controlled Pool[2]

Severe Adverse Event	Evinacumab 5 mg/kg N=36 n(%)	Evinacumab 15 mg/kg N=81 n(%)	Evinacumab All[3] N=117 n(%)	Placebo N=54 n(%)	Absolute Risk Difference (95% CI)[4]
Patients with at least 1 severe AE	**1 (2.8%)**	**4 (4.9%)**	**5 (4.3%)**	**1 (1.9%)**	**3.1% (-2.8%, 9.0%)**
Number of events	**4**	**6**	**10**	**1**	**-**
Hypertensive encephalopathy	1 (2.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Myalgia	1 (2.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Syncope	1 (2.8%)	1 (1.2%)	2 (1.7%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
Tendon rupture	1 (2.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Suicide attempt	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
Urosepsis	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
Coronary artery disease	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
Glioblastoma	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
Angina unstable	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
Dyspnea exertional	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	-1.9% (-5.4%, 1.7%)

Source: adae.xpt; Software: JMP.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; AE, adverse event.
1 Defined as an AE that produces significant impairment of functioning or incapacitation and is a definite hazard to patient's health. Treatment may be given and/or patient may be hospitalized.
2 Includes trial 1629 DBTP and trial 1643 DBTP. Duration = 24 weeks.
3 Includes evinacumab 5 mg/kg IV Q4W and 15 mg/kg IV Q4W.
4 Difference is shown between evinacumab 15 mg/kg and placebo.

8.4.5. Treatment-Emergent Adverse Events and Adverse Reactions

The most frequent adverse events, that also occurred with greater incidence than placebo, are provided in Table 43. Notable AEs that were consistent with the expected safety profile of a monoclonal antibody included dizziness; asthenia; nausea; upper respiratory symptoms such as rhinorrhea, nasopharyngitis, upper respiratory tract infection, and nasal congestion; influenza-like illness; and infusion site pruritus. Pain in extremity and constipation were also observed. Two cases of asthma occurred in current/former smokers with a baseline history of asthma and are unlikely related to evinacumab. Coronary artery disease occurred in patients with a baseline history of ASCVD and is unlikely related to evinacumab. Dental caries and neck pain occurred in 2 or fewer patients and are unlikely related to evinacumab based on biologic implausibility.

Reference ID: 4745518

Table 43. Patients with Common Treatment-Emergent Adverse Events[1] Occurring at ≥2% Incidence and ≥1.5% Over Placebo, Evinacumab 15 mg/kg versus Placebo, Safety Population, Placebo-Controlled Pool[2]

Preferred Term[3]	Evinacumab 5 mg/kg N=36 n(%)	Evinacumab 15 mg/kg N=81 n(%)	Evinacumab All[4] N=117 n(%)	Placebo N=54 n(%)	Absolute RD (95% CI)[5]
Dizziness	2 (5.6%)	5 (6.2%)	7 (6.0%)	0 (0.0%)	6.2% (0.9%, 11.4%)
Rhinorrhea	0 (0.0%)	4 (4.9%)	4 (3.4%)	0 (0.0%)	4.9% (0.2%, 9.7%)
Pain in extremity	3 (8.3%)	3 (3.7%)	6 (5.1%)	0 (0.0%)	3.7% (-0.4%, 7.8%)
Asthenia	0 (0.0%)	3 (3.7%)	3 (2.6%)	0 (0.0%)	3.7% (-0.4%, 7.8%)
Nausea	2 (5.6%)	4 (4.9%)	6 (5.1%)	1 (1.9%)	3.1% (-2.8%, 9.0%)
Nasopharyngitis	3 (8.3%)	13 (16.0%)	16 (13.7%)	7 (13.0%)	3.1% (-8.9%, 15.1%)
Constipation	2 (5.6%)	2 (2.5%)	4 (3.4%)	0 (0.0%)	2.5% (-0.9%, 5.8%)
Coronary artery disease	1 (2.8%)	2 (2.5%)	3 (2.6%)	0 (0.0%)	2.5% (-0.9%, 5.8%)
Upper respiratory tract infection	1 (2.8%)	2 (2.5%)	3 (2.6%)	0 (0.0%)	2.5% (-0.9%, 5.8%)
Asthma	0 (0.0%)	2 (2.5%)	2 (1.7%)	0 (0.0%)	2.5% (-0.9%, 5.8%)
Dental caries	0 (0.0%)	2 (2.5%)	2 (1.7%)	0 (0.0%)	2.5% (-0.9%, 5.8%)
Infusion site pruritus	0 (0.0%)	2 (2.5%)	2 (1.7%)	0 (0.0%)	2.5% (-0.9%, 5.8%)
Nasal congestion	0 (0.0%)	2 (2.5%)	2 (1.7%)	0 (0.0%)	2.5% (-0.9%, 5.8%)
Neck pain	0 (0.0%)	2 (2.5%)	2 (1.7%)	0 (0.0%)	2.5% (-0.9%, 5.8%)
Influenza-like illness	3 (8.3%)	6 (7.4%)	9 (7.7%)	3 (5.6%)	1.9% (-6.5%, 10.2%)

Source: adae.xpt; Software: JMP.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; RD, risk difference.
1 Treatment-emergent AE defined as an AE that developed or worsened during DBTP. MedDRA version 22.0.
2 Includes trial 1629 DBTP and trial 1643 DBTP. Duration = 24 weeks.
3 Coded as MedDRA preferred terms.
4 Includes evinacumab 5 mg/kg IV Q4W and 15 mg/kg IV Q4W.
5 Difference is shown between evinacumab 15 mg/kg and placebo.

Grouped medical queries (FDA-developed medical queries [FMQs] and custom medical queries [CMQs]) (Tables 44 and 45) were also performed on placebo-controlled data. Grouped queries combined similar PTs that represent the same medical concept (e.g., abdominal pain, abdominal pain upper, and abdominal pain lower) to detect any potential safety signals that could be diluted using individual PTs alone; FMQs utilized standard FDA PT combinations, whereas CMQs utilized reviewer-determined PT combinations. For any grouped query with a signal, contributing PTs were reviewed to determine the relatedness to evinacumab and potential need for inclusion in labeling.

Abdominal pain may be related to evinacumab and should be included in the adverse reaction section of labeling. The abdominal pain/discomfort CMQ (Table 45) was driven by the following PTs: constipation (already included in the adverse reaction table, Table 43), abdominal pain, and abdominal pain upper. Abdominal pain (PTs = abdominal pain and abdominal pain upper) occurred more frequently in patients treated with evinacumab 15 mg/kg (2.5%) versus those treated with placebo (1.9%). Abdominal pain also occurred more frequently in patients treated with evinacumab 5 mg/kg (11.1%) lending credibility to the observed association. Refer to Section 10 for additional discussion.

Reference ID: 4745518

No other grouped query will require labeling either because of more specific capture under individual PTs in Table 43 (fatigue; pruritus; upper respiratory infection; infection, all; dyspepsia) or because of lack of apparent drug relatedness, presence of confounders, or lack of a clear signal upon review of contributing PTs.

- The two AEs under the bronchospasm FMQ represented events of asthma in current/former smokers with a history of asthma.
- Amongst the 4 cases of hemorrhage, 2 patients had a history of allergic rhinitis and experienced epistaxis (1 patient was taking aspirin), and 1 patient experienced a hip contusion while taking the anticoagulant rivaroxaban. Coagulation parameters such as PT, PTT, or INR were not monitored during the trial; however, trends in hemoglobin, hematocrit, and platelet count do not suggest a hemorrhagic effect of evinacumab (Section 8.4.6).
- The arthritis FMQ included 1 case of gout and 1 case of spinal osteoarthritis, which represent distinct pathophysiologic events and are likely a chance finding.
- Amongst the 2 cases of erythema, 1 patient experienced bandage-associated redness (not drug-related). One additional patient experienced a local injection site reaction of erythema; however, it is difficult to draw any conclusions from such a small imbalance (1 drug versus 0 placebo).
- The viral infection CMQ included 6 distinct infectious sources with only a single patient impacted by each event: herpes simplex, herpes zoster, viral gastroenteritis, influenza, and viral upper respiratory infection amongst evinacumab-treated patients and parainfluenza infection in a single placebo patient. The small number of impacted patients and lack of a clear signal limit the ability to draw conclusions.
- Noncardiac chest pain included the following PTs: noncardiac chest pain, atypical chest pain, and chest pain. Noncardiac chest pain, atypical chest pain, and chest pain may represent distinct medical concepts. Without additional detail, it is difficult to draw conclusions regarding a drug-related association.

Reference ID: 4745518

Table 44. Patients with Treatment-Emergent Adverse Events[1] by FMQ (Narrow)[2] Occurring at ≥2% Incidence and ≥1% over Placebo, Evinacumab 15 mg/kg versus Placebo, Safety Population, Placebo-Controlled Pool[3]

FMQ (Narrow)	Evinacumab 5 mg/kg N=36 n(%)	Evinacumab 15 mg/kg N=81 n(%)	Evinacumab All[4] N=117 n(%)	Placebo N=54 n(%)	Absolute RD (95% CI)[5]
Bronchospasm	0 (0.0%)	2 (2.5%)	2 (1.7%)	0 (0.0%)	2.5% (-0.9%, 5.8%)
Hemorrhage	2 (5.6%)	2 (2.5%)	4 (3.4%)	0 (0.0%)	2.5% (-0.9%, 5.8%)
Fatigue	4 (11.1%)	4 (4.9%)	8 (6.8%)	2 (3.7%)	1.2% (-5.7%, 8.1%)
Pruritus	0 (0.0%)	4 (4.9%)	4 (3.4%)	2 (3.7%)	1.2% (-5.7%, 8.1%)
Arthritis	1 (2.8%)	1 (1.2%)	2 (1.7%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
Erythema	1 (2.8%)	1 (1.2%)	2 (1.7%)	0 (0.0%)	1.2% (-1.2%, 3.6%)

Source: adae.xpt; Software: JMP.
Abbreviations: CI, confidence interval; FMQ, FDA Medical Query; N, number of patients in treatment arm; n, number of patients with at least one event; RD, risk difference.
1 Treatment-emergent AE defined as an AE that developed or worsened during DBTP. MedDRA version 22.0.
2 Only those FMQs that provide additional information, beyond data already displayed in Table 43, are included.
3 Includes trial 1629 DBTP and trial 1643 DBTP. Duration = 24 weeks.
4 Includes evinacumab 5 mg/kg IV Q4W and 15 mg/kg IV Q4W.
5 Difference is shown between evinacumab 15 mg/kg and placebo.

Table 45. Patients with Treatment-Emergent Adverse Events[1] By CMQ[2] Occurring at ≥2% Incidence and ≥1% Over Placebo, Evinacumab 15 mg/kg versus Placebo, Safety Population, Placebo-Controlled Pool[3]

Grouped Medical Query	Evinacumab 5 mg/kg N=36 n(%)	Evinacumab 15 mg/kg N=81 n(%)	Evinacumab All[4] N=117 n(%)	Placebo N=54 n(%)	Absolute Risk Difference (95% CI)[5]
Upper respiratory infection	10 (27.8%)	24 (29.6%)	34 (29.1%)	9 (16.7%)	13.0% (-1.1%, 27.0%)
Infection, all	12 (33.3%)	28 (34.6%)	40 (34.2%)	12 (22.2%)	12.3% (-2.8%, 27.5%)
Abdominal pain/discomfort	6 (16.7%)	4 (4.9%)	10 (8.5%)	1 (1.9%)	3.1% (-2.8%, 9.0%)
Dyspepsia	3 (8.3%)	7 (8.6%)	10 (8.5%)	3 (5.6%)	3.1% (-5.6%, 11.7%)
Infection, viral	1 (2.8%)	3 (3.7%)	4 (3.4%)	1 (1.9%)	1.9% (-3.6%, 7.3%)
Non-cardiac chest pain	1 (2.8%)	3 (3.7%)	4 (3.4%)	1 (1.9%)	1.9% (-3.6%, 7.3%)

Source: adae.xpt; Software: JMP.
Abbreviations: CI, confidence interval; CMQ, Custom MedDRA Query; N, number of patients in treatment arm; n, number of patients with adverse event.
1 Treatment-emergent AE defined as an AE that developed or worsened during DBTP. MedDRA version 22.0.
2 Only those CMQs that provide additional information, beyond data already displayed in Tables 43 and 44, are included.
3 Includes trial 1629 DBTP and trial 1643 DBTP. Duration = 24 weeks.
4 Includes evinacumab 5 mg/kg IV Q4W and 15 mg/kg IV Q4W.
5 Difference is shown between evinacumab 15 mg/kg and placebo.

Reference ID: 4745518

8.4.6. Laboratory Findings

Laboratory values were assessed descriptively using measures of central tendency and categorically using clinically meaningful cutoffs.

There were no obvious trends in lab analyses associated with evinacumab exposure. More patients treated with evinacumab experienced extreme glucose values (Table 47); however, both hypoglycemia and hyperglycemia were observed with similar incidence, which calls into question the biologic plausibility of a glycemic effect. Additionally, there was no meaningful difference in mean glucose or HbA1c over time compared to placebo, and review of individual patients demonstrated that these were typically isolated events. Evinacumab patients were also more likely to experience an elevated WBC; however, the elevations were generally mild, occurred in only a handful of patients, and nonspecific (i.e., elevations were observed in different components of WBC including neutrophils, monocytes, eosinophils, and lymphocytes).

Notably, there was no evidence of CK, ALT, or AST elevation with evinacumab. One patient experienced an ALT/AST elevation >5x ULN; however, the elevation is unlikely evinacumab-related as the patient had discontinued evinacumab 112 days prior to elevation. While the lack of a signal is somewhat reassuring, the ability of the safety database to detect events occurring at low frequency is limited by the small total number of patient exposures.

