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RESEARCH**

APPLICATION NUMBER:

761181Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	John Sharretts
Subject	Deputy Division Director Summary Review
BLA #	BLA 761181
Applicant	Regeneron Pharmaceuticals, Inc.
Date of Submission	June 11, 2020
PDUFA Goal Date	February 11, 2021
Proprietary Name	Evkeeza
Established or Proper Name	Evinacumab-dgnb (formerly REGN1500)
Dosage Form(s)	Injection, for intravenous use
Applicant Proposed Indication(s)/Population(s)	as an adjunct to diet and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adult and adolescent patients aged 12 years and older with homozygous familial hypercholesterolemia (HoFH)
Action or Recommended Action:	<i>(Approval vs. Complete Response)</i>
Approved/Recommended Indication(s)/Population(s) (if applicable)	<i>as an adjunct to other low-density lipoprotein-cholesterol (LDL-C)-lowering therapies for the treatment of adult and pediatric patients, aged 12 years and older, with homozygous familial hypercholesterolemia (HoFH)</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Laura Higginbotham, M.D., M.P.H. Eileen Craig, M.D.
Statistical Review	Kyunghee K. Song, Ph.D.
Pharmacology Toxicology Review	Lydia Haile, Ph.D.
OPQ – Application Team Lead	Chana Fuchs, Ph.D.
OPQ – OBP	Jee Chung, Ph.D.
OPQ - Labeling	Vicky Borders-Hemphill, Pharm.D.
OPQ - Facilities	Wayne Seifert Thuy Thanh Nguyen, Ph.D.
Microbiology Review	Zhong Li, Ph.D. Wayne Seifert Candace Gomez-Broughton, Ph.D.
Clinical Pharmacology Review	Sze W. Johnny Lau, Ph.D. Jihye Ahn, Ph.D. Katarzyna Drozda, Pharm.D., M.S.

OPDP	Charuni Shah, Pharm.D.
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OND=Office of New Drugs
 OPQ=Office of Pharmaceutical Quality
 OBP=Office of Biotechnology Products
 OPDP=Office of Prescription Drug Promotion
 OSI=Office of Scientific Investigations
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRM=Division of Risk Management
 DPMH=Division of Pediatrics and Maternal Health

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Homozygous familial hypercholesterolemia (HoFH) is a rare, autosomal-recessive disorder characterized by marked elevations in low-density lipoprotein cholesterol (LDL-C) and increased risk for premature cardiovascular (CV) morbidity and mortality. HoFH results from mutations affecting the function of the LDL-C receptor (LDLR). The diagnosis may be made using clinical criteria or genetic testing.

Patients with HoFH are unable to effectively clear plasma of LDL-C, resulting in persistent, severe hypercholesterolemia beginning in childhood. Patients diagnosed with HoFH may have LDL-C values prior to treatment exceeding 400 to 1000 mg/dL. Clinical manifestations include early onset, progressive atherosclerotic cardiovascular disease (ASCVD), valvular and supra-aortic stenosis, increased risk of CV events, and premature mortality. Physical signs of cholesterol accumulation include cutaneous and tendinous xanthomata and corneal arcus.

The goal of therapy is LDL-C lowering to reduce the risk of ASCVD, CV events, and death. Approved pharmacotherapy includes statins, ezetimibe, evolocumab, and lomitapide, but lipid-lowering therapies do not achieve lipid targets for most patients. HoFH patients do not respond to statins or PCSK9 inhibitors as well as non-HoFH patients, because these drugs act by upregulating the defective LDLR. Use of lomitapide is limited by hepatotoxicity. LDL apheresis may achieve time-averaged substantial LDL-C reductions through repeated sessions but has a high patient burden because of issues such as time, cost, travel, and lack of access.

Evinacumab-dgnb is an angiotensin-like protein 3 (ANGPTL3) inhibitor monoclonal antibody (IgG4 isotype) produced by recombinant DNA technology. The drug product is a sterile, preservative-free solution for intravenous use.

Evinacumab-dgnb binds to and inhibits ANGPTL3, a member of the angiotensin-like protein family expressed primarily in the liver, that regulates lipid metabolism by inhibiting lipoprotein lipase (LPL) and endothelial lipase (EL). Inhibition of ANGPTL3 leads to reduction of LDL-C – independent of the presence of LDL receptor (LDLR) – by promoting EL-mediated very low-density lipoprotein (VLDL) processing and clearance upstream of LDL formation, and reduction of TG and HDL-C by rescuing LPL activity.

The application demonstrates substantial evidence of effectiveness to support approval of evinacumab-dgnb as an adjunct to other LDL-C-lowering therapies for the treatment of adult and pediatric patients, aged 12 years and older, for treatment of HoFH.

The application relies on a single adequate and well-controlled clinical investigation, the double-blind treatment period (DBTP) of Study R1500-CL-1629 (Study 1629), plus confirmatory evidence from the open-label trials, Study 1629 OLTP (open-label treatment period) and Study R1500-CL-1719. The randomized, controlled trial 1629 DBTP is highly persuasive, having demonstrated a large treatment effect on LDL-C, a highly statistically significant result, and consistent changes on secondary lipid endpoints. The statistical methods used by the applicant were acceptable. The FDA statistical reviewer confirmed the results of the primary endpoint and key secondary endpoints.

Percent change from baseline in LDL-C has served as the basis for conventional approval of other products intended to treat patients with HoFH. The treatment effect with evinacumab-dgnb was observed in patients with elevated LDL-C despite maximally tolerated lipid-lowering therapy and was similar across important subgroups.

The applicant provided confirmatory evidence of effectiveness from Study 1629 OLTP. The observed effect in treatment-naïve patients who crossed over to evinacumab-dgnb during the open-label extension period appeared similar to the effect observed in the randomized, controlled trial, although the open-label design, lack of control group, and missing data limit the interpretability of these data somewhat. Study 1719 provided additional evidence of the durability of the treatment effect and supportive efficacy data in pediatric patients. Pediatric efficacy data support expanding the indication to include pediatric patients aged 12 years and older.

The major risks associated with evinacumab-dgnb treatment are hypersensitivity reactions, including anaphylaxis and infusion reactions.

The most frequently observed adverse reactions occurring with evinacumab-dgnb and more frequently than with placebo include upper respiratory symptoms (such as nasopharyngitis, rhinorrhea, and nasal congestion), influenza-like illness, upper respiratory tract infection, dizziness, constipation, and abdominal pain. Transient decreases in diastolic blood pressure and increases in heart rate occurred more frequently during evinacumab-dgnb infusion than placebo infusion but are not anticipated to require intervention. Nevertheless, prescribers should be made aware of these relatively common findings.

Evinacumab-dgnb is teratogenic based on nonclinical evidence. The relevance to humans cannot be excluded. The risk of teratogenicity can be addressed through patient selection and use of contraception. Communication of the risks in labeling is necessary because of severity of fetal findings in rabbits and the occurrence at low exposure margins.

The potential risks do not outweigh the benefits in patients with HoFH. The small size of the safety database is a concern; however, despite the uncertainty, the benefit-risk consideration remains favorable because of the magnitude of the treatment effect in this rare population with high unmet medical need. Safety concerns are monitorable, generally reversible with treatment discontinuation, and may be adequately addressed in labeling.

It remains unknown whether the benefit-risk consideration would be favorable in other patient populations. Additional studies would be necessary to support other indications.

All other review disciplines support approval. The nonclinical findings of embryofetal toxicity, observed in a developmental toxicity study in rabbits, warrant inclusion in labeling, along with recommendations for pregnancy testing and contraception. The clinical pharmacology data are adequate. The dose selection is acceptable, and no dose adjustments are needed for intrinsic or extrinsic factors. Clinical inspections support the validity of the data in the randomized, placebo-controlled trial and the open-label extensions. The chemistry, manufacturing, and controls data and facilities inspections are adequate to support approval. The product quality team requested a postmarketing commitment to provide data from one media fill to support (b) (4) drug product manufacture.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> • Homozygous familial hypercholesterolemia (HoFH) is a rare autosomal recessive disease characterized by marked elevations of low-density lipoprotein cholesterol (LDL-C), caused by genetic mutations that affect the function of the LDL receptor (LDLR). <ul style="list-style-type: none"> ○ Estimated prevalence of 1 in 1,000,000 individuals or approximately 350 patients in the U.S. ○ Most common gene mutations result in defects in LDLR, apolipoprotein B-100 (ApoB-100), or LDL receptor adaptor protein-1 (LDLRAP1), or gain-of-function mutations of proprotein convertase subtilisin/kexin 9 (PCSK9) • Decreased expression or impaired function of the LDLR results in ineffective plasma clearance of LDL-C from the circulation <ul style="list-style-type: none"> ○ Persistent severe hypercholesterolemia (LDL-C >400-500 mg/dL) beginning in childhood ○ Premature atherosclerotic cardiovascular disease (ASCVD), valvular and supra- and sub-aortic stenosis, and CV death ○ Clinical manifestations also include xanthomata and corneal arcus • Decreased life expectancy (20s to mid-40s) without aggressive treatment <ul style="list-style-type: none"> ○ Typically respond poorly to approved lipid-lowering therapies, because most therapies target the defective LDLR 	<p>HoFH is a rare genetic condition that results in persistent severe hyperlipidemia, premature cardiovascular disease, and premature death.</p> <p>There is high unmet medical need in this population.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p>Current Treatment Options</p>	<ul style="list-style-type: none"> • The primary target of therapy is reduction of LDL-C with the goal of reducing atherosclerosis, CV events, and CV death <ul style="list-style-type: none"> ○ Published recommendations vary, but the LDL-C goal typically ranges from LDL-C <135 mg/dL to LDL-C <70 mg/dL or relative reduction of at least 50% from pretreatment baseline values • Approved pharmacotherapy includes: <ul style="list-style-type: none"> ○ Statins (-14% to -30% LDL-C reduction) ○ Ezetimibe (-21% to -27% as add-on to statin) ○ Evolocumab (-31%) ○ Lomitapide (-40%) – boxed warning for hepatotoxicity • LDL apheresis provides effective reduction in LDL-C, however practical factors such as cost, time-consumption, and availability limit its use • Outcomes trials are not feasible in HoFH because the condition is so rare, but LDL-C lowering is expected to reduce the risk of CV events and death • LDL-C reduction improves CV outcomes in other populations, including patients with heterozygous familial hypercholesterolemia (HeFH) <ul style="list-style-type: none"> ○ 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 ○ Outcomes trials of the two approved PCSK9 inhibitors demonstrated reduced risk of CV events as an adjunct to statins in patients with established ASCVD or HeFH ○ A single outcomes trials with ezetimibe demonstrated incremental benefit (6% relative risk reduction) with moderate LDL-C lowering as an adjunct to statin in patients with ASCVD 	<p>The goal of therapy is to reduce LDL-C levels with the intent of reducing CV risk.</p> <p>However, many patients with HoFH, especially those with defective synthesis of LDLR (negative or null mutations), respond poorly to traditional lipid-lowering therapies (statins, PCSK9 inhibitors) which typically require a functional LDL-C receptor.</p> <p>Most patients with HoFH are unable to meet lipid targets with available therapies.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	<ul style="list-style-type: none"> • In a 24-week, randomized, double-blind, placebo-controlled trial of patients with HoFH, evinacumab-dgnb as an add-on to background lipid-lowering therapy (including high-intensity statin, ezetimibe, and PCSK9 inhibitor +/- lomitapide or apheresis), lowered LDL-C by 49% compared to placebo • Evinacumab-dgnb'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 • Evinacumab-dgnb also lowered Apo B, TG, non-HDL-C, and TC • The effect of evinacumab-dgnb on cardiovascular morbidity and mortality has not been assessed 	<p>Evinacumab-dgnb has a large LDL-C reduction treatment effect, particularly in comparison to currently available therapies for LDL-C reduction in HoFH.</p> <p>Evinacumab-dgnb reduces LDL-C independent of the LDLR. In the clinical trial, evinacumab-dgnb was similarly effective in patients with genetic variants shown or likely to result in very limited LDLR function (either <15% function demonstrated on in vitro assays or mutations likely to have minimal or no LDLR function by genetic analysis).</p> <p>LDL-C reduction in the intended population is expected to result in CV risk reduction.</p>
Risk and Risk Management	<ul style="list-style-type: none"> • The most serious safety issues are hypersensitivity reactions, including anaphylaxis (0.9% evinacumab-dgnb vs. 0% placebo) and infusion reactions (7.7% evinacumab-dgnb vs. 3.7% placebo); in some cases, hypersensitivity reactions required treatment discontinuation • Transient decreases in diastolic blood pressure and increases in heart rate were observed during infusion administration but resolved spontaneously • Common adverse events included upper respiratory symptoms, influenza-like illness, infusion site reactions, and dizziness • Evinacumab-dgnb was not associated with other adverse reactions commonly associated with lipid-lowering therapy, including no signal of myopathy/rhabdomyolysis or liver enzyme abnormalities 	<p>The most concerning risk is hypersensitivity reactions, including anaphylaxis. Evinacumab-dgnb is administered in a healthcare setting, and the risk is clinically monitorable.</p> <p>Other adverse reactions associated with evinacumab-dgnb were generally mild to moderate severity and clinically manageable.</p> <p>All risks associated with evinacumab-dgnb can be adequately addressed through labeling</p>

