

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211617Orig1s000

INTEGRATED REVIEW

Executive Summary

Interdisciplinary Assessment

Appendices

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number	211617
Priority or standard	Standard
Submit date	2/26/2019
Received date	2/26/2019
PDUFA goal date	2/26/2020
Division/office	Division of Metabolism and Endocrinology Products (DMEP)
Review completion date	2/25/2020
Established name	Bempedoic acid and ezetimibe
(Proposed) trade name	Nexlizet
Pharmacologic class	an adenosine triphosphate-citrate lyase (ACL) inhibitor and a cholesterol absorption inhibitor
Code name	ETC-1002/ezetimibe
Applicant	Esperion Therapeutics, Inc.
Dose form/formulation	Tablets, 180 mg/10 mg
Dosing regimen	One tablet daily
Applicant proposed indication(s)/population(s)	Adjunct to diet (b) (4) who require additional lowering of low-density lipoprotein cholesterol (LDL-C).
Proposed SNOMED indication	55822004 (hyperlipidemia)
Regulatory action	Approval
Approved indication(s)/population(s) (if applicable)	adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C
Approved SNOMED indication	55822004 (hyperlipidemia)

Table of Contents

Table of Tables	v
Table of Figures	viii
Glossary.....	1
I. Executive Summary.....	3
1. Summary of Regulatory Action	3
2. Benefit-Risk Assessment.....	5
II. Interdisciplinary Assessment.....	9
3. Introduction	9
3.1. Approach to the Review	10
4. Patient Experience Data	12
5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology.....	13
5.1. Nonclinical Assessment of Potential Effectiveness.....	17
6. Evidence of Benefit (Assessment of Efficacy)	18
6.1. Assessment of Dose and Potential Effectiveness	18
6.2. Design of Clinical Trials Intended to Demonstrate Benefit to Patients.....	21
6.2.1. Trial Design.....	21
6.2.2. Eligibility Criteria	22
6.2.3. Statistical Analysis Plan.....	24
6.3. Results of Analyses of Clinical Trials/Studies Intended to Demonstrate Benefit to Patients.....	26
6.3.1. Patient Disposition, Demographics, and Baseline Characteristics	26
6.3.2. Efficacy Results	30
6.4. Review Issues Relevant to Evaluation of Benefit.....	35
6.4.1. Demonstration of Efficacy	35
6.4.2. Data Integrity Issue	35
6.4.3. Selection of LDL Analysis Windows	36
7. Risk and Risk Management.....	38
7.1. Potential Risks or Safety Concerns Based on Nonclinical Data.....	38
7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug- Specific Factors	39
7.3. Potential Safety Concerns Identified Through Postmarket Experience	39
7.4. FDA Approach to the Safety Review	40
7.5. Adequacy of the Clinical Safety Database	40
7.6. Safety Findings and Safety Concerns Based on Review of the Clinical Safety Database	41
7.6.1. Overall Adverse Event Summary.....	41
7.6.2. Deaths.....	41

7.6.3. Serious Adverse Events.....	41
7.6.4. Dropouts and/or Discontinuations Due to Adverse Events.....	42
7.6.5. Treatment-Emergent Adverse Events	44
7.6.6. Laboratory Findings	46
7.7. Review Issues Relevant to Evaluation of Risk.....	47
7.7.1. Hyperglycemia	47
7.7.2. Safety of Triple LMT Administration.....	50
8. Therapeutic Individualization	53
8.1. Intrinsic Factors	53
8.2. Drug Interactions	54
8.3. Pediatric Labeling/Plans for Pediatric Drug Development	54
8.4. Pregnancy and Lactation.....	54
9. Product Quality	58
9.1. Device or Combination Product Considerations	58
10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure	59
11. Advisory Committee Summary.....	60
III. Appendices.....	61
12. Summary of Regulatory History	61
13. Pharmacology Toxicology: Additional Information and Assessment	62
13.1. Summary Review of Studies Submitted Under IND	62
13.1.1. Pharmacology.....	62
13.1.1.1. Primary Pharmacology	62
13.1.1.2. Secondary Pharmacology	63
13.1.1.3. Safety Pharmacology.....	63
13.1.1.4. ADME/PK	64
13.1.1.5. Toxicokinetic Data	65
13.1.2. Toxicology	66
13.1.2.1. Genetic Toxicology	70
13.1.2.2. Carcinogenicity.....	71
13.1.2.3. Reproductive and Developmental Toxicity.....	72
13.2. Individual Reviews of Studies Submitted to the NDA.....	76
14. Clinical Pharmacology: Additional Information and Assessment	77
14.1. In Vitro Studies.....	77
14.2. In Vivo Studies	77
15. Trial Design: Additional Information and Assessment.....	88
16. Efficacy: Additional Information and Assessment	96

16.1. Patient Disposition, Demographics, and Baseline Characteristics: Full Analysis Set (Including Sites 1028, 1058, and 1068).....	96
16.2. Primary Endpoint, Additional Analyses	100
16.3. Secondary and Exploratory Endpoints	103
17. Clinical Safety: Additional Information and Assessment	106
17.1. Vital Signs	106
17.1.1. Trial 053, Excluding Sites 1028, 1058, and 1068	106
17.1.2. Trial 053, Full Analysis Set	106
17.2. ECGs.....	107
17.2.1. Trial 053, Excluding Sites 1028, 1058, and 1068	107
17.2.2. Trial 053, Full Analysis Set	107
17.3. Adverse Events	108
17.3.1. Recoded Adverse Events.....	108
17.3.2. Adverse Events for Trial 053, Full Analysis Set.....	109
18. Mechanism of Action/Drug Resistance: Additional Information and Assessment.....	115
19. Other Drug Development Considerations: Additional Information and Assessment.....	115
20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections).....	116
21. Labeling Summary of Considerations and Key Additional Information	128
22. Postmarketing Requirements and Commitments	128
23. Financial Disclosure	130
24. References	131
25. Review Team.....	131

Table of Tables

Table 1. Administrative Application Information	i
Table 2. Benefit-Risk Framework.....	5
Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations ¹ for Bempedoic Acid-Ezetimibe FDC.....	11
Table 4. Patient Experience Data Submitted or Considered.....	12
Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics.....	13
Table 6. Drug Exposure at Steady State	14
Table 7. Food Effect	15
Table 8. Dose-Ranging Studies Conducted for Bempedoic Acid.....	18
Table 9. Patient Screening and Randomization, Trial 053	26
Table 10. Patient Dispositions: Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053.....	27
Table 11. Patient Demographics, Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053.....	28
Table 12. Baseline Efficacy Parameters, Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053.....	29
Table 13. Primary Endpoint, Percent Change From Baseline to Week 12 in LDL-C, ¹ Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053	30
Table 14. Key Secondary Endpoint, Percent Change From Baseline to Week 12 in Non-HDL-C, ¹ Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053...31	
Table 15. Key Secondary Endpoint, Percent Change From Baseline to Week 12 in TC, ¹ Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053.....	32
Table 16. Key Secondary Endpoint, Percent Change From Baseline to Week 12 in Apo-B, ¹ Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053	32
Table 17. Key Secondary Endpoint, Percent Change From Baseline to Week 12 in hsCRP, ¹ Observed Values in Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053.....	33
Table 18. Percent Change in LDL-C From Baseline to Week 12, Observed Values in Full Analysis Set, Trial 053	36
Table 19. LDL-C Analysis Visit Windows Defined in Trial 053 SAP	37
Table 20. LDL-C Analysis Visit Windows Defined in Trials 040, 046, 047, and 048 SAP	37
Table 21. Bempedoic Acid and Ezetimibe Safety Margins for Coadministration in 91- Day Combination Rat Study	39
Table 22. Duration of Exposure, Safety Population, Trial 053, Excluding Sites 1028, 1058, and 1068.....	40
Table 23. Overview of Adverse Events, ¹ Controlled Trial Safety Population, Trial 053, Excluding Sites 1028, 1058, and 1068, 12 Weeks.....	41

Table 24. Serious Adverse Events by Descending Difference Order, Safety Population, Trial 053, Excluding Sites 1028, 1058, and 1068	42
Table 25. Adverse Events Leading to Discontinuation, Safety Population, Trial 053, Excluding Sites 1028, 1058, and 1068.....	43
Table 26. Adverse Events ¹ Occurring at 1% Higher Frequency in Treatment Arm Than Comparator Arm, ² Phase 3 Safety Population, Excluding Sites 1028, 1058, and 1068.....	44
Table 27. Patients Meeting Laboratory Abnormality Criteria, From Baseline Through Week 12, Safety Population, Trial 053, Excluding Sites 1028, 1058, and 1068	46
Table 28. Mean Change From Baseline in Selected Laboratory Parameters, Safety Population, Excluding Sites 1028, 1058, and 1068	47
Table 29. Mean and Median Change From Baseline in FPG	48
Table 30. Absolute FPG Values, Baseline to Week 12, by Diabetic Status	49
Table 31. Overview of Adverse Events, ¹ Safety Population, High CV Risk Pool, Trials 040 and 047, 52 Weeks, by Baseline LMT	50
Table 32. Serious Adverse Events by Descending Difference (>0.1%) Order, Safety Population, High CV Risk Pool, Trials 040 and 047, Patients on Background Statin + Ezetimibe Therapy	51
Table 33. Adverse Events Leading to Discontinuation by Descending Difference (>0.1%) Order, Safety Population, High CV Risk Pool, Trials 040 and 047, Patients on Background Statin + Ezetimibe Therapy	52
Table 34. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation, Bempedoic Acid	55
Table 35. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation, Ezetimibe	56
Table 36. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation, Bempedoic Acid and Ezetimibe FDC.....	56
Table 37. Summary of TK Data From Combination 90-Day General Toxicity and EFD Study With Bempedoic Acid and Ezetimibe.....	65
Table 38. TK Parameters for ETC-1002 and ESP15228 in the Rat 90-Day Combination Study	65
Table 39. TK Parameters for Ezetimibe and Ezetimibe-Glucuronide in the Rat 90-Day Combination Study	65
Table 40. TK Parameters for ETC-1002 and ESP15228 in the Rat Combination EFD Study (GD 17).....	66
Table 41. TK Parameters for Ezetimibe and Ezetimibe-Glucuronide in the Rat Combination EFD Study (GD 17)	66
Table 42. Methods of 91-Day Oral Combination Toxicity Study in the Rat.....	69
Table 43. Observations and Results of 91-Day Oral Combination Toxicity Study in the Rat	69

Table 44. Methods of Oral Combination Embryo-Fetal Developmental Study in the Rat	75
Table 45. Observations and Results of Oral Combination Embryo-Fetal Developmental Study in the Rat	76
Table 46. Clinical Studies Conducted Under FDC Development Program.....	77
Table 47. Arithmetic Mean (SD) PK Parameters for Bempedoic Acid and Ezetimibe, Study 1002FDC-034	78
Table 48. Geometric Mean T/R Ratio (90% CI) for PK Parameters of Bempedoic Acid and Ezetimibe, Study 1002FDC-034	80
Table 49. Geometric Mean T/R Ratio (90% CI) for PK Parameters of Bempedoic Acid and Ezetimibe, Trial 1002FDC-049	83
Table 50. Geometric Mean Fed/Fasted Ratio (90% CI) for PK Parameters of Bempedoic Acid and Ezetimibe, Study 1002FDC-055	85
Table 51. Validation Summary of Bioanalytical Method for Bempedoic Acid	86
Table 52. Validation Summary of Bioanalytical Method for Ezetimibe	87
Table 53. Patient Disposition, Full Analysis Set, Trial 053.....	96
Table 54. Patient Demographics, Full Analysis Set, Trial 053.....	97
Table 55. Baseline Efficacy Parameters, Full Analysis Set, Trial 053	99
Table 56. Sensitivity Analysis, Percent Change From Baseline to Week 12 in LDL-C, ¹ Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053	100
Table 57. LDL-C (mg/dL) Summary Statistics, Observed Values in Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053.....	100
Table 58. Subgroup Analysis on Percent Change in LDL-C From Baseline to Week 12, ¹ Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053.....	101
Table 59. Exploratory Analysis: Absolute Change From Baseline to Week 12 in hsCRP, ¹ Observed Values in Full Analysis Set Excluding Sites 1028, 1058, and 1068, ² Trial 053	103
Table 60. Exploratory Analysis: Patients Who Achieved Normal hsCRP ¹ at Week 12, Observed Values in Full Analysis Set Excluding Sites 1028, 1058, and 1068, ² Trial 053.....	104
Table 61. Exploratory Secondary Endpoint: Percent Change From Baseline to Week 12 in HDL-C, ¹ Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053.....	104
Table 62. Exploratory Secondary Endpoint: Percent Change From Baseline to Week 12 in TG, ¹ Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053	104
Table 63. Sensitivity Analysis Using Analysis Windows Defined by Trial 040 SAP From NDA 211616-Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053.....	105
Table 64. Vital Signs Mean Change From Baseline Over Time, Safety Population, Trial 053, Excluding Sites 1028, 1058, and 1068.....	106

Table 65. Vital Signs Mean (SD) Change From Baseline Over Time, Safety Population, Trial 053	106
Table 66. Patients Meeting ECG Abnormality Criteria, From Baseline Through Week 12, Safety Population, Trial 053, Excluding Sites 1028, 1058, and 1068	107
Table 67. Clinically Significant ECG Abnormalities, From Baseline Through Week 12, Safety Population, Trial 053, Excluding Sites 1028, 1058, and 1068	107
Table 68. Patients Meeting ECG Abnormality Criteria, From Baseline Through Week 12, Safety Population, Trial 053	107
Table 69. Clinically Significant ECG Abnormalities, From Baseline Through Week 12, Safety Population, Trial 053	108
Table 70. Recoded Adverse Events	108
Table 71. Overview of Adverse Events, ¹ Controlled Trial Safety Population, Trial 053, Week 12	109
Table 72. Serious Adverse Events by Descending Difference Order, Safety Population, Trial 053	110
Table 73. Adverse Events Leading to Discontinuation, Safety Population, Trial 053	111
Table 74. Adverse Events ¹ Occurring at 1% Higher Frequency in Treatment Arm Than Comparator Arm, ² Phase 3 Safety Population.....	112
Table 75. Patients Meeting Laboratory Abnormality Criteria, From Baseline Through Week 12, Safety Population, Trial 053	114
Table 76. Mean Change From Baseline in Selected Laboratory Parameters, Safety Population	115
Table 77. Covered Clinical Studies: FDC-053	130
Table 78. Reviewers of Integrated Assessment	131
Table 79. Additional Reviewers of Application	131
Table 80. Signatures of Reviewers	132

Table of Figures

Figure 1. Mechanism of Action of Bempedoic Acid and Ezetimibe.....	17
Figure 2. Placebo-Adjusted LS Mean Percent Change From Baseline by Daily Bempedoic Acid Dose Pooled Across Phase 2 Studies ¹ :.....	19
Figure 3. Study Design, Trial 053.....	21
Figure 4. Multiplicity Control for Primary and Key Secondary Endpoints.....	25
Figure 5. Median (IQR) LDL-C (mg/dL) Over Time, Observed Values in Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053.....	31
Figure 6. Median (IQR) hsCRP (mg/dL) Over Time, Observed Values in Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053.....	33

Figure 7. Arithmetic Mean Plasma Bempedoic Acid Concentration in Healthy Subjects Following Single Oral Dose of Bempedoic Acid 180 mg Coadministered With Ezetimibe 10 mg as Individual Tablets or Fixed-Dose Combination.....	79
Figure 8. Arithmetic Mean Plasma Ezetimibe Concentration in Healthy Subjects Following Single Oral Dose of Bempedoic Acid 180 mg Coadministered With Ezetimibe 10 mg as Individual Tablets or Fixed-Dose Combination.....	80
Figure 9. Overview of Study Design, Trial 1002FDC-049	81
Figure 10. Arithmetic Mean (+SD) Plasma Bempedoic Acid Concentrations in Healthy Subjects Following Administration of Single Oral Dose of Bempedoic Acid 180 mg Alone and With Steady-State Ezetimibe.....	82
Figure 11. Arithmetic Mean (+SD) Plasma Unconjugated Ezetimibe in Healthy Subjects Following Administration of Single Oral Dose of Ezetimibe 10 mg Alone and With Steady-State Bempedoic Acid.....	82
Figure 12. Box Plot for Trough Plasma Bempedoic Acid Concentration at Various Weekly Intervals in Patients With Hyperlipidemia	83
Figure 13. Box Plot for Trough Plasma Ezetimibe Concentration at Various Weekly Intervals in Patients With Hyperlipidemia.....	83
Figure 14. Arithmetic Mean (+SD) Plasma Bempedoic Acid Concentrations in Healthy Subjects Following Administration of Single Oral Dose of FDC Tablet Under Fasted and Fed Conditions	84
Figure 15. Arithmetic Mean (+SD) Plasma Ezetimibe Concentrations in Healthy Subjects Following Administration of Single Oral Dose of FDC Tablet Under Fasted and Fed Conditions.....	85
Figure 16. Treatment Difference of FDC vs. Placebo by Subgroup in Percent Change in LDL-C From Baseline to Week 12, Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053	102
Figure 17. Percent Change in LDL-C From Baseline to Week 12 vs. Baseline LDL-C, Observed Values in Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053.....	103

Glossary

ACL	adenosine triphosphate-citrate lyase
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AMPK	adenosine monophosphate-activated protein kinase
ANCOVA	analysis of covariance
Apo-B	apolipoprotein B
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BUN	blood urea nitrogen
CDER	Center for Drug Evaluation and Research
C _{max}	maximum plasma concentration
CoA	coenzyme A
CSR	clinical study report
CV	cardiovascular
CVD	cardiovascular disease
DPMH	Division of Pediatric and Maternal Health
eGFR	estimated glomerular filtration rate
EZE	ezetimibe
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GLP	good laboratory practice
HDL-C	high-density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolemia
HMG	3-hydroxy-3-methylglutaryl
hsCRP	high-sensitivity C-reactive protein
IC ₅₀	half maximal inhibitory concentration
IND	investigational new drug
LDL-C	low-density lipoprotein cholesterol
LMT	lipid-modifying therapy
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NOAEL	no observed adverse effect level
OCp	Office of Clinical Pharmacology
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OSIS	Office of Study Integrity and Surveillance
PCSK9	proprotein convertase subtilisin/kexin type 9
PK	pharmacokinetics
PMR	postmarketing requirement
PPAR	peroxisome proliferator activated receptor

NDA 211617

Nexlizet / bempedoic acid and ezetimibe

PPAR α	peroxisome proliferator activated receptor alpha
PPAR γ	peroxisome proliferator activated receptor gamma
QD	once daily
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
TC	total cholesterol
TG	triglycerides
T _{max}	time to maximum concentration
ULN	upper limit of normal
WBC	white blood cell

I. Executive Summary

1. Summary of Regulatory Action

The benefit-risk analysis for the fixed-dose combination (FDC) product of bempedoic acid and ezetimibe is favorable for an indication as an adjunct to maximally tolerated statin therapy (b) (4) with established cardiovascular disease (CVD) or heterozygous familial hypercholesterolemia (HeFH) who require additional low-density lipoprotein cholesterol (LDL-C) lowering. The data support approval for these conditions of use. All review disciplines support approval.

The pivotal trial (Trial 053) achieved its primary endpoint. The FDC product demonstrated a clinically meaningful reduction in LDL-C relative to placebo, and each component contributed to the overall effect.

A key limitation of the trial was potentially fraudulent data obtained at three clinical sites, which Food and Drug Administration (FDA) excluded from its analysis. The trial was adequately powered despite exclusion of data from these sites, and exclusion of the data did not introduce any apparent bias. On the contrary, data from the excluded sites appeared to be biased toward the null. The pattern of LDL-C lowering from baseline to Week 12 was unusual: approximately -19% with bempedoic acid alone, -14% with ezetimibe alone, but only -13% with combination bempedoic acid and ezetimibe. Approximately 50% of the patients in the active treatment groups at these sites had no detectable investigational product on random sampling, despite reporting compliance with treatment. Additionally, patients in the placebo arm at the three sites experienced LDL-C lowering similar to that observed in the three active treatment arms (-16% from baseline to Week 12). This was divergent from placebo patients at other sites, who experienced a small increase in LDL-C from baseline to Week 12.

The safety profile of the combination of bempedoic acid and ezetimibe appears consistent with the profiles of the individual components. There is no evidence of increased risk with concomitant therapy or triple therapy (bempedoic acid, ezetimibe, and high-intensity statin). There was only limited data from Trial 053 due to short trial duration and small sample size. Nonetheless, review of safety data from Trials 1002-040 and 1002-047 (pivotal trials supporting NDA 211616) demonstrated no difference in the safety profile of patients treated with statin/bempedoic acid compared to patients treated with statin/bempedoic acid/ezetimibe. In those trials, more than 90% of patients were taking statins and about one-half were on high-intensity statin.

In Trial 053, there was an apparent increase in mean fasting plasma glucose (FPG) in the group of patients assigned to the FDC, but this finding was an artifact caused by small sample size and skewed distribution. Neither bempedoic acid nor ezetimibe monotherapy is associated with elevated fasting glucose. Comparison of median and mean values and histogram plots showed that the FPG distribution in the FDC treatment arm was highly skewed, containing several outliers with elevated FPG. Review of median FPG values demonstrated no meaningful difference in absolute or change-from-baseline results among the four treatment arms.

The clinical pharmacology reviewer supports approval. Dose selection was reasonable based on the clinical program for bempedoic acid (NDA 211616) and the approved dose for the listed drug Zetia (NDA 21445). The systemic exposures of bempedoic acid and ezetimibe were similar when administered as the FDC product (to-be-marketed formulation) or as individual tablets. Although the Applicant used a different formulation of bempedoic acid from the to-be-marketed product in the relative bioavailability study, the Applicant provided sufficient evidence to bridge the formulations.

The nonclinical reviewer supports approval. The Applicant referenced nonclinical pharmacology data from the listed drug Zetia (NDA 21445). Nonclinical pharmacology for bempedoic acid was reviewed as part of the Integrated Review of NDA 211616.

To support safety of bempedoic acid, the Applicant conducted a full nonclinical toxicology program for bempedoic acid, which was also reviewed as part of the Integrated Review of NDA 211616. To support the safety of the FDC product, the Applicant submitted a good laboratory practice (GLP)-compliant 91-day rat repeat-dose general toxicity and an embryofetal toxicity study in rats, both with coadministration of bempedoic acid and ezetimibe. No new clinically relevant target organ toxicity and no additive or synergistic toxicity was observed. Although the safety margin for bempedoic acid was relatively low (<2 times the clinical exposure), the toxicities at that level were due to rodent-specific peroxisome proliferator activated receptor alpha (PPAR α) effects that are not considered relevant to humans.

The Office of Pharmaceutical Quality review team determined that the application meets all standards to support the identity, strength, quality, and purity that it purports, and supports approval.

In summary, the Applicant demonstrated clinically significant LDL-C lowering with the FDC product and contribution of both components to the effect. There were no new safety findings with the combination beyond the previously known safety profile of the components. LDL lowering is generally considered a surrogate for cardiovascular (CV) risk reduction if the reduction is sufficiently robust and the investigational product does not have safety signals raising concern that risk exceeds benefit. The FDC of bempedoic acid and ezetimibe represents an additional therapeutic option in high-risk patients unable to meet goals with standard therapy (maximally tolerated statin with or without a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor).

NDA 211617

Nexlizet / bempedoic acid and ezetimibe

2. Benefit-Risk Assessment

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	<p>Large burden of cardiovascular (CV) disease in United States</p> <ul style="list-style-type: none"> • 93 million U.S. adults (2018) • Leading cause of death in the United States • \$555 billion annual health-care expense (2016) <p>Low-density lipoprotein (LDL) cholesterol (LDL-C) reduction with statins and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors is associated with improved CV outcomes</p> <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 <p>LDL-C reduction with other agents is used in high-risk patients who require additional LDL-C lowering</p> <ul style="list-style-type: none"> • A single outcomes trial with ezetimibe demonstrated incremental benefit (6% relative risk reduction) with moderate LDL-C lowering • Other agents may be used as adjuncts to statins, PCSK9 inhibitors, and ezetimibe, but the incremental effects on outcomes are uncertain <p>Patients with elevated LDL-C treated for primary and secondary prevention of CV events</p> <ul style="list-style-type: none"> • Primary prevention: reduce the risk for development of CV disease • Secondary prevention: reduce the risk for additional CV events 	<p>LDL-C reduction with therapies targeting upregulation of the LDL receptor is a cornerstone of preventive treatment for CV disease. Reduction in LDL-C with statins and PCSK9 inhibitors is associated with decreased CV risk in clinical trials of LDL.</p>

NDA 211617

Nexlizet / bempedoic acid and ezetimibe

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	<p data-bbox="396 230 611 256"><u>Treatment options</u></p> <p data-bbox="396 263 554 289">Monotherapy</p> <ul data-bbox="405 302 1037 451" style="list-style-type: none"> <li data-bbox="405 302 894 328">• Statins (-28% to -60% LDL-C reduction) <ul data-bbox="426 347 1037 451" style="list-style-type: none"> <li data-bbox="426 347 905 373">– High-intensity statin, ≥50% reduction <li data-bbox="426 380 1037 406">– Moderate-intensity statin, 30% to 49% reduction <li data-bbox="426 412 900 438">– Low-intensity statin, <30% reduction <li data-bbox="405 457 848 483">• Ezetimibe (-18% to -20% reduction) <p data-bbox="396 503 579 529">Add-on therapy</p> <ul data-bbox="405 542 1125 604" style="list-style-type: none"> <li data-bbox="405 542 1062 568">• Statin + ezetimibe (-12% to -21% additional lowering)* <li data-bbox="405 574 1125 600">• Statin + PCSK9 inhibitor (-47% to -63% additional lowering) <p data-bbox="396 620 1199 678"><u>Treatment recommendations, 2018 American College of Cardiology/ American Heart Association guidelines</u></p> <p data-bbox="396 685 621 711">Primary prevention</p> <ul data-bbox="405 724 1226 782" style="list-style-type: none"> <li data-bbox="405 724 1226 782">• Moderate-intensity statin to reduce LDL-C by 30%-≥50% depending on calculated CV risk <p data-bbox="396 802 1058 828">Secondary prevention, not very high-risk for recurrence*</p> <ul data-bbox="405 841 1131 867" style="list-style-type: none"> <li data-bbox="405 841 1131 867">• High-intensity statin to reduce LDL-C by ≥50% +/- ezetimibe <p data-bbox="396 886 1012 912">Secondary prevention, very high-risk for recurrence*</p> <ul data-bbox="405 925 1178 984" style="list-style-type: none"> <li data-bbox="405 925 1178 984">• High-intensity statin to reduce LDL-C >70 mg/dL + ezetimibe +/- PCSK9 inhibitor <p data-bbox="396 1003 1226 1146">* Very high-risk for recurrence includes patients with history of multiple major ASCVD events (myocardial infarction, stroke, peripheral artery disease, or recent acute coronary syndrome); or one major ASCVD event plus multiple high-risk conditions (age ≥65, HeFH, diabetes mellitus, hypertension, chronic kidney disease, current smoker, LDL-C ≥100 mg/dL despite maximal therapy, or history of congestive heart failure/ coronary artery bypass graft/ percutaneous coronary intervention).</p> <p data-bbox="396 1166 747 1192"><u>Efficacy of ezetimibe + statins</u></p> <ul data-bbox="405 1205 1226 1354" style="list-style-type: none"> <li data-bbox="405 1205 957 1230">• Concurrent initiation (-12% to 15% reduction) <li data-bbox="405 1237 1136 1263">• Ezetimibe add-on to ongoing statin therapy (-21% reduction) <li data-bbox="405 1269 1226 1354">• Patient access to newer add-on therapies, such as PCSK9 inhibitors, has been challenging due to factors such as expense and refusal of payers to cover 	<p data-bbox="1276 230 1917 380">Current treatment guidelines for LDL-C reduction are based on an individualized approach which considers a patient's overall risk for a CV event, specifically established atherosclerotic cardiovascular disease (ASCVD) and additional risk factors.</p> <p data-bbox="1276 422 1917 756">Moderate- or high-intensity statins are considered first-line therapy for all patients who require LDL-C reduction, depending on risk category. Low-intensity statins are not recommended for any population. Ezetimibe and/or PCSK9 inhibitors are considered second-line, add-on drugs to a background of maximally tolerated statin therapy in patients at highest CV risk who require additional LDL-C reduction. Ezetimibe appears more effective when started as add-on therapy to ongoing background statin use, rather than with concurrent initiation.</p> <p data-bbox="1276 799 1917 857">Statins reduce LDL-C by 30% to 60% depending on the statin intensity.</p> <p data-bbox="1276 899 1917 1114">PCSK9 inhibitors lower LDL-C by an additional 50% to 60%. Other drug categories, such as fibrates or niacin, are generally not considered mainstays of therapy due to mild LDL-lowering ability, limited efficacy, and absence of outcomes data as an adjunct to statins. Additional agents may be used in patients who require additional LDL-C lowering despite optimum therapy.</p>

NDA 211617

Nexlizet / bempedoic acid and ezetimibe

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	<p>In patients with hyperlipidemia who received the fixed-dose combination (FDC) for primary or secondary prevention as add-on to zero lipid-modifying therapy (LMT) (28%) or background statin therapy (60%-70%), FDC lowers LDL compared to placebo by -38% at 12 weeks.</p> <ul style="list-style-type: none"> Both bempedoic acid and ezetimibe contribute to the observed efficacy. No treatment effect interaction was observed for primary versus secondary prevention. No treatment effect interaction was observed for baseline LMT. <p>30% of patients treated with the FDC achieved LDL-C <70 mg/dL, within goal.</p>	<p>The FDC has a reasonable treatment effect compared to currently available therapies for LDL-C reduction. The treatment effect appears similar to moderate-intensity statins, although this must be interpreted with caution given the large percentage of patients (28%) on no baseline LMT. LDL-lowering ability in this trial was demonstrated in patients who are ezetimibe-naïve. It is unknown whether the treatment effect would be similar in patients who switch from ezetimibe to the FDC product. However, patient access to newer add-on therapies, such as PCSK9 inhibitors, has been challenging (expense, refusal of payers to cover), so bempedoic acid may provide an additional option.</p>
Risk and risk management	<p><u>FDC's observed safety profile in clinical trials</u></p> <ul style="list-style-type: none"> The FDC is associated with a low risk for hyperuricemia (4.7%). The FDC is associated with changes across multiple lab parameters including hemoglobin, platelets, blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), and bone alkaline phosphatase. <p>Given the short duration of Trial 053 (12 weeks) and the limited sample size of patients exposed to the FDC product (n=85), the safety profile of the FDC must largely be inferred from the safety profiles of its individual components. However, no new safety signals emerged with coadministration.</p> <p><u>Additional Risks from Bempedoic Acid's Known Safety Profile (NDA 211616)</u></p> <ul style="list-style-type: none"> Bempedoic acid is associated with a low risk for tendon rupture (0.5%). Bempedoic acid is associated with a low risk for increased serum uric acid (3.5%), which may lead to development of gout (1.5%). Bempedoic acid is associated with a low risk for new-onset benign prostatic hyperplasia in men (1.3%). Bempedoic acid is associated with changes across multiple lab parameters including hemoglobin, total white blood cell (WBC), platelets, neutrophils, BUN, creatinine, estimated glomerular filtration 	<p>The safety profile of the FDC product appears generally consistent with bempedoic acid and ezetimibe monotherapies. Bempedoic acid is associated with several serious safety signals, including tendon rupture, development of gout, and new-onset benign prostatic hyperplasia. However, these risks are low incidence, monitorable, and can be adequately addressed through labeling.</p> <p>Bempedoic acid is also associated with numerous changes to lab parameters. These changes are generally amenable to physician monitoring, reversible upon drug discontinuation, and did not require additional medical intervention in clinical trials. Both bempedoic acid and ezetimibe are associated with asymptomatic, reversible elevations in liver enzymes. The incidence did not appear to increase with FDC exposure.</p>

NDA 211617

Nexlizet / bempedoic acid and ezetimibe

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>rate (eGFR), alanine aminotransferase (ALT)/AST, creatine kinase (CK), and bone alkaline phosphatase.</p> <ul style="list-style-type: none"> - Lab changes were generally small and reversible upon drug discontinuation. - For patients with the greatest changes, no evidence of untoward clinical consequence. 	
	<p><u>Additional Risks from Ezetimibe's Known Safety Profile</u> Ezetimibe is associated with asymptomatic elevations in liver enzymes that normalize upon treatment discontinuation.</p>	

Conclusions Regarding Benefit-Risk

Limited options exist for second-line, add-on therapy medications for patients at risk for CV events who have maximized their statin dose yet require additional LDL-C reduction. Approval of the fixed-dose combination (FDC) product of bempedoic acid and ezetimibe would provide an additional option to lower LDL-C in these patients. The treatment effect of the FDC product in the factorial study was a placebo-adjusted reduction of LDL-C of 38% from baseline, and the combination was superior to either product administered alone. The expected LDL-C lowering in clinical practice is clinically meaningful. Furthermore, the safety profile of combination therapy of bempedoic acid and ezetimibe, added on to baseline statin therapy, appears consistent with the known safety profiles of the individual drugs.