Reference ID: 4745518

Table 46. Mean Change from Baseline Over Time in Laboratory Values, by Treatment Arm, Safety Population, Placebo-Controlled Pool[1]

Parameter	Study Visit[2]	Evinacumab 15 mg/kg N=81			Placebo N=54			Absolute Difference in Mean Change
		n at Visit	Mean (SD)	Mean Change from Baseline (SD)	n at Visit	Mean (SD)	Mean Change from Baseline (SD)	
Hemoglobin (g/dL)	Baseline	75	13.8 (1.7)	-	51	13.6 (1.2)	-	-
	Week 24	75	13.5 (1.6)	-0.3 (0.8)	50	13.3 (1.2)	-0.4 (0.8)	0.1
Hematocrit (%)	Baseline	75	41.5 (4.9)	-	50	40.9 (4.1)	-	-
	Week 24	75	40.8 (4.6)	-0.7 (2.6)	49	40.0 (3.7)	-0.9 (3.0)	0.3
Platelets (10^9/L)	Baseline	74	229.1 (67.7)	-	51	223.2 (56.8)	-	-
	Week 24	74	239.2 (76.0)	8.6 (43.3)	49	236.2 (63.0)	12.6 (34.6)	-4.0
Creatinine (mg/dL)	Baseline	76	0.8 (0.2)	-	52	0.8 (0.2)	-	-
	Week 24	76	0.8 (0.2)	0.0 (0.1)	52	0.8 (0.2)	-0.01 (0.08)	0.01
BUN (mg/dL)	Baseline	76	15.4 (5.0)	-	51	14.8 (3.9)	-	-
	Week 24	76	15.4 (4.5)	0.0 (3.9)	51	14.0 (4.2)	-0.6 (3.1)	0.6
WBC (10^9/L)	Baseline	75	6.4 (2.1)	-	51	6.1 (1.9)	-	-
	Week 24	75	6.3 (2.2)	-0.2 (1.3)	50	6.1 (1.9)	-0.1 (1.7)	-0.1
Glucose (mg/dL)	Baseline	76	93.7 (14.4)	-	51	97.3 (27.0)	-	-
	Week 24	76	97.3 (16.2)	3.6 (12.6)	51	100.9 (39.6)	3.6 (28.8)	-0.9
HbA1c (%)	Baseline	76	5.5 (0.5)	-	48	5.6 (0.7)	-	-
	Week 24	76	5.5 (0.6)	0.0 (0.0)	50	5.5 (0.7)	0.0	0.0
ALT (U/L)	Baseline	76	24.6 (14.7)	-	52	21.8 (11.4)	-	-
	Week 24	76	22.1 (11.3)	-2.5 (11.6)	52	22.6 (17.5)	0.9 (11.1)	-3.4
AST (U/L)	Baseline	76	22.3 (9.3)	-	52	21.1 (8.9)	-	-
	Week 24	75	21.2 (8.4)	-1.1 (6.5)	52	20.6 (10.7)	-0.5 (7.1)	-0.6
Bilirubin (mg/dL)	Baseline	76	0.7 (0.3)		52	0.6 (0.4)	-	-
	Week 24	76	0.6 (0.3)	-0.09 (0.2)	52	0.6 (0.3)	-0.03 (0.3)	-0.06
Alkaline phosphatase (U/L)	Baseline	76	61.2 (18.2)	-	52	64.8 (33.2)	-	-
	Week 24	76	62.1	0.9 (10.8)	52	66.0	1.2 (13.3)	-0.3

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			(17.8)			(32.0)		
CK (U/L)	Baseline	76	136.8 (97.3)	-	52	142.0 (156.8)	-	-
	Week 24	76	141.1 (130.9)	4.4 (104.1)	52	131.7 (161.0)	-10.3 (175.0)	14.7
Albumin (g/L)	Baseline	76	44.0 (3.4)	-	51	43.7 (2.8)	-	-
	Week 24	76	43.1 (3.2)	-0.9 (2.5)	51	42.9 (3.3)	-0.8 (2.5)	-0.2
Protein (g/L)	Baseline	76	70.3 (4.9)	-	52	70.4 (4.5)	-	-
	Week 24	76	68.5 (5.1)	-1.8 (3.8)	52	68.8 (5.6)	-1.6 (4.3)	-0.2
Uric acid (mg/dL)	Baseline	76	5.4 (1.6)	-	52	5.6 (1.6)	-	-
	Week 24	76	5.6 (1.7)	0.2 (0.9)	52	5.6 (1.7)	-0.06 (1.0)	0.3

Source: adlb.xpt; Software: JMP.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; HbA1c, hemoglobin A1c; SD, standard deviation; WBC, white blood cell.
1 Includes trials 1629 DBTP and 1643 DBTP. Duration = 24 weeks.
2 For patients with more than one value at Week 24, the most extreme value is selected.

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Table 47. Patients with One or More Laboratory Values Exceeding Specified Levels, Safety Population, Placebo-Controlled Pool[1]

	Evinacumab 5 mg/kg N=36	Evinacumab 15 mg/kg N=81	Placebo N=54	Absolute RD (95% CI)[2]
Glucose, low (mg/dL)				
<70	3 (8.3%)	5 (6.2%)	1 (1.9%)	4.3% (-2.0%, 10.7%)
Glucose, high (mg/dL)				
≥126 fasting or ≥200 random	4 (11.1%)	7 (8.6%)	2 (3.7%)	4.9% (-3.0%, 12.9%)
HbA1c, high (%)				
>8	0 (0.0%)	0 (0.0%)	1 (1.9%)	-1.9% (-5.4%, 1.7%)
CK, high (U/L)				
>3x ULN	0 (0.0%)	1 (1.2%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
>5x ULN	0 (0.0%)	2 (2.5%)	1 (1.9%)	0.6% (-4.3%, 5.6%)
>10x ULN	0 (0.0%)	1 (1.2%)	1 (1.9%)	-0.6% (-4.9%, 3.7%)
ALT (U/L)				
>2x ULN	1 (2.8%)	1 (1.2%)	1 (1.9%)	-0.6% (-4.9%, 3.7%)
>3x ULN	0 (0.0%)	0 (0.0%)	1 (1.9%)	-1.9% (-5.4%, 1.7%)
>5x ULN	0 (0.0%)	1 (1.2%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
>10x ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
AST (U/L)				
>2x ULN	0 (0.0%)	2 (2.5%)	1 (1.9%)	0.6% (-4.3%, 5.6%)
>3x ULN	0 (0.0%)	0 (0.0%)	2 (3.7%)	-3.7% (-8.7%, 1.3%)
>5x ULN	0 (0.0%)	1 (1.2%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
>10x ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Bilirubin, total, high (mg/dL)				
>1.5x ULN	0 (0.0%)	1 (1.2%)	1 (1.9%)	-0.6% (-4.9%, 3.7%)
>2x ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Alkaline phosphatase, high (U/L)				
>1.5x ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
WBC, low (cells/µL)[3]				
<3500	2 (5.6%)	2 (2.5%)	5 (9.3%)	-6.8% (-15.2%, 1.6%)
<3000	0 (0.0%)	0 (0.0%)	2 (3.7%)	-3.7% (-8.7%, 1.3%)
<1000	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
WBC, high (cells/µL)[4]				
>10,800	1 (2.8%)	7 (8.6%)	2 (3.7%)	4.9% (-3.0%, 12.9%)
>13,000	0 (0.0%)	4 (4.9%)	0 (0.0%)	4.9% (0.2%, 9.7%)
>15,000	0 (0.0%)	1 (1.2%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
Eosinophils, high (cells/µL)[5]				
>500	4 (11.1%)	6 (7.4%)	2 (3.7%)	3.7% (-3.9%, 11.3%)

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>650	3 (8.3%)	2 (2.5%)	1 (1.9%)	0.6% (-4.3%, 5.6%)
>1500	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
>5000	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Lymphocytes, high (cells/µL)[6]				
>4000	0 (0.0%)	3 (3.7%)	0 (0.0%)	3.7% (-0.4%, 7.8%)
>10,000	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
>20,000	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Neutrophils, high (cells/µL)[7]				
>6000	6 (16.7%)	15 (18.5%)	10 (18.5%)	0.0% (-13.4%, 13.4%)
>8000	2 (5.6%)	6 (7.4%)	1 (1.9%)	5.6% (-1.2%, 12.3%)
>10,000	0 (0.0%)	2 (2.5%)	0 (0.0%)	2.5% (-0.9%, 5.8%)
Basophils, high (cells/µL)[8]				
>100	0 (0.0%)	0 (0.0%)	1 (1.9%)	-1.9% (-5.4%, 1.7%)
Monocytes, high (cells/µL)[9]				
>700	3 (8.3%)	11 (13.6%)	3 (5.6%)	8.0% (-1.6%, 17.7%)
Neutrophils, low (cells/µL)				
<1000	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)

Source: adlb.xpt; Software: JMP.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; CI, confidence interval; HbA1c, hemoglobin A1c; RD, risk difference; ULN, upper limit of normal; WBC, white blood cell.
1 Includes trials 1629 DBTP and 1643 DBTP. Duration = 24 weeks.
2 Difference is shown between evinacumab 15 mg/kg IV and placebo.
3 Amongst patients whose baseline was 3500 or greater.
4 Amongst patients whose baseline was 15 or less.
5 Amongst patients whose baseline was 5000 or less.
6 Amongst patients whose baseline was 8000 or less.
7 Amongst patients whose baseline was 5000 or less.
8 Amongst patients whose baseline was 300 or less.
9 Amongst patients whose baseline was 1000 or less.

8.4.7. Vital Signs

In the placebo-controlled pool, vital signs were obtained pre-infusion, 30 minutes post-infusion, and 60 minutes post-infusion. Vital signs were assessed descriptively using measures of central tendency and categorically using clinically meaningful cutoffs.

There were no clinically meaningful mean changes to SBP, DBP, or heart rate (HR) over time. However, there were subsets of patients who experienced elevated SBP and HR 30-60 minutes post-infusion, as well as patients who experienced decreased DBP post-infusion.

Patients treated with evinacumab 15 mg/kg were more likely to experience a SBP of 140 to 159 mmHg compared to placebo patients (Tables 48 and 49); the elevation most commonly occurred 60 minutes post-infusion (evinacumab 29.6% vs. placebo 18.5%; RD 11.1% [-3.2, 25.5]). The trend remained even when patients with elevated SBP at baseline or pre-infusion at the same study visit were removed from analyses (Table 49).

Reference ID: 4745518

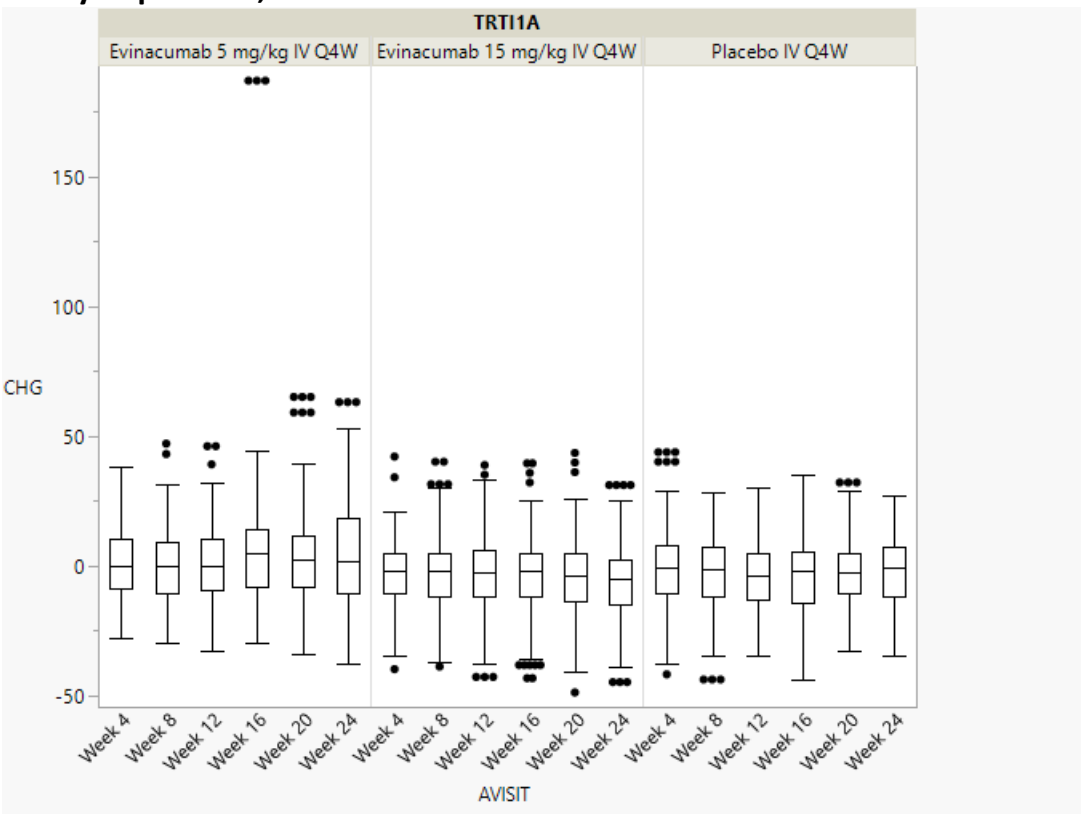
Evinacumab-treated patients (15 mg/kg dose) were also more likely to experience a post-infusion HR ≥100 bpm with concomitant increase ≥10 bpm from baseline compared to placebo-treated patients. The increased heart rate occurred 30-60 minutes post-infusion (30 minutes: evinacumab 2.5% vs. placebo 0%; RD 2.5% [-0.9, 5.8] and 60 minutes: evinacumab 3.7% vs. placebo 0%; RD 3.7% [-0.4, 7.8]). When patients with elevated HR pre-infusion were removed, the signal remained. Notably, the patients who experienced increased HR post-infusion were not the same patients as those identified by investigators as having an anaphylactic or infusion reaction.

Finally, patients treated with evinacumab 15 mg/kg were also more likely to experience a DBP <60 mmHg 30-60 minutes post-infusion than placebo-treated patients during the trial (evinacumab 37.0% vs. placebo 29.6%; RD 7.4% [-8.7, 23.5]) (Table 50). The signal remained when patients with low DBP at baseline or pre-infusion during the same study visit were removed (Table 51).

In summary, evidence suggests that evinacumab infusion may cause acute, transient changes to blood pressure and heart rate during the post-infusion period; however, changes appear to resolve between treatments. Hypotension and tachycardia during or post-administration are more commonly associated with monoclonal antibodies given the potential for hypersensitivity, including anaphylaxis and infusion reactions. However, hypertension has also been observed in infusion reactions with other monoclonal antibodies (such as the multiple myeloma drug, daratumumab). In these cases, hypertension is likely the result of a pathophysiologic compensatory mechanism.

Reference ID: 4745518

Figure 8. Mean Change in Systolic Blood Pressure Over Time by Treatment Group, Safety Population, Placebo-Controlled Pool



Source: advs.xpt; Software: JMP.
Abbreviations: AVISIT, study visit; TRT1A, actual treatment received.