2. Background

Analysis of Condition

Homozygous familial hypercholesterolemia (HoFH) is a rare, autosomal-recessive disorder characterized by marked elevations in low-density lipoprotein cholesterol (LDL-C) and increased risk for premature cardiovascular (CV) morbidity and mortality. Prevalence of HoFH in the United States is generally estimated as 1 per 1,000,000 persons, or approximately 350 individuals in the U.S., although genetic screening of unselected populations outside the US suggest that the prevalence may be as high as 1 in 160,000 to 1 in 300,000.¹

HoFH results from mutations affecting the function of the LDL-C receptor (LDLR). Approximately 90% of patients have mutations in the *LDLR* gene encoding the LDLR, and more than 1200 genetic variants have been identified. HoFH may also be caused by mutations of other genes encoding factors involved in metabolism of LDL-C, including the *APOB* gene that encodes apolipoprotein B-100 (ApoB-100, the LDLR ligand on LDL particles), and the *LDLRAP1* gene encoding LDL receptor adaptor protein-1 (LDLRAP1). Gain-of-function mutations in proprotein convertase subtilisin/kexin 9 (PCSK9), which regulates expression of the LDLR, are also implicated in HoFH.

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.

The clinical severity of HoFH depends on the residual activity of the LDLR, with less activity resulting in higher LDL-C levels and worse clinical outcomes.² Activity of the LDLR is categorized as null³ or negative⁴ when protein synthesis is defective, and patients with FH may be classified as either receptor negative (typically <2% residual activity) or receptor defective (2% to 25%).⁵ Patients with biallelic null variants are also sometimes described as null-null.⁶ Terminology varies in the literature, including the percentage of residual activity on in vitro assays that defines receptor-negative or null variants.

¹ Nordestgaard BG, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: Consensus Statement of the European Atherosclerosis Society. *Eur Heart J*. 2013; 34:3478–3490.

² Cartier JL, Goldberg AC. Familial Hypercholesterolemia: Advances in Recognition and Therapy. *Prog Cardiovasc Dis*. 2016; 59(2):125–134.

³ Hobbs HH, et al. The LDL receptor locus in familial hypercholesterolemia: mutational analysis of a membrane protein. *Annu Rev Genet*. 1990; 24:133-170.

⁴ Rader DJ, et al. Monogenic hypercholesterolemia: new insights in pathogenesis and treatment. *J Clin Invest*. 2003; 111(12):1795-1803.

⁵ Cuchel M, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. *Eur Heart J*. 2014; 35:2146–2157.

⁶ Raal FJ, et al. Evinacumab for Homozygous Familial Hypercholesterolemia. *N Engl J Med*. 2020; 383(8):711-720.

Clinical manifestations of HoFH include progressive and early heart disease, including premature atherosclerosis, valvular or supraaortic stenosis,⁷ increased risk for cardiovascular events, beginning in the second decade, and life expectancy of 40-50 years in the absence of therapy. Life expectancy of receptor-negative patients may be less than 20 years.

Physical signs of cholesterol accumulation include cutaneous and tendinous xanthomata and corneal arcus, generally presenting in childhood. Cardiac valvular abnormalities such as aortic stenosis and regurgitation commonly present in children or adolescents.

HoFH may be diagnosed by clinical criteria or confirmed with genetic testing.

Current Treatment Options

The goal of therapy in HoFH is LDL-C lowering to reduce the risk of ASCVD, CV events, and death. Treatment guidelines vary, but target LDL-C generally ranges from <135 mg/dL⁸ to <70 mg/dL,^{9,10} depending on age and risk, or alternatively, a relative reduction in LDL-C by $\geq 50\%$ from pretreatment values.¹¹

Approved pharmacotherapy includes statins, ezetimibe, evolocumab, and lomitapide, but lipid-lowering therapies do not achieve lipid targets for most patients. HoFH patients do not respond as well to statins or PCSK9 inhibitors as non-HoFH patients, because these drugs act by upregulating the LDLR. Lomitapide use is limited by hepatotoxicity.

LDL apheresis is an extracorporeal therapy that selectively removes LDL particles from plasma and may achieve time-averaged LDL-C reductions of approximately 50% through repeated sessions, typically performed weekly or biweekly. Use is limited by high patient burden, including time, cost, travel requirements, or lack of access to specialized centers.

Regulatory History

Evinacumab-dgnb is a new biological product not currently marketed in the U.S. The sponsor, Regeneron, opened IND 116398 in November 2012 to evaluate evinacumab-dgnb (then known as REGN1500) for the treatment of (b) (4) HoFH.

The sponsor submitted R1500-CL-1331 (Study 1331), a Phase 2, proof-of-concept study in planned 8 patients (study 1331) in July 2014.

⁷ Kolansky DM, et al. Longitudinal evaluation and assessment of cardiovascular disease in patients with homozygous familial hypercholesterolemia. *Am J Cardiol.* 2008; 102:1438–1443.

⁸ Raal FJ, et al. Familial hypercholesterolemia treatments: Guidelines and new therapies. *Atherosclerosis.* 2018; 277:483-492.

⁹ Catapano AL, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. *Atherosclerosis.* 2016; 253:281-344.

¹⁰ Harada-Shiba M, et al. Guidelines for Diagnosis and Treatment of Familial Hypercholesterolemia 2017. *J Atheroscler Thromb.* 2018; 25(8):751–770.

¹¹ Jacobson, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1--full report. *J Clin Lipidol.* 2015; 9(2):129-69.

In August 2016, the Applicant requested an end-of-phase 2 (EOP2) meeting, which was denied and converted to a Type C meeting because the Phase 2 trial was not complete. At the meeting, held in February 2017, FDA advised the sponsor on the design of a proposed Phase 3 trial R1500-CL-1629 (Study 1629).

A pre-BLA meeting was held in October 2019. Major topics of discussion at both meetings included the size of the safety database at the time of the BLA submission.

In February 2016, FDA granted evinacumab-dgnb Orphan Drug designation for the treatment of HoFH. In March 2017, FDA granted Breakthrough Therapy designation for the treatment of HoFH based on preliminary evidence from the completed Phase 2 trial 1331. FDA granted rolling review for the BLA application in February 2020.

The BLA application was submitted in 3 segments, with the final segment submitted on June 11, 2020. FDA granted Priority Review at the time of filing on August 11, 2020.

3. Product Quality

The Office of Pharmaceutical Quality (OPQ) recommends for approval. In the Integrated Quality Assessment (IQA), the Office of Biotechnology Products (OBP) Application Technical Lead, Dr. Chana Fuchs, concluded that the manufacture and control of the (b) (4) drug substance and drug product are controlled in a manner that is pure and potent for the duration of the shelf-life, and that the BLA is approvable from a product quality, microbiology, and stability assurance perspective. The Facilities team lead, Dr. Thuy Thanh Nguyen, recommends approval from the facility standpoint. I concur with the recommendations. Labeling review was provided by Dr. Vicki Borders-Hemphill, and I concur with her recommendations.

The following summarizes key findings from the IQA.

Evinacumab-dgnb is a recombinant human IgG4 monoclonal antibody of the kappa light chain isotype produced in Chinese Hamster Ovary (CHO) cells. It is a heterodimeric glycoprotein consisting of two 214-amino acid light chains and two 453-amino acid heavy chains covalently linked through inter- and intra-chain disulfide bonds. Each heavy chain is glycosylated at asparagine residue 303. The molecular weight is 146.08 kDa.

Evinacumab-dgnb binds to angiopoietin-like 3 (ANGPTL3) to inhibit its functions. Refer to the nonclinical and clinical pharmacology sections of this review for additional details on the mechanism of action. The potency of evinacumab drug substance and drug product is measured using a cell-free enzymatic bioassay.

(b) (4)

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The container closure system is suitable for evinacumab-dgnb based on stability data and maintenance of closure integrity. The dating period for evinacumab-dgnb drug substance stability is (b) (4) months when stored at (b) (4) °C with limited light exposure. Refer to the Drug Product portion of the OBP review authored by Dr. Chung for details.

The Evkeeza drug product is as a single-dose, sterile, preservative-free solution for IV infusion with two presentations: a 345 mg/vial and a 1200 mg/vial. The required volume from vials is transferred into an IV infusion bag consisting of 0.9 NaCl injection, USP or 5% Dextrose Injection, USP. The final concentration of the diluted solution should be between 0.5 mg/mL and 20 mg/mL. Based on the endotoxin specification for the Evkeeza drug product, the OPQ review team recommends that diluent should be limited to 250 mL per dose in order to achieve a two-fold safety factor for the infused solution. Refer to the Drug Substance and Drug Product microbiology reviews, authored by Dr. Zhong Li and Mr. Wayne Seifert, respectively.

The application provided adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy for the Regeneron Pharmaceuticals, Inc. (FEI: 1000514603) drug substance manufacturing facility, and the facility had recently been inspected for other applications. Because of the COVID-19 pandemic, inspection occurred through a 704(a)(4) records review.

The applicant provided adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination for the (b) (4) drug product manufacturer. The inspection was waived. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage, and the 704(a)(4) process. Refer to the Facilities Review by Dr. Li and Mr. Seifert for details.

OBP concluded that assay and assay parameters (including assay sensitivities, drug tolerance levels, and titer cut-points) used for assessment of the screening, confirmatory, titer, and a neutralizing activity are suitable for the evaluation of the clinical samples. Refer to the Immunogenicity Assay portion of the OBP review by Dr. Chung for details.

The OPQ team requested on postmarketing commitment: Provide data from one media fill using the product-specific container closure system and product specific setup equipment to demonstrate adequate evinacumab drug product (b) (4) manufacture. I concur with the recommendation.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer, Dr. Lydia Haile, concluded that the nonclinical data support approval. Dr. Haile recommends inclusion of the risk for embryofetal toxicity in labeling, because of major fetal malformations absent confounding maternal toxicity observed in a rabbit embryofetal developmental toxicity study. I concur with her recommendations.