The most significant risks associated with the FDC are those identified in the bempedoic acid clinical development program. These include tendon rupture and gout, which may result in significant morbidity, and multiple laboratory abnormalities (decreased hemoglobin and WBC, increased BUN and creatinine) that are monitorable and reversible upon drug discontinuation. Refer to the Integrated Review of NDA 211616 for details. There is no evidence that the combination of bempedoic acid and ezetimibe confers any additional risk compared to bempedoic monotherapy as an adjunct to maximally tolerated statin therapy. Overall, in the intended population, the benefit of the FDC product appears to outweigh any risk associated with taking the drug.

II. Interdisciplinary Assessment

3. Introduction

The Applicant, Esperion Therapeutics, Inc., submitted this New Drug Application (NDA) in support of the following indication:

NEXLIZET, which contains an ACL inhibitor and a cholesterol absorption inhibitor, is indicated as an adjunct to diet [REDACTED] (b) (4) [REDACTED] who require additional lowering of LDL-C. Limitations of Use: The effect of ezetimibe or bempedoic acid on cardiovascular morbidity and mortality has not been determined.

Nexlizet contains bempedoic acid and ezetimibe. Bempedoic acid is an inhibitor of adenosine triphosphate-citrate lyase (ACL), an enzyme in the cholesterol and fatty acid biosynthesis pathways. Ezetimibe is an inhibitor of intestinal cholesterol absorption. The bempedoic acid-ezetimibe fixed-dose combination (FDC) product is administered orally once daily as a 180 mg/10 mg tablet.

Patients with elevated low-density lipoprotein cholesterol (LDL-C) are treated to reduce the risk of developing cardiovascular (CV) disease (primary prevention) or to reduce the risk of additional events in patients with established CV disease (secondary prevention). The 2018 American College of Cardiology/American Heart Association treatment guidelines for LDL-C reduction emphasize an individualized treatment approach to LDL-C reduction based on a patient's CV risk category (primary versus secondary prevention) and calculated predicted risk for future CV events. Statins are considered first-line therapy for all patients who require LDL-C reduction, regardless of CV risk category. Ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are recommended as second-line treatment options as add-on therapy to a background of optimized statin in patients at highest CV risk who require additional LDL-C reduction. Other approved treatment options include fenofibrates and niacin; however, these drug classes are not considered mainstays of therapy due to limited efficacy.

Bempedoic acid (NDA 211616) was approved in the United States on February 21, 2020, for use as an adjunct to maximally tolerated statin therapy in patients with high-density lipoprotein cholesterol (HeFH) or established atherosclerotic cardiovascular disease (ASCVD). Postmarketing data are not yet available. Bempedoic acid is not marketed elsewhere worldwide. Ezetimibe is approved for the treatment of patients with primary hyperlipidemia as a monotherapy or in combination with statins or fenofibrates. The bempedoic acid/ezetimibe fixed-dose combination (FDC) IND was opened in June 2016.

Review issues relating to the evaluation of benefit include:

- Data quality issue at three clinical sites

- Selection of LDL analysis windows
- Selection of LDL analysis windows was not consistent with the analysis windows used in NDA 211616 (bempedoic acid monotherapy)

Selection of analysis windows favored earlier assessments, which may overestimate efficacy

Review issues relating to risk and risk management include:

- Apparent increases in serum fasting plasma glucose
- Safety of triple lipid-modifying therapy (LMT) administration
- The FDC (bempedoic acid plus ezetimibe) is indicated for patients on maximally tolerated statins

3.1. Approach to the Review

For the FDC product, the Applicant's phase 3 clinical development program consisted of a 12-week factorial trial in high CV risk patients on maximally-tolerated statin who required additional LDL-C lowering for primary or secondary prevention (FDC-053). The Applicant also referenced clinical trials conducted under its bempedoic acid application, NDA 211616.

NDA 211617

Nexlizet / bempedoic acid and ezetimibe

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations¹ for Bempedoic Acid-Ezetimibe FDC

Trial Identifier	Trial Population	Trial Design	Regimen (Number. Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
1002FDC-053	Primary and secondary prevention: Patients with hyperlipidemia on maximally-tolerated statin who require additional LDL lowering	Control Type: Placebo-controlled Randomization: 2:2:2:1, stratified by primary versus secondary prevention and baseline statin intensity Blinding: Double blind Biomarkers: LDL-C Innovative design features: Factorial trial	Drug: FDC (bempedoic acid+ezetimibe) Dose: 180 mg +10 mg Number treated: 108 Duration (quantity and units):12 wk Drug: Bempedoic acid Dose: 180 mg Number treated: 110 Duration (quantity and units): 12 wk Drug: Ezetimibe Dose: 10 mg Number treated: 109 Duration (quantity and units): 12 wk Drug: Placebo Number treated: 55 Duration (quantity and units):12 wk	Primary: Percent change from baseline to Week 12 in LDL-C Secondary: Percent change from baseline to Week 12 in non-HDL-C, TC, Apo-B, hsCRP, TG, and HDL	350/382	78 centers in 1 country (U.S.)

Source: Reviewer

¹ Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies

Abbreviations: Apo-B, apolipoprotein B; FDC, fixed-dose combination; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; wk, week

4. Patient Experience Data

No patient experience data were submitted with this application.

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical outcome assessment data submitted in the application		
<input type="checkbox"/>	Patient-reported outcome	
<input type="checkbox"/>	Observer-reported outcome	
<input type="checkbox"/>	Clinician-reported outcome	
<input type="checkbox"/>	Performance outcome	
Other patient experience data submitted in the application		
<input type="checkbox"/>	Patient-focused drug development meeting summary	
<input type="checkbox"/>	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Natural history studies	
<input type="checkbox"/>	Patient preference studies	
<input type="checkbox"/>	Other: (please specify)	
<input checked="" type="checkbox"/>	If no patient experience data was submitted by Applicant, indicate here.	
Data Considered in the Assessment (but Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Perspectives shared at patient stakeholder meeting	
<input type="checkbox"/>	Patient-focused drug development meeting summary report	
<input type="checkbox"/>	Other stakeholder meeting summary report	
<input type="checkbox"/>	Observational survey studies	
<input type="checkbox"/>	Other: (please specify)	

NDA 211617

Nexlizet / bempedoic acid and ezetimibe

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

A high-level summary of clinical pharmacology information is shown in Table 5.

Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information Pharmacologic Activity
Established pharmacologic class	Adenosine triphosphate-citrate lyase (ACL) inhibitor (bempedoic acid); Cholesterol absorption inhibitor (ezetimibe)
Mechanism of action	<p>Bempedoic acid is an ACL inhibitor that lowers low density lipoprotein cholesterol (LDL-C) by inhibition of cholesterol synthesis in the liver. ACL is an enzyme upstream of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase in the cholesterol (and fatty acid) biosynthesis pathway. Bempedoic acid and its active metabolite, ESP15228, require coenzyme A (CoA) activation by very long-chain acyl-CoA synthetase 1 (ACSVL1) to ETC-1002-CoA and ESP15228-CoA, respectively. ACSVL1 is expressed primarily in the liver. Inhibition of ACL by ETC-1002-CoA and ESP15228-CoA results in decreased cholesterol synthesis in the liver and lowers LDL-C in blood via upregulation of LDL receptors.</p> <p>Ezetimibe reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine. The molecular target of ezetimibe has been shown to be the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols. Ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in LDL receptors, resulting in clearance of cholesterol from the blood.</p>
Active moieties	Bempedoic acid-CoA, ESP15228-CoA
QT prolongation	<p>Ezetimibe is rapidly metabolized to ezetimibe-glucuronide. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10%–20% and 80%–90% of the total drug in plasma. In rat model, the metabolite was as potent as the parent compound in inhibiting the absorption of cholesterol.</p> <p>Thorough QT (TQT) study was conducted for the mono component, bempedoic acid. In a randomized, double-blind, placebo- and positive-controlled, parallel-design TQT study in healthy subjects, at a dose of 240 mg (1.3 times the approved recommended dose), bempedoic acid does not prolong the QT interval to any clinically relevant extent. (see <i>review in NDA 211616</i>). For ezetimibe component, no additional TQT study was conducted with the FDC product since an approved ezetimibe dose was used in combination with bempedoic acid.</p>

Characteristic	Drug Information General Information										
Bioanalysis	Plasma concentrations of bempedoic acid and its active metabolite, ESP15228 as well as ezetimibe and its active metabolite, ezetimibe-glucuronide, were determined by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS). The QC sample results for all the analytes met the acceptance criteria, i.e., at least 67% of the QC results were within $\pm 15\%$ of their nominal concentrations. The PK samples were stored and analyzed within the validated storage stability period and conditions.										
Healthy subjects versus patients	Bempedoic acid and ezetimibe PK from the FDC tablet are similar between healthy subjects and patients with hyperlipidemia.										
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	<p>Table 6. Drug Exposure at Steady State</p> <table border="1"> <thead> <tr> <th>Parameter</th> <th>ETC-1002 ($\mu\text{g/mL}$)</th> <th>ESP15228 ($\mu\text{g/mL}$)</th> <th>Ezetimibe (ng/mL)</th> <th>Ezetimibe- Glucuronide (ng/mL)</th> </tr> </thead> <tbody> <tr> <td>Mean C_{trough} (SD) at Week 12</td> <td>9.02 (9.18)</td> <td>1.27 (1.28)</td> <td>3.04 (3.86)</td> <td>87.6 (114)</td> </tr> </tbody> </table> <p>Source: NDA 211616. Module 2.7.2. Summary of Clinical Pharmacology studies</p>	Parameter	ETC-1002 ($\mu\text{g/mL}$)	ESP15228 ($\mu\text{g/mL}$)	Ezetimibe (ng/mL)	Ezetimibe- Glucuronide (ng/mL)	Mean C_{trough} (SD) at Week 12	9.02 (9.18)	1.27 (1.28)	3.04 (3.86)	87.6 (114)
Parameter	ETC-1002 ($\mu\text{g/mL}$)	ESP15228 ($\mu\text{g/mL}$)	Ezetimibe (ng/mL)	Ezetimibe- Glucuronide (ng/mL)							
Mean C_{trough} (SD) at Week 12	9.02 (9.18)	1.27 (1.28)	3.04 (3.86)	87.6 (114)							
Range of effective dose(s) or exposure	BA: LDL-C lowering effect reached a maximum at 180 mg QD, with similar effect size at 240 mg QD. For the FDC tablet, only one dose combination, i.e., 180 mg bempedoic acid/10 mg ezetimibe was investigated.										
Maximally tolerated dose or exposure	BA: Not identified. Doses up to 240 mg QD (the highest dose tested in clinical trials) raised no major safety concerns. The maximum tolerated dose for ezetimibe was not determined in human.										
Dose proportionality	Bempedoic acid steady-state pharmacokinetics are generally linear over a range of >60 mg to 220 mg. Ezetimibe pharmacokinetics were generally dose proportional between 5 and 20 mg.										
Accumulation	The mean accumulation ratio of bempedoic acid following once daily administration is 2.3-fold. Following once daily multiple dosing, conjugated ezetimibe and ezetimibe accumulated 2- to 3-fold. ¹										
Time to achieve steady state	Steady state is achieved with bempedoic acid in about 120 hours. Based on the reported half-life of 22 hours, steady state for ezetimibe is expected to be achieved in 7 days.										
Bridge between to-be marketed and clinical trial formulations	The final to-be-marketed formulation was used in the clinical study conducted with the FDC formulation. Hence, no bridging study is required. However, the Applicant relied upon the bempedoic acid application (NDA 211616) and the ezetimibe reference product for nonclinical, clinical pharmacology and clinical information. An adequate bridging study was conducted accordingly.										

¹ See https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21445_Zetia_biopharmr_P1.pdf.

NDA 211617

Nexlizet / bempedoic acid and ezetimibe

Characteristic	Drug Information																				
	Absorption																				
Bioavailability	Based on a radio-labelled PK study, at least 70% of the administered bempedoic acid dose was absorbed after oral administration. The absolute bioavailability of bempedoic acid was not determined in human. The absolute bioavailability of ezetimibe cannot be determined, as the compound is virtually insoluble in aqueous media suitable for injection.																				
T _{max}	T _{max} of bempedoic acid and ezetimibe are 3.5 hours and 5 hours, respectively, following single-dose administration of the FDC tablet in healthy subjects.																				
Food effect (fed/fasted) Geometric least square mean and 90% CI	<p>Table 7. Food Effect</p> <table border="1"> <thead> <tr> <th>Component</th> <th>AUC_{0-inf}</th> <th>C_{max}</th> <th>T_{max}</th> </tr> </thead> <tbody> <tr> <td>ETC-1002</td> <td>0.95 (0.90, 1.00)</td> <td>0.70 (0.61, 0.80)</td> <td>Prolonged from 2 to 4 hours</td> </tr> <tr> <td>ESP15228</td> <td>1.08 (1.00, 1.17)</td> <td>0.91 (0.83, 0.99)</td> <td>Unchanged</td> </tr> <tr> <td>Ezetimibe</td> <td>0.91 (0.81, 1.02)</td> <td>0.88 (0.70, 1.11)</td> <td>Prolonged from 1.6 to 4 hours</td> </tr> <tr> <td>Ezetimibe-glucuronide</td> <td>0.88 (0.75, 1.02)</td> <td>0.6 (0.43, 0.78)</td> <td>Prolonged from 0.8 to 2 hours</td> </tr> </tbody> </table>	Component	AUC _{0-inf}	C _{max}	T _{max}	ETC-1002	0.95 (0.90, 1.00)	0.70 (0.61, 0.80)	Prolonged from 2 to 4 hours	ESP15228	1.08 (1.00, 1.17)	0.91 (0.83, 0.99)	Unchanged	Ezetimibe	0.91 (0.81, 1.02)	0.88 (0.70, 1.11)	Prolonged from 1.6 to 4 hours	Ezetimibe-glucuronide	0.88 (0.75, 1.02)	0.6 (0.43, 0.78)	Prolonged from 0.8 to 2 hours
Component	AUC _{0-inf}	C _{max}	T _{max}																		
ETC-1002	0.95 (0.90, 1.00)	0.70 (0.61, 0.80)	Prolonged from 2 to 4 hours																		
ESP15228	1.08 (1.00, 1.17)	0.91 (0.83, 0.99)	Unchanged																		
Ezetimibe	0.91 (0.81, 1.02)	0.88 (0.70, 1.11)	Prolonged from 1.6 to 4 hours																		
Ezetimibe-glucuronide	0.88 (0.75, 1.02)	0.6 (0.43, 0.78)	Prolonged from 0.8 to 2 hours																		
	Distribution																				
Volume of distribution	The bempedoic acid apparent volume of distribution (V/F) was 18 L. The volume of distribution for ezetimibe has not been reported.																				
Plasma protein binding	Plasma protein binding of bempedoic acid, its glucuronide and its active metabolite, ESP15228, were 99.3%, 98.8% and 99.2%, respectively. Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins.																				
Drug as substrate of transporters	ETC-1002 and ESP15228 were not substrates for cellular transporters. Ezetimibe is a substrate of P-gp. In a hamster cell line, the V _{max} was approximately 270% of basal activity and the K _m was 21 μM.																				
	Elimination																				
Mass balance results	<p>Following single oral administration of 240 mg of bempedoic acid (1.3 times the approved recommended dose), approximately 70% of the total dose (bempedoic acid and its metabolites) was recovered in urine, primarily as the acyl glucuronide conjugate of bempedoic acid, and approximately 30% was recovered in feces. Less than 5% of the administered dose was excreted as unchanged bempedoic acid in feces and urine combined.</p> <p>Following oral administration of ¹⁴C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) accounted for approximately 93% of the total radioactivity in plasma. After 48 hours, there were no detectable levels of radioactivity in the plasma. Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively, over a 10-day collection period. Ezetimibe was the major component in feces and accounted for 69% of the administered dose, while ezetimibe-glucuronide was the major component in urine and accounted for 9% of the administered dose.</p>																				
Clearance	The steady-state clearance of bempedoic acid was 11.2 mL/min after once-daily dosing; renal clearance of unchanged bempedoic acid represented less than 2% of total clearance. The clearance of ezetimibe has not been reported.																				
Half-life	The half-life of bempedoic acid and ezetimibe are 19.8 hr and 22 hr, respectively.																				

NDA 211617

Nexlizet / bempedoic acid and ezetimibe

Characteristic	Drug Information
Metabolic pathway(s)	<p>The primary route of elimination for bempedoic acid is through metabolism of the acyl glucuronide. Bempedoic acid is also reversibly converted to an active metabolite (ESP15228) based on aldo-keto reductase activity observed in vitro from human liver.</p> <p>Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation with subsequent biliary and renal excretion. Minimal oxidative metabolism has been observed in all species evaluated. In humans, ezetimibe is rapidly metabolized to ezetimibe-glucuronide. Ezetimibe and ezetimibe-glucuronide are the major drug-derived compounds detected in plasma, constituting approximately 10% to 20% and 80% to 90% of the total drug in plasma, respectively.</p>
Primary excretion pathways (% dose)	(See mass balance results above)
Intrinsic Factors and Specific Populations	
Body weight	The pharmacokinetics of bempedoic acid were not affected by weight. Ezetimibe: Females had 13%–22% higher mean C_{max} and AUC compared to males, which may partly be attributed to the difference in body weight. The average body weight for male and female subjects were 76 pounds and 67 pounds, respectively.
Age	The pharmacokinetics of bempedoic acid were not affected by age. Ezetimibe: In a multiple-dose study with ezetimibe given 10 mg once daily for 10 days, plasma concentrations for total ezetimibe were about 2-fold higher in older (≥ 65 years) healthy subjects compared to younger subjects.
Renal impairment	The mean bempedoic acid AUC in subjects with mild renal impairment (n=8) were 1.5-fold higher compared to those with normal renal function (n=6). Relative to those with normal renal function, mean bempedoic acid AUCs were higher in patients with moderate (n=5) or severe (n=5) renal impairment by 2.3-fold and 2.4-fold, respectively. Ezetimibe: Patients with severe renal disease had 1.5-fold higher ezetimibe exposure than the healthy subjects.
Hepatic impairment	No dose adjustment is recommended for bempedoic acid in patients with mild or moderate hepatic impairment. Bempedoic acid was not studied in patients with severe hepatic impairment (Child Pugh C). Ezetimibe: After a single 10 mg ezetimibe, the exposure (AUC) was increased 1.7- and 4-fold in patients with mild hepatic insufficiency and moderate (including severe) hepatic impairment, respectively. Therefore, ezetimibe is not recommended in patients with moderate or severe hepatic impairment.
Drug Interaction Liability (Drug as Perpetrator)	
Inhibition/induction of metabolism	In vitro metabolic interaction studies suggest that bempedoic acid, as well as its active metabolite and glucuronide forms are not metabolized by and do not interact with cytochrome P450 enzymes. Ezetimibe had no significant effect on the activity of CYP1A2, CYP2C8/9, CYP2D6, CYP3A4 or N-acetyltransferase, suggesting no induction or inhibition of common CYP450 enzymes.
Inhibition/induction of transporter systems	Bempedoic acid weakly inhibits OAT3 at high multiples of clinically relevant concentrations, and bempedoic acid and its glucuronide weakly inhibit OATP1B1, and OATP1B3 at clinically relevant concentrations. Bempedoic acid weakly inhibits OAT2 in vitro, which is likely the mechanism responsible for minor elevations in serum creatinine and uric acid. Ezetimibe is an inhibitor of P-gp in vitro.

Abbreviations: BA, bempedoic acid; FDC, fixed-dose combination; P-gp, P-glycoprotein; PK, pharmacokinetics; QC, quality control; QD, once a day; SD, standard deviation

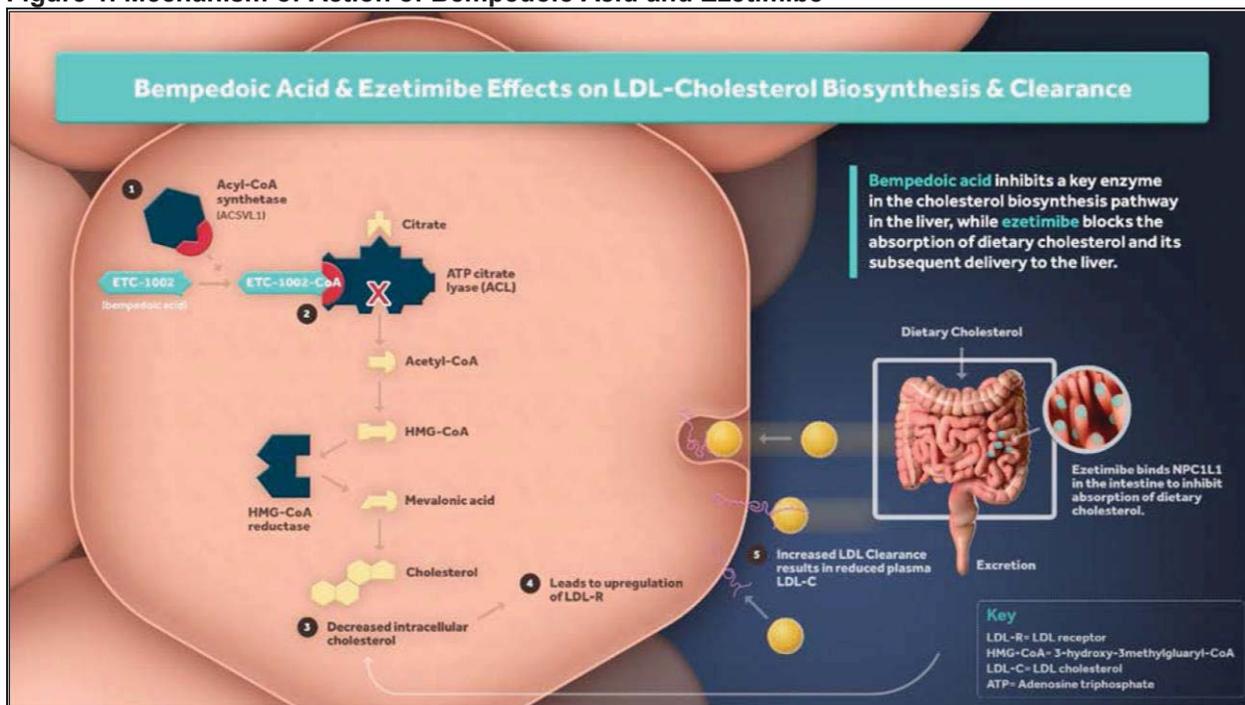
5.1. Nonclinical Assessment of Potential Effectiveness

The nonclinical pharmacology of bempedoic acid (Nexletol) and ezetimibe (Zetia) were previously reviewed under NDA 211616 and NDA 21445, respectively. The key findings are summarized below:

- Bempedoic acid is a prodrug that requires conversion into ETC-1002-coenzyme A (ETC-1002-CoA) by very long chain acyl-Coenzyme A synthetase 1 enzyme in the liver. The active ETC-1002-CoA inhibits ACL, a cytosolic enzyme upstream of HMG-CoA reductase (target for statins) that catalyzes the cleavage of citrate into oxaloacetate and acetyl-CoA in a concentration dependent manner ($K_i = 2\mu\text{M}$). Through ACL-dependent inhibition of cholesterol synthesis, bempedoic acid upregulates hepatic LDL receptors and enhances LDL-C clearance by the liver in a manner similar to statins. Bempedoic acid demonstrated inhibition of de novo lipid synthesis both in vitro and in various disease animal models.
- Ezetimibe reduces the absorption of cholesterol in the small intestine by blocking the sterol transporter Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and related phytosterols.

Therefore, the FDC is anticipated to reduce elevated LDL-C through complementary inhibition of cholesterol synthesis in the liver. This leads to increased hepatic LDL receptors expression, subsequent cholesterol efflux (bempedoic acid), and inhibition of cholesterol absorption in the intestine (ezetimibe), as shown in Figure 1.

Figure 1. Mechanism of Action of Bempedoic Acid and Ezetimibe



Source: Excerpted from the Applicant's submission

6. Evidence of Benefit (Assessment of Efficacy)

6.1. Assessment of Dose and Potential Effectiveness

Was the dose selected for the pivotal trial(s) reasonable?

Yes, the dose selected for the pivotal trial was reasonable. For the ezetimibe component of the FDC, a dose of 10 mg once daily (QD) was selected based on the approved product labeling of the listed drug, Zetia. The dose selection for the bempedoic acid component of the FDC product was based on a total of six dose-ranging studies conducted under the bempedoic acid monotherapy program (NDA 211616) (Table 8).

Table 8. Dose-Ranging Studies Conducted for Bempedoic Acid

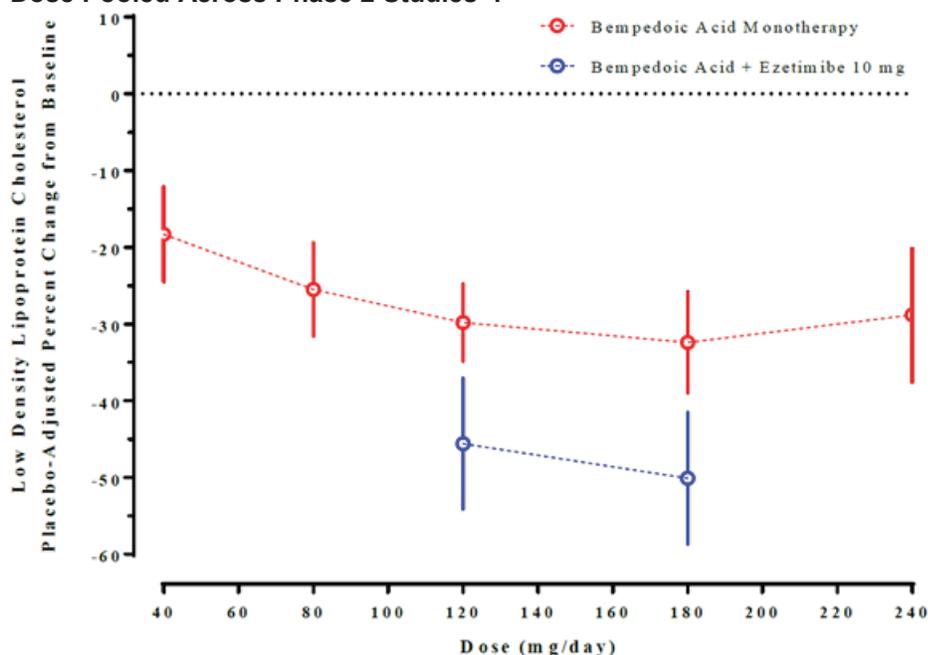
Study ID	Objectives	Population	Study Design	Treatment and Duration
1002-003	To assess the effect on LDL-C, TG and other biomarkers	Patients with elevated LDL-C (n=176)	R, DB, PC, ascending MD	BA: 40, 80 or 120 mg Placebo 12 weeks
1002-005	To assess the effect on LDL-C, glycemic parameters and other biomarkers	Patients with T2DM (n=60)	R, DB, PC, PG	BA: 80 mg for 14 days and 120 mg for 14 days Placebo 28 days
1002-006	To assess the effect on LDL-C, and lipid other biomarkers	Patients with elevated LDL-C and statin intolerance (n=54)	R, DB, PC, PG	BA: Starting dose 60 mg/day, with up-titration to 120, 180, then 240 mg Placebo 8 weeks
1002-007	Effect of BA when added to atorvastatin	Patients with elevated LDL-C (n=52)	R, DB, PC, PG	BA: starting dose 60 mg/day, with up-titration to 120 mg, 180 mg, then 240 mg; with oral atorvastatin 10 mg Placebo with oral atorvastatin 10 mg 8 weeks
1002-008	To assess the LDL-C lowering effect versus ezetimibe	Patients with elevated LDL-C and without statin intolerance (n=322)	R, DB, AC, PG	BA: 120-mg or 180-mg tablet Ezetimibe: 10-mg tablet BA: 120-mg or 180-mg tablet plus ezetimibe 10-mg tablet 12 weeks
1002-009	To assess the LDL-C lowering effect on a background of low and moderate dose statin	Patients with elevated LDL-C despite ongoing statin therapy	R, DB, PC, PG	BA: 120-mg or 180-mg Placebo 12 weeks

Source: NDA 211617, Module 5.2. Tabular listing of all clinical studies – Bempedoic acid
 Abbreviations: AC, active comparator-controlled; BA, bempedoic acid; DB, double-blind; LDL-C, low-density lipoprotein cholesterol; MD, multiple dose; n, number of subjects in study; PC, placebo-controlled; T2DM, type 2 diabetes mellitus; TG, triglycerides; R, randomized

Change from baseline in LDL-C with varying dose of bempedoic acid was assessed in patients with hyperlipidemia in a pooled analysis of 6 randomized, double-blind, placebo-controlled, parallel-group phase 2 studies. Mean LDL-C generally decreased with increasing bempedoic acid dose up to 180 mg (Figure 2). Placebo-adjusted LS mean percent change from baseline in LDL-C was -18.3%, -25.5%, -29.8%, -32.4%, and -28.8% with bempedoic acid 60, 80, 120, 180, and 240 mg QD, respectively. The 180 mg QD monotherapy dose lowered LDL-C approximately 3 percentage points more than the corresponding 120 mg QD monotherapy dose; but further LDL-C lowering at the 240 mg dose was not observed.