Reference ID: 4745518

Table 48. Percentage of Patients Experiencing Given Category of Systolic Blood Pressure, Post-Baseline[1], Safety Population, Placebo-Controlled Pool[2]

Systolic Blood Pressure (mmHg)	Evinacumab 5 mg/kg N=36	Evinacumab 15 mg/kg N=81	Evinacumab All[3] N=117	Placebo N=54	Absolute RD (95% CI)[4]
<90	0 (0.0%)	4 (4.9%)	4 (3.4%)	4 (7.4%)	-2.5% (-10.9%, 6.0%)
≥90 to <120	27 (75.0%)	67 (82.7%)	94 (80.3%)	47 (87.0%)	-4.3% (-16.5%, 7.8%)
≥120 to <140	34 (94.4%)	75 (92.6%)	109 (93.2%)	50 (92.6%)	0.0% (-0.9%, 9.0%)
≥140 to <160	17 (47.2%)	34 (42.0%)	51 (43.6%)	17 (31.5%)	10.5% (-5.9%, 26.9%)
≥160 to <180	7 (19.4%)	5 (6.2%)	12 (10.3%)	3 (5.6%)	0.6% (-7.4%, 8.7%)
≥160 and increase from BL ≥20	8 (22.2%)	2 (2.5%)	10 (8.5%)	1 (1.9%)	0.6% (-4.3%, 5.6%)
≥180	2 (5.6%)	0 (0.0%)	2 (1.7%)	1 (1.9%)	-1.9% (-5.4%, 1.7%)
≥180 and increase from BL ≥20	2 (5.6%)	0 (0.0%)	2 (1.7%)	1 (1.9%)	-1.9% (-5.4%, 1.7%)

Source: advs.xpt; Software: JMP.
Abbreviations: BL, baseline; CI, confidence interval; N, number of patients in treatment arm with available blood pressure data; n, number of patients with indicated blood pressure; RD, risk difference.
1 Any time post-baseline. Includes SBP assessments pre-infusion, 30 minutes post-infusion, and 60 minutes post-infusion.
2 Includes trial 1629 DBTP and trial 1643 DBTP. Duration = 24 weeks.
3 Includes evinacumab 5 mg/kg IV Q4W and 15 mg/kg IV Q4W.
4 Difference is shown between evinacumab 15 mg/kg and placebo.

Reference ID: 4745518

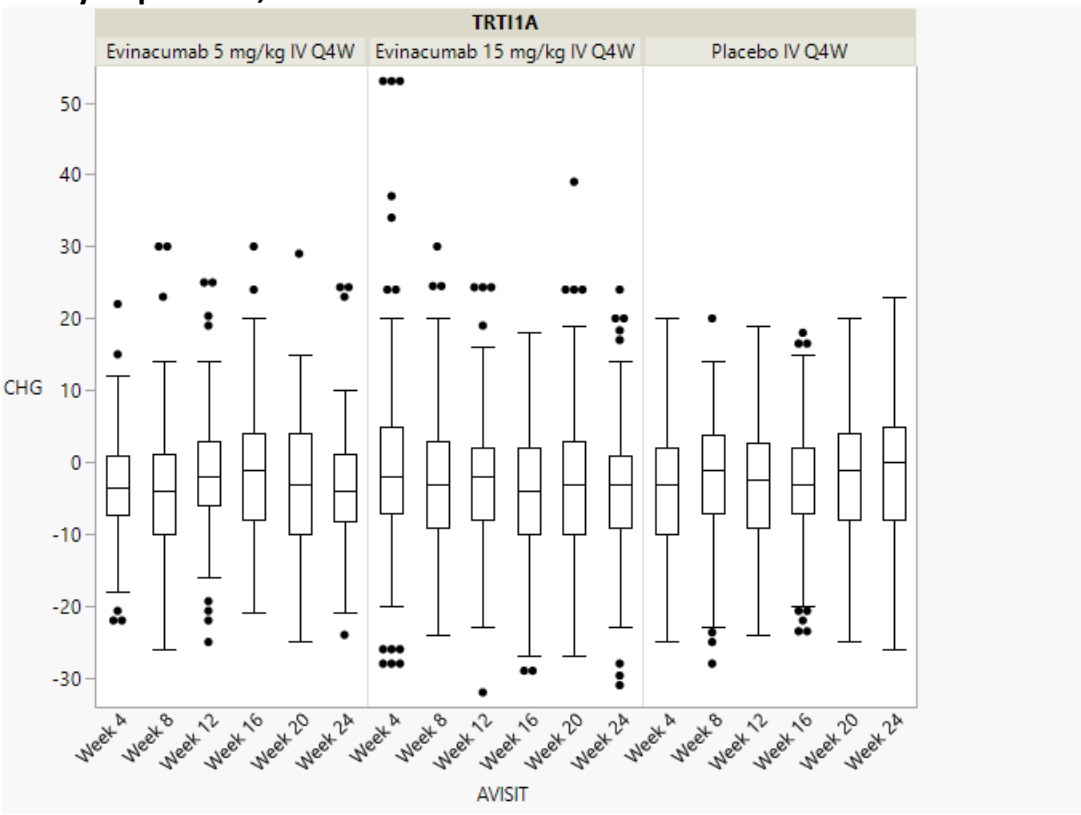
Table 49. Percentage of Patients Experiencing Given Category of Systolic Blood Pressure, Post-Infusion[1], Safety Population, Placebo-Controlled Pool[2]

Systolic Blood Pressure (mmHg)	Evinacumab 5 mg/kg N=36	Evinacumab 15 mg/kg N=81	Evinacumab All[3] N=117	Placebo N=54	Absolute RD (95% CI)[4]
<90	0 (0.0%)	4 (4.9%)	4 (3.4%)	3 (5.6%)	-0.6% (-8.3%, 7.1%)
≥90 to <120	24 (66.7%)	58 (71.6%)	82 (70.1%)	43 (79.6%)	-8.0% (-22.6%, 6.5%)
≥120 to <140	32 (88.9%)	71 (87.7%)	103 (88.0%)	48 (88.9%)	-1.2% (-12.3%, 9.8%)
≥140 to <160	15 (41.7%)	28 (34.6%)	43 (36.8%)	14 (25.9%)	8.6% (-7.0%, 24.3%)
≥140 to <160, 30 min post-infusion	11 (30.6%)	18 (22.2%)	29 (24.8%)	13 (24.1%)	-1.9% (-16.4%, 12.7%)
≥140 to <160, 60 min post-infusion	15 (41.7%)	24 (29.6%)	39 (33.3%)	10 (18.5%)	11.1% (-3.2%, 25.5%)
≥140 to <160, 60 min post-infusion; and <140 pre-infusion[5]	13 (36.1%)	16 (19.8%)	29 (24.8%)	7 (13.0%)	6.8% (-5.7%, 19.3%)
≥140 to <160, 60 min post-infusion; and increase from BL ≥10	8 (22.2%)	10 (12.3%)	18 (15.4%)	3 (5.6%)	6.8% (-2.6%, 16.2%)
≥140 to <160, 60 min post-infusion; and increase from BL ≥20	7 (19.4%)	7 (8.6%)	14 (12.0%)	1 (1.9%)	6.8% (-0.3%, 13.9%)
≥160 to <180	6 (16.7%)	2 (2.5%)	8 (6.8%)	2 (3.7%)	-1.2% (-7.3%, 4.8%)
≥160 and increase from BL ≥20	6 (16.7%)	0 (0.0%)	6 (5.1%)	1 (1.9%)	-1.9% (-5.4%, 1.7%)
≥180	1 (2.8%)	0 (0.0%)	1 (0.9%)	1 (1.9%)	-1.9% (-5.4%, 1.7%)
≥180 and increase from BL ≥20	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.9%)	-1.9% (-5.4%, 1.7%)

Source: advs.xpt; Software: JMP.
Abbreviations: BL, baseline; CI, confidence interval; N, number of patients in treatment arm with available blood pressure data; n, number of patients with indicated blood pressure; RD, risk difference.
1 Includes SBP assessments 30 minutes post-infusion and 60 minutes post-infusion.
2 Includes trial 1629 DBTP and trial 1643 DBTP. Duration = 24 weeks.
3 Includes evinacumab 5 mg/kg IV Q4W and 15 mg/kg IV Q4W.
4 Difference is shown between evinacumab 15 mg/kg and placebo.
5 On same study visit.

Reference ID: 4745518

Figure 9. Mean Change in Diastolic Blood Pressure Over Time by Treatment Group, Safety Population, Placebo-Controlled Pool



Source: advs.xpt; Software: JMP.
Abbreviations: AVISIT, study visit; TRT1A, actual treatment received.

Table 50. Percentage of Patients Experiencing Given Category of Diastolic Blood Pressure, Post-Baseline[1], Safety Population, Placebo-Controlled Pool[2]

Diastolic Blood Pressure (mmHg)	Evinacumab 5 mg/kg N=36	Evinacumab 15 mg/kg N=81	Evinacumab All[3] N=117	Placebo N=54	Absolute RD (95% CI)[4]
<60	7 (19.4%)	32 (39.5%)	39 (33.3%)	19 (35.2%)	4.3% (-12.3%, 20.9%)
≥60 to <90	34 (94.4%)	79 (97.5%)	113 (96.6%)	52 (96.3%)	1.2% (-4.8%, 7.3%)
≥90 to <110	16 (44.4%)	11 (13.6%)	27 (23.1%)	11 (20.4%)	-6.8% (-19.9%, 6.3%)
≥110 to <120	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
≥110 and increase from BL ≥10	1 (2.8%)	1 (1.2%)	2 (1.7%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
≥120	1 (2.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0.0% (0.0%, 0.0%)
≥120 and increase from BL ≥10	1 (2.8%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	0.0% (0.0%, 0.0%)

Source: advs.xpt; Software: JMP.
Abbreviations: BL, baseline; CI, confidence interval; N, number of patients in treatment arm with available blood pressure data; n, number of patients with indicated blood pressure; RD, risk difference.
1 Any time post-baseline. Includes DBP assessments pre-infusion, 30 minutes post-infusion, and 60 minutes post-infusion.
2 Includes trial 1629 DBTP and trial 1643 DBTP. Duration = 24 weeks.
3 Includes evinacumab 5 mg/kg IV Q4W and 15 mg/kg IV Q4W.
4 Difference is shown between evinacumab 15 mg/kg and placebo.

Reference ID: 4745518

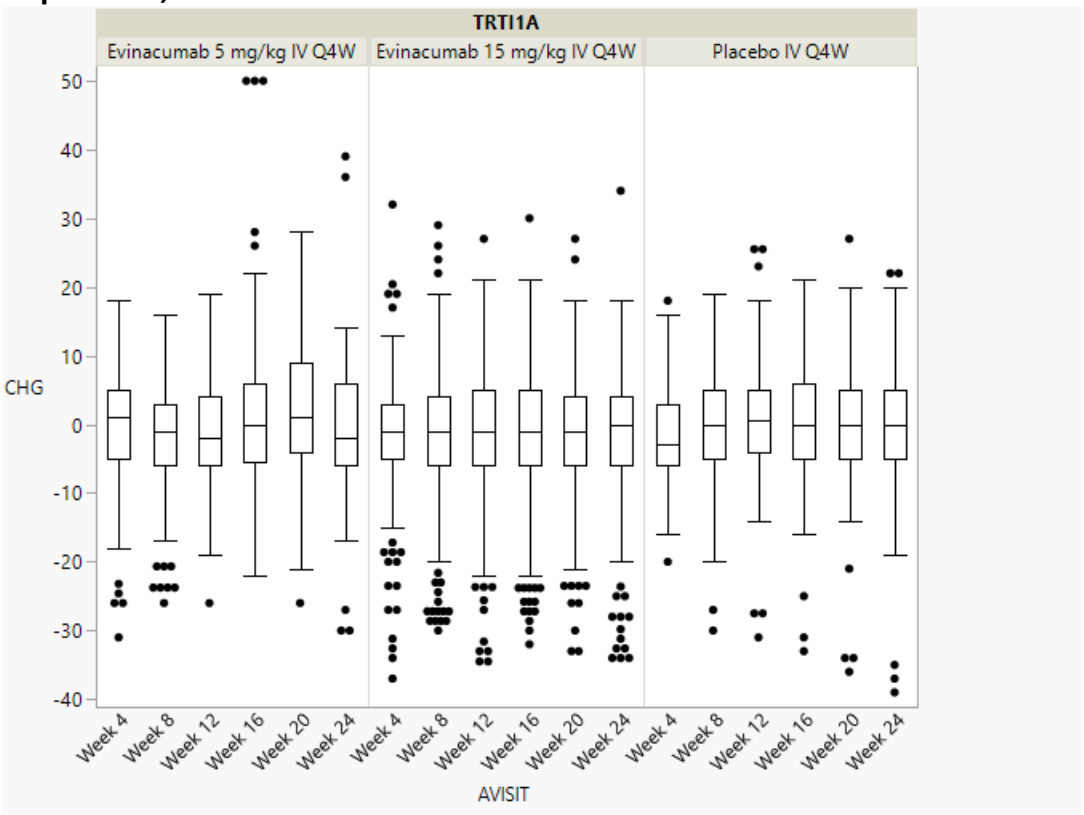
Table 51. Percentage of Patients Experiencing Given Category of Diastolic Blood Pressure, Post-Infusion[1], Safety Population, Placebo-Controlled Pool[2]

Diastolic Blood Pressure (mmHg)	Evinacumab 5 mg/kg N=36	Evinacumab 15 mg/kg N=81	Evinacumab All[3] N=117	Placebo N=54	Absolute RD (95% CI)[4]
<60	6 (16.7%)	30 (37.0%)	36 (30.8%)	16 (29.6%)	7.4% (-8.7%, 23.5%)
<60, 30 min post-infusion	3 (8.3%)	27 (33.3%)	30 (25.6%)	11 (20.4%)	13.0% (-1.9%, 27.8%)
<60, 60 min post-infusion	3 (8.3%)	26 (32.1%)	29 (24.8%)	14 (25.9%)	6.2% (-9.3%, 21.7%)
<60; and ≥60 pre-infusion[5]	6 (16.7%)	24 (29.6%)	30 (25.6%)	12 (22.2%)	7.4% (-7.5%, 22.3%)
<60; and decrease from BL ≤10	6 (16.7%)	22 (27.2%)	28 (23.9%)	8 (14.8%)	12.3% (-1.2%, 25.9%)
≥60 to <90	33 (91.6%)	76 (93.8%)	109 (93.2%)	51 (94.4%)	-0.6% (-8.7%, 7.4%)
≥90 to <110	10 (27.8%)	5 (6.2%)	15 (12.8%)	8 (14.8%)	-8.6% (-19.5%, 2.2%)
≥110 to <120	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
≥110 and increase from BL ≥10	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
≥120	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
≥120 and increase from BL ≥10	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)

Source: advs.xpt; Software: JMP.
Abbreviations: BL, baseline; CI, confidence interval; N, number of patients in treatment arm with available blood pressure data; n, number of patients with indicated blood pressure; RD, risk difference.
1 Includes DBP assessments 30 minutes post-infusion and 60 minutes post-infusion.
2 Includes trial 1629 DBTP and trial 1643 DBTP. Duration = 24 weeks.
3 Includes evinacumab 5 mg/kg IV Q4W and 15 mg/kg IV Q4W.
4 Difference is shown between evinacumab 15 mg/kg and placebo.
5 On same study visit.