The following summarizes the key nonclinical findings. For details, refer to Dr. Haile's review.

Dr. Haile concluded that the nonclinical program was conducted consistent with ICH guidelines. Although pivotal toxicity studies were conducted with subcutaneous administration, most studies included a high-dose group administered evinacumab-dgnb intravenously, consistent with the proposed clinical route of administration.

Animal species were clinically relevant, based on evinacumab-dgnb binding affinity and ANGPTL3 functional activity in vitro, and evidence of pharmacodynamic activity in vivo, i.e., blockage of ANGPTL3-mediated inhibition of LPL and EL, and lipid-lowering effects. Dr. Haile concluded that the LPL-mediated effects on TG and HDL-C were well-characterized, and she agreed that in vivo mechanistic studies (in LDLR-knockout and LDLR/EL-double-knockout models) provided evidence of EL-mediated VLDL-C processing and clearance independent of the LDLR. Dr. Haile also concluded that evinacumab-dgnb did not demonstrate potential for off-target Fc-mediated functions, such as cytotoxicity or complement fixation.

Intravenous pharmacokinetic studies demonstrated nonlinear kinetics at lower concentrations and linear kinetics at higher concentrations. The half-lives of elimination in rats (4 to 6 days) and monkeys (6 to 10 days) were shorter than that in humans (approximately 25 days) but were consistent with half-lives generally observed with human monoclonal antibody therapeutics in those species. The volumes of distribution for evinacumab-dgnb were consistent with the plasma volume. In accordance with current guidance for protein-based therapeutics, tissue distribution, drug metabolism and excretion studies were not conducted.

In repeat-dose toxicology studies in rats and monkeys (administered evinacumab-dgnb weekly via IV and SC dosing for up to 13 and 26 weeks, respectively), effects were consistent with intended pharmacology (TG and HDL lowering). LDL-C levels were unaffected in both species, which could indicate species-specific differences compared to humans or resistance to LDL-C reductions in healthy animals. There were no target organs of toxicity identified with chronic administration. Dr. Haile concluded that the NOAELs for chronic administration of evinacumab-dgnb in rats and monkeys were approximately 1- and 4-fold, respectively, the maximum recommended human dose (MRHD) of 15 mg/kg IV every 4 weeks based on AUC when administered intravenously, and 0.4- and 3-fold the MRHD, respectively, when administered subcutaneously. The NOAELs were assigned based on the absence of toxicity at the highest doses administered.

Evinacumab-dgnb did not affect surrogate markers of male and female fertility in the 6-month chronic toxicology study in sexually-mature male and female monkeys administered doses up to 3-fold MRHD, based on AUC.

In rats, a combined female fertility and early embryonic development and pre- and postnatal developmental study showed no effects on female fertility or early embryo-fetal development or pre- and postnatal development landmarks in the F1 generation. Dr. Haile concluded that

the NOAELs for maternal toxicity, female fertility, and pre- and postnatal toxicity in rats were less than the clinical exposure, based on the absence of adverse effects at the highest dose administered. There were no adverse fetal effects observed in an embryo-fetal development study in rats. The NOAEL for embryofetal developmental toxicity was less than clinical exposures, based on the absence of adverse effects at the highest dose administered.

In the definitive embryofetal development study in rabbits, subcutaneous evinacumab-dgnb administration during the period of organogenesis resulted in dose-dependent increases in the incidence of major fetal malformations (including internal hydrocephaly, characterized by domed heads and dilation of the lateral and third ventricles of the brain, and flexed fore/hind paws) at clinically relevant exposures. Notably, these particular findings occurred in the absence of maternal toxicity in a dose-range finding rabbit study and occurred at doses resulting in less than clinical exposures. Dr. Haile concluded that the NOAEL for drug-related major fetal malformations was less than the clinical exposure. Other fetal malformations observed in the definitive embryofetal developmental toxicity study were considered to be secondary to maternal toxicity.

There were no adverse effects noted on growth, sexual maturation, or neurobehavioral development in juvenile toxicity studies in rats and rabbits. Dr. Haile concluded that the NOAEL in juvenile rats was similar to clinical exposure, and that the NOAEL in juvenile rabbits was 5-fold the MRHD, based on AUC. NOAELs were based on the absence of adverse effects at the highest doses administered.

Because evinacumab-dgnb is not expected to interact directly with DNA, mutagenicity studies were not considered appropriate. The Applicant submitted a weight-of-evidence assessment to address the carcinogenic potential of evinacumab-dgnb consistent with recommendations in ICH guidances, which included information available from relevant literature and animal toxicology studies. The nonclinical team did not request any *in vivo* animal carcinogenicity studies after consulting with CDER's Executive Carcinogenicity Assessment Committee (April 18, 2017). In her review, Dr. Haile concluded that the sponsor's carcinogenicity assessment was adequate.

In her labeling review, Dr. Haile concluded that the established pharmacological class (EPC) of "ANGPTL3 (angiopoietin-like 3) inhibitor" is acceptable.

In the nonclinical review, Dr. Haile, in consultation with other members of the nonclinical and clinical teams, concluded that the observed rabbit embryo-fetal malformations represent a potential human risk, considering the unknown mechanism, the severity of the findings, their occurrence at below clinical exposures, the similarity of findings with other known human teratogens, and the unlikely relationship to maternal toxicity. She recommends inclusion of the risk in Section 5 - *Warnings and Precautions* of labeling.

Dr. Haile provided extensive revisions to Section 8.1 (Pregnancy) to include the embryofetal developmental toxicity findings, and recommendations for pregnancy testing and contraception for patients who may become pregnant.

Dr. Haile recommended including nonclinical fertility data in Section 13.1 and removing toxicology and pharmacology data from Section 13.2 that are either addressed clinically or represent negative findings that do not warrant inclusion in labeling.

5. Clinical Pharmacology

The clinical pharmacology reviewer, Dr. S.W. Johnny Lau, found the clinical pharmacology data submitted in support of the application to be acceptable, and he recommends approval for adults and pediatric patients, aged 12 years and older, with HoFH. I concur with the recommendation. Refer to the Office of Clinical Pharmacology (OCP) review co-authored by Dr. Lau, Dr. Jihye Ahn (pharmacometrics), and Dr. Katarzyna Drozda (genomics) for details.

Dr. Lau found the proposed evinacumab-dgnb dosing, 15 mg/kg administered via intravenous infusion over 60 minutes once every 4 weeks, acceptable and recommends no specific dosing adjustments in patient subgroups based on intrinsic or extrinsic factors, including age, sex, body weight (42 to 152 kg), race, renal impairment, apheresis, or concomitant lipid-lowering medications. The formulation used in Phase 2 and Phase 3 trials was identical to the to-be-marketed formulation.

General Topics

The following summarizes general clinical pharmacology data described in the OCP review.

Absorption: Mean serum evinacumab C_{max} at steady state is 689 mg/L.

Distribution: The estimated volume of distribution of evinacumab-dgnb is about 4.8 L.

Metabolism: Evinacumab-dgnb is likely degraded into small peptides and amino acids via catabolic pathways similar to metabolism of endogenous IgG. Elimination is mediated via parallel linear and non-linear pathways, a non-saturable proteolytic pathway at higher concentrations, and non-linear, saturable ANGPTL3 target-mediated disposition at lower concentrations.

Excretion: Because evinacumab-dgnb has a molecular weight of 146.08 kDa, the kidney is not likely to excrete evinacumab-dgnb unchanged. After the last steady state dose of 15 mg/kg IV every 4 weeks, the median time for evinacumab-dgnb concentrations to reach below the limit of quantitation of 78 ng/mL is 19 weeks.

Dose Linearity: A 3-fold increase in dose from 5 mg/kg to 15 mg/kg IV every 4 weeks results in a 4.3-fold increase in $AUC_{tau,SS}$ because of non-linear clearance.

Drug Interactions: The applicant did not conduct any in vitro or dedicated clinical drug-drug interaction studies. In clinical trial patients, the concentrations of statins (atorvastatin, rosuvastatin, simvastatin) were not meaningfully altered, either prior to receiving evinacumab-dgnb or at steady state of evinacumab-dgnb. Concentrations of evinacumab-dgnb were comparable either with or without background lipid lowering therapy.

Immunogenicity: The applicant measured anti-drug antibodies (ADA) in all clinical studies. No patient treated with evinacumab-dgnb exhibited treatment-emergent ADA responses.

Bioanalytical Methods: The applicant developed ELISA-based bioanalytical methods to measure total evinacumab-dgnb and total ANGPTL3 concentrations in sera in clinical trials. The applicant measured statin concentrations via liquid chromatography and mass spectrometry. Dr. Lau concluded that the validation of the bioanalytical methods was acceptable.

Genomics: Dr. Drozda, the genomics and targeted therapy reviewer, evaluated the applicant's proposed classification of the *LDLR* mutations for labeling. Although the categorization varies from the conventional classification in published literature, Dr. Drozda concluded that *LDLR* mutation status should not affect trial results, because the evinacumab-dgnb mechanism of action is independent of the LDLR. Refer to the OCP review for details.

In summary, the clinical pharmacology data support approval. Refer to the review for details of the development program and labeling recommendations.

6. Clinical Microbiology

The OPQ drug substance and drug product microbiology reviewers, Dr. Li and Mr. Seifert, respectively, support approval, and I concur with their recommendations. Refer to the Product Quality section of this review and the Microbiology review for details.

7. Clinical/Statistical-Efficacy

The Applicant submitted adequate clinical data to demonstrate substantial evidence that evinacumab-dgnb reduces LDL-C in adults and pediatric patients, aged 12 years and older, with HoFH. Dr. Laura Higginbotham was the primary clinical reviewer for the application. Dr. Eileen Craig reviewed efficacy and safety data from 13 pediatric patients enrolled in an open-label extension trial that were submitted as an amendment to the application during the review cycle. Dr. Kyunghee Song was the statistical efficacy reviewer. All reviewers support approval, and I concur with their recommendations. The remainder of this section summarizes efficacy issues related to approvability and labeling. Refer to the FDA clinical review co-authored by Dr. Higginbotham and Dr. Craig and the FDA statistical review authored by Dr. Song for additional details.

The BLA submission included a single, randomized, controlled trial to support efficacy supported by two open-label extension trials. Study R1500-CL-1629 (Study 1629) comprises two of the components of the submission, including the 24-week, randomized, double-blind, placebo-controlled treatment period (Study 1629 DBTP) – which is the primary source of efficacy data for the application – and a 24-week open-label treatment period (Study 1629 OLTP), which provides confirmatory evidence of effectiveness. Study R1500-CL-1719 (Study 1719) is an ongoing, long-term open-label extension trial providing additional confirmatory evidence of long-term efficacy.

Study R1500-CL-1629

Study Design

Study 1629 DBTP was a 24-week, randomized, double-blind, placebo-controlled trial. The primary objective was to evaluate the effect of evinacumab-dgnb 15 mg/kg administered intravenously every 4 weeks compared to placebo in patients with HoFH. The trial consisted of an 8-week run-in period for genotyping and stabilization of background therapies, followed by a 24-week treatment period. Eligible patients were assigned to evinacumab-dgnb or placebo infusion using a 2:1 randomization scheme, stratified by apheresis status and geographical region. Patients who completed the DBTP continued in the OLTP. Patients who completed the OLTP either entered Study 1719 or completed a 24-week follow-up period.