When bempedoic acid was administered in combination with ezetimibe, placebo-adjusted LS mean change from baseline in LDL-C was -45.6% for bempedoic acid 120 mg + ezetimibe 10 mg and -50.1% for bempedoic acid 180 mg + ezetimibe 10 mg. Thus, the 180 mg dose was associated with an additional 4.5 percentage-point decrease in mean LDL-C compared with 120 mg. Consequently, a fixed dose of 180 mg bempedoic acid and 10 mg ezetimibe was selected for the phase 3 study (1002FDC-053). Refer to the Integrated Review of NDA 211616 for additional details on dose-ranging studies for bempedoic acid.

Figure 2. Placebo-Adjusted LS Mean Percent Change From Baseline by Daily Bempedoic Acid Dose Pooled Across Phase 2 Studies¹:



¹ Bempedoic acid monotherapy: pooled data from Studies 003, 005, 006, and 008; Coadministration with ezetimibe (Study 008) Source: NDA 211617, Module 2.7.2. Cross-ref to NDA 2116 –Summary of Clinical Pharmacology Studies–Bempedoic acid Abbreviations: LS, least square

Is the proposed dosing regimen appropriate for the general patient population for which the Indication is being sought?

Yes, the proposed dosing regimen is appropriate for the general patient population for which the indication is being sought. For the ezetimibe component, the once daily dosing regimen was selected based on the approved dosing regimen for Zetia. For the bempedoic acid component, the

Applicant only investigated once daily dosing, which demonstrated efficacy of the product for the proposed indication. Refer to the Integrated Review of NDA 211616 for additional details on dose-ranging studies for bempedoic acid.

Is there bridging information which is important to the review of this application?

While Trial 1002FDC-053 demonstrated the safety/efficacy of the FDC product in patients with hyperlipidemia with maximally tolerated statin therapy for up to 12 weeks, the long-term safety and efficacy of the FDC tablet was not investigated. Instead, the Applicant relied on the bempedoic acid NDA (211616) for long-term safety and efficacy information. Hence, a scientific bridge between the FDC product and bempedoic acid is warranted. In addition, for the ezetimibe component, the Applicant relied on clinical pharmacology information from the Zetia label, which necessitates a scientific bridge between the FDC product and Zetia.

Study 1002FDC-034 was conducted to compare the relative bioavailability of bempedoic acid and ezetimibe administered as FDC tablet or concurrently as separate tablets. The study also investigated two FDC formulations (b) (4) to identify the optimum formulation for further clinical development. This was a randomized, open-label, single-dose, 3-period, 6-sequence, crossover study in which healthy subjects (n=24) received single doses of (i) bempedoic acid/ezetimibe 180 mg/10 mg FDC (b) (4) tablet, (ii) bempedoic acid/ezetimibe 180 mg/10 mg FDC (b) (4) tablet, and (iii) bempedoic acid 180 mg + ezetimibe 10 mg individual tablets under fasting conditions. The treatments were separated by a washout of 14 days.

Results from this study demonstrated that the systemic exposures of bempedoic acid were similar when administered as FDC (b) (4) tablet (the final to-be-marketed formulation) or individual tablets, i.e., 90% CI for the geometric mean ratio of maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) were within 0.80 to 1.25. Similarly, the systemic exposure of ezetimibe was generally comparable between FDC tablet and Zetia. The lower bound of 90% confidence interval for geometric mean ratio of ezetimibe C_{max} was outside 0.80. Since the Applicant demonstrated the efficacy of the FDC product in a pivotal phase 3 study (1002FDC-053), this marginal deviation is not expected to have any impact on the efficacy of the FDC product. Refer to Section 14 for additional details for this study.

While the systemic exposure of bempedoic acid was similar between the bempedoic acid tablet and the to-be-marketed FDC tablet, the bempedoic acid tablet used in this study was not the to-be-marketed formulation. The Applicant provided the following evidence to support the pharmacokinetics (PK) bridging evaluation: physicochemical properties of bempedoic acid, formulation composition, in vitro release profiles, and population pharmacokinetic analysis. Given the minor difference in formulation composition and in vitro dissolution profiles between the to-be-marketed formulation and the formulation used in this study, no clinical meaningful difference would be expected. Refer to the Integrated Review of NDA 211616 for additional details.

Is there dose response or other data that provides evidence of potential effectiveness but does not meet the criteria for an adequate and well-controlled trial?

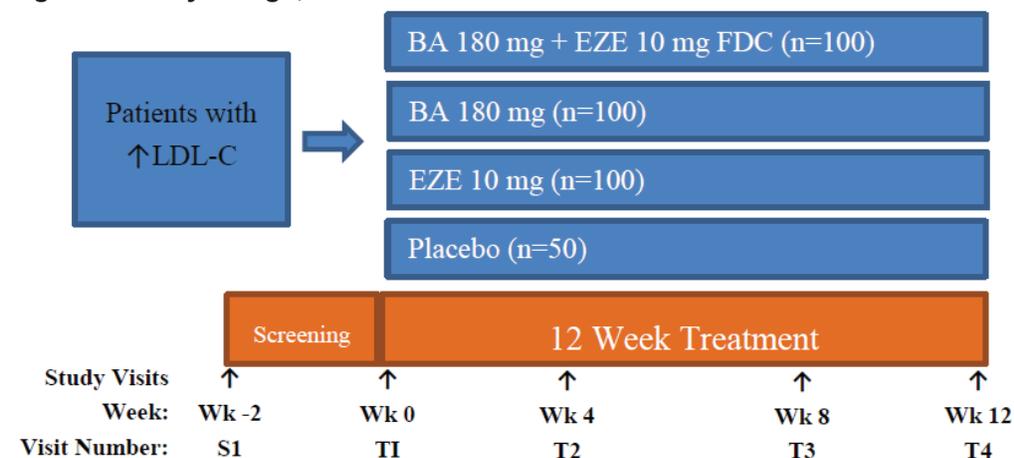
No such studies were submitted for this application.

6.2. Design of Clinical Trials Intended to Demonstrate Benefit to Patients

6.2.1. Trial Design

Trial 053 was a 12-week, randomized, double-blind, placebo-controlled, parallel group, multicenter factorial trial designed to compare the bempedoic acid + ezetimibe fixed-dose combination (FDC) product to its individual components and to placebo (Figure 3). The randomization ratio was 2:2:2:1 (FDC:bempedoic acid:ezetimibe (EZE):placebo), and randomization was stratified by primary versus secondary prevention and by baseline statin intensity. Screening occurred approximately 2 weeks prior to randomization. After randomization, patients were followed every 4 weeks for 3 months. Patients who withdrew from investigational medicinal product (IMP) treatment were asked to continue follow-up for safety and efficacy using the protocol-specified visit schedule and procedures.

Figure 3. Study Design, Trial 053



Source: SAP Figure 1

Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed-dose combination; LDL-C, low-density lipoprotein cholesterol; n, number of subjects in group; S, screening (period); T, treatment (period); Wk, week

Primary Endpoint

Mean percent change in LDL-C from baseline to Week 12 was the primary efficacy endpoint. Reduction of LDL-C is a surrogate endpoint for CV risk reduction and has been used as the basis for approval in previous trials of lipid-lowering drugs.

LDL-C was calculated using the Friedewald equation, which is generally considered reliable within <0.5 mg/dL of directly-measured LDL. For patients with triglycerides (TG) >400 mg/dL or LDL-C ≤50 mg/dL, the Friedewald equation loses accuracy; in these cases, direct LDL measurement was used. Baseline LDL-C was defined as the mean of values from Week -2 (Screening) and predose Day 1/Week 0. No adjustment to background LMT was allowed during the trials.

Secondary Endpoints

Key secondary endpoints included percent change in non-high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), apolipoprotein B (Apo-B), HDL, TG, and high-sensitivity C-reactive protein (hsCRP) from baseline to Week 12. Baseline for non-HDL-C, HDL-C, total cholesterol (TC), and TG were defined as the mean of values from Week -2 (screening) and predose Day 1/Week 0. Baseline for Apo-B and hsCRP were defined as the predose Day 1/Week 0 value.

In clinical practice, TC and Apo-B may be considered in treatment decisions regarding CV risk optimization. However, the utility of non-HDL-C as a biomarker is less clear. Review of changes to non-HDL-C's components, LDL-C and VLDL (TG carrier), are more clinically meaningful. Note also that the Division does not currently consider reduction in hsCRP as a surrogate endpoint for any clinically meaningful outcome.

Other endpoints of interest to practicing clinicians are changes in triglycerides (TG) and HDL from baseline. The Applicant did not include these biomarkers as prespecified secondary endpoints; however, the review team evaluated them as exploratory endpoints.

6.2.2. Eligibility Criteria

Study 053 was conducted in high CV risk patients who required additional LDL-C lowering for primary or secondary prevention despite use of maximally tolerated statin therapy. Use of any additional, nonstatin LMT at baseline was not allowed, including the exclusion of patients who used ezetimibe within the previous 5 weeks. Key inclusion and exclusion criteria are listed below. For more information, see Section 15.

Key Inclusion Criteria

1. Age ≥ 18 years
2. High cardiovascular risk, defined as:
 - HeFH (by genotyping, WHO criteria, or Simon Broome Register criteria)
 - ASCVD (established or risk-equivalent)
 - Established: history of acute or silent myocardial infarction, unstable angina, coronary revascularization, or positive diagnostic imaging
 - Risk-equivalent: peripheral arterial disease, cerebrovascular disease
 - Multiple risk factors (age ≥ 45 for males or ≥ 55 for females, family history in a first degree relative, current smoker, history of HTN, HDL < 40 mg/dL, or coronary calcium score $> 95\%$ for age/sex)
 - T2DM: 1 risk factor
 - Non-T2DM: ≥ 3 risk factors
3. On maximally-tolerated statin, stable (> 4 weeks) statin dose
4. Fasting LDL at screening
 - HeFH/ASCVD, ≥ 100 mg/dL
 - Multiple risk factors, ≥ 130 mg/dL

Key Exclusion Criteria

1. Ezetimibe use within previous 5 weeks
2. Triglycerides ≥ 500 mg/dL
3. Recent (within 3 months) cardiovascular event or intervention
4. Uncontrolled hypertension
5. Active liver disease
6. Hemoglobin < 10.0 g/dL at screening
7. Active malignancy within past 5 years
8. Renal dysfunction or estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m²
9. HbA1c $\geq 10\%$ at screening
10. Uncontrolled hypothyroidism
11. CK $> 3 \times$ upper limit of normal (ULN) at randomization
12. Body mass index ≥ 40 kg/m²
13. Use of the following concomitant medications within previous 5 weeks, unless otherwise stated
 - Simvastatin doses ≥ 40 mg daily
 - Nonstatin lipid-modifying therapies
 - Fibrates
 - Niacin
 - Bile acid sequestrants
 - Ezetimibe
 - Mipomersen or lomitapide
 - Apheresis
 - PCSK9 inhibitors within previous 4 months
 - Cholesterylester transfer protein inhibitors within previous 12 months
 - Red yeast rice extract-containing products within previous 2 weeks
 - Systemic corticosteroids
 - Hormone replacement, new or planned dose change
 - Thyroid replacement, new or planned dose change
 - Diabetes medications, new or planned dose change
 - Omega 3 fatty acids, new or planned dose change
 - Obesity medications, new or planned dose change within previous 6 months

Note that this trial used a different definition of high CV risk than the trials conducted under NDA 211616. In trial 53, the definition was expanded to include patients without established ASCVD or HeFH but who had multiple risk factors for CVD. As such, this trial is considered a trial of primary and secondary prevention.

6.2.3. Statistical Analysis Plan

Primary Efficacy Analysis

The prespecified efficacy analysis population is the full analysis set (FAS), which consists of all randomized patients. FDA's review of efficacy focuses on the subset of the FAS excluding sites 1028, 1058, and 1068, which had severe data quality issues. Additional details are provided under Benefit Review Issue #1.

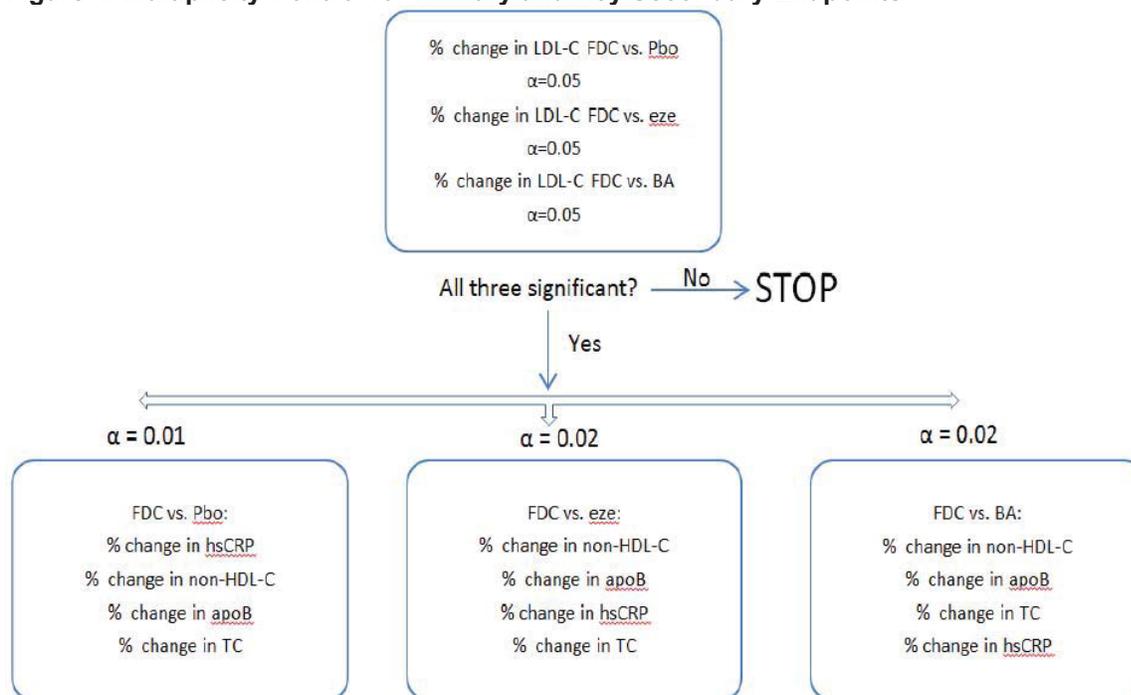
The analyses of the coprimary efficacy endpoints consist of three comparisons of the percent change from baseline to Week 12 in LDL-C: FDC versus placebo, FDC versus EZE; and FDC versus bempedoic acid. An analysis of covariance (ANCOVA) model with treatment group and randomization strata (baseline statin intensity and CVD risk category) as factors and baseline LDL-C as a covariate was performed. Considering that the randomization ratio is 2:2:2:1, the ANCOVA model accounts for possible unequal variances between treatment groups by assuming unequal residual variances.

Key secondary endpoints, which include the percent change from baseline to Week 12 in non-HDL-C, TC, and Apo-B, were analyzed in a similar manner as the primary efficacy endpoint. For hsCRP, a nonparametric analysis (Wilcoxon rank-sum test) with Hodges-Lehmann estimates and confidence interval was performed because hsCRP is known to be skewed by extreme values and have non-normal distribution.

Control of Type I Error

Each comparison for the coprimary endpoints was conducted at two-sided alpha of 0.05. If, and only if, all three tests for the coprimary endpoints achieve statistical significance, the study is claimed to meet its primary objective, and the key secondary endpoints will then be tested in sequential order within each comparison group as shown in Figure 4. The 0.05 alpha is split among the three comparison groups: alpha =0.01 for FDC versus placebo, alpha =0.02 for FDC versus EZE, alpha =0.02 for FDC versus bempedoic acid for testing the key secondary endpoints.

Figure 4. Multiplicity Control for Primary and Key Secondary Endpoints



Source: SAP of Trial 053

Abbreviations: Apo-B, apolipoprotein B; BA, bempedoic acid; eze, ezetimibe; FDC, fixed-dose combination; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PBO, placebo; TC, total cholesterol

Method for Handling Missing Data

All available measurements were included in the primary efficacy analysis regardless of treatment discontinuation. Missing values for the primary endpoint were imputed using a multiple imputation method. The Applicant's analyses showed the following:

- For patients with missing value and off-treatment at Week 12 (>7 days post last dose of IMP), missing LDL-C values were imputed as baseline values.
- For patients with missing value but on-treatment at Week 12, missing LDL-C values were imputed based on a regression model including treatment, stratification factor, and baseline LDL-C.

The reviewers consider placebo data as a better reference for imputing off-treatment missing values, since these values mimic the situation where the treatment effect is "washed out." The statistical reviewer's analyses showed the following:

- For patients with missing data and off-treatment at Week 12, and for patients with missing data in the placebo group, missing LDL-C values were imputed based on placebo completers. Observed intermediate values from active treatment groups were deleted prior to imputation.
- For patients with missing data while on active treatment at Week 12, missing LDL-C values were imputed based on treatment completers within each active treatment group. The imputation models include treatment, stratification factor, and all prior LDL-C measurements.

A sensitivity analysis was conducted, where all missing values were imputed based on placebo completers, regardless whether the patients were on active treatment or not. Given the small number of subjects who were on active treatment at Week 12 but had missing LDL-C, this sensitivity analysis was not expected to differ much from the main analysis. The results are shown in Table 56 in the Appendix.

Subgroup Analysis

Subgroup analysis for percent change in LDL-C from baseline to Week 12 was performed for baseline factors of sex, race, age group, cardiovascular disease (CVD) risk, and baseline statin intensity. Subgroup analysis by country was not performed, since all randomized patients in Trial 053 are from the United States. Results for treatment difference within subgroups are presented in Table 58 in the Appendix. Missing data were imputed in the same way as the primary efficacy analysis. A similar ANCOVA model was fit including additional factors of subgroup and subgroup-by-treatment interaction.

Sample Size Calculation

Assuming that the treatment difference between FDC and EZE or bempedoic acid would be 13% with an SD of 25%, 100 patients in each of these 2 groups would provide 95% power to detect such a difference using a t-test with 2-sided alpha =0.05. Additionally, 100 patients in the FDC arm and 50 patients in the placebo arm would provide >99% power to detect a treatment difference of 33% with SD of 25%. Under the same assumptions, 80 patients in each of the FDC arm and EZE or bempedoic acid arm, and 40 patients in the placebo arm would provide 90% power and >99% power for the same tests, respectively.

6.3. Results of Analyses of Clinical Trials/Studies Intended to Demonstrate Benefit to Patients

6.3.1. Patient Disposition, Demographics, and Baseline Characteristics

In Trial 053, more than half (53.5%) of screened patients were screen failures. The primary reason for screen failure was failure to meet LDL-C entry criteria, i.e., a baseline LDL-C value that did not require additional lowering.

Table 9. Patient Screening and Randomization, Trial 053

Disposition	Trial 053
Screened	821
Screen failure, n(%) ¹	439 (53.5)
Randomized, n(%) ¹	382 (46.5)

Source: adsl, statistical reviewer's analysis

¹Total number of screened patients was used as denominator

Abbreviations: n, number of subjects with disposition

As previously described, three sites had data irregularities indicating possible fraud, and data from these sites were excluded (see Benefit Review Issue #1). Patient disposition and demographics for Trial 053 from the FAS (including the three fraudulent sites) and from the subset of FAS excluding the three fraudulent sites are similar. Only results from the subset of FAS excluding the three fraudulent sites are presented in the main text. Results from the FAS are included in Section 16.1.

Patient disposition for Trial 053 is provided in Table 10. In general, no evidence of differential attrition was present. Similar proportions of randomized patients in each treatment group completed the 12-week treatment period on IMP: close to 90%. The most common reason for withdrawing from IMP was adverse events (AEs). The proportion of patients with a missing LDL-C value at Week 12 was low (3% to 9%).

Table 10. Patient Dispositions: Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053

Parameter	BA 180 mg +			
	EZE 10 mg FDC	BA 180 mg	EZE 10 mg	Placebo
Randomized/full analysis set, n	86	88	86	41
Safety population, ¹ n (%)	85 (98.8)	88 (100.0)	86 (100.0)	41 (100.0)
Completed IMP, n (%)	75 (87.2)	75 (85.2)	73 (84.9)	36 (87.8)
Withdrew from IMP, n (%)	10 (11.6)	13 (14.8)	13 (15.1)	5 (12.2)
Adverse event	7 (8.1)	9 (10.2)	10 (11.6)	2 (4.9)
Withdrawal by patient	3 (3.5)	2 (2.3)	3 (3.5)	1 (2.4)
Protocol violation	0	1 (1.1)	0	1 (2.4)
Lost to follow-up	0	1 (1.1)	0	0
Completed study, n (%)	81 (94.2)	82 (93.2)	81 (94.2)	40 (97.6)
Withdrew from study, n (%)	5 (5.8)	6 (6.8)	5 (5.8)	1 (2.4)
Missed LDL-C at Week 12, n (%)	3 (3.5)	8 (9.1)	6 (7.0)	2 (4.9)
Retrieved dropout, ² n (%)	7 (8.1)	7 (8.0)	8 (9.3)	4 (9.8)

Source: adsl, statistical reviewer's analysis

¹ Safety Population consists of all randomized patients who receive at least one dose of blinded IMP.

² Patients who were off-treatment and had LDL-C measurement at Week 12

Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC: fixed-dose combination; IMP: investigational medicinal product; LDL-C, low-density lipoprotein cholesterol; n, number of subjects with disposition

Patient demographics and baseline efficacy parameters for Trial 053 are provided in Table 11 and Table 12.

Baseline demographics and disease characteristics were generally well-balanced between bempedoic acid, ezetimibe, and placebo arms. Though patients assigned to the FDC were slightly younger, more obese, and had higher baseline triglycerides, patients assigned to placebo had slightly higher baseline LDL-C. Enrolled patients were more reflective of the U.S. population than trials conducted under NDA 211616. Most patients were white and non-Hispanic with a mean age of 64 years. All enrolled patients were from the United States. Most trial patients were overweight, most were current or former smokers, and most had hypertension. Nearly half of patients had diabetes. When patients from sites 1028, 1058, and 1068 were excluded, no changes in the trial makeup occurred with the exception of a decrease in Hispanic representation.

Although defined as a “high CV risk” patient population, enrollees were a mixture of primary and secondary prevention patients. Approximately 60% of patients had established ASCVD or HeFH, while 40% had risk factors for CVD only. Mean baseline LDL-C values were 146 to 152 mg/dL. According to the Applicant, 65% of patients were on maximally tolerated statin at

enrollment; however, only one-third of those patients were on high-intensity statin. Furthermore, 28% of patients were on no LMT at enrollment.

Given the large percentage of patients on zero or non-optimized antihyperlipidemia therapy at baseline, the Division does not consider the enrolled patient population to reflect adequately the intended clinical population. In clinical practice, standard of care therapy for hyperlipidemia is initiation of statin therapy with addition of ezetimibe or PCSK9 inhibitors as add-on therapy for those patients who require additional LDL-C lowering. As such, we would expect that most patients would be on baseline lipid-modifying therapy.

Table 11. Patient Demographics, Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053

Characteristic	BA 180 mg + EZE 10 mg FDC (N=86)	BA 180 mg (N=88)	EZE 10 mg (N=86)	Placebo (N=41)
Age (years)				
Mean (SD)	62.2 (9.46)	65.0 (9.77)	65.1 (8.43)	65.4 (10.75)
Median (min, max)	62 (56, 69)	65 (58, 71.5)	66 (59, 71)	64 (57, 73)
Age group (years), n (%)				
18-40	1 (1.2)	1 (1.1)	0	1 (2.4)
41-64	50 (58.1)	41 (46.6)	38 (44.2)	20 (48.8)
65-74	25 (29.1)	30 (34.1)	35 (40.7)	10 (24.4)
≥75	10 (11.6)	16 (18.2)	13 (15.1)	10 (24.4)
Gender, n (%)				
Male	42 (48.8)	40 (45.5)	43 (50.0)	24 (58.5)
Female	44 (51.2)	48 (54.5)	43 (50.0)	17 (41.5)
Race, n (%)				
American Indian or Alaska Native	1 (1.2)	0	0	0
Asian	2 (2.3)	1 (1.1)	1 (1.2)	0
Black or African American	16 (18.6)	17 (19.3)	12 (14.0)	7 (17.1)
Native Hawaiian or Other Pacific Islander	0	0	1 (1.2)	0
White	67 (77.9)	70 (79.5)	72 (83.7)	34 (82.9)
Other	0	0	0	0
Multiple	0	0	0	0
Ethnicity, n (%)				
Hispanic or Latino	10 (11.6)	11 (12.5)	9 (10.5)	6 (14.6)
Not Hispanic or Latino	76 (88.4)	77 (87.5)	77 (89.5)	35 (85.4)
Body mass index group (kg/m ²), n (%)				
<25	13 (15.1)	13 (14.8)	13 (15.1)	3 (7.3)
25 - <30	19 (22.1)	29 (33.0)	30 (34.9)	17 (41.5)
≥30	54 (62.8)	46 (52.3)	43 (50.0)	21 (51.2)
CVD Risk, n (%) ¹				
ASCVD and/or HeFH	53 (61.6)	57 (64.8)	53 (61.6)	27 (65.9)
Multiple CV risk factors	33 (38.4)	31 (35.2)	33 (38.4)	14 (34.2)
HeFH, n(%)				
Yes	3 (3.5)	1 (1.1)	2 (2.3)	1 (2.4)
No	83 (96.5)	87 (98.9)	84 (97.7)	40 (97.6)

Characteristic	BA 180 mg + EZE 10 mg FDC (N=86)	BA 180 mg (N=88)	EZE 10 mg (N=86)	Placebo (N=41)
Baseline statin intensity, n (%)				
High-intensity statin	31 (36.0)	29 (33.0)	28 (32.6)	16 (39.0)
Other intensity statin	22 (25.6)	32 (36.4)	26 (30.2)	11 (26.8)
None	33 (38.4)	27 (30.7)	32 (37.2)	14 (34.1)

Source: adsl, statistical reviewer's analysis

¹ There is small discrepancy from Applicant's number for CVD risk (Table 14.1.2.1a, CSR).

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BA, bempedoic acid; CVD, cardiovascular disease; EZE, ezetimibe; FDC, fixed-dose combination; HeFH, heterozygous familial hypercholesterolemia; N, number of subjects in group; n, number of subjects with characteristic; SD, standard deviation

Table 12. Baseline Efficacy Parameters, Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053

Characteristic	BA 180 mg + EZE 10 mg FDC (N=86)	BA 180 mg (N=88)	EZE 10 mg (N=86)	Placebo (N=41)
TC (mg/dL)				
Mean (Std Dev)	237.32 (48.69)	225.55 (43.16)	231.41 (50.48)	231.27 (50.21)
Median	225.75	222.50	215.00	234.00
Minimum, maximum	152.0, 371.5	156.0, 349.5	153.0, 394.5	156.0, 393.0
LDL-C (mg/dL)				
Mean (std dev)	153.80 (40.53)	145.13 (38.46)	148.80 (41.84)	152.80 (46.77)
Median	144.50	139.00	137.25	152.00
Minimum, maximum	83.5, 282.5	84.5, 266.0	83.5, 298.5	88.5, 306.5
HDL-C(mg/dL)				
Mean (std dev)	49.19 (14.57)	49.89 (12.38)	51.23 (15.90)	50.40 (14.07)
Median	46.50	49.00	46.50	45.00
Minimum, maximum	27.0, 117.0	29.0, 94.0	29.5, 127.0	28.0, 82.0
TG (mg/dL)				
Mean (std dev)	177.19 (94.90)	156.65 (71.98)	161.73 (79.92)	144.59 (55.81)
Median	157.00	141.00	143.50	139.50
Minimum, maximum	61.0, 449.5	63.0, 489.5	63.5, 478.5	50.0, 302.5
Non-HDL-C (mg/dL)				
Mean (std dev)	188.22 (46.66)	175.67 (40.47)	180.18 (47.31)	180.91 (49.72)
Median	175.75	170.25	168.25	179.50
Minimum, maximum	113.5, 315.0	113.0, 297.0	105.0, 340.0	107.0, 338.5
Apo-B (mg/dL)				
Mean (std dev)	121.12 (30.85)	113.41 (26.43)	115.54 (31.30)	115.05 (32.52)
Median	118.5	111.0	107.0	117.0
Minimum, maximum	61, 215	68, 187	66, 211	62, 197
hsCRP (mg/L)				
Mean (std dev)	5.74 (11.09)	4.60 (6.12)	4.54 (4.73)	4.26 (4.16)
Median	3.08	2.91	2.78	3.01
Minimum, maximum	0.2, 91.3	0.1, 37.6	0.4, 27.4	0.2, 15.9

Source: adsl, statistical reviewer's analysis

Abbreviations: Apo-B, apolipoprotein B; BA, bempedoic acid; EZE, ezetimibe; FDC, fixed-dose combination; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides

6.3.2. Efficacy Results

All three comparisons for the coprimary endpoints achieved statistical significance with significant p-values (Table 13). The primary objective was met. The FDC is superior to both bempedoic acid and EZE in terms of percent change in LDL-C from baseline to Week 12, suggesting both components contribute to the FDC's treatment effect. The placebo-adjusted treatment difference (LS mean) for FDC, bempedoic acid, and EZE is -38.2%, -19.3%, and -24.7%, respectively. Figure 5 shows change in LDL-C median over time in each treatment group. There is clear separation between FDC and other treatment groups starting at Week 4.