Reference ID: 4745518

Figure 10. Mean Change in Heart Rate Over Time by Treatment Group, Safety Population, Placebo-Controlled Pool



Source: advs.xpt; Software: JMP.
Abbreviations: AVISIT, study visit; TRT1A, actual treatment received.

Table 52. Percentage of Patients Experiencing Given Category of Heart Rate, Post-Baseline[1], Safety Population, Placebo-Controlled Pool[2]

Heart Rate (bpm)	Evinacumab 5 mg/kg N=36	Evinacumab 15 mg/kg N=81	Evinacumab All[3] N=117	Placebo N=54	Absolute RD (95% CI)[4]
≤50 and decrease from BL ≥10	2 (5.6%)	2 (2.5%)	4 (3.4%)	2 (3.7%)	-1.2% (-7.3%, 4.8%)
≥100 and increase from BL ≥10	1 (2.8%)	6 (7.4%)	7 (6.0%)	1 (1.9%)	5.6% (-1.2%, 12.3%)

Source: advs.xpt; Software: JMP.
Abbreviations: BL, baseline; bpm, beats per minute; CI, confidence interval; N, number of patients in treatment arm with available blood pressure data; n, number of patients with indicated heart rate; RD, risk difference.
1 Any time post-baseline. Includes HR assessments pre-infusion, 30 minutes post-infusion, and 60 minutes post-infusion.
2 Includes trial 1629 DBTP and trial 1643 DBTP. Duration = 24 weeks.
3 Includes evinacumab 5 mg/kg IV Q4W and 15 mg/kg IV Q4W.
4 Difference is shown between evinacumab 15 mg/kg and placebo.

Reference ID: 4745518

Table 53. Percentage of Patients Experiencing Given Category of Heart Rate, Post-Infusion[1], Safety Population, Placebo-Controlled Pool[2]

Heart Rate (bpm)	Evinacumab 5 mg/kg N=36	Evinacumab 15 mg/kg N=81	Evinacumab All[3] N=117	Placebo N=54	Absolute RD (95% CI)[4]
≤50 and decrease from BL ≥10	1 (2.8%)	2 (2.5%)	3 (2.6%)	2 (3.7%)	-1.2% (-7.3%, 4.8%)
≥100 and increase from BL ≥10	0 (0.0%)	4 (4.9%)	4 (3.4%)	0 (0.0%)	4.9% (0.2%, 9.7%)
≥100 and increase from BL ≥10, 30 min post-infusion	0 (0.0%)	2 (2.5%)	2 (1.7%)	0 (0.0%)	2.5% (-0.9%, 5.8%)
≥100 and increase from BL ≥10, 60 min post-infusion	0 (0.0%)	3 (3.7%)	3 (2.6%)	0 (0.0%)	3.7% (-0.4%, 7.8%)
≥100 and increase from BL ≥10; and pre-dose <100	0 (0.0%)	4 (4.9%)	4 (3.4%)	0 (0.0%)	4.9% (0.2%, 9.7%)

Source: advs.xpt; Software: JMP.
Abbreviations: BL, baseline; bpm, beats per minute; CI, confidence interval; N, number of patients in treatment arm with available blood pressure data; n, number of patients with indicated heart rate; RD, risk difference.
1 Includes HR assessments 30 minutes post-infusion and 60 minutes post-infusion.
2 Includes trial 1629 DBTP and trial 1643 DBTP. Duration = 24 weeks.
3 Includes evinacumab 5 mg/kg IV Q4W and 15 mg/kg IV Q4W.
4 Difference is shown between evinacumab 15 mg/kg and placebo.

Table 54. Individual Patients with Heart Rate Elevation ≥100 and Increase from Baseline ≥10, Post-Infusion[1], Safety Population, Placebo-Controlled Pool[2]

USUBJID	Treatment Arm	Study Visit	Pre-Infusion HR (bpm)	30 Min Post-Infusion HR (bpm) (Mean Change from Pre-Infusion)	60 Min Post-Infusion HR (bpm) (Mean Change from Pre-Infusion)
(b) (6)	Evinacumab 15 mg/kg	Week 8	68	85 (17)	104 (36)
	Evinacumab 15 mg/kg	Week 24	51	105 (54)	70 (19)
	Evinacumab 15 mg/kg	Week 20	60	103 (43)	100 (40)
	Evinacumab 15 mg/kg	Week 6	91	89 (-2)	101 (10)

Source: advs.xpt; Software: JMP.
Abbreviations: bpm, beats per minute; HR, heart rate; USUBJID, unique subject identification.
1 Includes HR assessments 30 minutes post-infusion and 60 minutes post-infusion.
2 Includes trial 1629 DBTP and trial 1643 DBTP. Duration = 24 weeks.

Reference ID: 4745518

8.4.8. Electrocardiograms (ECGs)

ECGs were obtained at baseline and Week 24 in trials contributing to the placebo-controlled pool. Changes in ECG parameters were assessed descriptively using measures of central tendency and categorically.

There was no evidence to suggest a proarrhythmic effect of evinacumab.

Table 55. Change in ECG Parameters from Baseline to Week 24, Placebo-Controlled Pool[1]

Parameter	Study Visit	Evinacumab 15 mg/kg N=81			Placebo N=54			Absolute Difference in Mean Change
		n(%) at Visit	Mean (SD)	Mean Change from Baseline (SD)	n(%) at Visit	Mean (SD)	Mean Change from Baseline (SD)	
QTcF (msec)	Week 24	75	413.1 (30.5)	3.2 (21.4)	51	426.7 (74.4)	7.4 (99.2)	-4.2
PR duration (msec)	Week 24	75	165.1 (35.4)	-1.1 (21.8)	51	163.8 (21.9)	-3.9 (66.4)	2.8
QRS duration (msec)	Week 24	75	92.6 (15.0)	0.3 (6.5)	51	92.7 (10.1)	-6.0 (45.5)	6.3
QT duration (msec)	Week 24	75	399.5 (32.5)	1.2 (25.8)	51	407.5 (31.7)	1.3 (29.3)	-0.1
RR duration (msec)	Week 24	75	911.2 (121.9)	-16.1 (125.3)	51	903.5 (214.4)	-29.9 (229.0)	13.8
			N=75 n(%)			**N=50 n(%)**		**Absolute RD (95% CI)**
Abnormal ECG[2]	Week 24		27 (36.0%)			18 (36.0%)		0.0% (-17.2%, 17.2%)
Clinically significant	Week 24		1 (1.3%)			0 (0.0%)		1.3% (-1.3%, 3.9%)
Not clinically significant	Week 24		26 (34.7%)			18 (36.0%)		-1.3% (-18.5%, 15.8%)

Source: adeg.xpt; Software: JMP.
Abbreviations: CI, confidence interval; QTcF, Fridericia's correction; RD, risk difference; SD, standard deviation.
1 Includes trials 1629 DBTP and 1643 DBTP.
2 As reported by investigator.

8.4.9. QT

No thorough QT study was conducted. The Division previously agreed to this during a Type C guidance meeting after input from the QTc review team.

Reference ID: 4745518

8.4.10. Immunogenicity

Development of ADA was assessed throughout all trials. No ADA were observed in any trial.

The Office of Biotechnology Products (OBP) determined that the immunogenicity assays, screening, confirmatory, and neutralizing activity assays were adequately validated for ADA detection. Refer to Dr. Chung's review for a review of product quality data.

Reference ID: 4745518

8.5. Analysis of Submission-Specific Safety Issues

Adverse events of special interest included events of concern based on evinacumab's chemical/physical structure (monoclonal antibody) and events of theoretical concern based on other lipid-lowering therapies. Definitions used to identify AESI are described in Section 8.3.2.

Table 56. Incidence of Treatment-Emergent Adverse Events of Special Interest, Placebo-Controlled Pool[1]

	Evinacumab 5 mg/kg N=36 n(%)	Evinacumab 15 mg/kg N=81 n(%)	Evinacumab All[2] N=117 n(%)	Placebo N=54 n(%)	Absolute Risk Difference (95% CI)[3]
Anaphylactic reaction	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
Infusion reaction	3 (8.3%)	6 (7.4%)	9 (7.7%)	2 (3.7%)	3.7% (-3.9%, 11.3%)
General allergic reaction	4 (11.1%)	9 (11.1%)	13 (11.1%)	6 (11.1%)	0.0% (-10.8%, 10.8%)
Immune complex disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Hepatic disorder event	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Musculoskeletal event	11 (30.6%)	17 (21.0%)	28 (23.9%)	11 (20.4%)	0.6% (-13.3%, 14.5%)
Neurocognitive or neurologic event	0 (0.0%)	1 (1.2%)	1 (0.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
New-onset T2DM[4]	1 (3.0%)	1 (1.4%)	2 (1.9%)	0 (0.0%)	1.2% (-1.2%, 3.6%)
Worsening T2DM[5]	0 (0.0%)	1 (14.3%)	1 (10.0%)	3 (42.9%)	-4.3% (-10.9%, 2.2%)
Pancreatitis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.0% (0.0%, 0.0%)
Cataract	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)	1.2% (-1.2%, 3.6%)

Source: Applicant, ISS.
Abbreviations: CI, confidence interval; T2DM, type 2 diabetes mellitus.
1 Includes trial 1629 DBTP and trial 1643 DBTP. Duration = 24 weeks.
2 Includes evinacumab 5 mg/kg IV Q4W and 15 mg/kg IV Q4W.
3 Difference is shown between evinacumab 15 mg/kg and placebo.
4 Amongst patients with no history of T2DM at baseline; denominators = 33 in evinacumab 5 mg/kg arm, 74 in evinacumab 15 mg/kg arm, 107 in evinacumab all arm, and 47 in placebo arm.
5 Amongst patients with history of T2DM at baseline; denominators = 3 in evinacumab 5 mg/kg arm, 7 in evinacumab 15 mg/kg arm, 10 in evinacumab all arm, and 7 in placebo arm.

Selected AESI are described in additional detail in the sections below.

Reference ID: 4745518

8.5.1. Anaphylactic Reaction

A single case of anaphylactic reaction, which occurred within five minutes of evinacumab 15 mg/kg infusion initiation and resolved with infusion discontinuation and oral diphenhydramine, was previously discussed under SAEs (Section 8.4.2). The event responded promptly to infusion interruption, required no further intervention, and had no prolonged sequelae.

Evinacumab is associated with hypersensitivity, including anaphylaxis. The risk is considered clinically monitorable since drug is administered during a healthcare encounter.

8.5.2. Infusion Reactions

Infusion reactions were identified by investigator report. Investigators were instructed to suspect infusion reaction when the following AEs occurred during an infusion or two hours post-infusion: visual impairment, infusion site pruritus, fatigue, pyrexia, facial edema, infusion site hypoesthesia, anaphylactic reaction, laryngeal/pharyngeal edema, severe bronchospasm, chest pain, seizure, severe hypotension, muscular weakness, headache, somnolence, nasal congestion, rash, or vascular pain.

Infusion reactions occurred more frequently with evinacumab treatment than with placebo (7.7% vs. 3.7%). Two patients (1.7%) experienced an infusion reaction leading to permanent drug discontinuation – the previously-described patient who experienced anaphylaxis at day 28 (Sections 8.4.2 and 8.5.1) and a second patient who developed a rash after an initial dose of evinacumab 5 mg/kg IV. All infusion reactions were mild to moderate. Because infusion reactions also occurred in the placebo arm, this suggests that some reactions may be due to excipients. However, the observed risk difference of 4.0% likely reflects the true incidence of evinacumab-related infusion reactions.

Reference ID: 4745518

Table 57. Infusion Reactions[1], Safety Population, Placebo-Controlled Data[2]

Trial	Patient	Arm	PT	Severity	SAE	Associated Dose	Infusion Interruption	Infusion Resumed	Required Treatment	Permanently D/C'ed Drug
1629 DBTP	1.	Evinacumab 15 mg/kg	Infusion site pruritus	Moderate	No	1st dose	Yes	Yes	No	No
	2.	Evinacumab 15 mg/kg	Infusion site pruritus	Mild	No	2nd and 4th dose	No	-	No	No
	3.	Evinacumab 15 mg/kg	Pyrexia, vascular pain	Mild	No	3rd dose	No	-	No	No
			Muscular weakness	Mild	No	4th dose	No	-	No	No
	4.	Placebo	Infusion site hypoesthesia	Mild	No	1st, 2nd, 3rd, 4th, and 5th doses	No	-		No
			Facial edema	Mild	No	2nd dose	No	-	No	No
1643 DBTP	1.	Evinacumab 15 mg/kg	Nausea	Mild	No	1st dose	No	-	No	No
	2.	Evinacumab 15 mg/kg	Anaphylactic reaction	Moderate	Yes	2nd dose	Yes	No	Yes	Yes
	3.	Evinacumab 15 mg/kg	Nasal congestion	Moderate	No	2nd and 5th dose	No	-	Yes	No
	4.	Evinacumab 5 mg/kg	Visual impairment	Mild	No	n/a	No	-	No	No
	5.	Evinacumab 5 mg/kg	Rash	Moderate	No	1st dose	No	-	Yes	Yes
	6.	Evinacumab 5 mg/kg	Fatigue	Mild	No	n/a	No	-	No	No
	7.	Placebo	Headache, somnolence	Mild	No	1st dose	No	-	Yes	No

Source: adae.xpt; Software: JMP.
Abbreviations: DBTP, double-blind treatment period; D/C, discontinue; PT, preferred term; SAE, serious adverse event.
1 As identified by investigators.
2 Includes trials 1629 DBTP and 1643 DBTP. Duration = 24 weeks.

Reference ID: 4745518

Evinacumab is associated with infusion reactions. The risk may lead to drug discontinuation but is clinically monitorable, promptly reversible, and results in no long-term sequelae.

8.5.3. Very Low LDL-C

Nearly 10% of patients taking evinacumab experienced an LDL-C value less than 25 mg/dL (9.4% vs. 0% placebo), and two patients (1.7%) had LDL-C values that dropped below 15 mg/dL. Low LDL-C values occurred at any time point, as early as Week 2, and were generally isolated to a single timepoint. No patients required a treatment pause or treatment discontinuation. Additionally, review of AEs for these patients revealed no convincing evidence of adverse consequence, such as a neurocognitive or neurologic event. One patient experienced mild weakness and one patient experienced mild headache; however, these events were also observed in patients who did not experience an LDL-C below 25 mg/dL and may represent adverse drug reactions related to evinacumab itself rather than sequelae of low LDL-C values.

Overall, data does not support any adverse consequence of dramatic LDL-C reduction or need for treatment interruption in patients experiencing this event.