The study population consisted of adult and adolescent patients ≥ 12 years of age with HoFH diagnosed by genetic or clinical criteria. Genetic criteria required confirmed mutations in both *LDLR*, *APOB*, *LDLRAP1*, or *PCSK9* alleles or double heterozygous mutations (mutations on different genes). Clinical criteria were an untreated total cholesterol (TC) > 500 mg/dL and triglycerides (TG) < 300 mg/dL, and either both parents with documented TC > 250 mg/dL or personal history of cutaneous or tendinous xanthomata before age 10 years. Dr. Higginbotham concluded that these definitions were reasonable, and I concur.

The applicant defined two subgroups based on LRLR function, patients with null/null mutations, defined as mutations in *LDLR* or *LDLRAP1* resulting in minimal LDLR activity ($< 15\%$) on in vitro assays, and patients with negative/negative mutations, defined as mutations in *LDLR* or *LDLRAP1*, such as premature stop codons, frame shifts, splice site changes, small and large insertions/deletions, and copy number variations (CNVs) predicted to result in the loss of function of both *LDLR* alleles.

The applicant proposed presenting LDL-C data in labeling for these subgroups. In lieu of the applicant's definitions, we proposed defining these categories collectively as "limited LDLR function." In published literature, the terms "null" and "negative" are used inconsistently. The term "receptor-negative" is used to describe patients with $< 2\%$ receptor function on in vitro assays,⁵ and there is no standard definition for mutations predicted to result in loss of function based on mutation analysis but not evaluated in functional assays. Furthermore, the categories as defined by the applicant are not mutually exclusive, such that the total number of patients in the two subgroups was unclear.

The trial included patients with LDL-C greater than 70 mg/dL despite maximally tolerated lipid-lowering therapy. Patients were instructed to follow a low-fat or heart-healthy diet. Exclusion criteria were generally appropriate and not overly restrictive. Examples of exclusions include diabetes or acute coronary syndrome diagnosed within 3 months of screening (conditions that might impact lipid levels acutely), and NYHA Class IV heart failure. Patients who withdrew from the trial were asked to attend an unscheduled visit for safety and pregnancy assessment and a final end-of-study visit for collection of efficacy and safety data.

The primary endpoint of the DBTP was the percent reduction in LDL-C from baseline to Week 24, calculated using the Friedewald equation. Although the protocol provided for direct

LDL-C measurement for patients with elevated TG or very low LDL-C, these conditions were of minimal importance in this trial of patients with a primary disorder of LDL-C who are resistant to other LDL-C-lowering therapies. The protocol pre-specified efficacy analysis procedures. The protocol also prespecified 9 key secondary endpoints, including other lipid parameters (ApoB, TC, non-HDL-C), categorical descriptions of LDL-C reduction (<30% and <50% reduction from baseline, and absolute LDL-C change from baseline). Analyses used a hierarchical testing procedure to control Type I error rate.

The Division had previously advised the applicant that absolute change and categorical changes in LDL-C would most likely not be considered for labeling inclusion, because these endpoints either do not additionally inform the primary (categorization of changes in a continuous variable) or are highly dependent on the magnitude of the baseline value (absolute change, proportion achieving various targets).

The applicant conducted primary and key secondary efficacy analyses on the Intent-To-Treat (ITT) population, using a mixed-effects repeated measures (MMRM) model assuming missing observations were missing-at-random (MAR), and tested at a 2-sided significance level of 0.05. In the statistical review, Dr. Song noted that MAR is not the appropriate assumption, but this choice had negligible impact on the results because of the small amount of missing data. The applicant evaluated key secondary continuous endpoints using the MMRM model and binary endpoints using a logistic regression model. Refer to the statistical review for details, including discussion of sensitivity analyses and subgroup analyses.

The applicant summarized lipid endpoints in the OLTP descriptively, without formal statistical testing or control for multiplicity. Refer to the clinical review for additional details of OLTP trial design.

Disposition

The trial enrolled patients in 30 centers from 11 countries in Europe, Asia, North America, and Australia. Investigators screened 75 patients and randomized 65 patients (10 from US centers), including 43 randomized to evinacumab-dgnb and 22 to placebo (2:1 randomization). One patient assigned to placebo withdrew consent after receiving one dose, and 64 completed the 24-week DBTP.

Protocol deviations were mostly minor and not anticipated to impact data integrity or the interpretation of trial results. Refer to the clinical review for details.

Demographics and Baseline Characteristics

The mean age at baseline was 42 years (range 12 to 75), including 2 pediatric patients. Most patients were White race (74%) and non-Hispanic ethnicity (89%). Demographics were similar between treatment arms. In the trial, 40% (26 of 65) patients had limited LDLR function (either null/null or negative/negative or both, as defined by the applicant).

The mean LDL-C at baseline was 255 mg/dL. In patients with limited LDLR function, the mean LDL-C at baseline was 307 mg/dL. At baseline, 94% of patients were taking statins (77% high-intensity), 75% were on ezetimibe, 77% were on a PCSK9 inhibitor antibody, 22%

were taking lomitapide, and 34% were receiving lipoprotein apheresis. Most patients were taking three lipid lowering therapies.

Results

The primary efficacy endpoint was the mean percent change in LDL-C from baseline to Week 24. At Week 24, the least squares (LS) mean treatment difference between evinacumab-dgnb and placebo was -49% (95% confidence interval: -65% to -33%; p<0.0001). The statistical reviewer, Dr. Song, was able to reproduce the applicant’s results of the primary analysis. Table 1 summarizes Dr. Song’s analysis of the primary endpoint.

Table 1: LDL-C Percent Change from Baseline to Week 24 in Patients with HoFH, Study R1500-CL-1629, ITT Population

	LS Mean ¹ (95% CI)	Difference (95% CI); p-value
Evinacumab-dgnb (n=43)	-47 (-56, -38)	
Placebo (n=22)	2 (-11, 15)	
		-49 (-65, -33); <0.0001

Source: Adapted from FDA Statistical Review.

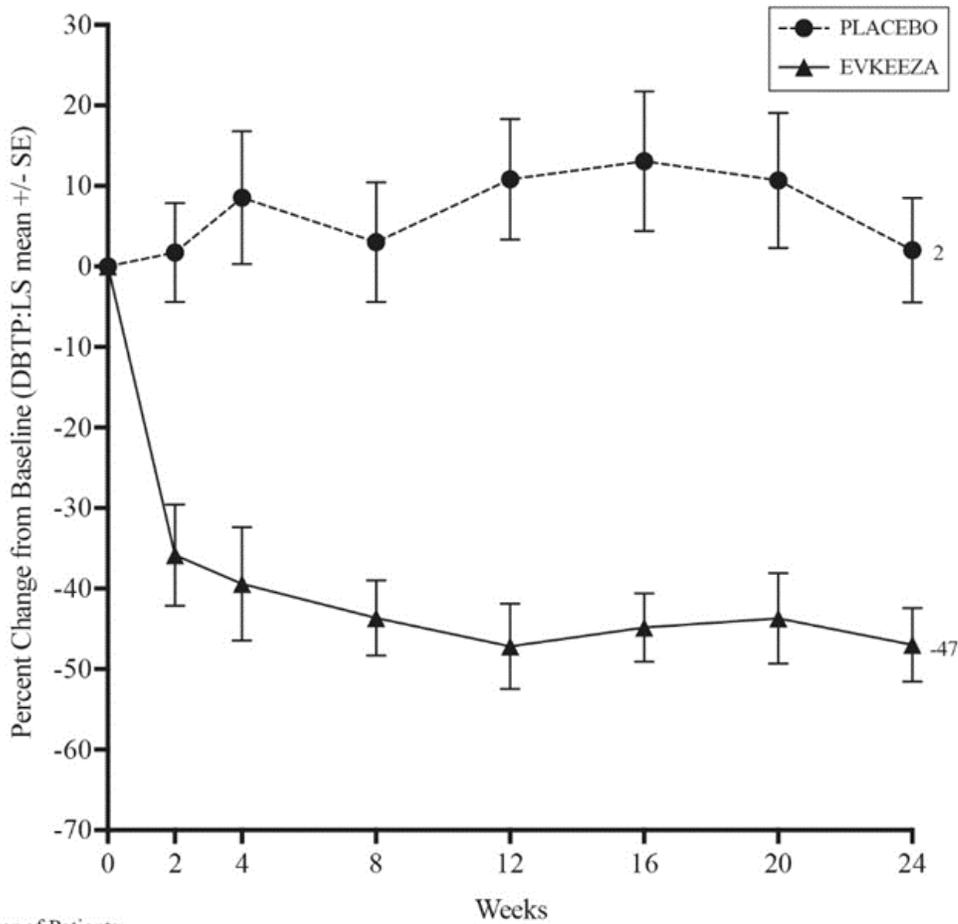
Abbreviations: LDL-C=low-density lipoprotein cholesterol, HoFH=homozygous familial hypercholesterolemia, ITT=intent-to-treat, n=number of randomized patients, LS mean=least squares mean, CI=confidence interval

¹ Model based mean estimates using mixed-model repeated measures (MMRM) model with treatment, stratification factor, time, treatment by time, strata by time as fixed effects, and baseline LDL-C, and baseline LDL-C by time as covariates.

Only one patient in the placebo arm had a missing value at Week 24. Not surprisingly, sensitivity analysis yielded results that were consistent with the primary efficacy analysis per Dr. Song’s review.

The treatment effect of evinacumab-dgnb at LDL-C reduction was similar regardless of a patient’s HoFH mutation status, baseline LDL-C, or the number or type of background lipid-lowering therapies, including apheresis status. Figure 1 depicts the percent change in LDL-C over time in the DBTP.

Figure 1: Percent Change in Calculated LDL-C (LS mean) from Baseline over Time in Patients with HoFH, Study R1500-CL-1629, ITT Population



Number of Patients		Weeks							
PLACEBO	22	19	20	21	20	20	20	21	21
EVKEEZA	43	38	43	42	42	40	43	43	43

Source: Applicant, Draft Prescribing Information

Abbreviations: LDL-C=low-density lipoprotein cholesterol, LS mean=least squares mean, HoFH=homozygous familial hypercholesterolemia, ITT=intent-to-treat, DBTP=double-blind treatment period, SE=standard error

In the evinacumab-dgnb group, three patients experienced an increase in LDL-C from baseline, while 40 experienced a decrease, ranging from -88% to 85% overall. Most evinacumab-dgnb patients experienced clinically meaningful LDL-C lowering. Figure 2 is a Waterfall plot that illustrates the individual responses from baseline to Week 24 of randomized patients in Study 1629 DBTP.

Figure 2: Waterfall Plot of Individual Patient Percent Change in LDL-C (mg/dL) from Baseline to Week 24, Study R1500-CL-1629, ITT Population



Source: Applicant response to information request, Feb. 9, 2021

Abbreviations: LDL-C=low density lipoprotein cholesterol, ITT=intent-to-treat, DB=double-blind, IV=intravenous, Q4W=every 4 weeks.

In addition to reducing LDL-C, evinacumab-dgnb also reduced Apo B, non-HDL-C, TC, TG, and HDL-C, at 24 weeks. TG and HDL-C were not included in the testing hierarchy but are presented because of potential clinical relevance. Table 2 summarizes these results.