Results from the key secondary endpoints are generally supportive, although this is not unexpected as LDL-C is a major component of non-HDL-C and TC. All three comparisons for non-HDL-C, TC, and Apo-B achieved statistical significance (Table 14, Table 15, Table 16). The FDC is superior to both bempedoic acid and EZE in terms of percent change in non-HDL-C, TC, and Apo-B from baseline to Week 12, suggesting both components contribute to FDC's treatment effects in these endpoints.

The FDC is superior to EZE in terms of percent change in hsCRP from baseline to Week 12. However, the difference between FDC and bempedoic acid is not significantly different from 0, suggesting the treatment effect of FDC in hsCRP is mostly due to bempedoic acid (Table 17). We also did an analysis for absolute change in hsCRP, considering that percent change may be sensitive to small baseline values of this variable. Results from this analysis are consistent with those from the prespecified analysis using percent change (Table 59). Figure 6 also supports the conclusion that EZE has little contribution to the treatment effect of FDC in hsCRP, showing overlapping trajectories of FDC and bempedoic acid, EZE, and placebo, respectively. Note that the Division does not consider CRP a validated surrogate endpoint for any clinically meaningful outcome.

Results for exploratory secondary endpoints HDL-C and TG are included in Table 61 and Table 62 in the Appendix. It appears that the effect of FDC in HDL-C is mostly due to bempedoic acid.

Table 13. Primary Endpoint, Percent Change From Baseline to Week 12 in LDL-C,¹ Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053

LDL-C	FDC (N=86)	BA (N=88)	EZE (N=86)	Placebo (N=41)
Baseline mean (mg/dL)	153.8	145.1	148.8	152.8
Percent change from baseline (LS mean ²) (SE)	-36.2 (2.7)	-17.3 (2.7)	-22.7 (2.5)	2.0 (3.6)
FDC vs. placebo (LS mean) (95% CI)	-38.2 (-46.9 to -29.4)			
P-value	<0.001 ³			
FDC vs. BA (LS mean) (95% CI)	-18.9 (-26.3 to -11.5)			
P-value	<0.001 ³			
FDC vs. EZE (LS mean) (95% CI)	-13.5 (-20.6 to -6.3)			
P-value	<0.001 ³			

Source: ad b adsl, statistical reviewer's analysis

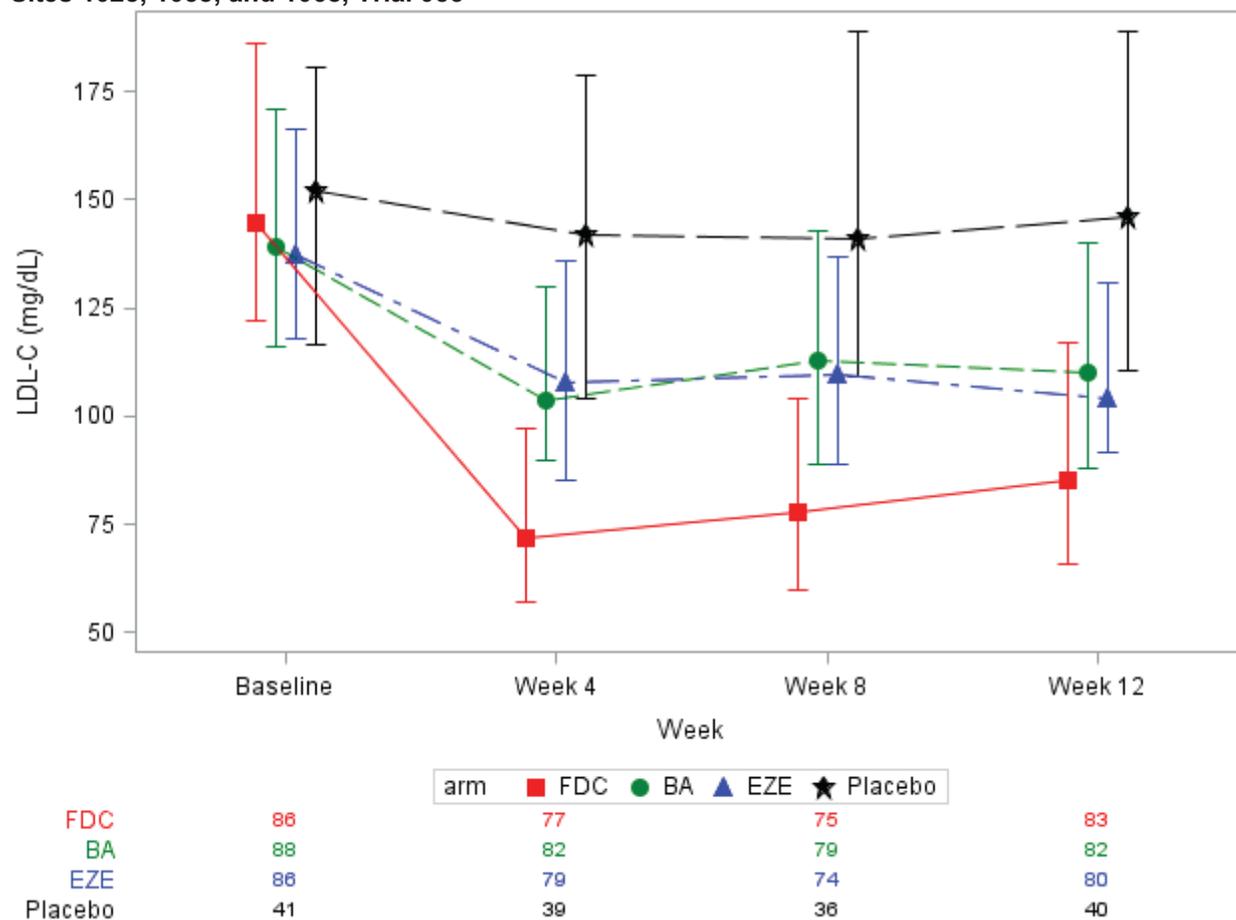
¹ For patients with missing data and being off-treatment or on placebo at Week 12, missing LDL-C values were imputed based on placebo completers; for patients with missing data and being on active treatment at Week 12, missing LDL-C values were imputed based on completers within each active treatment group; an ANCOVA model was fit including treatment group, randomization strata, and baseline LDL-C

² LS means adjusted according to distribution of baseline covariates

³ Statistically significant based on prespecified alpha allocation

Abbreviations: BA, bempedoic acid; CI, confidence interval; EZE, ezetimibe; FDC, fixed-dose combination; LDL-C, low-density lipoprotein cholesterol; LS, least square; N, number of subjects in group; SE, standard error

Figure 5. Median (IQR) LDL-C (mg/dL) Over Time, Observed Values in Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053



Source: adlb, statistical reviewer's analysis
 Baseline: defined as the mean of values from Week -2 (Screening) and predose Day 1/Week 0 in the SAP. If one value is available then the single value will be used as baseline.
 Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed-dose combination; LDL-C, low-density lipoprotein cholesterol; IQR, interquartile range

Table 14. Key Secondary Endpoint, Percent Change From Baseline to Week 12 in Non-HDL-C,¹ Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053

	FDC (N=86)	BA (N=88)	EZE (N=86)	Placebo (N=41)
Non-HDL-C				
Baseline mean (mg/dL)	188.2	175.7	180.2	180.9
Percent change from baseline (LS mean ²) (SE)	-31.9(2.3)	-14.1 (2.3)	-19.3 (2.3)	1.9 (3.3)
FDC vs. placebo (LS mean) (95% CI)	-33.8 (-41.8, -25.9)			
P-value	<0.001 ³			
FDC vs. BA (LS mean) (95% CI)	-17.9 (-24.3, -11.5)			
P-value	<0.001 ³			
FDC vs. EZE (LS mean) (95% CI)	-12.6 (-19.0, -6.2)			
P-value	<0.001 ³			

Source: ad b adsl, statistical reviewer's analysis
¹ Similar approach as analysis for primary efficacy endpoint
² LS means adjusted according to distribution of baseline covariates
³ Statistically significant based on prespecified alpha allocation
 Abbreviations: BA, bempedoic acid; CI, confidence interval; EZE, ezetimibe; FDC, fixed-dose combination; HDL-C, high-density lipoprotein cholesterol; LS, least square; N, number of subjects in group; SE, standard error

Table 15. Key Secondary Endpoint, Percent Change From Baseline to Week 12 in TC,¹ Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053

TC	FDC (N=86)	BA (N=88)	EZE (N=86)	Placebo (N=41)
Baseline mean (mg/dL)	237.3	225.6	231.4	231.3
Percent change from baseline (LS mean ²) (SE)	-26.4 (2.0)	-12.1 (1.9)	-15.8 (1.7)	0.8 (2.5)
FDC vs. placebo (LS mean) (95% CI)	-27.2 (-33.5, -21.0)			
P-value	<0.001 ³			
FDC vs. BA (LS mean) (95% CI)	-14.3 (-19.7, -8.9)			
P-value	<0.001 ³			
FDC vs. EZE (LS mean) (95% CI)	-10.6 (-15.7, -5.5)			
P-value	<0.001 ³			

Source: ad b adsl, statistical reviewer's analysis

¹ Similar approach as analysis for primary efficacy endpoint² LS means adjusted according to distribution of baseline covariates³ Statistically significant based on prespecified alpha allocation

Abbreviations: BA, bempedoic acid; CI, confidence interval; EZE, ezetimibe; FDC, fixed-dose combination; LS, least square; N, number of subjects in group; SE, standard error; TC, total cholesterol

Table 16. Key Secondary Endpoint, Percent Change From Baseline to Week 12 in Apo-B,¹ Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053

Apo-B	FDC (N=82)	BA (N=85)	EZE (N=84)	Placebo (N=38)
Baseline mean (mg/dL)	121.1	113.4	115.5	115.1
Percent change from baseline (LS mean ²) (SE)	-24.6 (2.5)	-11.3 (2.3)	-14.6 (2.2)	5.6 (3.0)
FDC vs. placebo (LS mean) (95% CI)	-30.3 (-37.9, -22.6)			
P-value	<0.001 ³			
FDC vs. BA (LS mean) (95% CI)	-13.3 (-20.0, -6.6)			
P-value	<0.001 ³			
FDC vs. EZE (LS mean) (95% CI)	-10.1 (-16.6, -3.6)			
P-value	0.002 ³			

Source: ad b adsl, statistical reviewer's analysis

¹ Similar approach as analysis for primary efficacy endpoint; 12 patients had no baseline Apo-B and were excluded from analysis² LS means adjusted according to distribution of baseline covariates³ Statistically significant based on prespecified alpha allocation

Abbreviations: Apo-B, apolipoprotein B; BA, bempedoic acid; CI, confidence interval; EZE, ezetimibe; FDC, fixed-dose combination; LS, least square; N, number of subjects in group; SE, standard error

Table 17. Key Secondary Endpoint, Percent Change From Baseline to Week 12 in hsCRP,¹ Observed Values in Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053

hsCRP	FDC (N=80)	BA (N=81)	EZE (N=79)	Placebo (N=39)
Baseline median (mg/L)	3.0	3.0	2.8	3.1
Percent change from baseline (median) (IQR)	-35.1 (54.2)	-31.9 (70.4)	-8.2 (66.4)	21.6 (87.0)
FDC vs. placebo (location shift) (95% CI)	-46.1 (-71.6, -22.6)			
P-value	<0.001 ²			
FDC vs. BA (location shift) (95% CI)	-2.6 (-18.5, 13.1)			
P-value	0.73			
FDC vs. EZE (location shift) (95% CI)	-25.6 (-41.4, -9.7)			
P-value	0.002 ²			

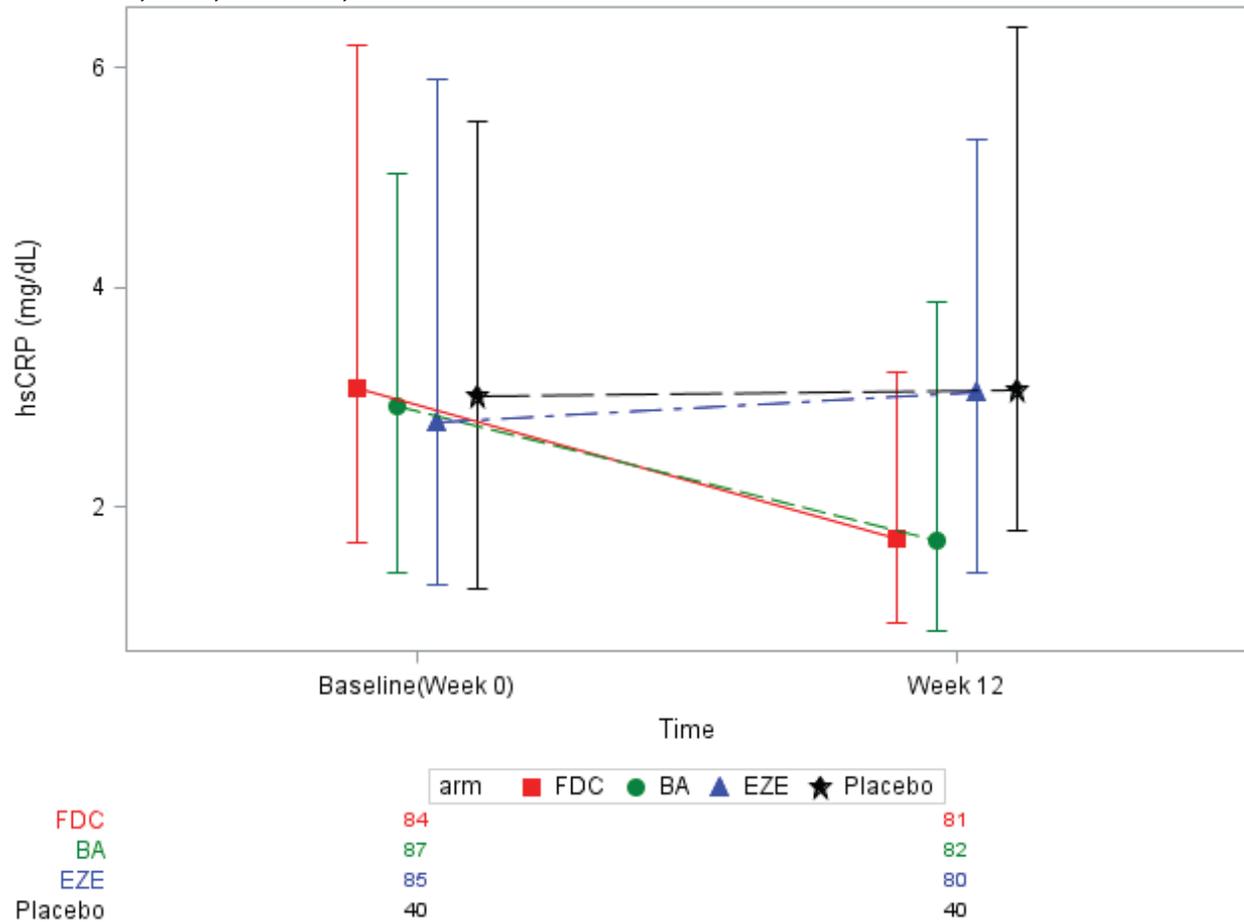
Source: ad b adsl, statistical reviewer's analysis

¹ Nonparametric (Wilcoxon rank-sum test) analysis with Hodges-Lehmann estimates and confidence interval was performed on observed data with no imputation for missing data

² Statistically significant based on prespecified alpha allocation

Abbreviations: Apo-B, apolipoprotein B; BA, bempedoic acid; CI, confidence interval; EZE, ezetimibe; FDC, fixed-dose combination; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; N, number of subjects in group; SE, standard error

Figure 6. Median (IQR) hsCRP (mg/dL) Over Time, Observed Values in Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053



Source: adlb, statistical reviewer's analysis

Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed-dose combination; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range

Subgroup Analyses

The treatment effect of the FDC relative to placebo appears to be similar across different subgroups (Table 58 and Figure 16 in the Appendix). There is no qualitative difference among any of the subgroups, including treatment difference of FDC relative to its components. Baseline LDL-C does not appear to be an effect modifier for the FDC in terms of percent change in LDL-C from baseline, i.e., the treatment difference of the FDC versus placebo is roughly constant at different baseline LDL-C values (Figure 17).

Clinical Meaningfulness of Efficacy Results

The FDC product containing bempedoic acid and ezetimibe lowers LDL-C to a clinically meaningful degree, -38% from baseline. Both bempedoic acid and ezetimibe contribute to the observed efficacy, although ezetimibe appears to contribute to the treatment effect more than bempedoic acid.

The treatment effect of the FDC product in Trial 053 (-38%) was larger than expected, given the effect size of the monotherapy product in pivotal trials conducted under NDA 211616 (-17%) and LDL-C reduction with ezetimibe (-15 to 20% per approved labeling). In Trial 053 the placebo-adjusted FDC treatment effect was slightly less than additive of each individual component administered alone, bempedoic acid -19% and ezetimibe -25%.

Differences in the enrolled trial populations—and background lipid-lowering therapy—may have contributed to the observed treatment effect. Although Trial 053 enrolled a “high CV risk” patient population, enrollees were actually a mixture of primary (40%) and secondary (60%) prevention patients, with higher baseline LDL-C values (~50 mg/dL higher) than patients in trials submitted with NDA 211616.

A greater proportion (approximately one-third) of patients in Trial 053 were treatment-naïve to any LMT (versus 1.5% in Trials 040 and 047, the pivotal trials supporting NDA 211616). A smaller proportion (approximately one-third) of patients were on high-intensity statin at baseline (versus 51% of patients in Trials 040 and 047). Because the enrolled population does not reflect the indicated population (patients on maximally tolerated statin therapy), trial results could differ from the LDL-C reduction that will be achieved in clinical practice.

The FDC product reduced non-HDL-C and TC; however, this was mostly due to reduction in LDL-C, a major component of both endpoints. The FDC also lowered TG by approximately 12% and Apo-B by 30% versus placebo. Both bempedoic acid and ezetimibe contributed to Apo-B reduction. For TG, most of the reduction was attributable to ezetimibe. The clinical significance of the observed change in TG is unclear. HDL-C decreased slightly with FDC exposure, but this is not considered clinically significant.

Although the FDC reduced hsCRP, the Division does not currently consider this a validated surrogate endpoint for any clinically meaningful outcome.

6.4. Review Issues Relevant to Evaluation of Benefit

6.4.1. Demonstration of Efficacy

Issue

Sufficiency of data to demonstrate a clinically meaningful reduction in LDL-C with FDC treatment and demonstration that both bempedoic acid and ezetimibe contribute to the observed treatment effect.

Conclusion

The FDC's treatment effect on LDL-C reduction is clinically meaningful. Both bempedoic acid and ezetimibe contribute to the observed effect.

Assessment

The above conclusion is based on the following assessments:

- Pivotal study (Trial 053) achieved statistical significance in the primary endpoint
- Bempedoic acid and ezetimibe monotherapy treatment arms also demonstrated LDL-C reduction
- The magnitude of LDL-C reduction was greatest in patients taking the FDC
- The FDC lowered LDL-C in high CV risk patients on a background of maximally tolerated statin who required additional LDL-C lowering
- LDL-C reduction is generally considered a surrogate for reduction in risk for CV events
- The FDC may represent an additional treatment option in patients unable to meet goals with currently available therapy (statins or PCSK9 inhibitors)

6.4.2. Data Integrity Issue

Issue

Three clinical trial sites were identified as potentially fraudulent.

Conclusion

Data from the involved sites was excluded from efficacy and safety analyses.

Assessment

In Trial 053, an unusual number of patients who reported routinely ingesting investigational medical product (IMP) had no detectable IMP in their PK blood samples. Most of these patients were from Sites 1028, 1058, and 1068 located in the Miami, Florida area. In fact, 34 of 65 patients in the active treatment arms from the three sites who reported completing 12 weeks of

treatment with IMP did not have detectable IMP in their PK blood samples at Week 12. Because of this concern, the Applicant conducted post hoc sensitivity analyses that excluded these sites; however, the primary analyses included all patients. During the review, we also noticed unusual results in the placebo group from the three sites that could not be explained by noncompliance. Patients randomized to placebo at the three sites had mean reduction of LDL-C at Week 12 of -16.09%, and this LDL-C decrease was similar in magnitude to that of the three active treatment groups at the three sites. In contrast, patients randomized to placebo at other trial sites showed small mean change from baseline of +1.22% (Table 18).

We later found unusual results in secondary endpoints from these sites as well. The lack of detectable IMP in the active treatment arms and the significant LDL-C reduction in placebo suggest that some patients at these sites received a different medication than they were assigned. Office of Scientific Investigation site inspections to determine the cause were inconclusive. The Applicant could also not explain the results. However, they acknowledged in response to an information request that “all data from the three sites are suspect and that the post hoc sensitivity analysis with data from the three sites removed more accurately represents the overall efficacy, safety and PK profile of the FDC.”

Including or excluding the three problematic sites did not alter interpretation of the primary endpoint, LDL-C reduction, but did alter the magnitude of the treatment effect, due to very distinct results from the three sites. However, given the uncertainty of treatment exposures from the three sites, we decided that exclusion of data from the three sites was the most valid way to proceed.

Table 18. Percent Change in LDL-C From Baseline to Week 12, Observed Values in Full Analysis Set, Trial 053

Planned Treatment	N	Mean	SD
Excluding sites 1028, 1058, 1068			
BA 180 mg + EZE 10 mg FDC	83	-37.86	23.05
BA 180 mg	82	-17.70	23.46
EZE 10 mg	80	-24.18	20.41
Placebo	40	1.22	22.55
Sites 1028, 1058, 1068			
BA 180 mg + EZE 10 mg FDC	22	-12.88	28.87
BA 180 mg	20	-19.35	24.54
EZE 10 mg	23	-13.50	23.72
Placebo	13	-16.09	18.84

Source: adlb, statistical reviewer's analysis

Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed-dose combination; LDL-C, low-density lipoprotein cholesterol; N, number of subjects in group; SD, standard deviation

6.4.3. Selection of LDL Analysis Windows

Issue

The LDL analysis windows used in FDC Trial 053 differed from those used in bempedoic acid phase 3 clinical studies conducted under NDA 211616, although they were prespecified in the Statistical Analysis Plan (SAP) prior to unblinding.

Conclusion

The selected analysis windows were acceptable and did not alter trial conclusions.

Assessment

The SAP outlined analysis visit windows for measurement of the primary endpoint, LDL-C (Table 19). The analysis visit windows used in Trial 053 differed from analysis windows used in pivotal trials submitted under NDA 211616 (Table 20). The selection of analysis windows in Trial 053 favored earlier endpoint assessment. Based on knowledge from trials conducted under NDA 211616, bempedoic acid’s peak efficacy occurs at early time points (Week 4), and we were concerned that the Applicant’s window selection may overestimate the efficacy of the FDC product.

Per FDA’s request, the Applicant conducted a sensitivity analysis for the primary and key secondary endpoints in Trial 053 using the analysis windows applied in NDA 211616. The primary and key secondary endpoints concerned only the last window, namely, [63, +∞] in the initial analysis, and [72, +∞] in the sensitivity analysis. Only three patients were affected. The sensitivity analyses show that this analysis window did not result in any clinically meaningful difference in the primary and key secondary endpoints in Trial 053. Refer to Table 63 in Section 16.3 for more details.

Table 19. LDL-C Analysis Visit Windows Defined in Trial 053 SAP

Visit	S1	T1	T2	T3	T4
Slotted Study Week	-2	0	4	8	12/EOS
Target Study Day	Day -13	Day 1	Day 29	Day 57	Day 85
Analysis Visit Windows	[-∞, -1]	[1]	[2,34]	[35, 62]	[63, +∞]
Protocol defined visit window	Day -16 to -5	Day 1	Day 29 ± 5	Day 57 ± 5	Day 85 ± 5

Source: Trial 053 SAP

Abbreviations: EOS, end of study; LDL-C, low-density lipoprotein cholesterol; S, screening visit; SAP, statistical analysis plan; T, treatment visit

Table 20. LDL-C Analysis Visit Windows Defined in Trials 040, 046, 047, and 048 SAP

Visit	S1	S2	S3	T1	T2	T3	T4, EOS
Slotted study week	-5	-4	-1	0	4	8	12
Target study day	-35	-28	-7	1	29	57	85
Analysis visit windows	[-∞,-32]	[-31,-18]	[-17,-1]	[1,1]	[2,43]	[44,71]	[72, ∞]

Abbreviations: EOS, end of study; LDL-C, low-density lipoprotein cholesterol; S, screening visit; SAP, statistical analysis plan; T, treatment visit

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The nonclinical safety profile of bempedoic acid was fully evaluated as described in the review for NDA 211616, which was informed by a complete nonclinical program designed to support clinical development and approval of a new molecular entity. Those data support this application, but only the nonclinical studies designed to support the fixed-dose combination (FDC) with ezetimibe will be discussed in detail in this review. The nonclinical safety of ezetimibe is supported by prior approval of ezetimibe (NDA 21445), as described in product labeling.

Briefly, the Applicant submitted a good laboratory practice (GLP)-compliant 91-day rat repeat dose general toxicity and an embryo-fetal toxicity study in rats, both with coadministration of bempedoic acid and ezetimibe, to support the safety of the FDC product. The results of the combination embryo-fetal development toxicity study and its implications for product labeling are described in section III.13. In the 91-day repeat dose combination rat toxicity study, bempedoic acid was administered at doses resulting in exposures 2 times the clinical exposure at the human dose of 180 mg (based on AUC). Ezetimibe was administered at doses resulting in up to 22 and 186 times the clinical exposure at the human dose of 10 mg (based on AUC) in male and female rats, respectively.

No new clinically relevant target organ toxicity and no additive or synergistic toxicity was observed. Overall, the toxicity profile observed predominantly reflected bempedoic acid exposure, and all toxicities were consistent with those observed in studies completed with bempedoic acid or ezetimibe alone. The completed combination toxicity study adequately supports the FDC product. Safety margins for coadministration correspond to <2 times the clinical exposure at the human dose of 180 mg (based on AUC) for bempedoic acid and 22 and 186 times the clinical exposure at the human dose of 10 mg (based on AUC) in male and female rats, respectively, for ezetimibe. The low safety margin established for bempedoic acid is acceptable, because the toxicities are due to dose-limiting but rodent-specific PPAR α -related effects at low multiples of clinical exposures with low or no relevance to humans.

Table 21. Bempedoic Acid and Ezetimibe Safety Margins for Coadministration in 91-Day Combination Rat Study

Treatment Group NOAEL (mg/kg)	Nonclinical Exposure (µg.hr/mL)	Safety Margins ¹ (multiples)	Basis for NOAEL
Bempedoic acid <30	513	<2	Adverse liver toxicities (necrosis) and liver enlargements at the only dose (30 mg/kg/day) tested.
Ezetimibe M: 750 F: 250	M: 15.6 F: 130	M: 22 F: 186	Absence of any significant systemic toxicity with ezetimibe at the highest dose tested (750 and 250 mg/kg/day in males and females, respectively).

¹ Exposure multiples for Bempedoic acid were based on population pharmacokinetics analysis from phase 3 trials, where the maximum clinical dose resulted in systemic geometric mean combined ETC-1002 and ESP15228 exposures (AUC_{0-24hr}) of 340 µg.hr/mL. Exposure (AUC) for ezetimibe at the maximum human dose of 10 mg/day (167 µg/kg) is 0.7 µg.hr/mL. Abbreviations: F, female; NOAEL, no observed adverse effect level; M, male

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

The following potential safety risks were reviewed based on information known about the statin drug class, which acts on the same cholesterol biosynthesis pathway as bempedoic acid and based on information known about ezetimibe.

- Myopathy and rhabdomyolysis
- Elevated liver enzymes
- Increases in fasting plasma glucose (FPG) and HbA1c

Common Risks Associated With FDC and Statins or Ezetimibe

- Myopathy: No cases of myopathy or CK elevations >5× were observed in Trial 053; MSK symptoms such as muscle spasm, pain in extremity, and myalgias were associated with the FDC and/or bempedoic acid treatment.
- Hepatic enzyme elevations: Isolated aspartate aminotransferase (AST) elevations >3× ULN were observed in the FDC treatment arm (1.9%) compared to 0% in other arms, but there was no evidence of drug-induced liver injury (DILI), such as Hy's Law cases (see Section 7.6.6).
- Increases in FPG are discussed in Section 7.7.1; HbA1c was not monitored in Trial 053.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Bempedoic acid (NDA 211616) was approved in the United States on February 21, 2020, for use as an adjunct to maximally tolerated statin therapy in patients with HeFH or established ASCVD. Postmarketing data are not yet available. Bempedoic acid is not marketed elsewhere worldwide.

7.4. FDA Approach to the Safety Review

For this review, the safety population was defined as randomized patients who received at least one dose of study drug. Patients were analyzed according to the actual treatment received.

The Division did not agree with the Applicant’s definition of treatment-emergent AEs, which excluded AEs that occurred during the trial period but more than 30 days after drug discontinuation, particularly since a greater proportion of active treatment patients discontinued drug than placebo-treated patients. The Applicant’s analysis approach introduced ascertainment bias in which collected safety data were more likely to be included for placebo-treated patients (who remain on drug) than for FDC-treated or bempedoic acid–treated patients. For this review, all AEs that occurred after the first dose of drug and during the trial period were included in analyses.

Several AEs were reclassified based upon review of verbatim to preferred term mapping (Appendix). In general, reclassification decisions were meant to capture an AE’s underlying etiology or to improve specificity. For example, “back pain due to fall” would be reclassified from “back pain” to “fall” or “bacteria in urine” would be reclassified from “bacterial test positive” to “bacteriuria.” Overall, reclassification decisions did not impact AE incidence. Additionally, AE terms that were considered to reflect the same clinical event were combined to avoid underestimation of incidence; these changes are indicated in footnotes of the affected tables.

7.5. Adequacy of the Clinical Safety Database

An adequate number of patients have been exposed to the individual components of the FDC product.