8.5.4. Myopathy/Rhabdomyolysis

Myopathy/rhabdomyolysis has been associated with other LLT. There were no events of rhabdomyolysis or significant CK elevation identified by the Applicant or by this clinical reviewer. Sensitivity to detect low-incidence AEs may be limited by the small safety database.

8.5.5. Hepatic Dysfunction

Hepatic dysfunction, most notably liver enzyme elevations, are commonly associated with other LLT. There were no events of hepatic impairment or significant LFT elevation identified by the Applicant or by this clinical reviewer. Ability to detect low-incidence AEs may be limited by the small safety database.

8.6. Safety Analyses by Demographic Subgroups

Elderly patients (≥65 years) were more likely to experience an adverse event than younger patients when treated with evinacumab 5 mg/kg or 15 mg/kg compared to placebo. It is plausible that older patients have increased sensitivity to drug adverse reactions due to altered body composition, decreased hepatic and renal function, and potential for concomitant medication interactions. Small sample size and small numbers of AEs limit interpretation of these subgroup data.

There was no effect of evinacumab on AEs by gender, race, or ethnicity.

Reference ID: 4745518

Table 58. Treatment-Emergent Adverse Events by Demographic Subgroup, Placebo-Controlled Pool[1]

Demographic Subgroup	Evinacumab 5 mg/kg N=36		Evinacumab 15 mg/kg N=81		Evinacumab All[2] N=117		Placebo N=54	
	n(%)	N	n(%)	N	n(%)	N	n(%)	N
Any TEAE	**27 (75.0%)**	**36**	**60 (74.1%)**	**81**	**87 (74.4%)**	**117**	**40 (74.1%)**	**54**
Age Group								
<65 years	20 (71.4%)	28	49 (71.0%)	69	69 (71.1%)	97	36 (76.6%)	47
≥65 years	7 (87.5%)	8	11 (91.7%)	12	18 (90.0%)	20	4 (57.1%)	7
Sex								
Female	19 (82.6%)	23	36 (85.7%)	42	55 (84.6%)	65	23 (79.3%)	29
Male	8 (61.5%)	13	24 (61.5%)	39	32 (61.5%)	52	17 (68.0%)	25
Race								
White	24 (72.7%)	33	49 (74.2%)	66	73 (73.7%)	99	29 (67.4%)	43
All Other	3 (100.0%)	3	11 (73.3%)	15	14 (77.8%)	18	11 (100.0%)	11
Ethnicity								
Hispanic	4 (57.1%)	7	3 (75.0%)	4	7 (63.6%)	11	0 (0.0%)	3
Non-Hispanic	23 (79.3%)	29	57 (74.0%)	77	80 (75.5%)	106	40 (78.4%)	51

Source: adsl.xpt, adae.xpt; Software: JMP.
Abbreviations: N, number of patients in treatment group; n, number of patients with specified characteristic; TEAE, treatment-emergent adverse event.
1 Includes trial 1629 DBTP and trial 1643 DBTP. Duration = 24 weeks.
2 Includes evinacumab 5 mg/kg IV Q4W and evinacumab 15 mg/kg IV Q4W.

8.7. Specific Safety Studies/Clinical Trials

This section discusses supportive safety data submitted by the Applicant in the 120-Day Safety Update on September 22, 2020 from ongoing, open-label trials. Included trials are 1629 OLTP (population: HoFH), 1719 (population: HoFH), and 1643 OLTP (population: HeFH or established ASCVD). The planned treatment durations are 24 weeks in trial 1629, 48 weeks in trial 1643, and up to 4 years in trial 1719 (mean treatment duration 22 weeks at the time of submission). Given the variation in treatment duration and the ongoing nature of the trials, incidence and risk differences must be interpreted with caution. As previously described, open-label trial results are presented separately and not pooled to avoid Simpson's paradox and underestimation of risk. Data is presented as of the data cutoff date of June 12, 2020.

Reference ID: 4745518

Table 59. Overview of Treatment-Emergent Adverse Events[1], Safety Population, Open-Label Data[2]

Event		1629 OLTP N=64 n(%)	1719 N=104 n(%)	1643 OLTP N=96 n(%)
Any AE		48 (75.0%)	63 (60.6%)	76 (79.2%)
	Mild	43 (67.2%)	49 (47.1%)	66 (68.8%)
	Moderate	16 (25.0%)	35 (33.7%)	38 (39.6%)
	Severe	5 (7.8%)	9 (8.7%)	6 (6.3%)
Death		0 (0.0%)	2 (1.9%)	0 (0.0%)
SAE		7 (10.9%)	13 (12.5%)	9 (9.4%)
AE leading to permanent drug discontinuation		0 (0.0%)	0 (0.0%)	0 (0.0%)
AE leading to dose interruption		1 (1.6%)	3 (2.9%)	4 (4.2%)

Source: adae.xpt; Software: JMP.
Abbreviations: AE, adverse event; SAE, serious adverse event; N, number of patients in treatment arm; n, number of patients with at least one event; OLTP, open-label treatment period.
1 Treatment-emergent AE defined as an AE that developed or worsened during OLTP. MedDRA version 22.0.
2 Duration = 24-48 weeks for trial 1629, 48-72 weeks for trial 1643 (ongoing), and up to 4 years for trial 1719 (ongoing).

In general, the incidence of overall, mild, and moderate TEAEs in open-label trials was similar to that observed in the 15 mg/kg evinacumab treatment arm of the placebo-controlled pool (Section 8.4). More severe TEAEs were observed in open-label data, but there was no difference in the incidence of SAEs (approximately 10% in placebo-controlled and open-label data).

8.7.1. Deaths

Two deaths occurred in trial 1719. Narratives are presented below.

Table 60. List of All Individual Patient Deaths in Safety Population, Open-Label Data[1]

Subject ID	Age Gender	Treatment Duration (days)	Study Day of Death (days)	Cause of Death	
				MedDRA Preferred Term	Verbatim Term
(b) (6)	54 M	235	235	Cardiac arrest	Sudden cardiac arrest
	54 F	366	366	Myocardial infarction	Cardiac infarction

Source: adae.xpt; Software: JMP.
Abbreviations: F, female; M, male.
1 Duration = 24-48 weeks for trial 1629, 48-72 weeks for trial 1643 (ongoing), and up to 4 years for trial 1719 (ongoing).

Narratives:

- Patient (b) (6) was a 54-year-old male with a past medical history notable for HoFH, hypertension, coronary artery disease s/p CABG, and aortic valve disease s/p valve replacement. The patient's background LLT included colestipol, rosuvastatin, ezetimibe, and alirocumab. During trial 1719, the patient experienced mild AEs of

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influenza-like illness and upper respiratory tract infection (days 45 and 48, respectively). He was also admitted to the hospital and treated for severe community-acquired pneumonia on day 85. On day 235, six days after the 8th dose of evinacumab, the patient experienced sudden cardiac arrest, and CPR was performed. No additional details are provided, and no autopsy was performed.

- Patient (b) (6) was a 54-year-old female with a past medical history notable for HoFH; coronary artery disease s/p MI, PCI, and CABG; and peripheral vascular disease s/p stenting. Her background LLT included atorvastatin, ezetimibe, and alirocumab. The patient was previously enrolled in trial 1629 and rolled into trial 1719. During trial 1719, she experienced moderate coronary artery stenosis on day 192 with a 4-stent PCI performed on day 201, severe chronic mesenteric ischemia secondary to an obstructed mesenteric artery on day 233 with an axillomesenteric bypass performed on day 241 complicated by a grade 3 liver laceration, severe myocardial infarction on day 245 with acute kidney injury on day 246, and insertion of a cardiac pacemaker on day 333. On day 366, the patient experienced another acute myocardial infarction with a peak troponin of 16,773 ng/L and died. No additional details are provided.

In both cases, the causes of death are consistent with the patients' underlying past medical history of extensive cardiovascular disease. The deaths are not likely related to evinacumab exposure.

8.7.2. Serious Adverse Events

In the open-label trials, 44 SAEs were experienced by 29 patients. The incidence of SAEs ranged from 9.4% to 12.5%. SAE incidence was generally consistent with that observed in the placebo-controlled data (Section 8.4.2).

The most frequent SOC involved was cardiac. There was no identifiable pattern to cardiac SAEs, and individual PTs were reported by 1-2 patients only (Table 61). Increased incidence of cardiac SAEs is consistent with the enrolled trial populations, which included established ASCVD in trial 1643 and patients with HoFH in trials 1629 and 1719, rather than with a drug-associated reaction.

Other organ systems experienced only a handful of SAEs with no discernible signal.

Review of patient narratives further corroborated that no SAEs were clearly or possibly related to drug.

Reference ID: 4745518

Table 61. Overview of Serious Adverse Events[1], Safety Population, Open-Label Data[2]

Event	1629 OLTP N=64 n(%)	1719 N=104 n(%)	1643 OLTP N=96 n(%)
SAE	**7 (10.9%)**	**13 (12.5%)**	**9 (9.4%)**
Fatal outcome	0 (0.0%)	2 (1.9%)	0 (0.0%)
Life-threatening	1 (1.6%)	0 (0.0%)	0 (0.0%)
Requiring hospitalization	6 (9.4%)	11 (10.6%)	7 (7.3)
Resulting in substantial disruption of normal life functions	0 (0.0%)	0 (0.0%)	0 (0.0%)
Congenital anomaly or birth defect	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	2 (2.1%)

Source: adae.xpt; Software: JMP.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; OLTP, open-label treatment period.
1 Defined as any untoward medical occurrence at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
2 Duration = 24-48 weeks for trial 1629, 48-72 weeks for trial 1643 (ongoing), and up to 4 years for trial 1719 (ongoing).

Table 62. Patients with Serious Adverse Events[1] by System Organ Class and Preferred Term, Safety Population, Open-Label Data[2]

System Organ Class *Preferred Term*	1629 OLTP N=64 n(%)	1719 N=104 n(%)	1643 OLTP N=96 n(%)
Proportion of patients with SAE	**7 (10.9%)**	**13 (12.5%)**	**9 (9.4%)**
Number of events	**11**	**20**	**13**
Cardiac disorders	**5 (7.8%)**	**10 (9.6%)**	**4 (4.2%)**
Angina unstable	1 (1.6%)	1 (1.0%)	0 (0.0%)
Acute myocardial infarction	1 (1.6%)	0 (0.0%)	0 (0.0%)
Coronary artery disease	1 (1.6%)	1 (1.0%)	0 (0.0%)
Angina pectoris	1 (1.6%)	0 (0.0%)	0 (0.0%)
Cardiac failure congestive	1 (1.6%)	1 (1.0%)	0 (0.0%)
Palpitations	0 (0.0%)	0 (0.0%)	1 (1.0%)
Atrial fibrillation	0 (0.0%)	0 (0.0%)	2 (2.1%)
Supravalvular aortic stenosis	0 (0.0%)	1 (1.0%)	0 (0.0%)
Aortic valve disease	0 (0.0%)	2 (1.9%)	0 (0.0%)
Coronary artery stenosis	0 (0.0%)	1 (1.0%)	0 (0.0%)
Cardiac arrest	0 (0.0%)	1 (1.0%)	0 (0.0%)
Myocardial infarction	0 (0.0%)	1 (1.0%)	0 (0.0%)
Eye disorders	**1 (1.6%)**	**1 (1.0%)**	**0 (0.0%)**
Glaucoma	1 (1.6%)	1 (1.0%)	0 (0.0%)
Gastrointestinal disorders	**0 (0.0%)**	**1 (1.0%)**	**1 (1.0%)**
Gastrointestinal motility disorder	0 (0.0%)	0 (0.0%)	1 (1.0%)
Intestinal ischemia	0 (0.0%)	1 (1.0%)	0 (0.0%)
General disorders and administration	**0 (0.0%)**	**1 (1.0%)**	**1 (1.0%)**
Chest pain	0 (0.0%)	1 (1.0%)	1 (1.0%)
Hepatobiliary disorders	**0 (0.0%)**	**0 (0.0%)**	**1 (1.0%)**
Gallbladder polyp	0 (0.0%)	0 (0.0%)	1 (1.0%)
Infections and infestations	**1 (1.6%)**	**1 (1.0%)**	**1 (1.0%)**
Pyelonephritis	1 (1.6%)	0 (0.0%)	0 (0.0%)

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Coronavirus infection	0 (0.0%)	0 (0.0%)	1 (1.0%)
Pneumonia	0 (0.0%)	1 (1.0%)	0 (0.0%)
Injury, poisoning, and procedural complications	**2 (3.1%)**	**3 (2.9%)**	**0 (0.0%)**
Cardiac procedure complication	1 (1.6%)	0 (0.0%)	0 (0.0%)
Carotid artery restenosis	1 (1.6%)	0 (0.0%)	0 (0.0%)
Cervical vertebral fracture	0 (0.0%)	1 (1.0%)	0 (0.0%)
Vascular pseudoaneurysm	0 (0.0%)	1 (1.0%)	0 (0.0%)
Inaccessible AV fistula	0 (0.0%)	1 (1.0%)	0 (0.0%)
Musculoskeletal and connective tissue	**0 (0.0%)**	**0 (0.0%)**	**1 (1.0%)**
Joint effusion	0 (0.0%)	0 (0.0%)	1 (1.0%)
Neoplasms	**0 (0.0%)**	**0 (0.0%)**	**1 (1.0%)**
Transitional cell carcinoma	0 (0.0%)	0 (0.0%)	1 (1.0%)
Nervous system disorders	**0 (0.0%)**	**0 (0.0%)**	**1 (1.0%)**
Carotid artery stenosis	0 (0.0%)	0 (0.0%)	1 (1.0%)
Renal and urinary disorders	**1 (1.6%)**	**2 (1.9%)**	**0 (0.0%)**
Nephrocalcinosis	1 (1.6%)	0 (0.0%)	0 (0.0%)
Renal infarct	0 (0.0%)	1 (1.0%)	0 (0.0%)
Reproductive system	**0 (0.0%)**	**1 (1.0%)**	**0 (0.0%)**
Ovarian cyst ruptured	0 (0.0%)	1 (1.0%)	0 (0.0%)
Respiratory, thoracic, and mediastinal	**0 (0.0%)**	**0 (0.0%)**	**2 (2.1%)**
Pulmonary embolism	0 (0.0%)	0 (0.0%)	1 (1.0%)
Dyspnea	0 (0.0%)	0 (0.0%)	1 (1.0%)
Vascular disorders	**1 (1.6%)**	**0 (0.0%)**	**0 (0.0%)**
Aortic stenosis	1 (1.6%)	0 (0.0%)	0 (0.0%)

Source: adae.xpt; Software: JMP.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; OLTP, open-label treatment period.
1 Defined as any untoward medical occurrence at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
2 Duration = 24-48 weeks for trial 1629, 48-72 weeks for trial 1643 (ongoing), and up to 4 years for trial 1719 (ongoing).