Table 2: Lipid Parameters in Patients with HoFH on Other Lipid-Lowering Therapies, Study R1500-CL-1629, ITT Population

	LDL-C	ApoB	Non-HDL-C	TC	TG ^a	HDL-C ^a
Baseline (mean), mg/dL (N=65)	255	171	278	322	124	44
LS Mean: EVKEEZA (N = 43)	-47%	-41%	-50%	-47%	-55%	-30% ^b

	LDL-C	ApoB	Non-HDL-C	TC	TG ^a	HDL-C ^a
LS Mean: Placebo (N = 22)	+2%	-5%	+2%	+1%	-5%	+1% ^b
LS Mean Difference from Placebo (95% CI)	-49% (-65 to -33)	-37% (-49 to -25)	-52% (-65 to -39)	-48% (-59 to -38)	-50% (-66 to -35)	- ^b

Source: Adapted from Applicant, Draft Prescribing Information (with FDA edits)

^a Neither TG nor HDL-C were pre-specified in the hypothesis testing

^b Mean percent change, based on safety population (EVKEEZA, n=44; placebo, n=20); HDL-C is presented for completeness but was not an efficacy endpoint that was statistically analyzed.

One subject in the placebo group discontinued study before Week 24. Treatment difference and 95% confidence interval (CI) were estimated using a mixed model repeated measures analysis.

Abbreviations: HoFH=homozygous familial hypercholesterolemia, ITT=intent-to-treat, LDL-C=low-density lipoprotein cholesterol, ApoB=apolipoprotein B, non-HDL-C=non-high-density-lipoprotein cholesterol, TC=total cholesterol, TG=triglycerides, HDL-C=high-density lipoprotein cholesterol, LS mean=least squares mean, N=number of randomized patients, CI=confidence interval

The Applicant also investigated LDL-C reduction by several categorical endpoints included in the testing hierarchy, including percentage of patients achieving at least 30% and 50% LDL-C reduction from baseline, absolute change from baseline in LDL-C, percentage of patients meeting apheresis criteria by US and EU standards, and percentage of patients achieving LDL-C <100 mg/dL. As described previously, the categorical endpoints and the absolute change in baseline are not considered clinically meaningful. A numerically smaller proportion of patients met US apheresis criteria compared to placebo, but the results were not statistically significant. Statistical hypothesis testing terminated after evaluation of the endpoint, and subsequent secondary endpoints (percentage achieving LDL-C <100 mg/dL, percentage meeting EU apheresis criteria) could not be tested per the prespecified method.

As noted above, evinacumab-dgnb lowered HDL-C by 30% from baseline. The significance of this reduction is unclear, as decreased HDL-C is considered an independent CV risk factor, but this magnitude of change does not outweigh the decrease in LDL-C.

There were two pediatric patients (one patient in each treatment arm). The observed change in calculated LDL-C at Week 24 was 60% in the placebo group and -73.3% in the evinacumab-dgnb group. Refer to Section 10 of this review for discussion of efficacy in pediatric patients obtained from Study 1719, the long-term, open-label extension trial.

OLTP Results

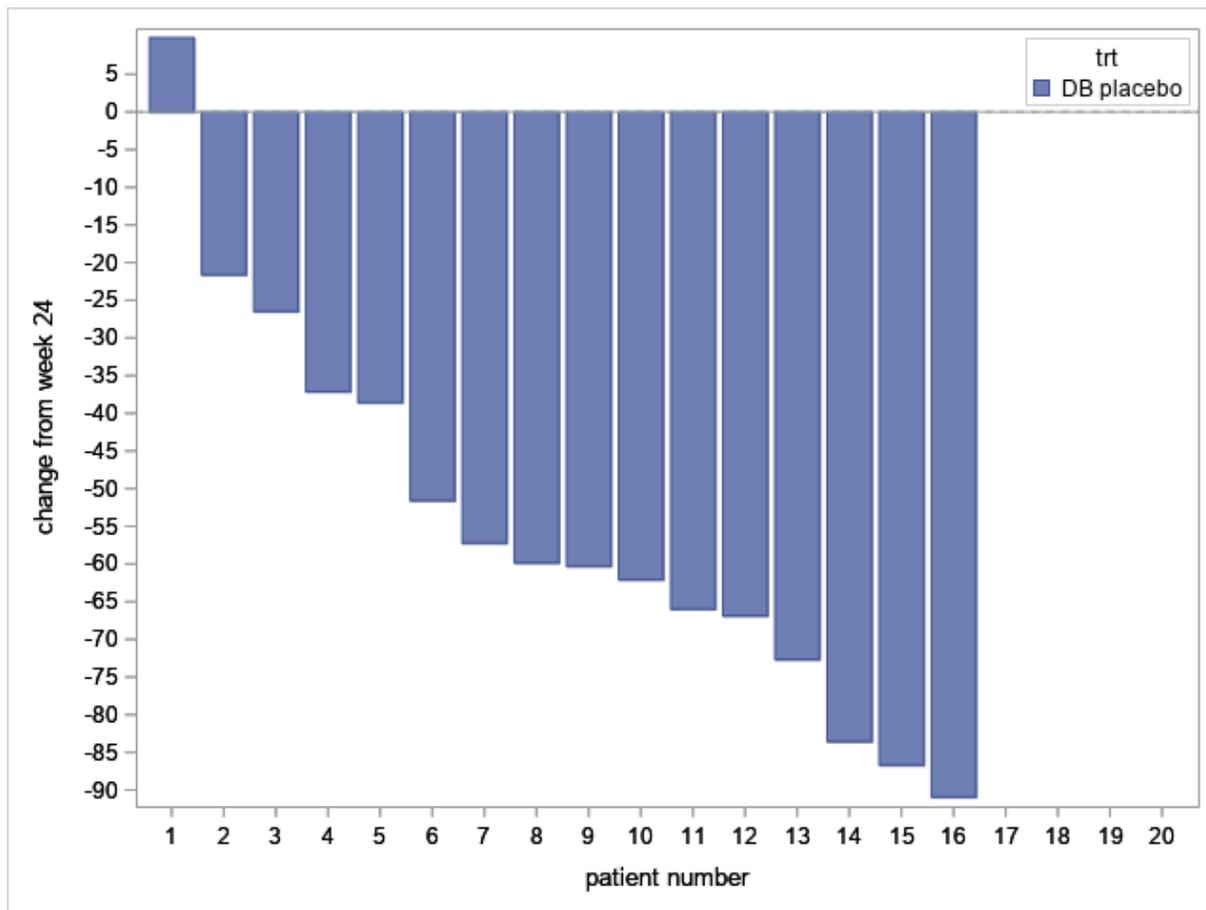
The OLTP set included 20 placebo and 44 evinacumab-dgnb patients from the DBTP. At Week 48, there were 6 patients with missing values; 4 from the DBTP placebo group and 2 from the DBTP evinacumab-dgnb group. In violation of the protocol, two patients initiated additional lipid-lowering treatment during the OLTP prior to assessment of Week 48 LDL-C reduction (both assigned to evinacumab-dgnb during the DBTP).

The mean change from baseline in LDL-C among patients in the OLTP was -46% after 24 to 48 weeks of treatment. The mean change from baseline for DBPT/evinacumab-dgnb patients was -43%, and the mean change for DBTP/placebo patients was -56% for patients with available data (n=42, n=16, respectively). Per the applicant's analysis, among the 16 DBTP/placebo patients with non-missing data at Week 48, all patients experienced a decrease from baseline ranging from -19% to -94%. Changes in other lipid parameters were similar to the results observed in the DBTP.

To estimate the mean change from baseline in the OLTP, the applicant used the baseline value obtained prior to the DBTP. While this baseline is appropriate for the DBTP/evinacumab-dgnb group – because the value represents the pre-treatment baseline, and the OLTP is an extension of therapy – it is unclear if the pre-DBTP baseline is appropriate for the DBTP/placebo group. Among the 21 DBTP/placebo patients with a non-missing LDL-C value at Week 24, seven patients had experienced a decrease from baseline to Week 24 and 14 had experienced an increase from baseline to Week 24, with changes overall ranging from -58% to 60%.

To account for the changes in LDL-C during the DBTP in the placebo group (that were, by definition, unrelated to evinacumab-dgnb), the statistical reviewer, Dr. Song calculated the change in LDL-C from Week 24 to Week 48 for the DBTP/placebo group. For the patients with non-missing values at Week 48, the mean change from Week 24 to Week 48 of the OLTP was -55%, similar to the results of the applicant's analysis (pre-DBTP baseline to Week 48). From Week 24 to Week 48, one patient experienced an increase in LDL-C, while 15 patients experienced decreases, ranging from +10% to -91%. Figure 3 presents a Waterfall plot of these data.

Figure 3: Waterfall Plot of Percentage Change in LDL-C from Week 24 to 48 in Patients assigned to Placebo during DBTP (Weeks 0 to 24), Study R1500-CL-1629



Source: FDA Statistical Reviewer

Patients with missing data at week 48 not shown.

Abbreviations: LDL-C=low-density lipoprotein cholesterol, DBTP=double-blind treatment period, trt=treatment, DB=double-blind

Study R1500-CL-1719

Study Design

Study 1719 is an ongoing, open-label, long-term extension trial designed to evaluate the safety, tolerability, and efficacy of evinacumab-dgnb in adult and pediatric patients with HoFH. After a ten-week run-in period for genotyping and stabilization of background therapies, all enrolled patients receive evinacumab-dgnb 15 mg/kg IV every 4 weeks for up to 4 years. The trial is being conducted at 25 sites in 10 countries, including the US. Enrolled patients were rolled over from Study 1629, the Phase 2 Study R1500-CL-1331, or were treatment-naïve.

Eligibility for Study 1719 is similar to Study 1629 but excludes patients with LDL-C <40 mg/dL (versus <70 mg/dL in Study 1629) and patients with either a significant protocol deviation or an adverse event leading to permanent drug discontinuation in a prior

evinacumab-dgnb trial. The primary endpoint is the incidence and severity of treatment-emergent adverse events. Efficacy endpoints, including LDL-C over time, are included as secondary endpoints.

Efficacy analyses will be conducted on the safety population. The applicant does not plan to conduct formal statistical testing or impute missing data.

Study Patients and Results

As of the BLA submission date, June 11, 2020, 64 of an anticipated 120 patients had enrolled into Study 1719. As of the September 24, 2019 data cutoff date, there were no treatment or study discontinuations, and mean treatment exposure was 22 weeks.

At baseline, the mean age was 41 years, and 55% of patients were female. Enrolled patients were predominantly White race (78%) and non-Hispanic ethnicity (80%). Most patients were enrolled outside of the U.S. (78%). Of the enrolled patients, 52% had limited LDLR function per the applicant's definitions of null-null and negative-negative mutations. Mean LDL-C at baseline was 266 mg/dL, and most patients were taking three lipid lowering therapies at baseline, including high-intensity statin (94%), PCSK9 inhibitors (67%), and ezetimibe (86%). Five (12%) rollover patients and one (5%) treatment-naïve patient had modified their baseline lipid-lowering therapies during the trial.

The mean percent change in LDL-C from baseline to Week 24 was -42% in the seven treatment-naïve patients and -47% in rollovers from other trials. Although interpretation of these values is somewhat limited by the open-label design, lack of a control arm, and small numbers of patients with available data, the results appear comparable to the results of Study 1629 DBTP, and support durability of the treatment effect beyond 24 to 48 weeks of treatment.

Pediatric Efficacy

With the initial BLA submission, the efficacy data included only one pediatric patient treated with evinacumab-dgnb. The applicant submitted a summary of efficacy for 13 pediatric patients with the 120-day safety update (including the patient treated with evinacumab-dgnb in Study 1629 DBTP), using a data cutoff of August 28, 2020, and the Division requested datasets for review. The applicant submitted the requested data as an amendment to the BLA on November 9, 2020.