Table 22. Duration of Exposure, Safety Population, Trial 053, Excluding Sites 1028, 1058, and 1068

Parameter	FDC N=85	BA N=88	Ezetimibe N=86	Placebo N=41
Duration of treatment (weeks)				
Mean (SD)	11.7 (2.1)	11.4 (2.4)	11.0 (3.0)	11.0 (3.3)
Median (min, max)	12.0 (1.1, 16.0)	12.0 (2.7, 16.6)	12.0 (0.4, 15.0)	12.1 (1.3, 14.0)
Patients treated, by duration, n (%)				
Any duration (at least one dose)	85 (100.0)	88 (100.0)	86 (100.0)	41 (100.0)
<1 month ¹	2 (2.4)	4 (4.5)	6 (7.0)	4 (9.8)
≥1 month	83 (97.6)	84 (95.5)	80 (93.0)	37 (90.2)
≥3 months	9 (10.6)	6 (6.8)	8 (9.3)	3 (7.3)
≥6 months	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥12 months	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Listing of data sources used by the reviewer in generating the table

¹ 1 month =30 days

Abbreviations: BA, bempedoic acid; FDC, fixed-dose combination; N, number of subjects in group; n, number of subjects with given treatment duration; SD, standard deviation

7.6. Safety Findings and Safety Concerns Based on Review of the Clinical Safety Database

This section presents safety findings from the full analysis set excluding the three fraudulent sites given the uncertainty about drug exposures in those patients. Results of analyses inclusive of those sites are provided in the Appendix.

7.6.1. Overall Adverse Event Summary

More bempedoic acid–exposed patients (FDC or monotherapy) experienced AEs than ezetimibe- or placebo-treated patients, and more of these patients temporarily interrupted drug. However, there were no differences in serious adverse events (SAEs) or drug discontinuation among the active treatment arms.

Table 23. Overview of Adverse Events,¹ Controlled Trial Safety Population, Trial 053, Excluding Sites 1028, 1058, and 1068, 12 Weeks

Event	FDC N=85 n (%)	BA N=88 n (%)	Ezetimibe N=86 n (%)	Placebo N=41 n (%)	Risk Difference ³ (95% CI)
Any AE	53 (62.3)	58 (65.9)	47 (54.7)	18 (43.9)	18.5 (0.1, 36.8)
Moderate or severe AEs ²	32 (37.6)	27 (30.7)	22 (25.6)	7 (17.1)	20.6 (5.1, 36.0)
SAE	9 (10.6)	8 (9.1)	9 (10.5)	1 (2.4)	8.1 (0.1, 16.2)
SAEs with fatal outcome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
AE leading to discontinuation of study drug	7 (8.2)	9 (10.2)	10 (11.6)	2 (4.9)	3.4 (-5.5, 12.2)
AE leading to interruption of study drug	10 (11.8)	5 (5.7)	3 (3.5)	0 (0.0)	11.8 (4.9, 18.6)

Source: Reviewer's analysis [adae.expt; Software: JMP]

¹ Includes treatment-emergent AE defined as any adverse event that occurred after the first dose of drug

² Moderate: events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities; severe: events interrupt the patient's usual daily activity, are incapacitating with inability to do usual activities, or significantly affect clinical status and warrant intervention and/or close follow-up

³ FDC versus placebo

Abbreviations: AE, adverse event; BA, bempedoic acid; CI, confidence interval; FDC, fixed-dose combination; N, number of subjects in group; n, number of subjects with at least one event; SAE, serious adverse event

7.6.2. Deaths

No deaths occurred in Trial 053.

7.6.3. Serious Adverse Events

There was no difference in overall SAEs experienced by FDC-treated patients compared to active control or placebo arms. Given the small sample size and short trial duration, most SAEs were experienced by only one patient. SAEs were generally cardiac or respiratory in etiology, but there were no important differences by treatment group. These SAEs are not unexpected for an older trial population at high risk for CV events.

NDA 211617

Nexlizet / bempedoic acid and ezetimibe

Table 24. Serious Adverse Events by Descending Difference Order, Safety Population, Trial 053, Excluding Sites 1028, 1058, and 1068

Adverse Event ¹	FDC	Bempedoic acid	Ezetimibe	Placebo	Risk Difference ³ (95% CI)
	N=85 n (%)	N=88 n (%)	N=86 n (%)	N=41 n (%)	
Patients with at least one SAE	9 (10.6)	8 (9.1)	9 (10.5)	1 (2.4)	8.1 (0.1, 16.2)
Myocardial infarction ²	1 (1.2)	3 (3.4)	3 (3.5)	1 (2.4)	-1.3 (-6.5, 4.0)
Angina unstable	1 (1.2)	1 (1.1)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)
Diverticulitis	1 (1.2)	1 (1.1)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)
Angina pectoris	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)
Atrial fibrillation	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)
Coronary artery disease	1 (1.2)	0 (0.0)	0 (0.0)	1 (2.4)	-1.3 (-6.5, 4.0)
Myocardial ischemia	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)
Hemiparesis	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)
Non-cardiac chest pain	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)
Rhinovirus infection	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)
Cardiac failure	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Chronic obstruction pulmonary disease	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Pneumonia	0 (0.0)	1 (1.1)	1 (1.2)	0 (0.0)	0.0 (0.0, 0.0)
Confusional state	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Supraventricular tachycardia	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Coronary vascular graft stenosis	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0.0 (0.0, 0.0)
Deep vein thrombosis	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0.0 (0.0, 0.0)
Chronic respiratory failure	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0.0 (0.0, 0.0)
Limb injury	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0.0 (0.0, 0.0)
Ovarian cancer	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0.0 (0.0, 0.0)
Renal artery occlusion	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0.0 (0.0, 0.0)
Respiratory failure	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0.0 (0.0, 0.0)

Source: Reviewer's analysis [adae.xpt; Software: JMP]

¹ Coded as MedDRA preferred terms² Includes acute myocardial infarction and myocardial infarction³ FDC versus placebo

Abbreviations: CI, confidence interval; FDC, fixed-dose combination; N, number of subjects in group; n, number of subjects with adverse event; SAE, serious adverse event

7.6.4. Dropouts and/or Discontinuations Due to Adverse Events

There was no difference in overall discontinuations due to AEs between FDC-treated patients and bempedoic acid- or ezetimibe-treated patients. More patients in the treatment and active control arms discontinued due to an AE than placebo patients. Given the small sample size and short trial duration, most events were experienced by fewer than three patients. Within the FDC arm, primary

NDA 211617

Nexlizet / bempedoic acid and ezetimibe

reasons for drug discontinuation were oral discomfort, fatigue, pain in extremity, and abdominal pain; although these events were experienced only by a handful of patients, they are consistent with safety profiles of bempedoic acid and ezetimibe.

Table 25. Adverse Events Leading to Discontinuation, Safety Population, Trial 053, Excluding Sites 1028, 1058, and 1068

Adverse Event¹	FDC N=85 n (%)	Bempedoic Acid N=88 n (%)	Ezetimibe N=86 n (%)	Placebo N=41 n (%)	Risk Difference² (95% CI)
Patients with at least one AE leading to discontinuation	7 (8.2)	9 (10.2)	10 (11.6)	2 (4.9)	3.4 (-5.5, 12.2)
Oral discomfort	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	2.4 (-0.9, 5.6)
Fatigue/lethargy ³	1 (1.2)	1 (1.1)	1 (1.2)	0 (0.0)	1.2 (-1.1, 3.5)
Pain in extremity	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)
Abdominal pain ⁴	1 (1.2)	0 (0.0)	1 (1.2)	0 (0.0)	1.2 (-1.1, 3.5)
Agitation	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)
Asthenia	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)
Blood glucose increased	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)
Dysgeusia	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)
Hypoglycemia	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)
Myalgia	0 (0.0)	3 (3.4)	1 (1.2)	0 (0.0)	0.0 (0.0, 0.0)
Confusional state	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Diarrhea	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Diverticulitis	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Myocardial infarction ⁵	0 (0.0)	1 (1.1)	1 (1.2)	0 (0.0)	0.0 (0.0, 0.0)
Hyperhidrosis	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Chronic respiratory failure	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0.0 (0.0, 0.0)
Constipation	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0.0 (0.0, 0.0)
Joint dislocation	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0.0 (0.0, 0.0)
Musculoskeletal discomfort	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0.0 (0.0, 0.0)
Non-cardiac chest pain	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0.0 (0.0, 0.0)
Renal artery occlusion	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0.0 (0.0, 0.0)
Urticaria	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0.0 (0.0, 0.0)
Wrist fracture	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)	0.0 (0.0, 0.0)
Muscular weakness	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	-2.4 (-7.2, 2.3)
Weight increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	-2.4 (-7.2, 2.3)

Source: Reviewer's analysis [adae.xpt; Software: JMP]

¹ Coded as MedDRA preferred terms² FDC versus placebo³ Includes fatigue and lethargy⁴ Includes abdominal pain and gastrointestinal pain⁵ Includes acute myocardial infarction and myocardial infarction

Abbreviations: AE, adverse event; CI, confidence interval; FDC, fixed-dose combination; N, number of subjects in group; n, number of subjects with adverse event

NDA 211617

Nexlizet / bempedoic acid and ezetimibe

7.6.5. Treatment-Emergent Adverse Events

The safety events in Trial 053 were generally consistent with the known safety profiles of bempedoic acid and ezetimibe. Notable events experienced by patients who received the FDC include hyperuricemia; gastrointestinal events (constipation, nausea, abdominal pain); upper respiratory events (nasopharyngitis, bronchitis, URI, cough); musculoskeletal events (muscle spasms, pain in extremity, myalgias); fatigue; elevated liver enzymes; increased creatinine; urinary tract infection; and oral discomfort.

Table 26. Adverse Events¹ Occurring at 1% Higher Frequency in Treatment Arm Than Comparator Arm,² Phase 3 Safety Population, Excluding Sites 1028, 1058, and 1068

Adverse Event	FDC N=85 n (%)	Bempedoic acid N=88 n (%)	Ezetimibe N=86 n (%)	Placebo N=41 n (%)	Risk Difference³ (95% CI)
Increased uric acid ⁴	4 (4.7)	1 (1.1)	0 (0.0)	0 (0.0)	4.7 (0.2, 9.2)
Constipation	4 (4.7)	0 (0.0)	2 (2.3)	0 (0.0)	4.7 (0.2, 9.2)
Nasopharyngitis	4 (4.7)	6 (6.8)	4 (4.7)	0 (0.0)	4.7 (0.2, 9.2)
Blood creatinine increased	3 (3.5)	1 (1.1)	0 (0.0)	0 (0.0)	3.5 (-0.4, 7.5)
Bronchitis	3 (3.5)	0 (0.0)	4 (4.7)	0 (0.0)	3.5 (-0.4, 7.5)
Fatigue	3 (3.5)	2 (2.3)	1 (1.2)	0 (0.0)	3.5 (-0.4, 7.5)
Nausea	3 (3.5)	1 (1.1)	0 (0.0)	0 (0.0)	3.5 (-0.4, 7.5)
Upper respiratory tract infection	3 (3.5)	1 (1.1)	0 (0.0)	0 (0.0)	3.5 (-0.4, 7.5)
Abdominal pain ⁵	3 (3.5)	1 (1.1)	1 (1.2)	0 (0.0)	3.5 (-0.4, 7.5)
Urinary tract infection	5 (5.9)	3 (3.4)	2 (2.3)	1 (2.4)	3.4 (-3.4, 10.3)
Cough	2 (2.4)	1 (1.1)	1 (1.2)	0 (0.0)	2.4 (-0.9, 5.6)
Elevated liver enzymes ⁶	2 (2.4)	1 (1.1)	0 (0.0)	0 (0.0)	2.4 (-0.9, 5.6)
Gastroenteritis viral	2 (2.4)	1 (1.1)	0 (0.0)	0 (0.0)	2.4 (-0.9, 5.6)
Hypokalemia	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	2.4 (-0.9, 5.6)
Muscle spasms	2 (2.4)	1 (1.1)	4 (4.7)	0 (0.0)	2.4 (-0.9, 5.6)
New/worsening diabetes ⁷	2 (2.4)	1 (1.1)	2 (2.3)	0 (0.0)	2.4 (-0.9, 5.6)
Oral discomfort	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	2.4 (-0.9, 5.6)
Acute otitis media	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	2.4 (-0.9, 5.6)
Prostatitis	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	2.4 (-0.9, 5.6)
Proteinuria ⁸	2 (2.4)	0 (0.0)	1 (1.2)	0 (0.0)	2.4 (-0.9, 5.6)
Spinal osteoarthritis	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	2.4 (-0.9, 5.6)
Syncope	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	2.4 (-0.9, 5.6)
Anxiety	1 (1.2)	2 (2.3)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)
Angina pectoris	1 (1.2)	1 (1.1)	1 (1.2)	0 (0.0)	1.2 (-1.1, 3.5)
Angina unstable	1 (1.2)	1 (1.1)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)

NDA 211617
Nexlizet / bempedoic acid and ezetimibe

Adverse Event	FDC N=85 n (%)	Bempedoic acid N=88 n (%)	Ezetimibe N=86 n (%)	Placebo N=41 n (%)	Risk Difference³ (95% CI)
Blood triglycerides increased	1 (1.2)	1 (1.1)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)
Diarrhea	1 (1.2)	2 (2.3)	2 (2.3)	0 (0.0)	1.2 (-1.1, 3.5)
Diverticulitis	1 (1.2)	1 (1.1)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)
Dizziness	1 (1.2)	2 (2.3)	2 (2.3)	0 (0.0)	1.2 (-1.1, 3.5)
Hemoglobin decreased	1 (1.2)	2 (2.3)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)
Hypertension	1 (1.2)	3 (3.4)	2 (2.3)	0 (0.0)	1.2 (-1.1, 3.5)
Hypoglycemia	1 (1.2)	1 (1.1)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)
Restless legs syndrome	1 (1.2)	1 (1.1)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)
Sinusitis ⁹	1 (1.2)	3 (3.4)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)
Vomiting	1 (1.2)	1 (1.1)	0 (0.0)	0 (0.0)	1.2 (-1.1, 3.5)

Source: Reviewer's analysis [adae.xpt; Software: JMP]

¹ Treatment-emergent adverse event defined as any adverse event that occurred after first dose of drug, coded as MedDRA preferred terms

² Adverse events that occurred only in one placebo-arm patient (and zero active treatment-arm patients) are not displayed

³ FDC versus placebo

⁴ Includes blood uric acid increased and hyperuricemia

⁵ Includes abdominal pain, abdominal pain upper, and gastrointestinal pain

⁶ Includes aspartate aminotransferase increased, liver function test abnormal, and liver function test increased

⁷ Includes diabetes mellitus inadequate control and new-onset diabetes mellitus

⁸ Includes protein urine present and proteinuria

⁹ Includes acute sinusitis and sinusitis

Abbreviations: CI, confidence interval; FDC, fixed-dose combination; N, number of subjects; n, number of subjects with adverse event

7.6.6. Laboratory Findings

Laboratory findings in Trial 053 were consistent with bempedoic acid's known effects. Refer to the Integrated Review of NDA 211616 for details of AEs in the registration trials. Two patients who received the FDC experienced an AST value $>3\times$ ULN. No CK elevations were observed. Patients treated with the FDC or bempedoic acid experienced decreases in hemoglobin and leukocyte count, increases in platelets, increased BUN and creatinine, decreased alkaline phosphatase, and increased uric acid.

Elevations in fasting plasma glucose were observed in the FDC and ezetimibe treatment arms. This finding is further discussed in Section 7.7.1.

Table 27. Patients Meeting Laboratory Abnormality Criteria, From Baseline Through Week 12, Safety Population, Trial 053, Excluding Sites 1028, 1058, and 1068

Laboratory Parameter	FDC N=85 n (%)	BA N=88 n (%)	Ezetimibe N=86 n (%)	Placebo N=41 n (%)
Creatine kinase (CK) elevations (BL normal to FU high)				
>3x-fold ULN	0 (0.0)	0 (0.0)	2 (2.3)	0 (0.0)
>5x-fold ULN	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
>10x-fold ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic enzyme elevations				
AST >3x-fold ULN	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
AST >5x-fold ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ALT >3x-fold ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ALT >5x-fold ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TB >2x-fold ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hemoglobin decrease				
≥ 2 g/dL from baseline	1 (1.2)	2 (2.3)	2 (2.3)	0 (0.0)
≥ 3 g/dL from baseline	0 (0.0)	1 (1.1)	1 (1.2)	0 (0.0)
≥ 5 g/dL from baseline	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
≥ 2 g/dL decline and $<$ LLN	1 (1.2)	2 (2.3)	1 (1.2)	0 (0.0)
WBC decrease				
$<4\times 10^9/L$ and normal at baseline	2 (2.4)	6 (6.8)	3 (3.5)	1 (2.4)
Creatinine increase				
>30% from baseline anytime	4 (4.7)	12 (13.6)	3 (3.5)	1 (2.4)
>30% from baseline by Week 4	2 (2.4)	2 (2.3)	0 (0.0)	0 (0.0)
>0.5 mg/dL from baseline	1 (1.2)	1 (1.1)	1 (1.2)	0 (0.0)
>1 mg/dL from baseline	0 (0.0)	0 (0.0)	1 (1.2)	0 (0.0)
BUN increase				
Normal baseline to $>$ ULN	20 (23.5)	24 (27.3)	8 (9.3)	1 (2.4)
Normal baseline to $>2\times$ -fold increase	5 (5.9)	2 (2.3)	1 (1.2)	1 (2.4)
Normal baseline to $>2\times$ -fold increase and $>$ ULN	3 (3.5)	1 (1.1)	0 (0.0)	0 (0.0)

Source: Reviewer's analysis [ad b.xpt; Software: JMP]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BA, bempedoic acid; BL, baseline; BUN, blood urea nitrogen; FDC, fixed-dose combination; FU, follow-up; LLN, lower limit of normal; N, number of subjects in group; n, number of subjects with abnormality; TB, total bilirubin; ULN, upper limit of normal; WBC, white blood cell

Table 28. Mean Change From Baseline in Selected Laboratory Parameters, Safety Population, Excluding Sites 1028, 1058, and 1068

Laboratory Parameter	FDC	BA	Ezetimibe	Placebo
	N=85 Mean (SD)	N=88 Mean (SD)	N=86 Mean (SD)	N=41 Mean (SD)
Alkaline phosphatase (U/L)				
Week 4	-17.6 (26.2)	-12.9 (10.0)	-1.5 (10.5)	-0.6 (8.1)
Week 8	-19.3 (17.9)	-14.3 (11.0)	-1.8 (10.6)	-2.5 (12.5)
Week 12	-16.7 (24.2)	-16.0 (14.3)	-2.3 (14.0)	-1.1 (9.3)
Fasting plasma glucose (mg/dL)				
Week 4	7.9 (29.6)	-1.8 (21.0)	5.7 (22.4)	2.8 (14.6)
Week 8	8.3 (28.1)	-1.2 (25.1)	1.3 (20.4)	6.1 (15.2)
Week 12	7.8 (32.4)	-4.5 (23.6)	-2.5 (23.9)	-0.4 (20.1)
Uric acid (mg/dL)				
Week 4	0.7 (1.0)	0.8 (0.9)	-0.2 (0.7)	-0.2 (0.6)
Week 8	0.7 (1.1)	0.9 (1.1)	-0.1 (0.7)	0.0 (0.7)
Week 12	0.6 (1.2)	0.8 (1.1)	0.1 (0.8)	-0.1 (0.8)
WBC (10⁹/L)				
Week 4	0.0 (2.0)	-0.3 (1.4)	0.2 (1.3)	-0.1 (1.2)
Week 8	-0.3 (1.8)	-0.2 (1.6)	0.1 (1.4)	-0.3 (1.1)
Week 12	-0.3 (1.3)	-0.3 (1.7)	0.2 (1.4)	-0.2 (1.3)
Platelets (10⁹/L)				
Week 4	29.8 (56.4)	21.9 (41.3)	-0.3 (37.8)	1.9 (32.5)
Week 8	23.0 (42.7)	17.1 (37.6)	-3.2 (36.2)	-2.6 (34.5)
Week 12	15.0 (43.2)	12.4 (45.9)	-1.2 (34.2)	-6.4 (31.9)

Source: Reviewer's analysis [ad b.xpt; Software: JMP]
 Abbreviations: BA, bempedoic acid; FDC, fixed-dose combination; N, number of subjects in group; n, number of subjects with abnormality; SD, standard deviation; WBC, white blood cell

7.7. Review Issues Relevant to Evaluation of Risk

7.7.1. Hyperglycemia

Issue

FDC patients experienced apparent increases in FPG during the trial.

Conclusion

Hyperglycemia is unlikely to be associated with exposure to the FDC.

Assessment

Detailed analyses were conducted to evaluate the potential etiology of hyperglycemia observed within the FDC treatment arm. The above conclusion is based on the following assessments:

- Bempedoic acid monotherapy is associated with decreased, rather than increased, FPG
- Ezetimibe monotherapy, marketed since 2002, has no known association with hyperglycemia or elevation of FPG

- There is no suspected drug-drug interaction that would lead to increased FPG with coadministration of bempedoic acid and ezetimibe
- The FDC does not contain any glucose, sucrose, or other sugar-based inactive ingredients
- The small sample size allowed for highly skewed FPG data

Comparison of mean and median FPG values, as well as review of histogram plots, revealed that the FPG distribution within the FDC arm was highly skewed to the right by a handful of outliers with FPG >150 mg/dL. Given this, median FPG values were compared between treatment arms for improved accuracy.

Review of median FPG values indicated that both absolute FPG values and FPG change from baseline did not differ between treatment arms.

Table 29. Mean and Median Change From Baseline in FPG

Patient Group	FDC N=107	BA N=110	Ezetimibe N=109	Placebo N=55
All patients				
Fasting plasma glucose (mg/dL), mean (SD)				
Week 4	8.6 (29.8)	-1.3 (22.6)	6.5 (30.2)	3.6 (17.4)
Week 8	8.0 (26.9)	-1.0 (30.4)	4.2 (25.9)	5.1 (15.8)
Week 12	9.1 (31.8)	-4.3 (27.9)	0.1 (28.3)	1.6 (19.8)
FPG, median (IQR)				
Week 4	3.0 (-2.0, 13.0)	0.0 (-0.9, 7.0)	3.0 (-3.0, 10.5)	2.0 (-5.0, 10.0)
Week 8	3.0 (-4.0, 12.5)	4.0 (-10.5, 12.0)	1.0 (-7.5, 11.0)	5.0 (-7.0, 13.0)
Week 12	1.0 (-5.3, 12.3)	0.5 (-10.0, 9.0)	1.5 (-8.3, 9.0)	0.0 (-7.0, 11.5)
T2DM patients				
	n=48	n=62	n=59	n=24
Fasting plasma glucose (mg/dL), mean (SD)				
Week 4	16.2 (42.0)	-2.5 (27.7)	8.7 (39.0)	3.7 (23.5)
Week 8	15.2 (38.8)	-1.6 (38.6)	8.0 (32.9)	6.2 (19.8)
Week 12	17.4 (42.6)	-6.0 (34.9)	0.0 (37.5)	1.2 (25.1)
FPG, median (IQR)				
Week 4	6.5 (-3.3, 29.3)	-1.0 (-11.0, 7.0)	4.0 (-4.5, 16.8)	1.0 (-10.0, 15.0)
Week 8	3.0 (-7.0, 26.5)	5.0 (-15.0, 14.0)	1.0 (-10.0, 27.0)	6.0 (-8.5, 17.5)
Week 12	3.0 (-6.0, 24.0)	-1.0 (-17.3, 14.0)	2.0 (-11.5, 13.5)	4.0 (-15.0, 23.0)
Non-T2DM patients				
	n=58	n=48	n=48	n=31
Fasting plasma glucose (mg/dL), mean (SD)				
Week 4	2.2 (8.7)	0.1 (14.2)	3.7 (10.0)	3.5 (11.6)
Week 8	2.7 (9.3)	-0.2 (14.6)	-0.4 (12.3)	4.2 (11.5)
Week 12	1.9 (14.5)	-2.3 (15.5)	0.3 (10.7)	2.0 (14.7)
FPG, median (IQR)				
Week 4	2.0 (-1.3, 5.3)	0.0 (-7.0, 7.0)	3.0 (-1.0, 8.5)	3.0 (-3.8, 10.0)
Week 8	3.0 (-2.0, 8.8)	0.0 (-7.3, 8.3)	1.0 (-6.0, 5.5)	4.0 (-4.0, 10.5)
Week 12	-1.0 (-5.0, 9.0)	1.5 (-9.8, 6.8)	1.0 (-6.0, 6.5)	-1.5 (-6.0, 8.5)

Source: Reviewer's analysis [adlb.xpt; Software: JMP]

Abbreviations: BA, bempedoic acid; FDC, fixed-dose combination; FPG, fasting plasma glucose; IQR, interquartile range; N, number of subjects in treatment group; n, number of subjects in subgroup; SD, standard deviation; T2DM, type 2 diabetes mellitus

Table 30. Absolute FPG Values, Baseline to Week 12, by Diabetic Status

Patient Group	FDC N=107	BA N=110	Ezetimibe N=109	Placebo N=55
All patients				
Fasting plasma glucose (mg/dL), mean (SD)				
Baseline	108.4 (26.0)	115.7 (35.6)	122.6 (47.8)	108.5 (29.8)
Week 4	116.2 (42.7)	111.6 (33.3)	128.3 (53.4)	111.6 (31.9)
Week 8	117.0 (40.2)	116.9 (36.5)	124.2 (52.0)	115.1 (31.9)
Week 12	117.9 (41.5)	111.0 (31.3)	123.7 (46.2)	111.2 (30.2)
FPG, median (IQR)				
Baseline	101.0 (90.0, 116.0)	105.0 (93.0, 127.0)	103.0 (94.0, 132.5)	102.0 (89.0, 120.0)
Week 4	102.0 (92.3, 125.3)	103.0 (89.8, 124.3)	108.0 (95.0, 141.5)	103.0 (93.0, 120.0)
Week 8	106.0 (91.0, 125.0)	106.0 (91.5, 133.0)	106.0 (92.0, 133.5)	106.5 (95.5, 126.3)
Week 12	105.5 (89.8, 134.0)	103 (90, 121.8)	105.5 (95.0, 136.0)	102.0 (90.0, 128.5)
T2DM patients				
	n=48	n=62	n=59	n=24
Fasting plasma glucose (mg/dL), mean (SD)				
Baseline	125.8 (28.0)	130.9 (39.5)	142.5 (55.2)	124.9 (36.6)
Week 4	140.0 (52.7)	124.7 (37.0)	149.6 (61.3)	129.1 (40.3)
Week 8	144.0 (48.3)	133.5 (39.7)	148.1 (59.2)	131.4 (39.5)
Week 12	142.0 (47.8)	124.8 (34.0)	145.4 (52.9)	127.2 (36.5)
FPG, median (IQR)				
Baseline	115.5 (108.0, 151.0)	120.5 (103.0, 153.5)	124.0 (102.5, 164.5)	120.0 (106.5, 144.3)
Week 4	128.5 (107.0, 161.3)	116.0 (96.0, 144.0)	127.0 (106.3, 180.3)	120.0 (95.0, 146.0)
Week 8	134.0 (109.0, 172.5)	120.0 (107.0, 159.0)	129.0 (106.0, 194.0)	133.0 (101.5, 154.5)
Week 12	130.0 (110.0, 172.0)	113.5 (102.0, 144.5)	126.0 (104.5, 176.5)	123.0 (102.0, 145.0)
Non-T2DM patients				
	n=58	n=48	n=48	n=31
Fasting plasma glucose (mg/dL), mean (SD)				
Baseline	94.2 (11.9)	95.6 (14.2)	97.2 (13.2)	95.9 (13.8)
Week 4	95.8 (11.0)	95.2 (17.2)	99.9 (15.6)	99.0 (15.2)
Week 8	96.7 (11.5)	95.6 (15.1)	95.5 (16.5)	101.0 (12.0)
Week 12	96.8 (16.8)	93.9 (15.7)	98.7 (14.8)	98.5 (15.2)
FPG, median (IQR)				
Baseline	96.0 (85.0, 99.0)	95.5 (85.5, 105.0)	95.5 (90.0, 101.8)	96.0 (88.0, 102.0)
Week 4	95.0 (87.8, 102.0)	93.0 (84.0, 104.0)	98.0 (89.5, 107.5)	100.5 (85.3, 106.0)
Week 8	93.5 (87.3, 105.8)	93.5 (86.8, 103.5)	94.5 (88.0, 102.3)	100.0 (92.0, 111.5)
Week 12	94.0 (86.0, 105.0)	91.5 (83.3, 104.5)	99.0 (89.0, 105.0)	96.5 (95.8, 105.0)

Source: Reviewer's analysis [adlb.xpt; Software: JMP] Abbreviations: BA, bempedoic acid; FDC, fixed-dose combination; FPG, fasting plasma glucose; IQR, interquartile range; N, number of subjects in treatment group; n, number of subjects in subgroup; SD, standard deviation; T2DM, type 2 diabetes mellitus

HbA1c was not monitored during the trial. However, baseline mean (SD) HbA1c was similar between all treatment arms: FDC 6.27 (0.95), bempedoic acid 6.36 (1.04), ezetimibe 6.58 (1.16), and placebo 6.16 (0.81).

There were no differences in changes to baseline antidiabetic therapy during the trial. Fewer patients in the FDC arm received dose adjustments to antidiabetic therapy during the trial: FDC n=3 (3.8%), bempedoic acid n=5 (6.2%), ezetimibe n=5 (6.3%), and placebo n=1 (2.7%).

7.7.2. Safety of Triple LMT Administration

Issue

The Applicant seeks an indication as add-on therapy to maximally tolerated statins. Limited data were available to evaluate the safety of triple therapy (FDC + high-intensity statin) given the short trial duration and small sample size in Trial 053.

Conclusion

Administration of the FDC with maximally tolerated statin therapy appears safe.

Assessment

Data from Trials 040 and 047, completed under NDA 211616, were reviewed. In these trials, 90% to 100% of enrolled patients were taking statins, and 50% to 53% were on high-intensity statin.

The safety profiles of patients who were taking statins plus ezetimibe at baseline were reviewed and compared between bempedoic acid and placebo treatment arms. They were also compared to the overall safety profiles of bempedoic acid and to the safety profiles of patients taking statin therapy alone.

No differences in fatal events, SAEs, adverse discontinuations, or overall treatment-emergent AEs were apparent between patients taking triple therapy (statin+ezetimibe+bempedoic acid) compared to patients taking statin+ezetimibe or statin+bempedoic acid.