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Table 63. List of All Individual Patients with Serious Adverse Events in Safety Population, Open-Label Data[1]

Study Arm	Subject ID	Age Gender	Study Day	MedDRA PT	Severity	Action Taken	Outcome
1629 OLTP	(b) (6)	66 M	248	Angina pectoris	Moderate	Dose not changed	Recovered
			385	Glaucoma	Moderate	Dose not changed	Recovered
		68 F	354	Carotid artery restenosis	Moderate	Dose not changed	Recovered
		66 M	351	Congestive cardiac failure	Severe	n/a	Recovering
		51 M	294	Angina unstable	Severe	Dose not changed	Recovered
		38 M	254	Coronary artery disease	Severe	Dose not changed	Recovered
		20 F	173	Nephrocalcinosis	Severe	Dose not changed	Recovered
			188	Pyelonephritis	Severe	Dose not changed	Recovered
		52 F	285	Cardiac procedure complication (verbatim: complication of aortic valve surgery)	Severe	Dose not changed	Recovered
			285	Aortic stenosis (verbatim: worsening of aortic stenosis)	Severe	Dose not changed	Recovered
			303	Acute myocardial infarction	Severe	Dose not changed	Recovered
1643 OLTP		62 M	512	Transitional cell carcinoma	Moderate	n/a	Recovered

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			558	Atrial fibrillation	Moderate	n/a	Not recovered
	(b) (6)	64 F	228	Carotid artery stenosis	Mild	Dose not changed	Recovered
		69 F	392	Palpitations	Severe	Dose not changed	Recovered
			392	Dyspnea	Severe	Dose not changed	Recovered
			398, 402	Atrial fibrillation	Severe	Dose not changed	Recovered
		55 F	404	Gallbladder polyp	Mild	Dose not changed	Recovered
		68 F	267	Gastrointestinal motility disorder	Moderate	Dose not changed	Recovered
		57 F	380	Joint effusion	Severe	Dose not changed	Recovered
		57 M	250	Pulmonary embolism	Severe	Dose not changed	Recovered
		76 M	394	Coronavirus infection	Moderate	Drug interrupted	Recovered
		60 F	432	Chest pain	Severe	Dose not changed	Recovered
1719		54 F	192	Coronary artery stenosis	Moderate	n/a	Recovered
			233	Intestinal ischemia	Severe	n/a	Recovered
			366	Myocardial infarction	Severe	n/a	Fatal
		23 F	129	Supravalvular aortic stenosis	Severe	Dose not changed	Recovered
		66 M	21	Glaucoma	Moderate	Dose not changed	Recovered
		68 F	49	Cervical vertebral fracture	Moderate	Dose not changed	Recovering

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	(b) (6)	66 M	-	Cardiac failure congestive	Severe	n/a	Recovering
		20 F	159	Chest pain	Moderate	Dose not changed	Recovered
		20 F	202	Renal infarct	Severe	Dose not changed	Recovered
			203	Renal infarct	Moderate	Dose not changed	Recovered
		30 F	307	Aortic valve disease	Severe	Dose not changed	Recovered
		40 F	15, 167	Angina unstable	Moderate	Dose not changed	Recovered
		60 M	146	Aortic valve disease	Moderate	Dose not changed	Recovered
			146	Coronary artery disease	Mild	Dose not changed	Recovered
		40 F	152	Ovarian cyst ruptured	Severe	Dose not changed	Recovered
		12 M	47	Inaccessible AV fistula	Severe	Dose not changed	Recovered
			192	Vascular pseudoaneurysm	Severe	Dose not changed	Recovered
		54 M	85	Pneumonia	Severe	Dose not changed	Recovered
			235	Cardiac arrest	Severe	n/a	Fatal

Source: adae.xpt; Software: JMP.
Abbreviations: F, female; M, male; PT, preferred term.
1 Duration = 24-48 weeks for trial 1629, 48-72 weeks for trial 1643 (ongoing), and up to 4 years for trial 1719 (ongoing).

Reference ID: 4745518

8.7.3. Dropouts and/or Discontinuations Due to Adverse Effects

Across the 3 open-label trials, no patient experienced an adverse event that led to permanent drug discontinuation.

8.7.4. Treatment-Emergent Adverse Events and Adverse Reactions

The most frequent adverse events observed in the open-label trials are displayed in Table 64. The safety profile was largely consistent with that previously identified during the DBTP. Additional detected AEs included gastrointestinal-related symptoms (dyspepsia, GERD, diarrhea, gastroenteritis), upper and lower respiratory symptoms (oropharyngeal pain, cough, influenza, sinusitis, bronchitis, respiratory tract infection), neurologic symptoms (headache, insomnia, anxiety), and musculoskeletal symptoms (arthralgia, arthritis, myalgias, muscle spasms). Urinary tract infection and back pain were also commonly observed.

Interpretation of TEAE data is difficult without inclusion of a control arm for comparison. For example, some AEs are common even outside of clinical trials (e.g., back pain) and some AEs may be associated with concomitant LLT (e.g., myalgia). A determination of evinacumab relatedness is unable to be made.

Reference ID: 4745518

Table 64. Patients with Common Treatment-Emergent Adverse Events[1] Occurring at ≥2% Frequency and in ≥3 Patients[2], Safety Population, Open-Label Data[3]

Preferred Term[4]	1629 OLTP N=64 n(%)	1719 N=104 n(%)	1643 OLTP N=96 n(%)	Open-Label Pool[5] N=203 n(%)
Nasopharyngitis	6 (9.4%)	10 (9.6%)	12 (12.5%)	26 (12.8%)
Headache	6 (9.4%)	7 (6.7%)	10 (10.4%)	22 (10.8%)
Influenza-like illness	2 (3.1%)	4 (3.8%)	8 (8.3%)	14 (6.9%)
Urinary tract infection	1 (1.6%)	5 (4.8%)	8 (8.3%)	14 (6.9%)
Upper respiratory tract infection	2 (3.1%)	4 (3.8%)	8 (8.3%)	13 (6.4%)
Back pain	3 (4.7%)	5 (4.8%)	4 (4.2%)	12 (5.9%)
Diarrhea	1 (1.6%)	5 (4.8%)	4 (4.2%)	9 (4.4%)
Nausea	3 (4.7%)	4 (3.8%)	2 (2.1%)	8 (3.9%)
Cough	1 (1.6%)	4 (3.8%)	3 (3.1%)	8 (3.9%)
Influenza	1 (1.6%)	5 (4.8%)	3 (3.1%)	8 (3.9%)
Arthralgia	0 (0.0%)	4 (3.8%)	4 (4.2%)	8 (3.9%)
Gastroenteritis[6]	2 (3.1%)	3 (2.9%)	3 (3.1%)	6 (3.0%)
Abdominal pain[7]	1 (1.6%)	1 (1.0%)	4 (4.2%)	6 (3.0%)
Muscle spasms	2 (3.1%)	3 (2.9%)	1 (1.0%)	6 (3.0%)
Myalgia	0 (0.0%)	3 (2.9%)	3 (3.1%)	6 (3.0%)
Fatigue	0 (0.0%)	1 (1.0%)	5 (5.2%)	6 (3.0%)
Toothache	2 (3.1%)	2 (1.9%)	3 (3.1%)	6 (3.0%)
Pruritus	1 (1.6%)	3 (2.9%)	2 (2.1%)	5 (2.5%)
Gastroesophageal reflux disease	1 (1.6%)	2 (1.9%)	2 (2.1%)	5 (2.5%)
Bronchitis	0 (0.0%)	1 (1.0%)	4 (4.2%)	5 (2.5%)
Chest pain	0 (0.0%)	1 (1.0%)	4 (4.2%)	5 (2.5%)
Insomnia	1 (1.6%)	2 (1.9%)	3 (3.1%)	5 (2.5%)
Anxiety	0 (0.0%)	2 (1.9%)	3 (3.1%)	5 (2.5%)
Dizziness	0 (0.0%)	3 (2.9%)	1 (1.0%)	4 (2.0%)
Sinusitis	0 (0.0%)	1 (1.0%)	3 (3.1%)	4 (2.0%)
Oropharyngeal pain	0 (0.0%)	3 (2.9%)	1 (1.0%)	4 (2.0%)
Oral herpes	1 (1.6%)	1 (1.0%)	3 (3.1%)	4 (2.0%)
Nasal congestion	0 (0.0%)	0 (0.0%)	3 (3.1%)	3 (1.5%)
Respiratory tract infection	0 (0.0%)	0 (0.0%)	3 (3.1%)	3 (1.5%)
Dyspepsia	0 (0.0%)	0 (0.0%)	3 (3.1%)	3 (1.5%)
Blood CPK increased	0 (0.0%)	0 (0.0%)	3 (3.1%)	3 (1.5%)
Coronavirus infection	0 (0.0%)	0 (0.0%)	3 (3.1%)	3 (1.5%)
Osteoarthritis	0 (0.0%)	3 (2.9%)	0 (0.0%)	3 (1.5%)

Source: adae.xpt; Software: JMP.
Abbreviations: CPK, creatine phosphokinase; N, number of patients in treatment arm; n, number of patients with adverse event; OLTP, open-label treatment period.
1 Treatment-emergent AE defined as an adverse event that developed or worsened during the trial. MedDRA version 22.0.
2 Three or more patients within an individual trial or within the open-label pool.
3 Duration = 24-48 weeks for trial 1629, 48-72 weeks for trial 1643 (ongoing), and up to 4 years for trial 1719 (ongoing).
4 Coded as MedDRA preferred terms.
5 Totals do not add up, since some AEs in rollover patients were reported in trial 1629 OLTP and trial 1719.
6 Includes gastroenteritis and gastroenteritis viral.
7 Includes abdominal pain, abdominal pain lower, and abdominal discomfort.

Reference ID: 4745518

Infusion reactions occurred in 10 patients, with an incidence of 3.1% to 4.7% across individual trials. The lower incidence, when compared to infusion reactions experienced by 7.7% of evinacumab patients in the placebo-controlled pool, is likely due to selection bias in the open-label trials. Patients only entered the OLTP or rolled into trial 1719 if they successfully tolerated evinacumab during the DBTP.

No patients experienced an infusion reaction leading to permanent drug discontinuation. Two patients required a temporary infusion interruption but were able to successfully complete the infusion on the same day. Two patients required treatment with an antihistamine. All infusion reactions were mild to moderate. No cases of anaphylaxis were observed.

Overall, the open-label data support that evinacumab is associated with infusion reactions. The reactions may occasionally require infusion interruption or discontinuation but are clinically monitorable, promptly reversible, and result in no long-term sequelae.

Reference ID: 4745518

Table 65. Infusion Reactions[1], Safety Population, Open-Label Data[2]

Trial	Patient	Treatment Status	PT	Severity	SAE	Associated Dose	Infusion Interruption	Infusion Resumed	Required Treatment
1629 OLTP	1.	-	Drug hypersensitivity (facial/eyes/hand edema and pruritus)	Moderate	No	1st dose	Yes	Yes	Yes[3]
	2.	-	Abdominal pruritus and rash	Mild	No	1st dose	No	-	No
		-	Asthenia	Mild	No	4th and 6th doses	No	-	No
	3.	-	Generalized pruritus	Moderate	No	2nd dose	No	-	Yes[4]
		-	Generalized pruritus	Mild	No	4th dose	No	-	Yes[4]
1719	1.	Treatment-naïve	Headache, facial edema	Mild	No	1st dose	No	-	No
		Treatment-naïve	Feeling hot, paresthesia	Mild	No	2nd dose	Yes	Yes	No
	2.	Treatment-naïve	Infusion site pruritus	Mild	No	2nd and 3rd doses	No	-	No
	3.	Treatment-naïve	Muscle spasm	Moderate	No	3rd dose	No	-	No
	4.	Rollover	Infusion site discomfort	Mild	No	2nd dose	No	-	No
1643 OLTP	1.	-	Fatigue	Mild	No	1st dose	No	-	No
	2.	-	Malaise	Mild	No	6th and 7th doses	No	-	No
	3.	-	Pain (verbatim: generalized pain)	Mild	No	7th dose	No	-	Yes[5]

Source: adae.xpt; Software: JMP.
Abbreviations: OLTP, open-label treatment period; PT, preferred term; SAE, serious adverse event.
1 As reported by PI.
2 Duration = 24-48 weeks for trial 1629, 48-72 weeks for trial 1643 (ongoing), and up to 4 years for trial 1719 (ongoing).
3 Required treatment with the antihistamine dexchlorpheniramine.
4 Required treatment with the antihistamine bepotastine and topical betamethasone.
5 Instructed to discontinue ezetimibe.

Reference ID: 4745518

8.7.5. Laboratory Findings

Laboratory values were assessed descriptively using measures of central tendency and categorically using clinically meaningful cutoffs.

There were no changes to lab parameters over time associated with evinacumab exposure. Five percent (5%) of patients experienced a CK elevation >5x ULN, and 2% experienced an elevation >10x ULN (Table 68). Without a control arm, however, it is difficult to attribute the elevation to evinacumab given the presence of confounders, such as concomitant LLT, including high-intensity statin, ezetimibe, and PCSK9i. Additionally, amongst the 4 patients who experienced a CK >10x ULN (Table 66), at least 2 had additional confounders beyond LLT, such as strenuous exercise or weightlifting.

Table 66. Individual Patients Experiencing CK >10x ULN, Safety Population, Open-Label Data[1]

Subject ID	Age / Gender	Study Visit (Day)	CK (U/L)	Comments
(b) (6)	15 M	Baseline OL Week 48 (168)	88 2050	Recovered
	32 M	Baseline OL Week 24 (337)	132 3423	Strenuous exercise Recovered
	59 M	Baseline OL Week 36 (423)	267 11,288	Weight lifting Recovered within 12 weeks
	50 M	Baseline OL Week 52 (534)	100 2274	Recovered within 1 week

Source: adlb.xpt, adcm.xpt; Software: JMP.
Abbreviations: CK, creatine kinase; M, male; OL, open-label; ULN, upper limit of normal.
1 Duration = 24-48 weeks for trial 1629, 48-72 weeks for trial 1643 (ongoing), and up to 4 years for trial 1719 (ongoing).

ALT/AST elevations >3x ULN were observed in four patients – 2 patients with ALT/AST elevations and 2 patients with isolated AST elevations. No patient had concomitant bilirubin elevation. In addition to evinacumab, all patients were taking a PCSK9i and statin (3 patients on high-intensity and 1 patient on low-intensity), and two patients were also taking ezetimibe. In all cases, the ALT/AST elevation seemingly resolved without intervention. No patient required evinacumab interruption or discontinuation, and no patient experienced a modification to background LLT. Additional details, such as narrative summaries, were not provided. Without inclusion of a control arm for comparison, it is difficult to determine the relatedness of observed ALT/AST elevations to evinacumab versus background LLT or other alternative etiology.