Dr. Eileen Craig reviewed the pediatric submission and concluded that the data provide substantial evidence to support expanding the indication to pediatric patients, aged 12 and older. I concur with her recommendations. Refer to the sections of the clinical review describing the pediatric data authored by Dr. Craig for details. The following summarizes the major issues affecting approvability and labeling described in her review.

Study Patients

The 13 pediatric participants enrolled at 7 sites in 6 countries: Australia, France, Italy, Japan, Netherlands, and South Africa. Despite some differences in clinical guidelines among participating countries, the management of pediatric HoFH is applicable to US practice.

The mean age was 14 years (range 12 to 17); 62% of patients were male; 46% were White race, 8% were Black, and 15% were Asian; 85% were non-Hispanic ethnicity; and 15% had missing demographic data for race and ethnicity.

The median time from diagnosis of HoFH was 9 years. Mean baseline LDL-C was 300 mg/dL. All patients were on a statin at baseline, 77% were on high-intensity statin, 46% were taking a PCSK9 inhibitor, 69% were taking ezetimibe, and 62% were receiving apheresis.

Among the 13 pediatric participants enrolled and treated, 11 were treatment-naïve and 2 were rollovers from Study 1629. All patients were ongoing in the trial and none had discontinued study treatment prematurely. The median duration of treatment was 33 weeks.

No patients had modified their baseline lipid-lowering medications during the trial, but 8 patients had deviated from their baseline apheresis schedule. Four of five had had a reduction in frequency (longer time since last apheresis) prior to the Week 24 endpoint. Two patients who had a change prior to Week 16 assessments had had a reduced frequency.

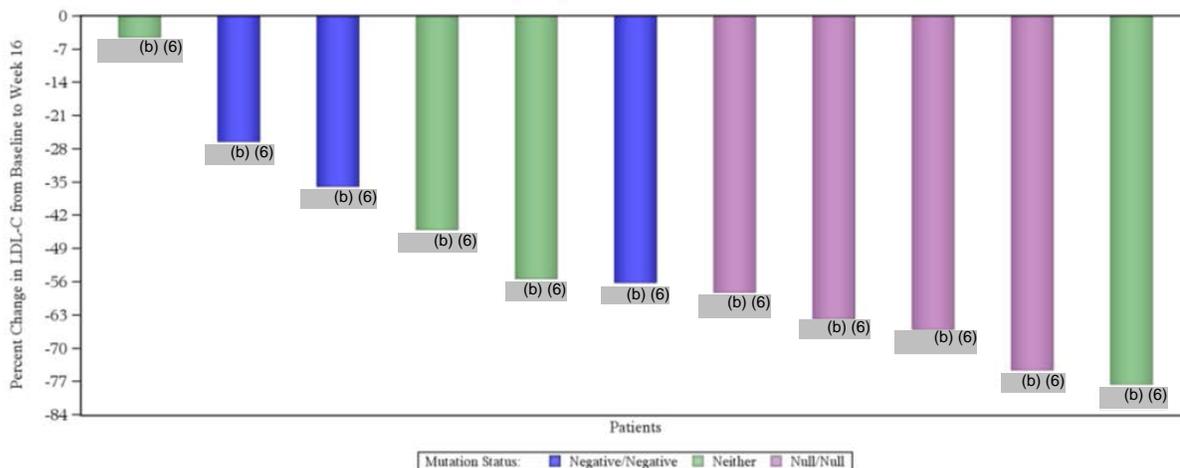
The applicant evaluated lipid endpoint results for 11 patients at Week 16 and 9 patients at Week 24 in the safety analysis set. Two of the thirteen pediatric patients had less than 12 weeks of data at the cutoff, and two patients had missing data at Week 24, one because of COVID-19 and the other because the lab collection occurred after the start of apheresis, and thus the lipid results for these patients were excluded.

Efficacy Results

For the patients with available data, the mean change from baseline in LDL-C was -51% at 16 weeks and -52% at 24 weeks. Other lipid parameters, including HDL-C, TG and TC, were also reduced at these timepoints.

Evinacumab-dgnb treatment was associated with a large decrease in LDL-C in most pediatric patients, including patients with null/null or negative/negative mutations per the applicant's definitions. Figure 4 is a Waterfall Plot of the pediatric patients depicting percent change from baseline to LDL-C at Week 16 by mutation status (null/null, negative/negative, or neither).

Figure 4: Waterfall Plot of Calculated LDL-C Percent Change from Baseline at Week 16 by Mutation Status (null/null vs negative/negative vs neither) – Study R1500-CL-1719, Safety Analysis Set, Pediatric Patients



Source: Applicant’s response to FDA IR submitted December 4, 2020 (Figure 14.9.3.56A)

Negative/negative defined as defined as mutations in *LDLR* or *LDLRAP1*, such as premature stop codons, frame shifts, splice site changes, small and large insertions/deletions, and copy number variations (CNVs) predicted to result in the loss of function of both LDLR alleles; null/null defined as mutations in *LDLR* or *LDLRAP1* resulting in minimal LDLR activity (<15%) on in vitro assays

Abbreviations: LDL-C=low-density lipoprotein

In summary, the effects of evinacumab-dgnb on LDL-C and other lipid parameters were similar in pediatric and adult patients with HoFH. In Study 1719, the mean percent change from baseline to Week 24 in LDL-C was -52%, a change similar in magnitude to that of adults in Study 1629 DBTP. The pediatric data from Study 1719 would not alone constitute substantial evidence, but the observed effect in the population studied may leverage the adult data submitted with the application, because the disease process is similar in adults and children (defective LDLR function leads to impaired processing of LDL-C) and the observed treatment effect in the cohort of pediatric patients was comparable to that observed in adults.

Efficacy Summary

In summary, the application demonstrates substantial evidence of effectiveness to support approval as an adjunct to other LDL-C-lowering therapies for the treatment of adult and pediatric patients, aged 12 years and older, for treatment of HoFH.

The application relies on a single adequate and well-controlled clinical investigation, Study 1629 DBTP, plus confirmatory evidence from the open-label trials, Study 1629 OLTP and Study 1719. The randomized, controlled trial, 1629 DBTP, is highly persuasive, evidenced by a large treatment effect on LDL-C, a highly statistically significant result, and consistent changes on secondary endpoints (such as ApoB, non-HDL-C, and TC). The large observed effects cannot be attributed to other influences, such as spontaneous change, placebo effect, or biased observation. The primary endpoint, percent change from baseline in LDL-C, has served as the basis for conventional approval of other products intended to treat patients with HoFH.

The treatment effect was observed in patients with elevated LDL-C despite maximally tolerated lipid-lowering therapy and was similar across important subgroups, including age, sex, presence of genetic variants consistent with limited LDLR activity, concomitant treatment with lipoprotein apheresis, and concomitant background lipid-lowering medications.

Confirmatory evidence from Study 1629 OLTP includes the observed effect of evinacumab-dgnb from Week 24 to 48 in patients assigned placebo in the DBTP. Missing data from 4 patients in this cohort limits the interpretability of the magnitude of the treatment effect somewhat, but the value was comparable to the percent change from baseline in the DBTP, and the range of individual profiles was similar in character. Study 1629 and 1719 also provided additional evidence of the durability of the treatment effect. Considering the rarity of HoFH and the high unmet medical need, reliance on a single adequate and well-controlled trial with confirmatory evidence is appropriate. Conduct of a second randomized, controlled trial would probably not be ethical or practicable.

Pediatric efficacy data support expanding the indication to include pediatric patients aged 12 years and older. The observed treatment effect in pediatric patients in the open-label extension trial, Study 1719, was similar to the effect observed in adults in Study 1629 DBTP, even considering the limitations of the data.

The applicant's proposed indication was reasonable—as an adjunct to diet and other lipid-lowering therapies. Although diet is a component of standard-of-care for patients with HoFH, I recommend removing the language about diet for the HoFH indication. Because of the severity of the condition, treatment guidelines recommend initiation of lipid-lowering pharmacotherapy at the time of diagnosis and do not require a trial of diet or lifestyle intervention. Such interventions would likely have only a minimal impact on LDL-C and cardiovascular outcomes; therefore, treatment should not be delayed for a trial of dietary intervention.

The indication should include a Limitation of Use statement to acknowledge that the effects on CV morbidity and mortality is unknown.

The applicant proposed including data in Section 14 of labeling for all secondary endpoints that achieved statistical significance. As discussed previously, categorical descriptions of the mean change in LDL-C do not additionally inform the primary endpoint. It is hardly surprising that a higher proportion of patients treated with evinacumab-dgnb experienced a 50% or 30% decrease in LDL-C from baseline, given the large treatment effect observed with evinacumab-dgnb and the mean change with placebo that was near zero. The percentage of patients achieving various thresholds is not useful information for providers, because an individual patient's likelihood of achieving goal is highly dependent on the baseline LDL-C value.

The applicant included language in Section 14 describing the treatment effect in patients with null/null and negative/negative mutations, as defined in the protocol. I recommend revising the language and clarifying that the categories of patients with limited LDLR function were defined by the applicant. Additionally, I recommend combining the categories (limited LDLR function diagnosed by in vitro assays and limited LDLR function inferred from mutation analysis), because the categories are not mutually exclusive.

Other minor revisions to Section 14 include edits to the proposed table depicting changes in lipid parameters to remove p-values and unnecessary decimal places, removal of data describing the efficacy results from Study 1629 OLTP that do not additionally inform the primary endpoint, replacement of a Forest Plot showing similar treatment effect across subgroups with a sentence in text, and addition of pediatric data from Study 1719 supporting the indication in patients aged 12 and older.

8. Safety

In the clinical review, Dr. Higginbotham concluded that the risks of evinacumab-dgnb are monitorable and reversible with treatment discontinuation, and that the risks do not outweigh the benefits in patients with HoFH. The major risks associated with evinacumab-dgnb treatment identified in Dr. Higginbotham's review are hypersensitivity, including anaphylaxis and infusion reactions, and teratogenicity.

The most frequently observed treatment-emergent adverse events (TEAEs) occurring with evinacumab-dgnb and more frequently than with placebo include upper respiratory symptoms (such as nasopharyngitis and rhinorrhea), influenza-like illness, upper respiratory tract infection, dizziness, constipation, and abdominal pain. Transient decreases in diastolic blood pressure and increases in heart rate during infusion occurred more frequently with evinacumab-dgnb than placebo.

Dr. Higginbotham concluded that the small size of the safety database and limited long-term data are the major limitations, but despite the uncertainty, the benefit-risk consideration remains favorable because of the magnitude of the treatment effect in this rare population with high unmet medical need. I concur with Dr. Higginbotham's recommendation.

This section of the review focuses on the key safety issues affecting approvability and labeling, and it includes only a high-level summary of other general safety topics. Refer to the clinical review for details of the safety analyses supporting the application.

Sources of Safety Data

The primary sources of safety data were two randomized, placebo-controlled trials, Study 1629 DBTP – the 24-week clinical trial in 65 patients with HoFH, and Study R1500-CL-1643 – a 24-week, randomized, three-arm, placebo-controlled trial of 106 patients with ASCVD randomized to evinacumab-dgnb 5 mg/kg, 15 mg/kg, or placebo administered intravenously every 4 weeks, denoted the placebo-controlled pool. Supportive safety data were obtained from three single-arm, open-label trials of evinacumab-dgnb, including the 24-week Study 1629 OLTP, the 48-week OLTP of Study 1643, and the long-term safety trial 1719. Study 1643 OLTP and Study 1719 remain ongoing.

Exposure

In phase 2 and 3 trials, 216 patients were exposed to evinacumab-dgnb 15 mg/kg IV every 4 weeks for a mean exposure duration of 55 weeks.