Table 31. Overview of Adverse Events,¹ Safety Population, High CV Risk Pool, Trials 040 and 047, 52 Weeks, by Baseline LMT

Event	Statin+Ezetimibe		Statin Alone	
	BA N=138 n (%)	Placebo N=69 n (%)	BA N=1,686 n (%)	Placebo N=837 n (%)
Any AE	109 (79.0)	63 (91.3)	1,303 (77.3)	637 (76.1)
Moderate or severe AEs (Grade 3-5) ²	69 (50.0)	35 (52.2)	953 (56.5)	447 (53.4)
SAE	14 (10.1)	9 (13.0)	316 (18.7)	142 (17.0)
SAEs with fatal outcome	1 (0.7)	1 (1.4)	24 (1.4)	6 (0.7)
AE leading to discontinuation of study drug	8 (5.8)	7 (10.1)	194 (11.5)	61 (7.3)
AE leading to interruption of study drug	12 (8.7)	4 (5.8)	209 (12.4)	84 (10.0)

Source: Reviewer's analysis [include source dataset(s) and tools used]

¹ Includes treatment-emergent AE defined as any adverse event that occurred after first dose of drug

² Moderate: events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities; severe: events interrupt the patient's usual daily activity, are incapacitating with inability to do usual activities, or significantly affect clinical status and warrant intervention and/or close follow-up

Abbreviations: AE, adverse event; BA, bempedoic acid; CI, confidence interval; CV, cardiovascular; LMT, lipid-modifying therapy; N, number of subjects in group; n, number of subjects with at least one event; SAE, serious adverse event

Table 32. Serious Adverse Events by Descending Difference (>0.1%) Order, Safety Population, High CV Risk Pool, Trials 040 and 047, Patients on Background Statin + Ezetimibe Therapy

Adverse Event ^{1,2}	Bempedoic Acid	Placebo	Risk Difference (95% CI)
	N=138 n (%)	N=69 n (%)	
Patients with at least one SAE	14 (10.1)	9 (13.0)	-2.9 (-12.3, 6.5)
Angina pectoris	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Aortic stenosis	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Cardiac failure	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Cellulitis	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Cerebrovascular accident	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Chronic obstructive pulmonary disease	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Coronary artery disease	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Diarrhoea	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Diverticulitis	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Goitre	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Lymphoma	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Obstructive pancreatitis	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Peripheral arterial occlusive disease	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Peripheral ischaemia	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Pneumonia	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Radius fracture	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Tendon rupture	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Upper gastrointestinal haemorrhage	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Myocardial infarction ³	1 (0.7)	1 (1.4)	-0.7 (-3.9, 2.4)
Breast cancer	1 (0.7)	1 (1.4)	-0.7 (-3.9, 2.4)
Acute kidney injury	0 (0.0)	1 (1.4)	-1.4 (-4.3, 1.4)
Aortic aneurysm	0 (0.0)	1 (1.4)	-1.4 (-4.3, 1.4)
Atrioventricular block complete	0 (0.0)	1 (1.4)	-1.4 (-4.3, 1.4)
Basal cell carcinoma	0 (0.0)	1 (1.4)	-1.4 (-4.3, 1.4)
Cardiac arrest	0 (0.0)	1 (1.4)	-1.4 (-4.3, 1.4)
Death	0 (0.0)	1 (1.4)	-1.4 (-4.3, 1.4)
Depression	0 (0.0)	1 (1.4)	-1.4 (-4.3, 1.4)
Dyspnoea exertional	0 (0.0)	1 (1.4)	-1.4 (-4.3, 1.4)
Inguinal hernia	0 (0.0)	1 (1.4)	-1.4 (-4.3, 1.4)
Orthostatic hypotension	0 (0.0)	1 (1.4)	-1.4 (-4.3, 1.4)

Source: Reviewer's analysis [adsl.xpt and addd.xpt; Software: Python]

¹ Coded as MedDRA preferred terms

² Terms included are those that occurred more often in the treatment than comparator group.

³ Includes acute myocardial infarction and myocardial infarction

Abbreviations: CI, confidence interval; N, number of subjects in group; n, number of subjects with adverse event; SAE, serious adverse event

Table 33. Adverse Events Leading to Discontinuation by Descending Difference (>0.1%) Order, Safety Population, High CV Risk Pool, Trials 040 and 047, Patients on Background Statin + Ezetimibe Therapy

Adverse Event^{1,2}	Bempedoic Acid N=138 n (%)	Placebo N=69 n (%)	Risk Difference (95% CI)
Patients with at least one AE leading to discontinuation	8 (5.8)	7 (10.1)	-4.3 (-12.5, 3.8)
Cognitive disorder	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Decreased appetite	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Gastritis	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Hyperkalaemia	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Hyponatraemia	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Insomnia	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Prothrombin time abnormal	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Tinnitus	1 (0.7)	0 (0.0)	0.7 (-0.7, 2.1)
Myocardial infarction ³	1 (0.7)	1 (1.4)	-0.7 (-3.9, 2.4)
Myalgia	1 (0.7)	1 (1.4)	-0.7 (-3.9, 2.4)
Arthralgia	0 (0.0)	1 (1.4)	-1.4 (-4.3, 1.4)
Breast cancer	0 (0.0)	1 (1.4)	-1.4 (-4.3, 1.4)
Cardiac arrest	0 (0.0)	1 (1.4)	-1.4 (-4.3, 1.4)
Ligament sprain	0 (0.0)	1 (1.4)	-1.4 (-4.3, 1.4)
Dizziness	0 (0.0)	2 (2.9)	-2.9 (-6.9, 1.1)

Source: Reviewer's analysis [adae.xpt; Software: Python]

¹ Coded as MedDRA preferred terms

² Terms included are those that occurred more often in the treatment than comparator group

³ Includes myocardial infarction and acute myocardial infarction

Abbreviations: AE, adverse event; CI, confidence interval; CV, cardiovascular; N, number of subjects in group; n, number of subjects with adverse event

8. Therapeutic Individualization

8.1. Intrinsic Factors

Effect of intrinsic factors on bioavailability of bempedoic acid and ezetimibe were not investigated under the FDC development program. For the ezetimibe component, the effect of intrinsic factors was cross-referenced to Zetia. For the bempedoic acid component, NDA 211616 assessed the effect of intrinsic factors as briefly outlined below.

Hepatic Impairment

Based on the hepatic impairment study (Study 032), both AUC_{inf} and C_{max} of bempedoic acid were similar between subjects with normal hepatic function and mild/moderate hepatic function. No dose adjustment is required (for detailed information, refer to the Integrated Review of NDA 211616).

Renal Impairment

Based on findings from the renal impairment study (Study 023), both AUC_{inf} and C_{max} of bempedoic acid increased approximately 50% in subjects with mild renal impairment (eGFR >90 mL/min) and 130% in subjects with moderate (eGFR 60 to 89 mL/min) and severe (eGFR 30 to 59 mL/min) renal impairment. Similar renal impairment effect on bempedoic acid systemic exposure was demonstrated based on observed bempedoic acid trough concentrations at steady state.

Based on the assessment of data between patients with normal renal function or mild renal impairment and patients with moderate renal impairment on LDL-C lowering effect for efficacy evaluation, uric acid, eGFR, creatinine, BUN, hemoglobin for safety evaluation, no dose adjustment in patients with moderate renal impairment is required (for detailed information, refer to the Integrated Review of NDA 211616).

Other Factors

Based on population pharmacokinetic analysis, age, gender, race, and bodyweight had no clinically meaningful impact on bempedoic acid systemic exposure. No dose adjustment is necessary for these intrinsic factors (for detailed information, refer to the Integrated Review of NDA 211616).

8.2. Drug Interactions

Are there clinically relevant drug-drug interactions impacting benefit or risk, and what is the appropriate management strategy?

No studies were conducted specifically to assess the effect of the FDC tablet on the PK of other drugs. The Applicant is relying on bempedoic acid (NDA 211616) and the listed drug, Zetia (NDA 21445), for relevant drug interaction information for bempedoic acid and ezetimibe, respectively.

The effect of steady-state bempedoic acid on the PK of single-dose ezetimibe was investigated in Trial 1002FDC-049. The same study also evaluated the effect of steady-state ezetimibe on the PK of single-dose bempedoic acid. This was an open-label, two-cohort, parallel group study in healthy subjects. In Cohort 1 (n=20), subjects received a single dose of 180 mg bempedoic acid tablet on Day 1 followed by once daily doses of 10 mg ezetimibe from Days 10 to 21. On Day 17, subjects received a single dose of 180 mg bempedoic acid along with ezetimibe. In Cohort 2 (n=20), subjects received a single dose of 10 mg ezetimibe tablet on Day 1 followed by once daily doses of 180 mg bempedoic acid from Days 10 to 21. On Day 17, subjects received a single dose of 10 mg ezetimibe along with bempedoic acid. Results from this study demonstrated that steady-state plasma levels of ezetimibe and bempedoic acid did not impact the PK of bempedoic acid and ezetimibe, respectively. Refer to Section 14 for additional information.

8.3. Pediatric Labeling/Plans for Pediatric Drug Development

As a new combination product, this application is subject to Pediatric Research Equity Act requirements. The Applicant was granted a partial waiver for pediatric patients with HeFH less than 10 years of age as studies are impossible or highly impractical. The Applicant will be issued postmarketing requirements (PMRs) to conduct a phase 2 pharmacokinetic/pharmacodynamic study and a phase 3 efficacy and safety study evaluating bempedoic acid in patients with HeFH ages 10 years to less than 18 years.

8.4. Pregnancy and Lactation

Animal Data

Product labeling for this fixed-dose combination (FDC) of bempedoic acid and ezetimibe will be based on reproduction studies conducted with bempedoic acid and ezetimibe administered separately in studies designed to cover the entire cycle of reproduction in rats and the period of organogenesis in rabbits. Additionally, the Applicant conducted a combination embryofetal developmental toxicity study in rats with coadministration of bempedoic and ezetimibe to support the safety of the FDC. The following section describes the outcomes and conclusions of these studies. Because the studies directly support product labeling, the results of studies

conducted to support each individual component of the FDC are provided, in addition to a description of the combination embryofetal developmental toxicity study with the combination. Summaries of the reproductive toxicity studies are provided in the Section III.13 and the final recommended labeling is shown in Section III.21.

Table 34. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation, Bempedoic Acid

Labeling Section	Nonclinical Data
8.1. Pregnancy	<p>Embryo-fetal developmental toxicity studies in rats showed increases in the incidence of nonadverse fetal skeletal variations (bent long bones, bent scapula and incomplete ossification) at doses ≥ 10 mg/kg/day (below the clinical exposure at human dose of 180 mg, based on AUC). Bempedoic acid also caused decreases in the numbers of viable fetuses, increases in postimplantation loss and increased total resorptions at 60 mg/kg/day (11 times the clinical exposure at the human dose of 180 mg based on AUC) and reduced fetal body weight at ≥ 30 mg/kg/day (4 times the clinical exposure at the human dose of 180 mg, based on AUC). Maternal toxicities in the form of reduced body weight and food consumption were noted at ≥ 30 mg/kg/day (4 times the clinical exposure at the human dose of 180 mg, based on AUC).</p> <p>Bempedoic acid caused no adverse developmental outcomes in pregnant rabbits at doses up to 80 mg/kg/day (12 times the clinical exposure at the human dose of 180 mg, based on AUC).</p> <p>In a rat pre- and postnatal development study, treatment with bempedoic acid was associated with adverse delivery outcomes including, increases in stillborn pup, reductions in numbers of live pups, pup survival, pup growth and slight delays in learning and memory at ≥ 10 mg/kg/day (below the clinical exposure at human dose of 180 mg, based on AUC). However, doses ≥ 10 mg/kg/day were associated with maternal toxicities.</p>
8.2. Lactation	<p>The partitioning of bempedoic acid into animal milk is not studied.</p>
13.1. Carcinogenesis, mutagenesis, impairment of fertility	<p>In a rat fertility study, no adverse effect on male fertility was observed even though there were drug-related decreases in sperm count that occurred at 60 mg/kg/day (9 times the clinical exposure at the human dose of 180 mg, based on AUC).</p> <p>In females, there were decreases in the numbers of corpora lutea, implants, viable embryos and litter size at ≥ 30 mg/kg/day (4 times the clinical exposure at the human dose of 180 mg, based on AUC) and changes in estrus cyclicity were observed in females treated at 60 mg/kg/day (9 times the clinical exposure at the human dose of 180 mg, based on AUC).</p> <p>General toxicity was noted in both males and females at ≥ 30 mg/kg/day.</p>

Table 35. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation, Ezetimibe

Labeling Section	Nonclinical Data
8.1. Pregnancy	<p>In embryo-fetal development studies in rats and rabbits, there was no adverse effect on maternal health and embryoletality at any of the dose tested (10-150-fold MRHD, based on AUC, in rats and rabbits).</p> <p>In rats, increased incidences of common fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) were observed at 1,000 mg/kg/day (approximately 10 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe). In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1,000 mg/kg/day (150 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe).</p> <p>Ezetimibe crossed the placenta when pregnant rats and rabbits were given multiple oral doses.</p> <p>In fetal transfer study, the fetal maternal plasma exposure ratio (total ezetimibe) was 1.5 for rats on gestation day 20 and 0.03 for rabbits on gestation day 22.</p> <p>In rat pre-and postnatal development study, no maternal toxicity or adverse developmental outcomes were observed up to the highest dose tested (17 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe).</p>
8.2. Lactation	Ezetimibe was detected in the milk of lactating rats. The pup to maternal plasma ratio for total ezetimibe was 0.5 on lactation day 12.
13.1. Carcinogenesis, mutagenesis, impairment of fertility	Exposure to ezetimibe was not associated with adverse effects on fertility at doses up to 1,000 mg/kg/day in male or female rats (approximately 7 times the human exposure at 10 mg daily based on AUC _{0-24hr} for total ezetimibe).

Abbreviations: MRHD, maximum recommended human dose

Table 36. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation, Bempedoic Acid and Ezetimibe FDC

Labeling Section	Nonclinical Data
8.1 Pregnancy	<p>In a combination embryofetal development study in rats, no adverse or additive/synergistic developmental toxicities were observed up on coadministration of bempedoic acid (4 times the clinical exposure at the human dose of 180 mg, based on AUC) with ezetimibe up to 112 times the clinical dose at the human dose of 10 mg (AUC) in pregnant rats.</p> <p>Consistent with the findings with bempedoic acid alone, there were nonadverse fetal skeletal variations (bent bones of the limbs, scapula, ribs and incomplete ossification of bones of the skull) observed in pregnant females treated with bempedoic acid alone and those given combination of bempedoic with ezetimibe.</p> <p>The fetal skeletal variations occurred in the presence of maternal toxicities and these variations are generally consistent with effects seen in other rat studies with significant maternal toxicity. This indicates the effects are unlikely to be drug-specific.</p>

Abbreviations: FDC, fixed-dose combination

Human Data

The Division of Pediatric and Maternal Health (DPMH) completed a consult review regarding proposed labeling to comply with the Pregnancy and Lactation labeling rule. The following summarizes DPMH's conclusions.

Pregnancy

There are minimal human pregnancy data (and no outcome data) for bempedoic acid in the published literature and in the Applicant's PVDB. The findings in animal studies with minor skeletal variations at doses below the clinical exposure were not worrisome. The Applicant recommended a (b) (4) regarding the use in pregnancy based on the animal studies and mechanism of action. DPMH recommends removing the (b) (4) and replacing it with a notice of the possibility of fetal harm based on mechanism of action in Section 8.

Because there are insufficient human data available to inform the safety of bempedoic acid use during pregnancy from clinical trial experience and the Applicant's pharmacovigilance database, DPMH recommends a PMR for a pregnancy exposure registry and a postmarketing pregnancy study of a different design to assess the safety of bempedoic acid during pregnancy.

Lactation

Based on the high protein binding (99%), it is unlikely that significant amounts of bempedoic acid would be present in human milk. However, because of theoretical concerns, DPMH proposes a PMR for a milk-only lactation study to confirm a low level being present in human milk. Should a significant amount of bempedoic acid be found in the milk-only lactation study, a milk-plasma study should be considered.

DPMH proposes the following for the "Risk Summary" labeling in Section 8.2:

(b) (4)
There is no information about the presence of ezetimibe in human milk. Ezetimibe is present in rat milk (see Data). When a drug is present in animal milk, it is (b) (4) likely that the drug will be present in human milk. There is no information about the effects of ezetimibe on the breastfed infant or the effects on milk production.

(b) (4)

9. Product Quality

Approval.

The Office of Pharmaceutical Quality Review team has assessed NDA 211617 with respect to chemistry, manufacturing, and controls and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, OPQ recommends approval of this NDA from a quality perspective.

Nexlizet (bempedoic acid and ezetimibe) tablet contains 180 mg of bempedoic acid and 10 mg of ezetimibe. Nexlizet tablets are blue, oval-shaped film-coated tablets debossed with “ESP” on one side and with “818” on the other side. Nexlizet tablets are packaged in 30ct or 90ct HDPE bottles supplied with desiccant or as 7ct PVC blister packaging. Nexlizet should be stored in original packaging at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

9.1. Device or Combination Product Considerations

N/A

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

The inspection for this new drug application (NDA) consisted of five domestic sites in addition to the Applicant. In general, based on the inspections of the five clinical sites, the inspectional findings support validity of data as reported by the Applicant under this NDA.

The Esperion Therapeutics, Inc. (Applicant) site inspection included a focus on the lack of any drug product found by the Applicant after database lock in pharmacokinetic (PK) blood samples from certain subjects at certain clinical sites who had reported that they took the investigational drug product. The inspections did not reveal a definitive root cause. The clinical investigators and their staff did not appear to be aware of the PK discrepancies and each site had followed the protocol. The assumption that subjects may have been perpetuating some level of subject misconduct is likely and, therefore, data from these sites (1028, 1058, and 1068) are suspect. We agree with the Applicant's decision to do post hoc sensitivity analyses of key safety, efficacy, and PK study results with all data from sites 1028, 1058, and 1068 removed. In general, the Applicant handled this issue appropriately, and had proper oversight of Trial 1002FDC-053. Data from this Applicant inspection appear acceptable to support this submitted application.

For more information, see Section 20.

11. Advisory Committee Summary

N/A

III. Appendices

12. Summary of Regulatory History

IND 130707 was submitted May 27, 2016, for a fixed-dose combination (FDC) 1 tablet of bempedoic acid (180 mg) and ezetimibe (10 mg), an inhibitor of intestinal cholesterol (and related phytoosterol) absorption.

Although the preferred description is “fixed-combination drug product” (FCDP), this document will use the term FDC for consistency with the Applicant’s terminology.

An end-of-phase 2 meeting was requested March 15, 2017, and granted March 24, 2017. Preliminary responses were issued May 15, 2017, which the Applicant accepted as the final minutes, and the meeting was subsequently cancelled.

A pre-NDA chemistry, manufacturing, and controls meeting, for both applications, was requested May 21, 2018, granted May 31, 2018, and written responses issued August 1, 2018.

Initial agreement letters for the pediatric study plans were issued May 4, 2016, for bempedoic acid and January 11, 2018, for the FDC.

The May 25, 2018, pre-NDA meeting request includes the following proposed indication for the initial submission:

Bempedoic acid is indicated as an adjunct to diet and maximally tolerated statin therapy for treatment of adults with Heterozygous Familial Hypercholesterolemia (HeFH) or Atherosclerotic Cardiovascular Disease (ASCVD) who require additional LDL-C lowering.

According to the meeting package submitted June 29, 2018, the Applicant revised the proposed indication as follows:

[TRADENAME] is indicated as an adjunct to diet [REDACTED] (b) (4) [REDACTED] who require additional lowering of LDL-C.

The Applicant is proposing to submit two NDAs simultaneously: one for the bempedoic acid tablet and one for the FDC tablet. The NDA for bempedoic acid will contain results from the following phase 3 trials:

- 1002-040: A randomized, double-blind, placebo-controlled, multicenter long-term safety and tolerability study of ETC-1002 in patients with hyperlipidemia at high cardiovascular risk who are not adequately controlled by their lipid-modifying therapy
- 1002-046: A randomized, double-blind, parallel group, multicenter study to evaluate the efficacy and safety of bempedoic acid (ETC-1002) 180 mg compared to placebo added to background lipid-modifying therapy in patients with elevated low-density lipoprotein cholesterol (LDL-C) who are statin intolerant

- 1002-047: A long-term, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy of bempedoic acid (ETC-1002) in patients with hyperlipidemia at high cardiovascular risk not adequately controlled by their lipid-modifying therapy
- 1002-048: A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of bempedoic acid (ETC-1002) 180 mg/day as add-on to ezetimibe therapy in patients with elevated LDL-C on low dose or less than low dose statins

The FDC tablet NDA (211617) will largely reference the monotherapy NDA (211616) but will also contain results from Trial 1002FDC-053, titled, A Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of Bempedoic Acid 180 mg + Ezetimibe 10 mg Fixed-Dose Combination Compared to Bempedoic Acid, Ezetimibe, and Placebo Alone in Patients Treated with Maximally Tolerated Statin Therapy.

Bempedoic acid tablets and the FDC tablets are intended for once daily oral chronic therapy.

Following the initial approval, the Applicant (b) (4) 1002-043, titled, A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Effects of Bempedoic Acid (ETC 1002) on the Occurrence of Major Cardiovascular Events in Patients With, or at High Risk for, Cardiovascular Disease Who Are Statin Intolerant (b) (4)

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under IND

13.1.1. Pharmacology

13.1.1.1. Primary Pharmacology

Bempedoic acid (ETC-1002) is a pro-drug that is converted to ETC-1002-coenzyme A (ETC-1002-CoA) in the liver and inhibits adenosine triphosphate-citrate lyase (ACL) ($K_i=2\mu\text{M}$), an enzyme that generates cytosolic acetyl-CoA from citrate used as substrate for the de novo synthesis of cholesterol and fatty acids. By reducing hepatic cholesterol biosynthesis, bempedoic acid causes upregulation of hepatic LDL receptors that enhances LDL-C clearance by the liver in a manner similar to statins.

Ezetimibe reduces the absorption of cholesterol by the small intestine by blocking sterol transporter Niemann-Pick C1-like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols. It is approved to reduced elevated total-C, LDL-C, apolipoprotein B (Apo-B), and non-HDL in patients with hyperlipidemia.

Bempedoic acid and ezetimibe FDC is anticipated to reduce elevated LDL-C levels through distinct but complementary mechanisms involving inhibition of cholesterol synthesis in the liver by bempedoic acid and inhibition of cholesterol absorption in the intestine by ezetimibe.

The safety of bempedoic acid was evaluated in a comprehensive nonclinical program reviewed in detail under NDA 211616. Ezetimibe is supported by FDA's finding of safety as described in approved product labeling. The following is a summary of important information from studies conducted to support approval of the monotherapies, while studies conducted specifically to support the FDC are discussed in greater detail.

Drug Activity Related to Proposed Indication

- Bempedoic acid demonstrated potent inhibition of de novo lipid synthesis in vitro upon incubation with primary human hepatocytes with a mean IC_{50} of 9.7 μ M.
- In high fat high cholesterol containing diet fed hamsters and apolipoprotein E-deficient mice—both accepted animal models of hyperlipidemia—treatment with bempedoic acid lowered plasma LDL-C by up to 38 and 60%, respectively. Moreover, changes in other lipid parameters including reductions in hepatic triglycerides, cholesteryl esters, and free cholesterol were noted in bempedoic acid treated dyslipidemic hamsters.
- Ezetimibe inhibits cholesterol absorption in the gut in animals and modestly lowers LDL-C, (~15% to 20%).

13.1.1.2. Secondary Pharmacology

- Bempedoic acid and its active metabolite (ESP15288) are weak PPAR α/γ agonists. Bempedoic acid also activates adenosine monophosphate-activated protein kinase (AMPK) signaling pathway. However, weight of evidence and mechanistic studies have excluded the likelihood of involvement of PPAR and AMPK signaling pathways in bempedoic acid-mediated lowering of LDL-C.
- No off-target pharmacology of ezetimibe has been reported.

13.1.1.3. Safety Pharmacology

- Bempedoic acid was not associated with any acute safety concerns in safety pharmacology studies at clinically relevant exposures.
- Ezetimibe had effects on behavioral (passivity, body elevation), neurologic (change in gait, limb position), and autonomic parameters at ≥ 10 mg/kg (1.6-fold maximum recommended human dose, based on area under the concentration-time curve (AUC)) in the CNS safety pharmacology study. These effects were neither recapitulated in the chronic repeat dose nonclinical studies or in human use.

13.1.1.4. ADME/PK

Bempedoic Acid

- The pharmacokinetics (PK) parameters of bempedoic acid were adequately characterized in humans, rats, monkeys, and rabbits and were reviewed in NDA 211616.
- Oral bioavailability was not determined; however, approximately >86% of oral dose was absorbed in bile duct–cannulated rats.
- Time to maximum concentration (T_{max}) was achieved within 1 to 2 hours in rats and monkeys, 8 hours in rabbits, and 3.5 hours in humans.
- Bempedoic acid has a relatively long half-life of ~18 hours in rats and monkeys, 10 hours in rabbits, and 19 hours in human.
- In vitro plasma protein binding of bempedoic acid was high >95% in all tested species (mouse, rat, monkey, and human plasma).
- Bempedoic acid distributes rapidly into all tissues, and highest drug levels were achieved in gastric and intestinal content, kidney (tissues associated with absorption and elimination), and liver (main site of pharmacological activity).
- Bempedoic acid was predominantly metabolized through glucuronidation via UGT2B7 to an inactive metabolite, ETC-1002-glucuronide (M11). In addition, it undergoes interconversion into an active and pharmacologically equipotent metabolite ESP15228 (M1) by aldo-keto reductase. ESP15228 further converted to inactive glucuronide conjugate. There was no unique human metabolite identified, and the metabolic profile of bempedoic acid is conserved across species. Bempedoic acid is primarily excreted renally (86%) in monkeys and (70%) in human. It is excreted into the bile in bile duct–cannulated rats (86%) and through feces (78%) in intact rats.

Ezetimibe

- After oral administration, ezetimibe is absorbed and extensively metabolized in the small intestine and liver via glucuronide conjugation to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide) with subsequent biliary and excretion.
- Minimal oxidative metabolism (a phase 1 reaction) has been observed in all species evaluated.
- Ezetimibe and ezetimibe-glucuronide are highly bound (>90%) to human plasma proteins.
- Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with a half-life of approximately 24 hours for both ezetimibe and ezetimibe-glucuronide.
- Ezetimibe was the major component in feces, and only small amounts were present in urine.

13.1.1.5. Toxicokinetic Data

In the 90-day rat combination study, systemic exposure to ETC-1002 and ESP15228 were not affected by coadministration with ezetimibe in both sexes. In contrast, systemic exposure (maximum plasma concentration (C_{max}) and AUC) to ezetimibe-glucuronide was increased up to 3- and 10-fold in males and females coadministered with bempedoic acid, respectively, as compared to ezetimibe alone. Similar increases in exposure to ezetimibe-glucuronide (5 to 7-fold) was observed in pregnant rats treated from GD 6 to 17 with a combination of bempedoic acid and ezetimibe. This is not of safety concern considering the absence of additive or synergetic toxicological interaction upon coadministration of bempedoic acid and ezetimibe.

Table 37. Summary of TK Data From Combination 90-Day General Toxicity and EFD Study With Bempedoic Acid and Ezetimibe

Study/Study No.	Major Findings
-----------------	----------------

General Toxicology Studies

RR 1002-500-061: 90-day repeat dose oral combination toxicity study in rats

Sample collection times: predose and at 1, 2, 4, 8, 12 and 24 hours post dose

Accumulation: none

Dose Proportionality: greater than

NOAEL:

Bempedoic acid: <30 mg/kg/day

Ezetimibe:
M: 750 mg/kg/day
F: 250 mg/kg/day

Safety margin:
Bempedoic acid: <2

Ezetimibe: M: 22, F: 186

Table 38. TK Parameters for ETC-1002 and ESP15228 in the Rat 90-Day Combination Study

Sex	Ezetimibe (mg/kg/day)	Bempedoic Acid (mg/kg/day)	ETC-1002		ESP15228		ETC-1002 + ESP15228	
			C_{max} (ng/mL)	AUC (ng.hr/mL)	C_{max} (ng/mL)	AUC (ng.hr/mL)	C_{max} (ng/mL)	AUC (ng.hr/mL)
M	0	30	58,400	356,000	4,950	31,000	63,350	387,000
	150	30	74,600	511,000	5,850	45,700	80,450	556,700
	375	30	87,200	447,000	5,090	35,600	92,290	482,600
	750	30	89,300	475,000	5,230	38,300	94,530	513,300
F	0	30	108,000	925,000	6,430	62,700	17,230	987,700
	50	30	91,200	730,000	4,740	53,900	95,940	783,900
	125	30	86,800	698,000	4,490	43,300	91,290	741,300
	250	30	125,000	800,000	5,450	47,400	130,450	847,400

Table 39. TK Parameters for Ezetimibe and Ezetimibe-Glucuronide in the Rat 90-Day Combination Study

Sex	Ezetimibe (mg/kg/day)	Bempedoic Acid (mg/kg/day)	Ezetimibe		Ezetimibe Glucuronide		Ezetimibe + Ezetimibe Glucuronide	
			C_{max} (ng/mL)	AUC (ng.hr/mL)	C_{max} (ng/mL)	AUC (ng.hr/mL)	C_{max} (ng/mL)	AUC (ng.hr/mL)
M	750	0	59.8	416	506	6,110	566	6,526
	150	30	18.7	103	1,470	10,700	1,489	10,803
	375	30	33.9	264	1,230	13,800	1,264	14,064
	750	30	57.4	333	1,660	15,300	17,717	15,633
F	250	0	13.3	154	1,780	14,200	1,793	14,354
	50	30	14.1	113	4,900	63,300	4,914	63,413
	125	30	15.3	138	9,780	66,800	9,795	66,938
	250	30	27.5	297	18,500	130,000	18,528	130,297

Study/Study No. Major Findings

Reproductive Toxicology Studies

RR 1002-500-041: Oral embryo-fetal developmental toxicity study in rats

NOAEL:

Bempedoic acid: 30 mg/kg/day

Ezetimibe: 100 mg/kg/day

Safety margin:

Bempedoic acid: 4

Ezetimibe: 112

Table 40. TK Parameters for ETC-1002 and ESP15228 in the Rat Combination EFD Study (GD 17)

Analyte	Group	Treatment	Dose (mg/kg)	C _{max} (ng/mL)	T _{max} (hr)	AUC _{0-24hr} (hr*ng/mL)	M:P ^a	BA:EZ ^b	TR ^c
ETC-1002	8	BA Alone/Vehicle B	30	149000	2	1420000	NA	NA	NA
ETC-1002	11	BA/Low-EZ	30	144000	1.28	1300000	NA	66500	0.915
ETC-1002	12	BA/High-EZ	30	146000	1.34	1050000	NA	110000	0.739
ESP15228	8	BA Alone/Vehicle B	30	7680	2	91400	0.0643	NA	NA
ESP15228	11	BA/Low-EZ	30	6680	1.28	78200	0.0600	NA	0.856
ESP15228	12	BA/High-EZ	30	6700	1.34	67000	0.0637	NA	0.733

NA - Not applicable
a: Metabolite to Parent Ratio (M:P) = AUC_{0-24hr} ESP15228/AUC_{0-24hr} ETC-1002
b: BA:EZ = AUC_{0-24hr}/Dose Bempedoic acid ÷ AUC_{0-24hr}/Dose Ezetimibe
c: Treatment Ratio (TR) = AUC_{0-24hr} 30 mg/kg BA in combination with EZ/AUC_{0-24hr} 30 mg/kg BA alone

Table 41. TK Parameters for Ezetimibe and Ezetimibe-Glucuronide in the Rat Combination EFD Study (GD 17)

Analyte	Group	Treatment	Dose (mg/kg)	C _{max} (ng/mL)	T _{max} (hr)	T _{last} (hr)	AUC _{0-24hr} (hr*ng/mL)	M:P ^a	TR ^b
Ezetimibe	9	Vehicle A/Low-EZ Alone	183	19.0	4	24	179	NA	NA
Ezetimibe	10	Vehicle A/High-EZ Alone	720	24.0	1.21	24	187	NA	NA
Ezetimibe	11	BA/Low-EZ	183	13.7	1.28	24	120	NA	0.670
Ezetimibe	12	BA/High-EZ	720	26.5	2	24	229	NA	1.22
Ezetimibe Glucuronide	9	Vehicle A/Low-EZ Alone	183	1090	1.15	24	11400	63.4	NA
Ezetimibe Glucuronide	10	Vehicle A/High-EZ Alone	720	1080	1.21	24	11300	60.0	NA
Ezetimibe Glucuronide	11	BA/Low-EZ	183	8180	1.28	24	57000	477	5.00
Ezetimibe Glucuronide	12	BA/High-EZ	720	12200	1.34	24	78300	341	6.93

NA - Not applicable
a: Metabolite to Parent Ratio (M:P) = AUC_{0-24hr} ezetimibe glucuronide/AUC_{0-24hr} ezetimibe
b: Treatment Ratio (TR) = AUC_{0-24hr} 720 or 183 mg/kg EZ in combination with 30 mg/kg BA/AUC_{0-24hr} 720 or 183 mg/kg EZ Alone

Abbreviations: BA, bempedoic acid; EFD, embryo-fetal development; EZ, ezetimibe; NOAEL, no observed adverse effect level; TK, toxicokinetic

13.1.2. Toxicology

Bempedoic Acid

Subchronic and chronic toxicology studies conducted with the administration of bempedoic acid alone were reviewed under NDA 211616 and include pivotal 26-week rat and 52-week monkey studies. Here, the summary of findings from the pivotal bempedoic acid studies and additional information pertinent to the bempedoic acid and ezetimibe FDC product is described.