In summary, both CK and ALT/AST elevations were observed in long-term, open-label trials of evinacumab. However, it remains unclear whether the elevations can be attributed to

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evinacumab or confounders. Placebo-controlled data to 6 months of treatment failed to reveal evidence that evinacumab causes these elevations, although the sample size was limited (N=171). At this time, given the questionable relatedness to evinacumab and presence of alternative etiologies, the observed CK and ALT/AST elevations do not raise concern enough to recommend inclusion in labeling (particularly since such risks are adequately labeled under statins, PCSK9i, and ezetimibe).

Table 67. Mean Change from Baseline Over Time in Laboratory Values, Safety Population, Open-Label Data[1]

Parameter	Study Visit	Evinacumab 15 mg/kg N=202		
		n(%) at Visit	Mean (SD)	Mean Change from Baseline (SD)
Hemoglobin (g/L)	Baseline	114	13.7 (1.3)	-
	Week 48	111	13.6 (1.4)	-0.1 (0.8)
	Week 60	32	14.2 (1.6)	-0.05 (0.0)
	Week 72	9	12.9 (2.1)	-0.2 (1.0)
Hematocrit (%)	Baseline	114	41.3 (4.2)	-
	Week 48	111	41.0 (4.0)	-0.2 (2.5)
	Week 60	32	43.1 (4.2)	-0.06 (3.4)
	Week 72	9	38.9 (5.8)	-1.1 (3.1)
Platelets (10^9/L)	Baseline	113	231.6 (61.2)	-
	Week 48	110	242.8 (64.8)	10.4 (34.3)
	Week 60	32	247.2 (63.3)	8.9 (42.0)
	Week 72	9	248.4 (93.6)	19.0 (51.2)
Creatinine (mg/dL)	Baseline	115	0.8 (0.2)	-
	Week 48	115	0.8 (0.2)	0.02 (0.1)
	Week 60	34	0.8 (0.1)	0.02 (0.1)
	Week 72	9	0.7 (0.2)	-0.01 (0.1)
BUN (mg/dL)	Baseline	115	15.4 (4.8)	-
	Week 48	115	15.7 (4.5)	0.1 (3.6)
	Week 60	34	16.2 (3.9)	0.6 (3.4)
	Week 72	9	15.1 (4.5)	1.1 (5.3)
WBC (10^9/L)	Baseline	114	6.2 (1.9)	-
	Week 48	111	6.1 (1.9)	0.04 (1.2)
	Week 60	32	6.1 (2.0)	0.3 (1.7)
	Week 72	9	5.5 (1.1)	-0.6 (1.1)
Glucose (mg/dL)	Baseline	114	95.5 (16.2)	-
	Week 48	113	100.9 (18.0)	3.6 (10.8)
	Week 60	34	104.5 (21.6)	7.2 (21.6)
	Week 72	9	102.7 (16.2)	-0.7 (9.0)
HbA1c (%)	Baseline	114	5.6 (0.5)	-
	Week 48	116	5.7 (0.6)	0.1 (0.3)
	Week 60	62	5.6 (0.6)	0.03 (0.3)
	Week 72	9	5.7 (0.8)	0.0 (0.3)
ALT (U/L)	Baseline	115	23.4 (13.1)	-
	Week 48	115	23.8 (12.6)	0.4 (11.9)

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	Week 60	34	24.8 (16.8)	4.9 (13.2)
	Week 72	9	20.9 (9.7)	-0.6 (6.9)
AST (U/L)	Baseline	115	21.4 (9.3)	-
	Week 48	115	21.3 (9.6)	-0.1 (9.8)
	Week 60	34	22.5 (12.4)	3.6 (11.1)
	Week 72	9	19.8 (7.1)	0.9 (3.6)
Bilirubin (mg/dL)	Baseline	115	0.6 (0.4)	-
	Week 48	115	0.6 (0.3)	-0.06 (0.2)
	Week 60	34	0.7 (0.3)	-0.02 (0.2)
	Week 72	9	0.6 (0.2)	0.1 (0.2)
Alkaline phosphatase (U/L)	Baseline	114	64.0 (26.0)	-
	Week 48	114	66.5 (25.0)	2.5 (15.5)
	Week 60	34	74.9 (37.9)	5.1 (18.7)
	Week 72	9	56.6 (22.3)	-0.2 (11.5)
CK (U/L)	Baseline	115	134.2 (111.1)	-
	Week 48	115	154.6 (205.8)	20.4 (199.8)
	Week 60	34	117.0 (80.4)	-12.0 (118.8)
	Week 72	9	97.1 (36.5)	13.1 (29.9)
Albumin (g/L)	Baseline	115	43.5 (3.0)	-
	Week 48	115	43.0 (2.8)	-0.5 (2.7)
	Week 60	34	42.9 (2.5)	-0.6 (2.3)
	Week 72	9	43.1 (2.3)	-0.4 (3.4)
Protein (g/L)	Baseline	115	69.6 (4.6)	-
	Week 48	115	69.5 (4.8)	-0.05 (4.1)
	Week 60	34	71.3 (4.7)	0.9 (3.7)
	Week 72	9	69.0 (5.6)	0.2 (4.4)
Uric acid (mg/dL)	Baseline	115	5.3 (1.6)	-
	Week 48	115	5.4 (1.5)	0.09 (0.9)
	Week 60	34	5.6 (1.4)	0.2 (0.7)
	Week 72	9	5.4 (1.5)	0.2 (0.9)

Source: adlb.xpt; Software: JMP.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; HbA1c, hemoglobin A1c; SD, standard deviation; WBC, white blood cell.
1 Duration = 24-48 weeks for trial 1629, 48-72 weeks for trial 1643 (ongoing), and up to 4 years for trial 1719 (ongoing).

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Table 68. Patients with One or More Values Exceeding Specified Levels for Selected Laboratory Tests, Safety Population, Open-Label Data[1]

Parameter		Evinacumab 15 mg/kg N=202 n(%)
Glucose, low (mg/dL)		
	<70	6 (3.0%)
Glucose, high (mg/dL)		
	≥200 random	4 (2.0%)
HbA1c, high (%)		
	>8	2 (1.0%)
CK, high (U/L)		
	>3x ULN	16 (7.9%)
	>5x ULN	9 (4.5%)
	>10x ULN	4 (2.0%)
ALT (U/L)		
	>3x ULN	2 (1.0%)
	>5x ULN	0 (0.0%)
	>10x ULN	0 (0.0%)
AST (U/L)		
	>3x ULN	2 (1.0%)
	>5x ULN	0 (0.0%)
	>10x ULN	0 (0.0%)
Bilirubin, total, high (mg/dL)		
	>1.5x ULN	8 (4.0%)
	>2x ULN	3 (1.5%)
Alkaline phosphatase, high (U/L)		
	>1.5x ULN	1 (0.5%)

Source: adlb.xpt; Software: JMP.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; HbA1c, hemoglobin A1c; ULN, upper limit of normal.
1 Duration = 24-48 weeks for trial 1629, 48-72 weeks for trial 1643 (ongoing), and up to 4 years for trial 1719 (ongoing).

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

No formal clinical trials to assess the carcinogenic effect of evinacumab were conducted.

In the placebo-controlled pool, 0.9% (n=1) of evinacumab patients reported a TEAE in the neoplasm SOC compared to 0% of placebo patients. The reported TEAE, glioblastoma diagnosis, was reported by a single patient only. There is no clinical or nonclinical evidence to suggest a carcinogenic effect of evinacumab.

8.8.2. Human Reproduction and Pregnancy

Based on nonclinical data in rabbits, evinacumab is teratogenic. One patient in trial 1629

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became pregnant two weeks after receiving the first dose of study drug. The patient discontinued drug and delivered a healthy term infant.

The Division of Pediatric and Maternal Health (DPMH) (see consult by Dr. Ceresa in DARRTS dated 11/2/2020; Reference ID: 4695852) recommends issuing a postmarketing requirement (PMR) for a Single-Arm Pregnancy Safety Study in women exposed to evinacumab during pregnancy and a PMR for a milk-only lactation study in lactating women who received therapeutic doses of evinacumab using a validated assay to assess concentrations of evinacumab in breast milk and the effects on the breastfed infant. DPMH also provided labeling recommendations for subsections 5.2, 8.1, 8.2, 8.3, and 17 of labeling in compliance with the PLLR.

DDLO agrees with the pregnancy study but recommends against the lactation study given feasibility concerns. Human IgG is expressed in breast milk, and thus it is highly likely that evinacumab, a human IgG, is also expressed in breast milk. Although pregnant patients may be exposed to evinacumab early in gestation because of its long half-life, it is unlikely that any patient would remain on drug and carry a pregnancy to term given the risk of embryofetal toxicity and labeling language that includes a Warning and Precaution statement and recommendations for pregnancy testing and contraception during evinacumab use. Thus, it would be highly challenging to recruit lactating patients currently taking evinacumab, especially in this exceedingly rare population. Even if one or more patients were successfully recruited to confirm that evinacumab is present in breast milk, it would not be possible to draw meaningful conclusions about the effects on the breastfed infant given the small sample size. DDLO met with DPMH on January 13, 2021 to discuss the lactation study and agreed not to issue a lactation PMR. A lactation study could be considered if evinacumab is subsequently approved for use in a larger population.

8.8.3. Pediatrics and Assessment of Effects on Growth

The Applicant's sought-after indication includes pediatric patients with HoFH. Thirteen adolescent patients, ages 12 to 17 years, were exposed to evinacumab in trials 1629 and 1719.

Refer to the R1500-CL-1719-Pediatric Update in Section 6.3 for a more detailed description of the pediatric database and the duration of exposure to evinacumab.

A total of 13 pediatric participants received at least 1 dose or part of a dose of open-label study treatment (safety analysis set [SAF] for adolescent subpopulation). The data was presented as of the data cutoff date of August 28, 2020. The median duration of evinacumab treatment for the pediatric subpopulation was 32.8 weeks (mean 34.5 weeks), ranging from 4 to 61 weeks. Eleven patients had ≥32 weeks and 3 patients had greater than 48 weeks of treatment exposure.

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There were no deaths, suspected cardiovascular events, or treatment discontinuation in any pediatric patient. No pediatric patients experienced an infusion reaction and no cases of anaphylaxis were reported in study 1719.

Serious Adverse Events

One (1.7%) patient from the Treatment-Naïve group had two SAEs (PT: Vascular pseudoaneurysm, Arteriovenous fistula site complication). Both events were severe and resolved during the treatment period. The patient was a 12-year-old male receiving weekly apheresis via an AV fistula that was initially placed in 2017. On study day 215, the patient was hospitalized for the treatment of a vascular pseudoaneurysm of the AV fistula and had surgical removal of the pseudoaneurysm and surgical superficialization or fistula elevation of the AV fistula. The patient recovered from both events 4 days later on study day 219. Evinacumab was unlikely to be a factor in this SAE.

Treatment-Emergent Adverse Events and Adverse Reactions

The open-label TEAE period was defined as the day of the first open-label study treatment administration to the day of the last open-label study treatment administration + 168 days (24 weeks). As summarized in the table below, TEAEs occurred in 6 (46%) pediatric patients (5 in the Treatment-Naïve and 1 in the Rollover group). The TEAEs were: rhinitis, paronychia, headache, or gastroenteritis viral, each in a different patient; vascular pseudoaneurysm, influenza-like illness, and arteriovenous fistula site complication in 1 patient; and influenza and nasopharyngitis in 1 patient.

The safety profile was consistent with that previously identified during the DBTP. Interpretation of TEAE data is difficult without inclusion of a control arm for comparison and also because of the small sample size. A determination of evinacumab relatedness to adverse events is unable to be made in most cases.

Table 69. Pediatric Patients with Treatment-Emergent Adverse Events[1] by SOC and PT, Safety Population, Study 1719

System Organ Class *Preferred Term*	**Treatment-Naïve** **N=11** **n (%)**	**Rollovers** **N=2** **n (%)**	**Total** **N=13** **n (%)**
Patients with at least one TEAE	5 (45.5%)	1 (50.0%)	6 (46.2%)
General disorders and administration site conditions	1 (9.1%)	0	1 (7.7%)
Influenza like illness	1 (9.1%)	0	1 (7.7%)
Infections and infestations	3 (27.3%)	1 (50.0%)	4 (30.8%)
Gastroenteritis viral	0	1 (50.0%)	1 (7.7%)
Influenza	1 (9.1%)	0	1 (7.7%)
Nasopharyngitis	1 (9.1%)	0	1 (7.7%)

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Paronychia	1 (9.1%)	0	1 (7.7%)
Rhinitis	1 (9.1%)	0	1 (7.7%)
Injury, poisoning and procedural complications	1 (9.1%)	0	1 (7.7%)
Arteriovenous fistula site complication	1 (9.1%)	0	1 (7.7%)
Vascular pseudoaneurysm	1 (9.1%)	0	1 (7.7%)
Nervous system disorders	1 (9.1%)	0	1 (7.7%)
Headache	1 (9.1%)	0	1 (7.7%)

Source: adae.xpt; Software: JMP and Applicant CSR Post-text Table 14.7.1.4A.
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.
1 Treatment-emergent AE defined as an adverse event that developed or worsened during the trial. MedDRA version 22.0.

Adverse Events of Special Interest

AESI results for the pediatric patients include potentially clinically significant values (PCSV) for ALT or AST in 2 adolescent patients (both in the New Evinacumab/Treatment Naïve group) with ALT >2x ULN and ≤3x ULN and ≤2x ULN at baseline. None of the adolescent patients met the criteria for drug-induced liver injury per Hy's law.

- One female patient (b) (6)) developed an ALT elevation of 2.2x ULN (67 U/L at week 24; normal range: 5 – 30 U/L) at the last assessment prior to the cutoff date; baseline ALT was elevated at 55 U/L. No changes to evinacumab were made as a result of the elevation.
- One male patient (b) (6)) developed an ALT elevation of 2.1x ULN (64 U/L and 63 U/L at weeks 16 and 24; normal range: 5 – 30 U/L) at the last 2 assessments prior to the cutoff date; baseline ALT was elevated at 44 U/L. No changes to evinacumab were made due to the elevation. This patient also had a CK elevation, as described below.

PCSV for CK occurred in 3 patients (2 in the New Evinacumab/Treatment Naïve group and 1 in the Continue Evinacumab/Rollover group).