Demographics and Baseline Characteristics

In the placebo-controlled pool, 38% of patients had HoFH, and 50% had heterozygous familial hypercholesterolemia (HeFH), mean age was 50 years, 45% of patients were male, 83% were White race, and 89% were non-Hispanic ethnicity. The mean baseline LDL-C was 187 mg/dL, 41% were taking a high-intensity statin at baseline, 83% were on a PCSK9 inhibitor, and 88% were taking ezetimibe. Mean BMI was 28 kg/m², 10% of patients had type 2 diabetes, and 59% had never smoked. Baseline characteristics were generally balanced.

Dr. Higginbotham concluded that the submission was high-quality, complete, and well-organized. Planned assessments were appropriate. Adverse Events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 22.0. Refer to the clinical review for details.

General Safety Issues

Deaths, Serious Adverse Events, and Discontinuations

No deaths occurred in either trial in the placebo-controlled pool. The percentage of patients who experienced at least one serious adverse event (SAE) was higher in patients assigned to evinacumab-dgnb 15 mg/kg (10%) compared to the 5 mg/kg group (6%) and placebo (2%). Despite the apparent dose-dependent trend, most SAEs were CV-related, such as unstable angina, coronary artery disease, and atrial fibrillation, events that are expected for the population. Refer to the clinical review for details.

One patient treated with evinacumab-dgnb 15 mg/kg experienced an SAE of anaphylaxis during the second infusion of investigational product on Day 28. The patient was a 53-year-old Hispanic female in Study 1643 with a history of asthma and allergic rhinitis. Approximately 5 minutes after infusion initiation she developed dizziness, racing heart, chest pressure, tingling, shortness of breath, itching, and lethargy. Physical exam findings included flushed face and chest, and hypotension to 78/57 mmHg. The event resolved approximately 11 minutes after infusion discontinuation and treatment with oral diphenhydramine. She was monitored for 2 hours, discharged to home, and evinacumab-dgnb was permanently discontinued.

Five patients experienced nine adverse events leading to permanent drug discontinuation, including numerically more evinacumab-dgnb-treated patients (3%) than placebo-treated patients (2%). All discontinuations were in Study 1643. Reasons for discontinuation assessed by the investigator as drug-related were anaphylactic reaction, headache, and rash.

Treatment Emergent Adverse Events

Table 3 summarizes the percentage of patients experiencing TEAE at a greater frequency with evinacumab-dgnb than with placebo. For inclusion in labeling, the table will include only the approved evinacumab-dgnb 15 mg/kg dose and events occurring in >3% of patients. Review of grouped queries, such as Standardized MedDRA Queries (SMQs) and FDA MedDRA Queries (FMQs) indicated imbalances in events below the threshold but occurring more frequently than placebo, including constipation, upper respiratory tract infection, nasal congestion, and abdominal pain. These events will be described in text below the table in Section 6 of the Prescribing Information.

Table 3: Patients with Treatment-Emergent Adverse Events¹ Occurring at ≥2% Incidence and ≥1.5% Over Placebo, Safety Population, Placebo-Controlled Pool²

Preferred Term ³	Placebo N=54 n (%)	Evinacumab-dgnb 5 mg/kg N=36 n (%)	Evinacumab-dgnb 15 mg/kg N=81 n (%)
Nasopharyngitis	7 (13%)	3 (8%)	13 (16%)
Influenza-like illness	3 (6%)	3 (8%)	6 (7%)
Dizziness	0 (0%)	2 (6%)	5 (6%)
Rhinorrhea	0 (0%)	0 (0%)	4 (5%)
Nausea	1 (2%)	2 (6%)	4 (5%)
Pain in extremity	0 (0%)	3 (8%)	3 (4%)
Asthenia	0 (0%)	0 (0%)	3 (4%)
Constipation	0 (0%)	2 (6%)	2 (3%)
Coronary artery disease	0 (0%)	1 (3%)	2 (3%)
Upper respiratory tract infection	0 (0%)	1 (3%)	2 (3%)
Asthma	0 (0%)	0 (0%)	2 (3%)
Dental caries	0 (0%)	0 (0%)	2 (3%)
Infusion site pruritus	0 (0%)	0 (0%)	2 (3%)
Nasal congestion	0 (0%)	0 (0%)	2 (3%)
Neck pain	0 (0%)	0 (0%)	2 (3%)

Source: Adapted from Clinical Review.

Abbreviations: N=number of patients in treatment arm; n= number of patients with adverse event.

¹ Treatment-emergent adverse event (AE) defined as an AE that developed or worsened after the first dose of investigational product.

² Study R1500-CL-1629 DBTP and Study R1500-CL-1643 DBTP. Duration = 24 weeks. DBTP=double-blind treatment period

³ Adverse events coded with the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.

Laboratory

Laboratory values were assessed descriptively using changes in measures of central tendency and categorically using shifts from baseline. There were no notable trends, including no changes in hepatic enzymes, creatinine, or glycemia parameters, such as HbA1C and plasma glucose. Refer to the clinical review for details.

Vital Signs

In the placebo-controlled pool, vital signs were obtained pre-infusion, 30 minutes post-infusion, and 60 minutes post-infusion, and assessed descriptively using changes in measures of central tendency and categorically using individual shifts from baseline.

There were no clinically meaningful mean changes to systolic blood pressure (SBP), diastolic blood pressure (DBP), or heart rate (HR) over time. Nevertheless, subsets of patients experienced transient elevated SBP 140-159 mmHg (19% placebo versus 30% evinacumab-dgnb) or decreased DBP <60 mmHg (30% placebo versus 37% evinacumab-dgnb) 30-60 minutes post-infusion. Additionally, a small number of patients (3% at 30 minutes and 4% at 60 minutes) treated with evinacumab-dgnb experienced increased HR ≥100 bpm with increase ≥10 bpm from baseline compared with none in placebo. These changes warrant inclusion in labeling. Although the changes are relatively small and resolved without intervention,

prescribers should be made aware because they occurred relatively frequently. Refer to Dr. Higginbotham's analyses in the clinical review for additional details.

ECG

ECGs were obtained at baseline and Week 24 in trials contributing to the placebo-controlled pool. Changes in ECG parameters were assessed descriptively using changes in measures of central tendency and categorically using shifts from baseline. There were no meaningful mean changes or shifts. In a consult memorandum dated March 5, 2017 authored by Dr. Christine Garnett, the QT Interdisciplinary Review Team agreed that a thorough QT study would not be required to support registration, because the monoclonal antibodies have a low likelihood of direct ion channel interactions, and nonclinical and clinical QTc data collected during the clinical development program to that point did not suggest an effect on the QTc interval.

Immunogenicity

Development of anti-drug antibodies (ADA) was assessed throughout the trials all trials. No patients developed ADA in any trial.

Adverse Events of Special Interest

Anaphylactic Reactions

Anaphylactic reactions were an Adverse Event of Special Interest (AESI). The single case is discussed in detail earlier in this section of this review, under the sub-heading, *Deaths, Serious Adverse Events, and Discontinuations*.

Infusion Reactions

Investigators were instructed to suspect infusion reaction when certain TEAEs (including infusion site pruritus, pyrexia, weakness, nausea, and nasal congestion observed in the placebo-controlled trials) occurred during an infusion or within two hours post-infusion. Infusion reactions occurred more frequently in patients treated with evinacumab-dgnb than those receiving placebo (7% vs. 4%). Infusion reactions warrant inclusion in Section 6 of labeling.

Of note, the placebo infusion in clinical trials contained the same components (Water for injection, histidine, L-arginine-HCl, L-proline, polysorbate 80) as the evinacumab-dgnb investigational product, excluding the evinacumab-dgnb purified protein. Thus, the observed imbalance may underestimate the incidence relative to inert placebo.

There were no significant findings for other AESIs including allergic reactions (no difference from placebo), hepatic events, musculoskeletal disorders (including myopathy), neurologic or neurocognitive events, new-onset or worsening diabetes mellitus, pancreatitis, or cataracts.

Demographic Subgroups

A numerically higher percentage of patients ≥ 65 years of age than younger patients experienced at least one adverse event compared to placebo when treated with evinacumab-dgnb 5 mg/kg or 15 mg/kg. Overall, 74% of patients in both the evinacumab-dgnb and placebo arms experienced at least one TEAE. In contrast, in the subset of patients ≥ 65 years of age, 90% of patients experienced at least one TEAE compared to 57% placebo. Conversely, in the

subset of patients <65 years of age, 71% experienced a TEAE versus 77% placebo. The percentages of patients experiencing at least one TEAE was similar between the evinacumab-dgnb 5 mg and 15 mg treatment arms for all subgroups. Small sample size and small numbers of AEs limit interpretation of these subgroup data.

Supportive Safety Data

In general, the incidence of overall, mild, and moderate TEAEs in open-label trials was similar to that observed in the placebo-controlled pool. Slightly more severe TEAEs were observed in open-label data, but there was no difference in the incidence or character of SAEs (10% in placebo-controlled versus 9-12% in open-label data). Refer to the clinical review for details.

There were two deaths in open-label extension trials, both male patients in their 50s with extensive ASCVD history who experienced CV events.

The most frequent adverse events observed in the open-label trials were generally consistent with those observed in the placebo-controlled trials. Refer to the clinical review for details.

Elevations in CK >10× the upper limit of normal (ULN) occurred in four patients and ALT/AST elevations >3× (ULN) occurred in two patients in long-term, open-label trials of evinacumab-dgnb, but lack of a control group and presence of confounders in case narratives (strenuous exercise, concomitant medication) limit interpretation of these findings.

Teratogenicity, Pregnancy, and Lactation

Nonclinical data in rabbits suggest that evinacumab-dgnb is teratogenic. The findings warrant inclusion in labeling (Section 8), because the relevance of the animal findings to humans cannot be excluded, the severity of fetal findings in rabbits, and the occurrence at systemic exposures below the human dose. The risk can be addressed through patient selection and use of contraception. One patient in Study 1629 became pregnant two weeks after receiving the first dose of evinacumab-dgnb. The patient discontinued investigational product and delivered a healthy term infant.

The Division of Pediatric and Maternal Health (DPMH) recommends issuing a postmarketing requirement (PMR) for a single-arm Pregnancy Safety Study in women exposed to evinacumab-dgnb during pregnancy and a PMR for a milk-only lactation study to assess concentrations of evinacumab-dgnb in breast milk and the effects on the breastfed infant.

The clinical team agrees with the pregnancy study but recommends against the lactation study. Although it is quite likely that pregnant patients will be exposed to evinacumab-dgnb early in gestation because of its long half-life, it is unlikely that any patients would remain on the drug and carry a pregnancy to term. Human IgG is expressed in breast milk, and thus it is highly likely that evinacumab-dgnb, a human IgG, is expressed in breast milk. Even if a small number of patients were successfully recruited to confirm that evinacumab-dgnb is present in breast milk, it would not be possible to draw meaningful conclusions about the effects on the breastfed infant with such a small sample size. DDLO met with DPMH on January 13, 2021 to discuss the lactation study and DPMH agreed with the decision not to issue a lactation PMR. A

lactation study could be considered if evinacumab-dgnb is subsequently approved for use in a broader population.

Pediatrics

Overall, 13 pediatric participants received at least one dose of open-label study treatment. The median duration of evinacumab-dgnb treatment at the time of the 120-day Safety Update cutoff was 33 weeks, and the range was 4 to 61 months. The clinical reviewer, Dr. Craig, concluded that the findings were generally consistent with those in adult patients, but that lack of a control arm and small sample size limit interpretability of the data. I concur. Refer to Dr. Craig's review (the pediatric sections within the FDA clinical review) for details.