Rat: 26-week Oral (Gavage) Toxicity Study in Rats/RR 1002-500-038

10, 30, 60 mg/kg/day

Exposure margins

0.2, 2, and 7.5 times the clinical dose at the human dose of 180 mg, based on AUC

Key study findings

- Mortality occurred in one toxicokinetic female treated at 60 mg/kg/day due to bempedoic acid–related severe hepatocyte necrosis in the liver.
- Targets and target organs of toxicity were red blood cell (RBC) mass and the liver and kidney.
- Consistent with findings in shorter-term studies, bempedoic acid caused mildly (5% to 15%) reduced RBC mass. This reduction included decreases in hemoglobin, hematocrit, MCV, and MCH at ≥ 10 mg/kg/day and reticulocytes at ≥ 30 mg/kg/day in both sexes. No correlative effects were noted upon analysis of bone marrow smears and no evidence of increased RBC consumption or hemolysis was seen.
- In the liver, bempedoic acid caused minimal hepatocyte necrosis at ≥ 30 mg/kg in females and 60 mg/kg in males; minimal subcapsular necrosis in one male at 60 mg/kg/day; minimal to severe centrilobular vacuolation in both sexes at ≥ 30 mg/kg; bile duct hyperplasia in males only at 60 mg/kg; and increases in brown pigment that was not iron reactive in males and females at all doses. These histological changes occurred concomitantly with elevation of LFTs and total bilirubin predominantly at highest dose tested 60 mg/kg/day. Vacuolation correlated with increased hepatocellular lipid content (positive staining for Oil Red O).
- In addition, treatment with bempedoic acid caused dose-related increases in absolute and relative liver weights (+23% to 154%) and minimal to moderate centrilobular to panlobular hepatocellular hypertrophy in both sexes at ≥ 10 mg/kg/day. These liver changes are attributable to bempedoic acid's PPAR α activity as evidenced by electron microscopy findings of qualitative increases in liver peroxisome at all doses.
- In the kidney, dose-related nonadverse minimal to mild brown tubular pigment (cortex) that was not iron reactive was observed ≥ 10 mg/kg/day in both sexes.
- The no observed adverse effect level (NOAEL) was established as 10 mg/kg/day, which resulted in exposures that approximate the human exposure at the 180 mg dose, based on AUC. The NOAEL is based on adverse liver hepatocyte necrosis and $\geq 93\%$ increases in liver weight in animals treated at ≥ 30 mg/kg/day.

Rat: 52-week Oral (Gavage) Toxicity Study in Monkeys/RR 1002-500-037

6, 20, 60 mg/kg/day

Exposure margins

0.6, 2.4, and 13 times the clinical dose at the human dose of 180 mg, based on AUC

Key study findings

- Bempedoic acid produced mild increases (up to 62%) in creatinine in both sexes treated at ≥ 20 mg/kg/day without any correlating histological kidney changes. Higher creatinine levels were apparent as early as 13 weeks of treatment in females. The increase in creatinine might be attributed to ETC-1002 mediated inhibition of organic anion

transporter 2 ($IC_{50} \sim 7 \times C_{max}$ at the human dose of 180 mg), a transporter mediating the secretion of creatinine in the kidney.

- Electron microscopy showed qualitatively increased peroxisomes in the liver in all treated females and MD and high-dose males. However, the peroxisomal proliferation occurred in the absence of correlative increase in liver weight and adverse histological changes.
- There was diffuse or periportal vacuolation of hepatocytes present in the liver of MD and high-dose animals that stained positive (mild) for Oil Red O staining (lipid content) in the liver. Nevertheless, these changes were not considered adverse, and due to the absence of frank toxicity, the NOAEL was established as 60 mg/kg/day (13 times exposure at the human dose of 180 mg, based on AUC).

Ezetimibe

- Chronic rat and dog dietary toxicity studies were completed to support the approval of ezetimibe (NDA 021445) and prior human use supports the safety of ezetimibe.

FDC Bempedoic Acid/Ezetimibe

Rat: 91-Day Oral Combination Toxicity Study in Rats/RR 1002-500-061

Key study findings

- No additive or synergistic toxicity was observed between bempedoic acid and ezetimibe.
- All the toxicity findings in rats coadministered with bempedoic acid alone or in combination with ezetimibe were consistent with bempedoic acid-related findings in multiple previous rat studies. These findings include significant reduction in body weights, decreases in RBC and clinical chemistry parameters (increases in alkaline phosphatase, calcium, albumin, albumin/globulin ratios, increases in cholesterol and triglyceride levels), and enlargement of the liver and histological findings (minimal to marked centrilobular hepatocellular hypertrophy and increased eosinophilia) in the liver. None of these changes were exacerbated upon coadministration with ezetimibe.
- The NOAEL for the individual agents was the same for monotherapy and combination groups and was established as <30 mg/kg/day (<2 times the clinical exposure at human dose of 180 mg, based on AUC) for bempedoic acid based on adverse liver toxicities (necrosis) and liver enlargements at the only dose (30 mg/kg/day) tested. The NOAEL for ezetimibe was established as the highest dose tested: 250 mg/kg/day in females or 750 mg/kg/day (22 and 186 times the clinical exposure at the human dose of 10 mg, based on AUC) in males due to the absence of ezetimibe-mediated significant systemic toxicity.

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

Table 42. Methods of 91-Day Oral Combination Toxicity Study in the Rat

Study Features	Methods Details
Dose and frequency of dosing	Bempedoic acid: 0 (vehicle 1), 30 mg/kg/day Ezetimibe (male): 0 (vehicle 2), 150, 375, 750 mg/kg/day, Ezetimibe (female): 0 (vehicle 2), 50, 125, 250 mg/kg/day, once daily for 91 days
Route of administration	Oral gavage
Formulation/vehicle	Bempedoic acid (vehicle 1): high viscosity 0.5% carboxymethylcellulose Ezetimibe (vehicle 2): low viscosity 0.5% carboxymethylcellulose
Species/strain	Rat/Wistar Han (b) (4)
Number/sex/group	15/sex/group
Age	7 weeks at initiation
Satellite groups/unique design	TK (3-9/sex/group)
Deviation from study protocol affecting interpretation of results	None

Table 43. Observations and Results of 91-Day Oral Combination Toxicity Study in the Rat

Parameters	Major Findings
Mortality	None
Clinical signs	None
Body weights	Bempedoic acid: Reduction in body weight gain (12%-18%) and loss in body weight (~6%) were noted in both males and females. Bempedoic acid/ezetimibe: Reduction in body weight gain (9-25%) and body weight loss (3%-12%) in both sexes. The differences in mean BW gain and loss were considered bempedoic acid-related; and adverse. Ezetimibe did not exacerbate the body weight effect of ETC-1002 in both sexes. No change in food consumption in noted.
Ophthalmoscopy	None
ECG	N/A
Hematology	Decreases in red blood cell mass including, Hgb (6%-13%), MCV (3%-8%) and MCH (5%-10%) with concomitant increases in RDW (10%-22%) were observed in males and females treated with 30 mg/kg/day of bempedoic acid and all doses of the combination of bempedoic acid and ezetimibe relative to vehicle treated animals. The decreases in red blood cell parameters were likely related to bempedoic acid and were not affected by ezetimibe alone and is consistent with earlier observation with bempedoic acid monotherapy.
Coagulation	Statistically significant mild decreases in APTT were observed in male and females treated with bempedoic acid alone (27%-32%) and in animals treated with all combination doses of bempedoic acid /ezetimibe (19%-27%).

Parameters	Major Findings
Clinical chemistry	<p>ALP was increased (~2-fold) in males and females treated at bempedoic acid alone and in combination with ezetimibe.</p> <p>All bempedoic acid treated groups had test article-related minimal to mild increases in albumin concentration, occasionally associated with minimal increases in calcium concentration (albumin is the major serum binding protein for calcium), albumin/globulin ratios relative to controls. None of these changes increased in an additive or synergistic manner in combination groups.</p> <p>In contrast to the expected pharmacology of the both drugs, all females treated with combination of bempedoic acid /ezetimibe and bempedoic acid alone demonstrated mild increases in cholesterol and triglyceride concentrations relative to controls. This increase might be attributed to compensatory increase in lipid in response to lipid lowering drugs.</p>
Urinalysis	Unremarkable
Gross pathology	There was no test article related macroscopic findings.
Organ weights	<p>Bempedoic acid alone: liver (94%-107%) and relative liver-to-body weight (103%-113%) and liver-to-brain weight (108%) were increased adversely in both males and females.</p> <p>Bempedoic acid and ezetimibe: Increases in absolute liver (65%-112%), relative to liver to body weight (85%-114%), and liver-to-brain weight (72%-107%) were observed in both sexes.</p> <p>Ezetimibe alone: none</p> <p>The increases in liver weight were attributed to weak PPARα activity of bempedoic acid and considered adverse. Ezetimibe did not exacerbate the enlargement of liver induced with bempedoic acid.</p>
Histopathology Adequate battery: Yes	<p>Liver: Mild to marked centrilobular hepatocellular hypertrophy and increased eosinophilia were observed in the liver of males and females given bempedoic acid and all doses of the combination of bempedoic acid and ezetimibe. However, the coadministration of ezetimibe did not increase the incidence and/or severity of bempedoic acid-mediated liver toxicities.</p>

Abbreviations: ALP, alkaline phosphatase; APTT, activated partial prothrombin time; ECG, electrocardiogram; Hgb, hemoglobin; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; N/A, not applicable; PPAR, peroxisome proliferator-activated receptor; RDW, red cell distribution width

13.1.2.1. Genetic Toxicology

Bempedoic Acid

Bempedoic acid was evaluated for genotoxic potential in a standard battery of valid genotoxicity assays. It was negative in an in vitro microbial reverse mutation (Ames assay), positive in in vitro human lymphocyte cytogenetic assay at toxic concentration, and negative in both in vivo mouse micronucleus and in vivo rat bone marrow micronucleus/liver comet assay. By the weight of evidence, bempedoic acid is not considered genotoxic.

Ezetimibe

As described in product labeling, no evidence of mutagenicity based on in vitro Ames and clastogenicity in the in vitro chromosomal aberration and in vivo mouse micronucleus test was observed.

Since both bempedoic acid and ezetimibe are not genotoxic there is not a genotoxic concern with the FDC product

13.1.2.2. Carcinogenicity

Bempedoic Acid

Rat and mouse carcinogenicity studies with administration of bempedoic acid alone were reviewed under NDA 211616.

In the 2-year carcinogenicity study conducted in male and female Wistar Han rats, bempedoic acid was administered daily at doses of 3, 10, or 30 mg/kg/day in accordance with Executive Carcinogenicity Assessment Committee dosing recommendations. There were statistically significant drug-related neoplastic findings in the liver (hepatocellular adenomas and hepatocellular adenoma combined with carcinomas), thyroid (follicular cell adenoma and follicular cell adenoma combined with carcinoma), and pancreas (islet cell adenomas combined with carcinomas) in the male rat at 30 mg/kg/day. The NOAEL for neoplasms was set at the mid dose of 10 mg/kg/day (exposure below the clinical exposure at the human dose of 180 mg, based on AUC). The mechanism for tumorigenesis for the liver and thyroid tumors is likely secondary to a rodent-specific PPAR alpha activation and increased metabolism of thyroid hormones, respectively, and these tumors are not considered a human risk. The human relevance of the pancreatic islet cell tumor findings in male rats is unclear.

In the 2-year carcinogenicity study conducted in male and female CD-1 mice, bempedoic acid was administered daily at doses of 25, 75, or 150 mg/kg/day, in accordance with Executive Carcinogenicity Assessment Committee dosing recommendations. There were statistically significant drug-related neoplastic findings in the liver (hepatocellular adenomas, hepatocellular carcinoma and hepatocellular adenoma combined with carcinomas) in male mice at 75 and 150 mg/kg/day. The NOAEL for neoplasms was set at 25 mg/kg/day (exposure below the clinical exposure at the human dose of 180 mg, based on AUC).

Ezetimibe

As described in product labeling, a 104-week dietary carcinogenicity study with ezetimibe was conducted in rats at doses up to 1,500 mg/kg/day (males) and 500 mg/kg/day (females). This is approximately 20 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe. A 104-week dietary carcinogenicity study with ezetimibe was also conducted in mice at doses up to 500 mg/kg/day (>150 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe). There were no statistically significant increases in tumor incidences in drug-treated rats or mice.

13.1.2.3. Reproductive and Developmental Toxicity

Bempedoic Acid

Reproductive and developmental toxicities were assessed in fertility, early embryonic development, embryo-fetal, pre- and postnatal development, and juvenile animal toxicity studies and was reviewed under NDA 211616.

Fertility and Early Embryonic Development in Rats/RR-1002-500-039

10, 30, 60 mg/kg

- The NOAEL for general toxicity (male and female) was 10 mg/kg/day (below the clinical exposure at the human dose of 180 mg, based on AUC) based on body weight and food consumption observed at ≥ 30 mg/kg/day. No effect was seen on mating and fertility indices in males treated at up to 60 mg/kg/day (9 times the clinical exposure at human dose of 180 mg, based on AUC) in spite of a drug-related statistically significant decrease in sperm count at 60 mg/kg/day.
- In females, there were adverse reproductive indices including increase in early embryonic deaths, lower corpora lutea, implants, and litter sizes at ≥ 30 mg/kg/day and prolonged estrus cyclicity at 60 mg/kg/day but occurred in the presence of significant maternal toxicities.
- The NOAEL for male fertility is 60 mg/kg/day (~7.5 times the clinical exposure at the human dose of 180 mg, based on AUC) considering the absence of direct adverse effect on male mating and fertility at all dose tested. The NOAEL for female fertility was 10 mg/kg/day based on adverse reproductive indices including, increase in early embryonic deaths, lower corpora lutea, implants, and litter sizes at ≥ 30 mg/kg/day).

Embryo-Fetal Development Study in Rats/RR-1002-500-041

10, 30, 60 mg/kg

- Bempedoic acid was not teratogenic when administered to pregnant rats during the period of organogenesis (GD 6 to 17) up to 11 times the clinical exposure at the human dose of 180 mg, based on AUC.
- There were nonadverse fetal skeletal variations (bent long bones, bent scapula, and incomplete ossification) reported at all doses ≥ 10 mg/kg/day in the absence of maternal body. This is below the clinical exposure at human dose of 180 mg, based on AUC.
- Bempedoic acid at maternally toxic doses caused decreases in the numbers of viable fetuses and increases in postimplantation loss and increased total resorptions at 60 mg/kg/day (11 times the clinical exposure at the human dose of 180 mg, based on AUC). It also reduced fetal body weight at ≥ 30 mg/kg/day (4 times the clinical exposure at the human dose of 180 mg, based on AUC).

Embryo-Fetal Development Study in Rabbits/RR-1002-500-044

20, 50, 80 mg/kg/day

Bempedoic acid was not teratogenic when administered to pregnant rabbits during the period of organogenesis (GD 6 to 18) up to 12 times the clinical exposure at the human dose of 180 mg, based on AUC.

No adverse developmental change was apparent in pregnant rabbits treated up to 80 mg/kg/day (12 times the clinical exposure at the human dose of 180 mg, based on AUC), whereas maternal toxicities were noted the same dose.

Pre- and Postnatal Development Study in Rats/RR-1002-500-042

5,10, 20, 30 and 60 mg/kg/day

- Bempedoic acid caused excessive maternal toxicities, including decreased activity, lower body weight, and high neonatal and maternal mortality during gestation and soon after birth in the 30 and 60 mg/kg/day dose groups. These groups were terminated early in lactation (LD 0 to 2).
- In the F0 generation, adverse maternal toxicities as evidenced by lower dam body weight and food consumption were observed throughout pregnancy and lactation at 20 mg/kg/day and transiently (lactation phase only) at 10 mg/kg/day. These coincided with increases in the occurrence of stillborn pup index at 10 and 20 mg/kg/day
- In the F1 generation, there was lower pup survival and lower body weight at 10 and 20 mg/kg/day. Slight delays in developmental landmarks (differences in learning and memory) and female sexual maturation (vaginal opening) were observed at 10 and 20 mg/kg/day.
- The maternal F0 NOAEL was established as 5 mg/kg/day based on effect on body weight and adverse delivery data (increase in stillborn pups) at ≥ 10 mg/kg/day. These exposures approximate the human exposure at the 180 mg dose, based on AUC.
- The NOAEL for F1 pup growth, survival, and behavioral assessments was 5 mg/kg/day (below the clinical exposure at the human dose of 180 mg, based on AUC). This was a result of lower viability index and delays in development (learning and memory) at ≥ 10 mg/kg/day.
- The NOAEL for the postweaning maturation and reproductive performance of the F1 generation was 20 mg/kg/day (11 times the clinical exposure at the human dose of 180 mg, based on AUC), considering the absence of significant drug-related effect on mating and fertility indices during postweaning phase.

Oral Juvenile Toxicity Study in Rats/RR 1002-500-055

1, 3, and 10 mg/kg/day

- Bempedoic acid did not affect growth, neurobehavior (FOB, startle response, motor activity, learning and memory) and sexual maturation in juvenile rats treated up to 10 mg/kg/day.

- The NOAEL is established as 10 mg/kg/day (at doses resulting in exposures below the clinical exposure, based on AUC) considering the absence of effect on growth and neurobehavior in juvenile rats treated at the high dose (10 mg/kg/day) tested.
- Low safety margin is not of clinical concern, because the toxicological profile of bempedoic acid in juvenile rats was comparable to that observed in adult rats. Further, toxicities observed in juvenile rats were related to dose-limiting, rodent-specific PPAR-related effects (increase in liver weight and hepatocellular hypertrophy), which are not considered relevant to humans.

Reproductive Toxicity of Ezetimibe

As described in the product labeling, in oral embryo-fetal development studies of ezetimibe conducted in rats and rabbits during organogenesis there was no evidence of embryo-lethal effects at the doses tested (250, 500, 1,000 mg/kg/day). In rats, increased incidences of common fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) were observed at 1,000 mg/kg/day (~10 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe). In rabbits treated with ezetimibe, an increased incidence of extra thoracic ribs was observed at 1,000 mg/kg/day (150 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe). Ezetimibe crossed the placenta when pregnant rats and rabbits were given multiple oral doses. In oral (gavage) fertility studies of ezetimibe conducted in rats, there was no evidence of reproductive toxicity at doses up to 1,000 mg/kg/day in male or female rats (~7 times the human exposure at 10 mg daily based on AUC_{0-24hr} for total ezetimibe).

Combination embryo-fetal developmental toxicity study with coadministration of bempedoic acid and ezetimibe was conducted, and the data are described below.

A Combination Developmental Toxicity Study in Rats With ETC-1002 and Ezetimibe and a Toxicokinetic Evaluation/RR-1002-500-062

Key study findings

- In general, maternal and embryofetal toxicities were consistent with those observed with bempedoic acid monotherapy.
- Maternal toxicities related to bempedoic acid administration were reflected as lower gestation body weights and decreased food consumption in dams treated with bempedoic acid alone at 30 mg/kg/day and combination of bempedoic acid (30 mg/kg/day) and ezetimibe (≥250 mg/kg/day).
- Incidence of fetal skeletal variations (bent bones of the limbs, scapula, ribs, and incomplete ossification of bones of the skull) were statistically increased in pregnant females treated with bempedoic acid alone and those given combination of bempedoic with ezetimibe. Fetal skeletal variations (bent bones and incomplete ossifications) were likely related to bempedoic acid administration and were consistent with skeletal abnormalities observed in a previously conducted developmental toxicity study with bempedoic acid monotherapy. The skeletal muscle variations were likely reversible postnatally and occurred primarily at dose associated with maternal toxicities.

- Ezetimibe had no additive or synergistic effect on bempedoic acid maternal and developmental effects.
- Therefore, the developmental NOAEL for coadministration of bempedoic acid and ezetimibe were established as 30 mg/kg/day (4 times the clinical exposure at the human dose of 180 mg, based on AUC) and 1,000 mg/kg/day (112 times the clinical exposure at the human dose of 180 mg, based on AUC), respectively.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 44. Methods of Oral Combination Embryo-Fetal Developmental Study in the Rat

Parameter	Method Details
Dose and frequency of dosing	Bempedoic acid: 30 mg/kg/day Ezetimibe: 250 and 1,000 mg/kg/day; Once daily; GD 6 to GD 17
Route of administration	Oral gavage
Formulation/Vehicle	Bempedoic acid (vehicle 1): 0.5% carboxymethylcellulose (high viscosity) Ezetimibe (vehicle 2): 0.5% carboxymethylcellulose (low viscosity)
Species/strain	Time-mated female rats/Wistar Han (b) (4)
Number/sex/group	23/sex/group
Satellite groups	TK: 4 time-mated females/Control group; 12 time-mated females/dose group
Study design	Standard; pregnant female Wistar Han rats dosed from GD 6 to GD 17 and euthanized on GD 20
Deviation from study protocol affecting interpretation of results	Deviations reported to not have affected interpretation of study findings

Abbreviations: GD, gestation day; TK, toxicokinetics

Table 45. Observations and Results of Oral Combination Embryo-Fetal Developmental Study in the Rat

Parameters	Major Findings
Mortality	None
Clinical signs	None
Body weights	<p>Decreases in body weight gain (23%) were observed in animals treated with bempedoic acid alone and in those coadministered with ≥ 250 mg/kg/day ezetimibe (18%).</p> <p>Gestation food consumption was lower in pregnant females treated with bempedoic acid alone (11%) and coadministered with ezetimibe (6%).</p> <p>There were no additive/synergistic increases in body weight effect with coadministration with ezetimibe.</p>
Necropsy findings Cesarean section data	Mean number of implantation sites, viable fetuses, nonviable fetuses, litter size, resorption sites (early, late, and total), and pre- and postimplantation loss were similar across the treated groups and were comparable to vehicle controls. These is consistent with earlier observation where by effects on these parameters were noted only in pregnant females treated at 60 mg/kg/day.
Necropsy findings Offspring	A statistically significant increases in the individual incidence of fetal skeletal variations (bent bones of the limbs, scapula, ribs and incomplete ossification of bones (jugal bone, supra occipital bone, intraparietal bone) were observed in groups treated with 30 mg/kg/day bempedoic acid and combination of 30 mg/kg/day of bempedoic acid and ≥ 250 mg/kg/day of ezetimibe in comparison to controls. No fetal effect was noted with ezetimibe alone. Therefore, these skeletal malformations and variations were considered related to administration of bempedoic acid and consistent with skeletal abnormalities observed in a previously conducted developmental toxicity study with bempedoic acid alone. Coadministration with ezetimibe did not have an additive or synergistic effect on the developmental effect of bempedoic acid in pregnant rats. The skeletal muscles deviations or variations were considered nonadverse since it is transient and known to reverse postnatally.

13.2. Individual Reviews of Studies Submitted to the NDA

N/A

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

No in vitro studies with human biomaterials were conducted specifically for the FDC product. The Applicant is relying on the bempedoic acid NDA (211616) and the listed drug, Zetia (NDA 21445), for relevant in vitro studies on bempedoic acid and ezetimibe, respectively. Refer to the Integrated Review of NDA 211616 for additional details on in vitro studies for bempedoic acid.

14.2. In Vivo Studies

The clinical program for bempedoic acid/ezetimibe 180 mg/10 mg FDC tablet included one relative bioavailability study (Study 1002FDC-034) and one food-effect study (Study 1002FDC-055) in healthy subjects. The Applicant also conducted a 12-week safety/efficacy study in patients with hyperlipidemia (Trial 1002FDC-053). All three studies were conducted with the to-be-marketed FDC product. In addition, a drug-drug interaction study between bempedoic acid and ezetimibe, which is relevant to this FDC application, was conducted in healthy subjects (Trial 1002FDC-049). Table 46 summarizes the clinical studies conducted for the FDC development program.

Table 46. Clinical Studies Conducted Under FDC Development Program

Study ID	Objectives	Population	Study Design	Treatment and Duration
1002FDC-034	Relative BA	Healthy subjects (n=24)	R, OL, SD, 3-period, CO	Bempedoic acid/ezetimibe 180 mg/10 mg FDC; monolayer tablet (TBM) Bempedoic acid/ezetimibe 180 mg/10 mg FDC; bilayer tablet Bempedoic acid 180 mg + ezetimibe 10 mg; coadministration of individual tablet
1002FDC-055	Food-effect	Healthy subjects (n=16)	R, OL, SD, 2-sequence, 2-period, CO	Bempedoic acid/ezetimibe 180 mg/10 mg FDC; fasted Bempedoic acid/ezetimibe 180 mg/10 mg FDC; fed
1002FDC-049	Drug interaction	Healthy subjects (n=40)	R, OL, single-sequence	Bempedoic acid 180 mg Ezetimibe 10 mg
1002FDC-053	Safety/efficacy	Patients with hyperlipidemia treated with maximally tolerated statin (n=350)	R, DB, PC, PG	Bempedoic acid/ezetimibe 180 mg/10 mg FDC tablet Bempedoic acid 180 mg tablet Ezetimibe 10 mg tablet Placebo 12 weeks

Source: NDA 211617, Module 5.2. Tabular listing of all clinical studies – bempedoic acid + Ezetimibe (FDC)
 Abbreviations: BA, bioavailability; CO, concept outline; DB, double-blind; FDC, fixed-dose combination; n, number of subjects in group; OL, open-label; PC, placebo-controlled; PG, parallel group; R, randomized; SD, single dose; TBM, to-be-marketed

Is there a scientific bridge established for bempedoic acid and ezetimibe between the FDC product and the respective individual components?

Yes, the Applicant established a scientific bridge for bempedoic acid and ezetimibe between the FDC product and the respective individual components (see also Section 6.1)

Study 1002FDC-034 was conducted to compare the relative bioavailability of bempedoic acid and ezetimibe administered as FDC tablet or concurrently as separate tablets. The study also investigated two FDC formulations (b) (4) to identify the optimum formulation for further clinical development. This was a randomized, open-label, single-dose, 3-period, 6-sequence, crossover study in which healthy subjects (n=24) received single doses of (a) bempedoic acid/ezetimibe 180 mg/10 mg FDC monolayer tablet, (b) bempedoic acid/ezetimibe 180 mg/10 mg FDC bilayer tablet, and (c) bempedoic acid 180 mg + ezetimibe 10 mg individual tablets under fasting conditions. The treatments were separated by a washout of 14 days. PK samples for bempedoic acid were collected at predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 19, 12, 24, 48, 96, 144, 192, and 240 hours postdose. For ezetimibe, PK samples were collected at predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 19, 12, 24, 48, 96, and 144 hours postdose.

The PK parameters from this study are summarized in Table 47. In general, the systemic exposure of bempedoic acid was similar when administered as FDC (b) (4) tablet (the final to-be-marketed formulation) or individual tablets, i.e., 90% CI for the geometric mean ratio of C_{max} and AUC were within 0.80 to 1.25 (Table 48). Similarly, the systemic exposure of ezetimibe was generally comparable between FDC tablet and Zetia (Table 48). The lower bound of 90% confidence interval for geometric mean ratio of ezetimibe C_{max} was outside 0.80. Since the Applicant demonstrated the safety and efficacy of the FDC product in a pivotal phase 3 study (1002FDC-053), this marginal deviation is not expected to have any impact on the efficacy of the FDC product.