- One male patient (b) (6), described above with an ALT elevation) had a CK elevation of 3.2x ULN (956 U/L at week 8; normal range: 25 – 300 U/L); baseline CK was 295 U/L, and CK was also elevated during screening at 1644 U/L (5.5 x ULN) on study day -7 and 651 U/L (2.2x ULN) on study day -4. The elevation at week 8 was reported to be due to exercise. The CK did subsequently decrease and was 147 U/L at the next study visit at week 16. No changes to evinacumab were made because of the elevation.
- One male patient (b) (6)) had a CK elevation of 4.7x ULN (1408 U/L at week 32; normal range: 25 – 300 U/L) at the last assessment prior to the cutoff date; baseline CK was elevated at 502 U/L. No changes to evinacumab treatment were made because of the elevation.
- One male patient (b) (6)) had a CK elevation of 6.8x ULN (2050 U/L at week 24; normal range: 25 – 300 U/L); baseline CK was within the normal range at 245 U/L. The elevation was reported to be due to intense physical activity during the 48 hours preceding collection of the blood samples. The CK did decrease and was 156 U/L at the next study visit at week 32. No changes to evinacumab treatment were made because of the elevation.

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No pediatric patient experienced AESIs of Anaphylactic Reactions, General Allergic Events, Infusion Reactions, Pregnancy, Symptomatic Overdose, Neurocognitive Events, Neurologic Events, Pancreatitis, Cataracts, Immune Complex Disease, Diabetic Complications, New Onset Diabetes (NOD), Muscle Events, or Hepatic Disorders.

Of the 13 pediatric patients, 12 had at least 1 post-baseline ADA result in the anti-evinacumab antibody assay; one patient in the New Evinacumab group ([redacted] (b) (6)) had only a baseline sample. None of the pediatric patients had a positive response in the ADA assay.

Three patients (two from the New Evinacumab and one from the Continue Evinacumab group) experienced episodes of diastolic blood pressure ≤ 45 mg Hg with decease ≥ 10 mm Hg from baseline. One patient (from the New Evinacumab group) experienced a heart rate ≥ 120 bpm and increase from baseline ≥ 20 bpm. These were isolated post-infusion vital signs changes, and no patient consistently experienced a change after each dosing. No intervention or adverse events were reported as a result of these vital signs changes.

All patients were evaluated for growth and development, including sexual maturation. A review of weight, Tanner staging, and sex hormones did not reveal any significant safety findings; however, the number of patients was too small to make any meaningful assessment of growth and development.

Overall, the open-label data with evinacumab in pediatric patients with HoFH demonstrated an acceptable safety profile and was consistent with that previously observed in the adult population. No new safety findings were identified.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdoses of evinacumab were defined as accidental or intentional overdose of at least two times the intended dose of study drug. No cases of overdose occurred in any trial of evinacumab.

Evinacumab's potential for drug abuse is low based on required administration in a healthcare setting and its low likelihood of crossing the blood-brain barrier.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable.

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8.9.2. Expectations on Safety in the Postmarket Setting

The use and administration of evinacumab in the postmarket setting is anticipated to be generally similar to its use and administration in clinical trials, as evinacumab delivery requires an in-person healthcare encounter for IV infusion. The most serious reactions associated with evinacumab, such as anaphylaxis or infusion reactions requiring intervention, are anticipated to occur during, or within several hours after, infusion administration. Patients will be directly monitored by healthcare personnel during this time.

Most patients in the safety database were taking concomitant high-intensity statin, ezetimibe, and PCSK9i, which mimics the anticipated real-world use of evinacumab. Overall, exposure in the postmarket setting is not expected to increase patient risk in the indicated population of HoFH.

Clinicians may be tempted to prescribe off-label evinacumab for other patient populations requiring LDL-C reduction, such as HeFH or established ASCVD. For patients with HoFH whose hyperlipidemia is generally resistant to other therapies, the magnitude of LDL-C reduction with evinacumab clearly outweighs its risks. However, in other patient populations such as HeFH or established ASCVD, where the urgent need for LDL-C reduction is less, and the treatment effect is comparable to that of other approved therapies (high-intensity statins and PCSK9i), it remains unknown whether the benefit would outweigh the risks. Thus, evinacumab administration should be restricted to patients with HoFH until efficacy and safety are established in other patient populations.

Adolescent patients were included, but not well-represented in the safety database. Although the safety data were limited, evinacumab was well tolerated in the 13 pediatric patients with HoFH in the open-label study R1500-CL-1719, and no new safety concerns were identified. Treatment with evinacumab resulted in clinically meaningful reductions in LDL-C of approximately 50% in the 13 pediatric participants, aged 12 years and older, with HoFH enrolled in the open-label study R1500-CL-1719, regardless of genetic mutations or background LLT (including apheresis). These results are especially meaningful for individuals with mutations (null/null and negative/negative) that cause absent or deficient LDLR activity <15% and are most resistant to other lipid-lowering therapies.

8.9.3. Additional Safety Issues From Other Disciplines

Not applicable.

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8.10. Integrated Assessment of Safety

The primary risks associated with evinacumab are systemic hypersensitivity and teratogenicity.

Systemic Hypersensitivity

Evinacumab is associated with systemic hypersensitivity, including anaphylaxis and infusion reactions, which may be serious, require intervention, or lead to drug discontinuation. Refer to Sections 8.4.2-8.4.3, 8.4.5, 8.5.1-8.5.2, and 8.7.4 for data and analyses.

The risk of hypersensitivity can be mitigated through patient selection, clinical monitoring, and temporary drug interruption. Evinacumab should be contraindicated in patients with known drug hypersensitivity, and a description of the risk should be included in Warnings and Precautions for all other patients. Evinacumab administration will be performed during an in-person healthcare encounter, which ensures that patients will be closely monitored during the time of greatest risk. In clinical trials, hypersensitivity reactions were reversible with infusion cessation.

Overall, the risk of hypersensitivity can be adequately addressed via labeling.

Teratogenicity

Evinacumab is teratogenic based on nonclinical evidence. Clinical exposures to evinacumab in pregnancy are limited. Refer to Section 4.4 and Dr. Haile's pharmacology/toxicology review for additional discussion.

The risk of teratogenicity can be addressed through patient selection and use of contraception. Based on the severity of fetal findings in rabbits and the occurrence at low exposure margins, a Warnings and Precaution for the use of evinacumab in pregnancy is necessary. Refer to Section 10 for additional discussion.

Overall, the risk of teratogenicity can be adequately mitigated with labeling.

Transient Blood Pressure and Heart Rate Changes

Evinacumab is associated with transient changes to vital signs during infusion administration, including increased systolic blood pressure, decreased diastolic blood pressure, and increased heart rate. Changes are temporary and resolve between treatments. There is no evidence of long-term impact on blood pressure or heart rate. Blood pressure and heart rate changes occurred in patients with normal and abnormal baseline values. No patients required intervention.

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Any risk associated with transient blood pressure and heart rate changes can be mitigated with labeling.

Myopathy/Rhabdomyolysis

Myopathy/rhabdomyolysis was identified as a potential evinacumab-associated risk during clinical development, as it is commonly associated with other lipid-lowering therapies. No events of myopathy/rhabdomyolysis were identified in the clinical program. Asymptomatic CK elevations >5x and >10x ULN were observed in open-label data at low incidence (in patients with alternative etiologies for elevation, such as concomitant LLT or muscle injury) but were not observed in placebo-controlled data. Overall, the evidence does not support that evinacumab is associated with myopathy, rhabdomyolysis, or CK elevation. Refer to Sections 8.4.6, 8.5.4, and 8.7.5.

Hepatic Dysfunction

Hepatic dysfunction was identified as a possible evinacumab-associated risk during clinical development based on the routine association of other lipid-lowering therapies with liver enzyme elevations. No adverse events of hepatic dysfunction or hepatic disorders occurred in any trial of evinacumab. Asymptomatic ALT/AST elevations >3x ULN were observed at low incidence in open-label trials but not in placebo-controlled trials. Overall, the evidence does not support an association between evinacumab treatment and hepatic dysfunction. Refer to Sections 8.4.6, 8.5.5, and 8.7.5 for additional discussion.

Decreased HDL-C

Decreased HDL-C with evinacumab exposure was identified as a concern during clinical development and at the start of the BLA review. However, the observed benefit of LDL-C reduction in a patient population at risk for CV events beginning in the 2nd decade of life and early-onset CV death, outweighs any theoretical risk associated with HDL-C reduction, particularly given the unclear nature of the HDL-C / CV risk relationship. Refer to Section 6.1.2 for additional discussion.

Very Low LDL-C

Very low LDL-C values, to <25 mg/dL or <15 mg/dL, was identified as a potential concern at the start of the BLA review. Although evinacumab is associated with very low LDL-C in approximately 10% of patients, data does not support any adverse consequence associated with this lowering. Refer to Section 8.5.3 for primary data and analyses.

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Conclusion

The major risks associated with evinacumab treatment are hypersensitivity, including anaphylaxis and infusion reactions, and teratogenicity. Transient increases in blood pressure and heart rate during evinacumab infusion were also observed but are not anticipated to require intervention. Other adverse reactions observed with evinacumab exposure include upper respiratory and flu-like symptoms, nausea, and dizziness. With the exception of teratogenicity, evinacumab's adverse reaction profile is typical for a monoclonal antibody. Theoretical risks associated with evinacumab's mechanism of action also include decreased HDL-C and very low LDL-C, although no evidence of adverse consequence was observed in clinical trials.

Evinacumab does not appear to be associated with adverse reactions commonly associated with other lipid-lowering therapies, including myopathy, rhabdomyolysis, or CK elevation; hepatic dysfunction or liver enzyme elevations; neurocognitive events; or elevated HbA1c and fasting plasma glucose (FPG).

The primary limitations of evinacumab's safety evaluation are the limited sample size and lack of long-term exposure data (although data collection remains ongoing).

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee was not planned.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Prescribing Information (PI)

A complete labeling review was conducted separately and incorporated into the draft label sent to the Applicant. Major recommendations on the Applicant's submitted PI include:

- Addition of Limitation of Use statements to indicate that evinacumab has not been investigated in patient populations outside of HoFH and that its effect of CV morbidity and mortality is unknown
- Recommendation on the timing of LDL-C assessment in Dosage and Administration
- Inclusion of additional details under Warnings and Precautions, Hypersensitivity Reactions
- Addition of Embryo-Fetal Toxicity to Warnings and Precautions
- Revision to Adverse Reactions to include only those observed with the to-be-marketed

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dose of 15 mg/kg
- Addition of infusion reactions and transient changes to blood pressure and heart rate as separate subheadings in Adverse Reactions
- Revision to the description of genetic variants in Section 14
- Revision to Section 14 to omit reference to open-label data
- Removal of categorical LDL-C endpoints from Section 14 of labeling
- Removal of Forest plot displaying subgroup analyses given the lack of meaningful differences
- Addition of pediatric data from the open-label extension study

Patient Labeling

Changes to the Applicant's submitted patient labeling materials should include:

- Limitation of Use disclaimer
- Inclusion of language on pregnancy testing

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not deemed necessary. The risks of evinacumab can be adequately mitigated through product labeling.

12. Postmarketing Requirements and Commitments

The following PMR will be issued:

> Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to evinacumab during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The study will collect information for a minimum of 10 years. Results will be analyzed and reported descriptively.

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13. Appendices

13.1. References

Medical and scientific literature is referenced throughout the document.

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13.2. Financial Disclosure

The Applicant adequately disclosed financial interests/arrangements with investigators. One sub-investigator, participating in trials 1629 and 1719, received a total of $38,032 for speaker programs and consulting agreements from 01/01/2018 to 04/12/2020. This sub-investigator's site enrolled 1 patient in trial 1629 and 0 patients in trial 1719 (trial is ongoing). No other investigators held financial interests or were sponsor employees.

Based on the study design (use of objective endpoints, double-blind masking in trial 1629, randomized treatment allocation via IVRS, independent DMC) and the sub-investigator's minimal contribution to study data, no questions are raised about data integrity.

Covered Clinical Study (Name and/or Number): R1500-CL-1629, R1500-CL-1719

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 100 in trial 1619, 119 in trial 1719		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 One sub-investigator received a total of $38,032 for speaker programs and consulting agreements from 01/01/2018 – 04/12/2020. Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Reference ID: 4745518

13.3. Verbatim to PT Coding of Adverse Events

Verbatim Term	Preferred Term	Remove PT?	Add
ACUTE CORONARY ARTERY DISEASE (UNSTABLE ANGINA)	Coronary artery disease	no	angina unstable
CHRONIC ASYMPTOMATIC CYSTITIS	Cystitis	yes	interstitial cystitis
DRUG ALLERGY (SKIN ITCH)	Drug hypersensitivity	no	pruritus
INTERCOSTAL PAIN	Musculoskeletal chest pain	yes	intercostal pain
INTERMITTENT BILATERAL LEG PAIN OF THIGHS & CALVES	Pain in extremity	no	myalgia
MUSCLE SORENESS FROM FALL	Myalgia	no	fall
PAIN IN LOWER LEFT CALF	Pain in extremity	no	myalgia
RED SKIN RESPONSE WHERE BANDAIDS AND WHERE IV TUBING WAS STABILIZED	Infusion site erythema	yes	application site erythema

Source: Clinical reviewer, adae.xpt; Software: JMP.

Reference ID: 4745518

13.4. Neurocognitive Disorders CMQ

MedDRA level	MedDRA Term Label
PTCD	Amnesia
PTCD	Amnestic disorder
PTCD	Anterograde Amnesia
PTCD	Behavioural and Psychiatric Symptoms of Dementia
PTCD	Change in sustained attention
LLTCD	Cognitive Deterioration
PTCD	Cognitive Disorder
LLTCD	Confusion
LLTCD	Confusion Aggravated
PTCD	Confusional State
PTCD	Delirium
PTCD	Dementia
PTCD	Dementia Alzheimer's type
LLTCD	Dementia Nos
LLTCD	Dementia Nos Aggravated
LLTCD	Dementia of the Alzheimer's type NOS
PTCD	Dementia with Lewy Bodies
PTCD	Disorientation
PTCD	Disturbance in attention
PTCD	Executive dysfunction
PTCD	Frontotemporal Dementia
LLTCD	Global Amnesia
PTCD	Illogical Thinking
PTCD	Impaired reasoning
PTCD	Incoherent
PTCD	Judgement impaired
PTCD	Memory Impairment
PTCD	Mental Impairment
LLTCD	Mental Impairment Nos
LLTCD	Mental State Abnormal Aggravated
PTCD	Mental Status Changes
PTCD	Mini Mental Status Examination Abnormal
PTCD	Presenile Dementia
PTCD	Retrograde Amnesia
PTCD	Senile Dementia
LLTCD	Senile Dementia Nos
LLTCD	Short-term Memory Loss
PTCD	Thinking Abnormal
LLTCD	Thinking Slowed
PTCD	Transient Global Amnesia
PTCD	Vascular Dementia

Source: Applicant, ISS Statistical Analysis Plan.

Reference ID: 4745518

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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02/11/2021 10:33:07 AM

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02/11/2021 10:38:36 AM