There were no deaths, suspected cardiovascular events, or treatment discontinuations in any pediatric patient. No pediatric patients experienced an infusion reaction or anaphylaxis. One patient experienced two SAEs because of vascular complications of apheresis access.

AESI occurring in pediatric patients included potentially clinically significant value (PCSV) for alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in two pediatric patients with ALT >2× ULN but ≤3× ULN and for CK above baseline in 3 patients, none >10× ULN and one >5× ULN associated with exercise. No pediatric patient experienced other AESIs.

There were no notable findings in Dr. Craig's review related to growth and development or sexual maturation safety findings, but the number of patients was too small to make any meaningful assessment of growth and development.

No pediatric patients had a positive response in the ADA assay.

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

Postmarketing

The use and administration of evinacumab-dgnb in the postmarket setting is anticipated to be similar to its use and administration in clinical trials. The most serious reactions associated with evinacumab-dgnb, such as anaphylaxis or infusion reactions, are anticipated to occur during, or within several hours after, infusion administration, when patients are being observed by healthcare personnel.

For patients with HoFH whose hyperlipidemia is generally resistant to other therapies, the significant magnitude of LDL-C reduction with evinacumab-dgnb clearly outweighs its risks. It remains unknown whether the benefit-risk consideration would be favorable in other patient populations in whom the anticipated treatment effect would be comparable to that of other approved therapies (high-intensity statins and PCSK9 inhibitors). The limited safety database warrants a Limitation of Use in labeling, stating that the safety and effectiveness have not been established in patients with other causes of hypercholesterolemia, including those with HeFH.

Conclusions

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

Systemic hypersensitivity, including anaphylaxis, may be serious, require intervention, or lead to treatment discontinuation. The risk can be mitigated with monitoring and treatment interruption. Communication of the risk can be addressed adequately in labeling.

Evinacumab-dgnb is teratogenic based on nonclinical evidence. 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-dgnb in pregnancy is necessary

Evinacumab-dgnb is associated with transient changes to vital signs during and shortly after infusion, including decreased diastolic blood pressure and increased heart rate. Changes are transient but should be communicated to prescribers.

Evinacumab-dgnb 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. Theoretical risks include decreased HDL-C and very low LDL-C, although no evidence of adverse consequence was observed in clinical trials.

For patients with HoFH whose hyperlipidemia is generally resistant to other therapies, the significant magnitude of LDL-C reduction with evinacumab-dgnb clearly outweighs its risks. It remains unknown whether the benefit-risk consideration would be favorable in other patient populations.

9. Advisory Committee Meeting

An Advisory Committee Meeting was not convened for this application. The Division and the Applicant had achieved general agreement on the necessary components of the development program at the Type C meeting conducted in February 2017 and the appropriate data cutoffs to support filing of an application at the pre-BLA meeting held in October 2019.

The design of the Phase 3 trials, including the primary endpoint, was consistent with other development programs for HoFH. Percent change in LDL-C has previously served as the basis for conventional approval in this population.

Efficacy data were convincing and clinically meaningful, and safety concerns would not preclude a favorable benefit-risk consideration in the intended population.

10. Pediatrics

Efficacy and Safety in Pediatric Patients

The application provides substantial evidence of effectiveness to support an indication for pediatric patient with HoFH aged 12 years and older. Refer to the *Pediatric Efficacy* and *Pediatrics* sub-headings within the *Efficacy* and *Safety* sections of this review, respectively, and the FDA clinical review for details. The data are summarized here.

With the initial BLA submission, the efficacy data included only one pediatric patient. The applicant submitted additional open-label data for 13 pediatric patients during the review cycle. Among the 13 pediatric participants enrolled and treated, 11 were treatment-naïve and 2 were rollovers from Study 1629. All patients were ongoing in the trial and none had discontinued study treatment prematurely.

In the patients with available data, the mean change from baseline in LDL-C was -51% at 16 weeks (n=11) and -52% at 24 weeks (n=9). Other lipid parameters, including HDL-C, TG and TC, were also reduced at these timepoints. Refer to the *Pediatric Efficacy* subheading in the *Efficacy* section of this review for additional discussion.

Safety findings were generally consistent with those in adult patients, but lack of a control arm and small sample size limit interpretability of the data. The benefit-risk consideration remains favorable, nonetheless. Refer to the *Pediatrics* subheading in the *Safety* section of this review for additional discussion.

Other Pediatric Issues

FDA granted Orphan Designation to evinacumab-dgnb for the treatment of HoFH; therefore, the application is exempt from the requirements of the Pediatric Research Equity Act (PREA). No additional pediatric assessment is required.

11. Other Relevant Regulatory Issues

Clinical Inspections

The Office of Scientific Investigations (OSI) concluded that the clinical site inspections support the validity of the data. Refer to the Clinical Inspection Summary authored by Dr. Cynthia Kleppinger for details. I concur with Dr. Kleppinger's recommendation.

The inspection consisted of two domestic clinical investigator sites, one foreign clinical investigator site, and the sponsor. Planned foreign onsite inspections could not be completed because of the ongoing COVID-19 pandemic. A remote regulatory assessment of source records was performed for Dr. Frederick Raal's site in South Africa, but remote data investigation of source records was not feasible for Dr. Genovefa Kolovou's site in Greece because of local restrictions.

Clinical inspections and regulatory assessment (for the foreign site) were conducted for Study 1629, the 24-week, double-blind, placebo-controlled trial with a 24-week open-label extension,

and Study 1719, the long-term, open-label study. All three clinical sites assessed enrolled patients in both trials, including both rollover and de novo patients in Study 1719.

Inspection of the two domestic clinical sites for Dr. Robert Rosenson in New York, NY and Dr. Traci Turner in Cincinnati, OH, inspection of the sponsor, and regulatory review of Dr. Raal's site all revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

In summary, clinical inspections support validity of the data.

Financial Disclosures

The Applicant disclosed financial interests and arrangements with investigators. One sub-investigator, whose site contributed one patient, had disclosable interests. The disclosed interest did not impact overall data integrity, because of the trial design features (randomized, double-blind design, central laboratory, and independent DMC) and the minimal contribution of the site to overall trial data.

Proprietary and Non-Proprietary Names

On February 28, 2020, the Division of Medication Error Prevention and Analysis (DMEPA) found the proposed suffix -dgnb acceptable and recommended revision of the nonproprietary name throughout labeling to evinacumab-dgnb. I concur with the recommendation. Refer to the DMEPA Suffix Review for Non-Proprietary Name authored by Carlos Mena-Grillasca, BS Pharm and finalized on May 21, 2020, for details.

The applicant submitted a list of 8 suffixes, in their order of preference, to be used in the nonproprietary name of their product. DMEPA concluded that the second proposed suffix, -dgnb, is not too similar to any other products' suffix designation, does not look similar to the names of other currently marketed products, is devoid of meaning, does not include any abbreviations that could be misinterpreted, and does not make any misrepresentations with respect to safety or efficacy of the product.

DMEPA also concluded that the proposed proprietary name Evkeeza is acceptable, and I concur with the recommendation. Refer to the proprietary name memorandum authored by Dr. Melina Fanari for details. DMEPA identified no concerns related to potential misbranding or name confusion with other products.

12. Labeling

Labeling recommendations also encompass recommendations from DMEPA described in the labeling review authored by Dr. Ariane Conrad, recommendations from the Office of Prescription Drug Promotions (OPDP) authored by Dr. Charuni Shah, and recommendations regarding Pregnancy and Lactation Labeling Rule (PLLR) from the DPMH consult authored by Dr. Carrie Ceresa.

Prescribing Information

The following summarizes changes to proposed labeling and highlights areas of disagreement with the applicant.

- **INDICATIONS AND USAGE section:**
 - Removed adjunct to diet.
 - Retained the proposed pediatric indication.
 - Added *Limitation of Use* stating that the safety and effectiveness have not been established in other populations with hyperlipidemia, including HeFH.
 - Added *Limitation of Use* stating that the effect on cardiovascular morbidity and mortality has not been established.
- **DOSAGE AND ADMINISTRATION section:**
 - Added instruction on timing of assessing the effects of therapy.
 - Made substantial edits on administration instructions as advised by DMEPA.
- **CONTRAINDICATIONS section:**
 - Retained contraindication for history of serious hypersensitivity reaction.
- **WARNINGS AND PRECAUTIONS section:**
 - Retained serious hypersensitivity reactions but added data (patient with anaphylaxis) and removed information about infusion-site reactions.
 - Added potential for embryofetal toxicity, recommendation to consider pregnancy testing prior to initiation, and recommendations for contraception in patients who may become pregnant.
- **ADVERSE REACTIONS**
 - Revised adverse reactions table and text, consistent with review findings.
 - Created separate sections for serious hypersensitivity reaction and infusion reactions.
 - Added data on transient changes in blood pressure and heart rate.
- **USE IN SPECIFIC POPULATIONS section:**
 - Revised information about embryofetal toxicity consistent with nonclinical review.
 - Added pregnancy testing and contraception recommendations.
 - Revised geriatric section to state that the safety data were insufficient to determine if older patients respond differently; [REDACTED] (b) (4)
- **CLINICAL PHARMACOLOGY section:**
 - Removed [REDACTED] (b) (4)
- **CLINICAL STUDIES section:**
 - Revised description of patients with genetic variants consistent with limited LDLR function on in vitro assays and variants predicted to result in limited LDLR function by mutation analysis.
 - Removed [REDACTED] (b) (4)
 - Removed [REDACTED] (b) (4)

- Removed inferential statistics and recommended formatting revisions to table summarizing percent change from baseline in LDL-C and other lipid parameters.
- Removed (b) (4).
- Replaced Forest Plot of treatment effect across subgroups with a statement in the text describing that the treatment effect was similar across subgroups.
- *PATIENT COUNSELING* section:
 - Revised for consistency with changes described above.

Other Labeling

With guidance from the Division of Medical Policy Programs (DMPP) and OPDP, we revised the Patient Prescribing Information, consistent with the Prescribing Information and current practices.

13. Postmarketing

Postmarketing Risk Evaluation and Mitigation Strategies

A Risk Evaluation and Mitigation Strategy (REMS) is not required to ensure safe use of the product. The clinical reviewers and the Division of Risk Management (DRM) agree that the benefit-risk profile for evinacumab-dgnb is favorable in the intended population, and that the identified risks may be adequately mitigated with labeling. I concur with the team’s recommendation. Refer to the DRM review authored by Dr. Mei-Yean Chen for additional details.

Other Postmarketing Requirements and Commitments

Postmarketing Requirements

1. Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Evkeeza (evinacumab) during pregnancy to assess the 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. Data collected retrospectively will be analyzed separately and reported with the interim and final study reports.

Draft Protocol Submission:	August 2021
Final Protocol Submission:	February 2022
Interim Study Report:	February 2023
	February 2024
	February 2025
	February 2026
	February 2027
	February 2028
	February 2029
	February 2030

	February 2031
	February 2032
	February 2033
Study Completion:	February 2033
Final Report Submission:	August 2033

Postmarketing Commitments

1. Provide data from one media fill using the product-specific container closure system and product specific setup equipment to demonstrate adequate evinacumab-dgnb drug product (b) (4) manufacture.

Final Report Submission: May 2021

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/

JOHN M SHARRETTS
02/11/2021 11:24:50 AM

ELLIS F UNGER
02/11/2021 11:49:24 AM

I was involved in the drafting of this review memorandum and I agree with its contents and conclusions. The document serves as the summary review for the Office of Cardiology, Hematology, Endocrinology, and Nephrology.