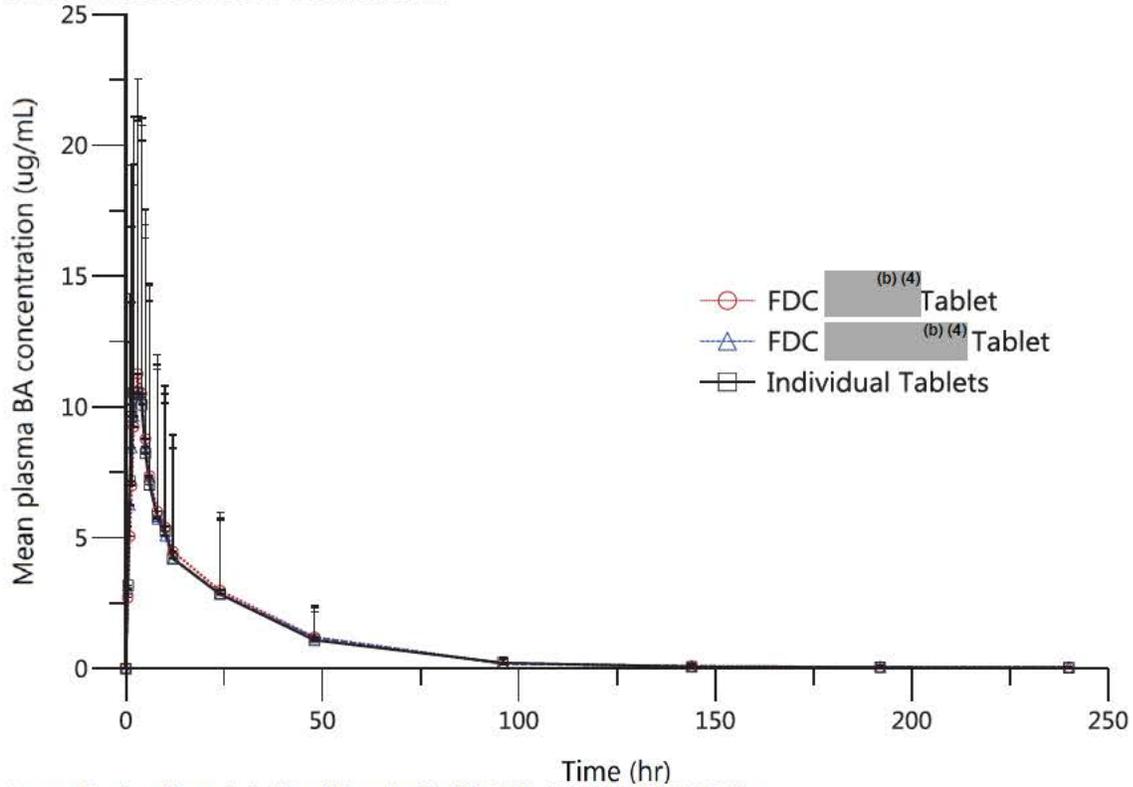
Table 47. Arithmetic Mean (SD) PK Parameters for Bempedoic Acid and Ezetimibe, Study 1002FDC-034

Formulation	Bempedoic Acid			Ezetimibe	
	C _{max} (µg/mL)	AUC _t (µg.hr/mL)	AUC _{inf} (µg.hr/mL)	C _{max} (ng/mL)	AUC _t (ng.hr/mL)
FDC (b) (4)	12.6 (2.80)	200 (42.8)	201 (50.0)	3.56 (1.90)	56.5 (26.1)
Individual tablet	13.4 (3.01)	199 (50.3)	202 (43.4)	3.95 (1.69)	53.0 (22.1)

Source: NDA 211617, Module 5.3.1. CSR Study 1002FDC-034

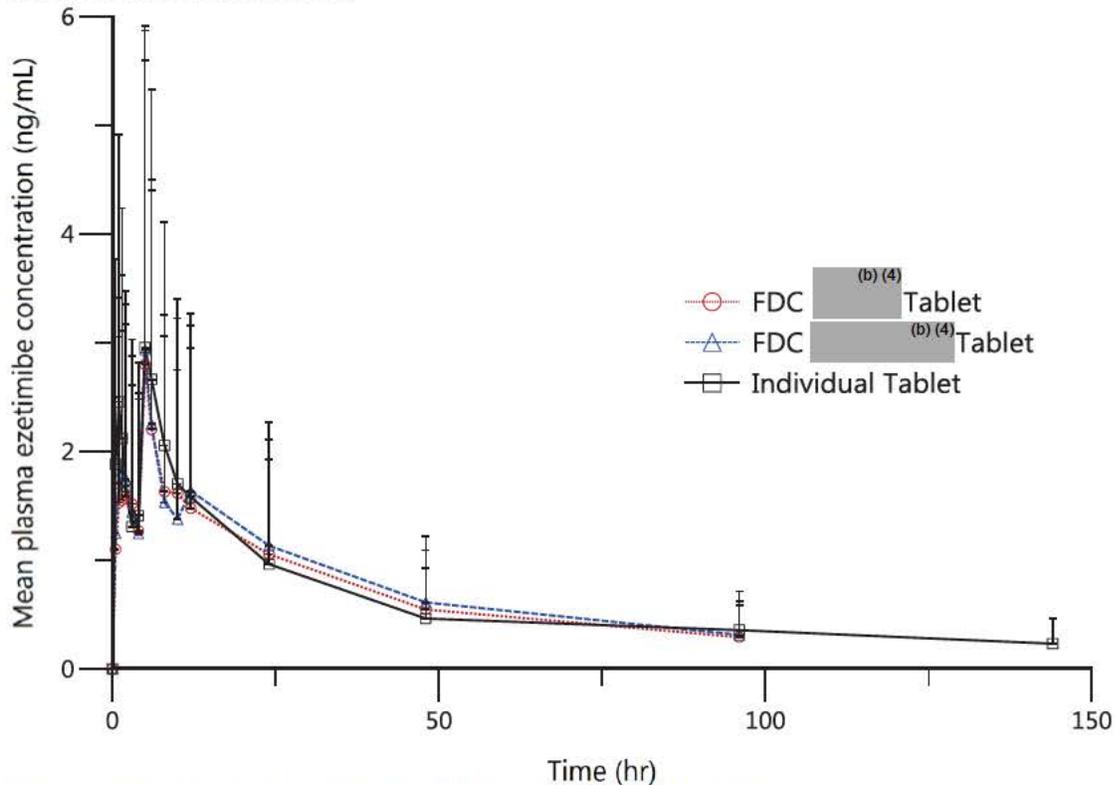
Abbreviations: FDC, fixed-dose combination; PK, pharmacokinetics; SD, standard deviation

Figure 7. Arithmetic Mean Plasma Bempedoic Acid Concentration in Healthy Subjects Following Single Oral Dose of Bempedoic Acid 180 mg Coadministered With Ezetimibe 10 mg as Individual Tablets or Fixed-Dose Combination



Source: Reviewer's analysis from data submitted in CSR (Study 1002FDC-034)
Abbreviations: BA, Bempedoic acid; FDC, fixed-dose combination

Figure 8. Arithmetic Mean Plasma Ezetimibe Concentration in Healthy Subjects Following Single Oral Dose of Bempedoic Acid 180 mg Coadministered With Ezetimibe 10 mg as Individual Tablets or Fixed-Dose Combination



Source: Reviewer's analysis from data submitted in CSR (Study 1002FDC-034)
 Abbreviations: FDC, fixed-dose combination

Table 48. Geometric Mean T/R Ratio (90% CI) for PK Parameters of Bempedoic Acid and Ezetimibe, Study 1002FDC-034

Parameter (unit)	Bempedoic Acid	Ezetimibe
C _{max}	0.93 (0.86, 1.01)	0.87 (0.74, 1.03)
AUC _t	0.99 (0.95, 1.04)	1.00 (0.86, 1.16)
AUC _{inf}	0.99 (0.95, 1.03)	-

Source: NDA 211617, Module 5.3.1. CSR Study 1002FDC-034

T/R: FDC (b) (4) tablet/individual tablet

Abbreviations: CI, confidence interval; FDC, fixed-dose combination; PK, pharmacokinetic; T/R, test/reference

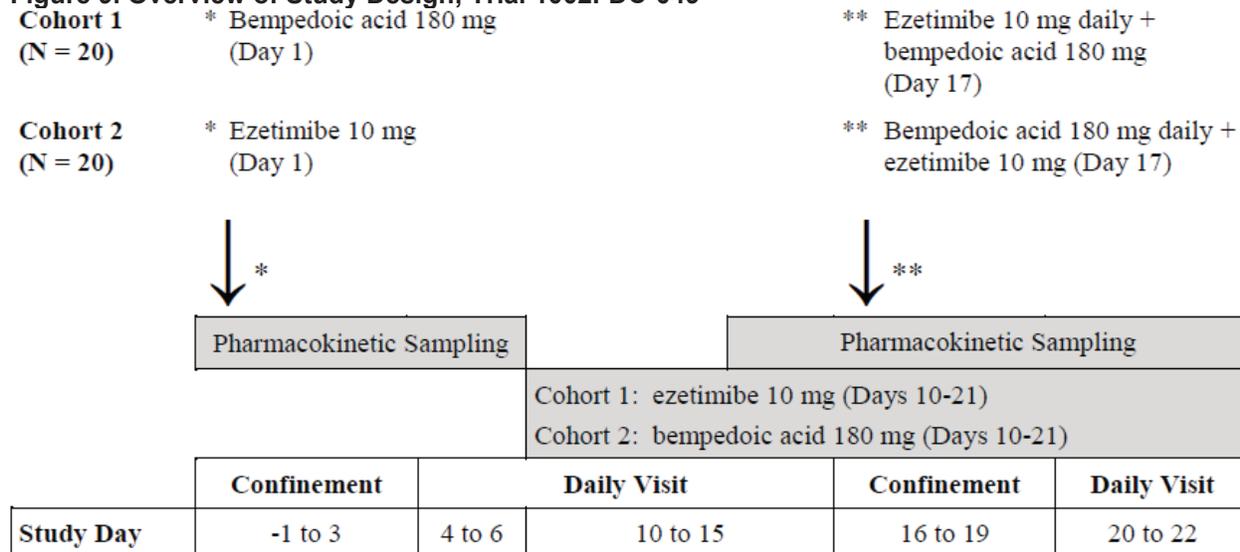
While the systemic exposure of bempedoic acid was similar between the bempedoic acid tablet and the to-be-marketed FDC tablet, the bempedoic acid tablet used in this study was not the to-be-marketed formulation for NDA 211616.

The Applicant provided the following evidence to support the PK bridging evaluation: physicochemical properties of bempedoic acid, formulation composition, in vitro release profiles, population pharmacokinetic analysis. Given the minor difference in formulation composition and in vitro dissolution profiles between formulation to to-be-marketed and the formulation used in this study, no clinically meaningful difference between formulation 2A and formulation 2 would be expected. Refer to the Integrated Review of NDA 211616 for additional details.

Is there a drug-drug interaction between bempedoic acid and ezetimibe?

To investigate the drug interaction potential between bempedoic acid and ezetimibe, the Applicant conducted Trial 1002FDC-049. This was an open-label, two-cohort, parallel group study in healthy subjects. In Cohort 1 (n=20), subjects received a single dose of 180 mg bempedoic acid tablet on Day 1 followed by once daily doses of 10 mg ezetimibe from Days 10 to 21. On Day 17, subjects received a single dose of 180 mg bempedoic acid along with ezetimibe. In Cohort 2 (n=20), subjects received a single dose of 10 mg ezetimibe tablet on Day 1 followed by once daily doses of 180 mg bempedoic acid from Days 10 to 21. On Day 17, subjects received a single dose of 10 mg ezetimibe along with bempedoic acid. Figure 9 provides a schematic of the study design. Blood samples for PK assessments were collected predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, and 120 hours after administration of the single dose of bempedoic acid or ezetimibe on Day 1; before the morning dose of bempedoic acid or ezetimibe on Days 14, 15, and 16; and before and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, and 120 hours after coadministration of bempedoic acid + ezetimibe on Day 17.

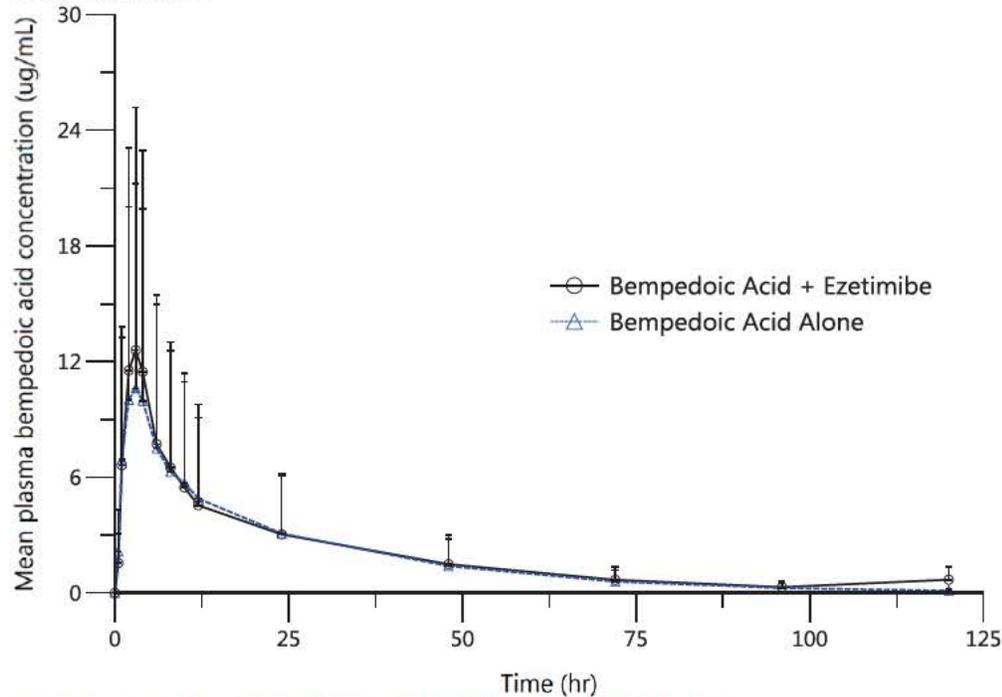
Figure 9. Overview of Study Design, Trial 1002FDC-049



Source: NDA 211617, Module 5.5.3. CSR Trial 1002FDC-049
 Abbreviations: FDC, fixed-dose combination; N, number of subjects in cohort

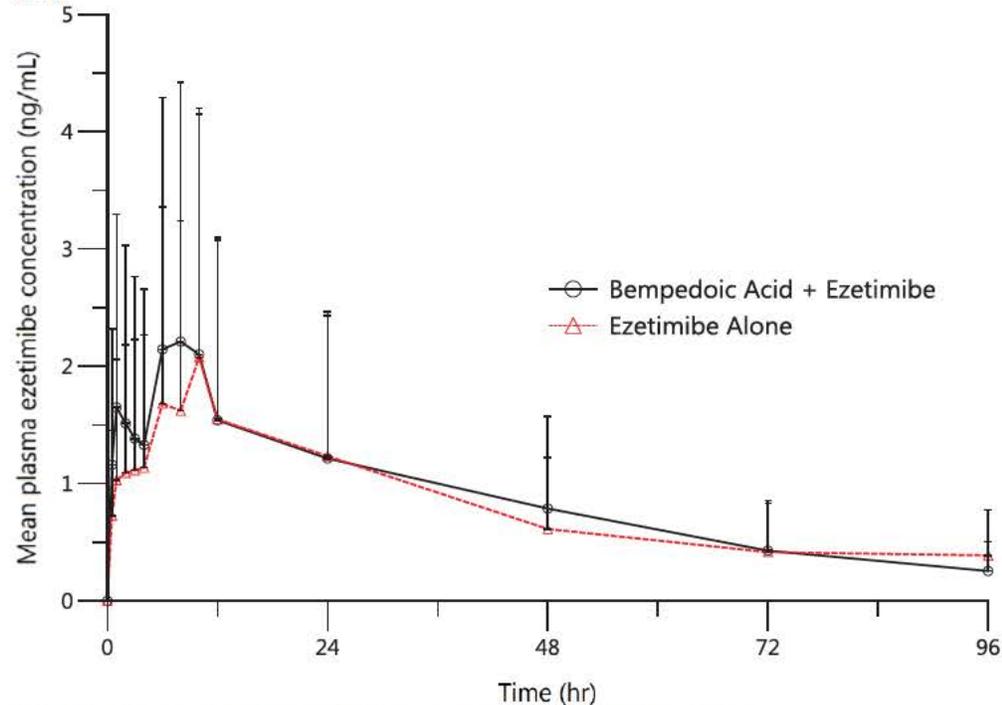
The results from this study demonstrated that steady-state plasma levels of ezetimibe and bempedoic acid generally did not impact the PK of bempedoic acid and ezetimibe, respectively (Table 49).

Figure 10. Arithmetic Mean (+SD) Plasma Bempedoic Acid Concentrations in Healthy Subjects Following Administration of Single Oral Dose of Bempedoic Acid 180 mg Alone and With Steady-State Ezetimibe



Source: Reviewer's analysis from data submitted in CSR (Trial 1002FDC-049)
Abbreviations: SD, standard deviation

Figure 11. Arithmetic Mean (+SD) Plasma Unconjugated Ezetimibe in Healthy Subjects Following Administration of Single Oral Dose of Ezetimibe 10 mg Alone and With Steady-State Bempedoic Acid



Source: Reviewer's analysis from data submitted in CSR (Trial 1002FDC-049)
Abbreviations: SD, standard deviation

Table 49. Geometric Mean T/R Ratio (90% CI) for PK Parameters of Bempedoic Acid and Ezetimibe, Trial 1002FDC-049

Parameter (unit)	Bempedoic Acid	Ezetimibe
C _{max}	1.08 (0.98, 1.18)	1.16 (0.99, 1.36)
AUC _t	1.05 (1.01, 1.08)	1.20 (1.02, 1.41)
AUC _{inf}	1.05 (1.02, 1.09)	-

Source: NDA 211617, Module 5.3.3. CSR Trial 1002FDC-049

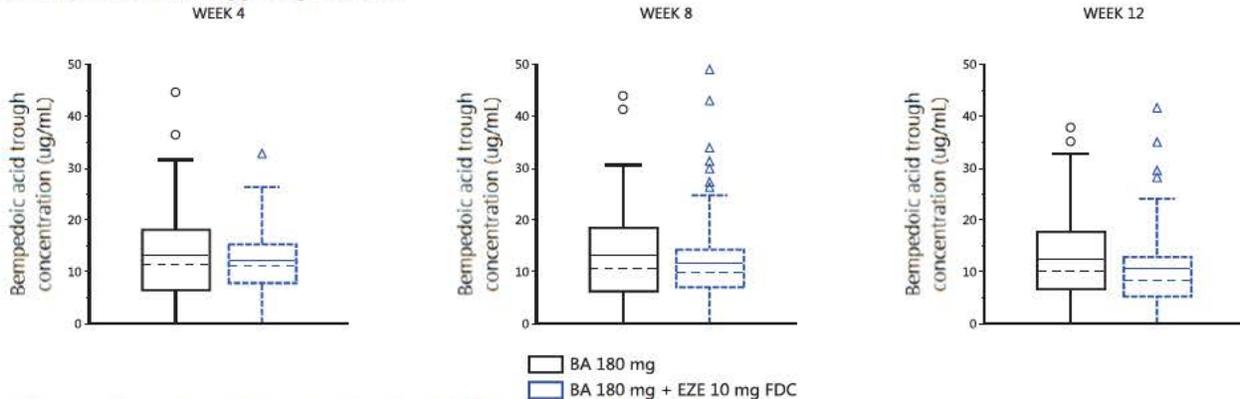
T/R for bempedoic acid: Bempedoic acid alone/Bempedoic acid + SS ezetimibe

T/R for ezetimibe: Ezetimibe alone/Ezetimibe + SS bempedoic acid

Abbreviations: CI, confidence interval; FDC, fixed-dose combination; PK, pharmacokinetic; T/R, test/reference

Trough plasma concentration of bempedoic acid and ezetimibe were also measured following administration of the FDC tablet and the individual component products. Data suggest that the trough concentrations at various weekly intervals were generally comparable between the FDC and both bempedoic acid and ezetimibe alone, suggesting no drug interaction between the two components (Figure 12 and Figure 13).

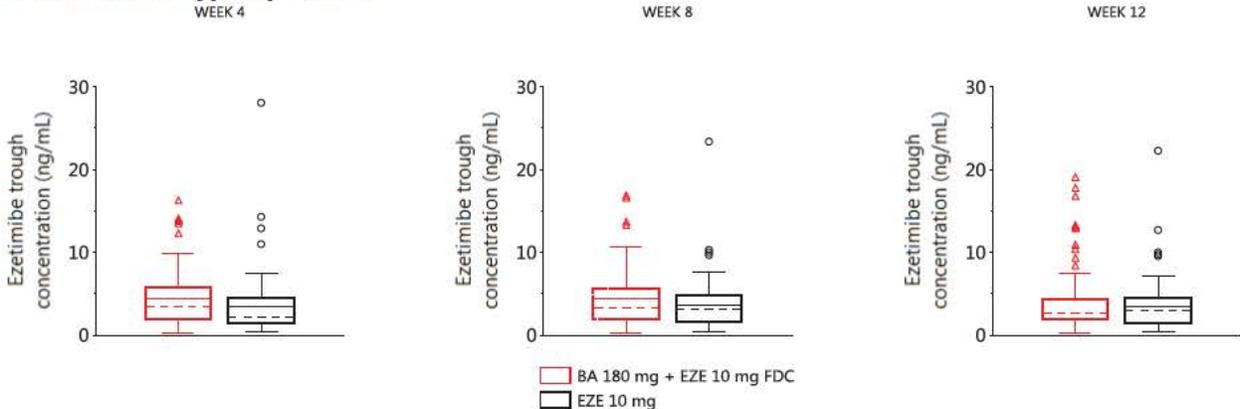
Figure 12. Box Plot for Trough Plasma Bempedoic Acid Concentration at Various Weekly Intervals in Patients With Hyperlipidemia



Source: Reviewer's analysis from data submitted in CSR (Trial 1002FDC-053)

Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed-dose combination

Figure 13. Box Plot for Trough Plasma Ezetimibe Concentration at Various Weekly Intervals in Patients With Hyperlipidemia



Source: Reviewer's analysis from data submitted in CSR (Trial 1002FDC-053)

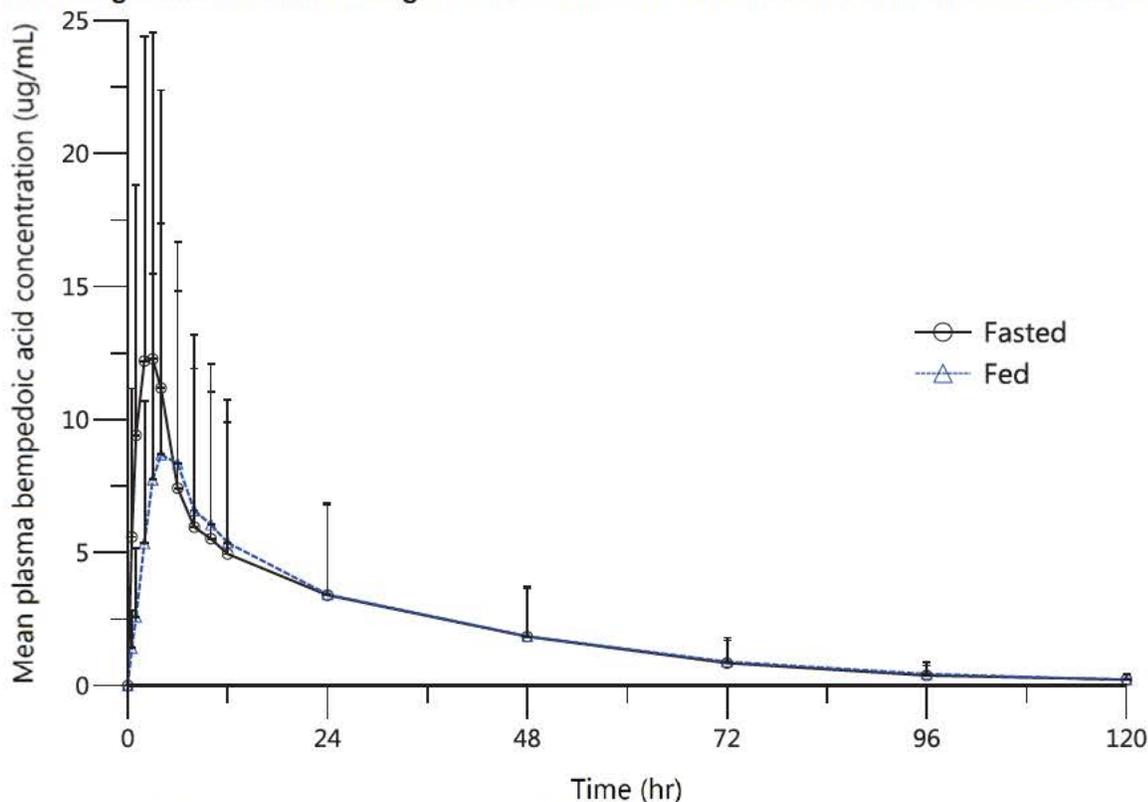
Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed-dose combination

Does food affect the systemic exposure of bempedoic acid and ezetimibe from the FDC tablet?

The effect of food on the systemic exposure of bempedoic acid and ezetimibe from the FDC tablet was investigated in Study 1002FDC-055. This was a randomized, open-label, 2-sequence, 2-period, crossover study in which healthy subjects (n=16) were given a single dose of the FDC tablet in a fasted state and after consumption of a standardized high-fat, high-calorie meal. The treatments were separated by a washout period of 14 days. PK samples were collected predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96 and 120 hr postdose.

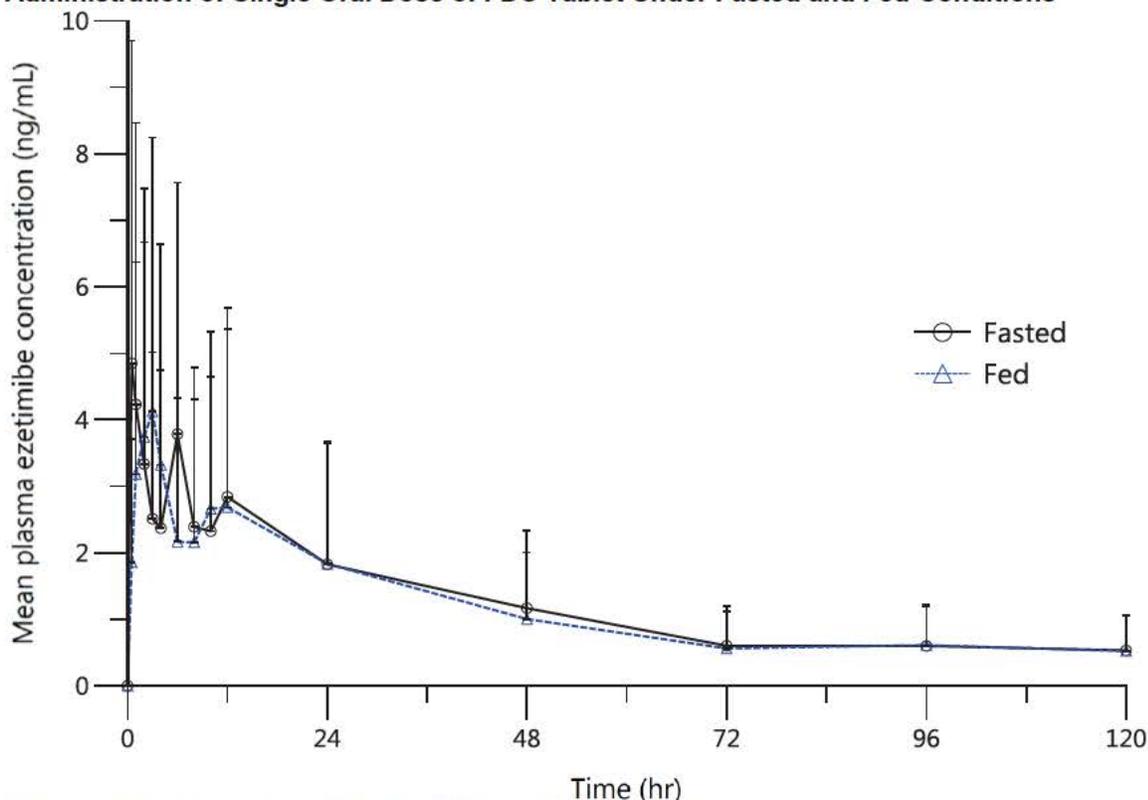
There was no effect of a high-fat meal on the extent of bempedoic acid absorption based on the fed-to-fasted AUC ratio and the 90% CIs. However, there was an effect on the rate of absorption as indicated by a 30% reduction in mean C_{max} and a 2-hour delay in median T_{max} for bempedoic acid. Similarly, a high-fat meal did not affect the extent of ezetimibe exposure as measured by fed-to-fasted AUC ratio and its 90% CI. The mean ezetimibe C_{max} was reduced by 12%, and the median T_{max} was prolonged by 2.5 hours under fed conditions relative to fasted conditions, in a manner similar to bempedoic acid. In the pivotal phase 3 study (1002FDC-053), the to-be-marketed FDC product was administered with or without food. Hence, the observed difference in C_{max} under fed condition does not appear to impact the efficacy of the drug product.

Figure 14. Arithmetic Mean (+SD) Plasma Bempedoic Acid Concentrations in Healthy Subjects Following Administration of Single Oral Dose of FDC Tablet Under Fasted and Fed Conditions



Source: Reviewer's analysis from data submitted in CSR (Trial 1002FDC-049)
Abbreviations: FDC, fixed-dose combination; SD, standard deviation

Figure 15. Arithmetic Mean (+SD) Plasma Ezetimibe Concentrations in Healthy Subjects Following Administration of Single Oral Dose of FDC Tablet Under Fasted and Fed Conditions



Source: Reviewer's analysis from data submitted in CSR (Trial 1002FDC-049)
 Abbreviations: FDC, fixed-dose combination; SD, standard deviation

Table 50. Geometric Mean Fed/Fasted Ratio (90% CI) for PK Parameters of Bempedoic Acid and Ezetimibe, Study 1002FDC-055

Parameter (unit)	Bempedoic Acid	Ezetimibe
C _{max}	0.70 (0.61, 0.80)	0.88 (0.70, 1.11)
AUC _t	0.95 (0.90, 1.00)	0.97 (0.83, 1.14)
AUC _{inf}	0.95 (0.91, 1.00)	-

Source: NDA 211617, Module 5.3.1. CSR Study 1002FDC-055
 Abbreviations: CI, confidence interval; FDC, fixed-dose combination; PK, pharmacokinetic

How is the proposed to-be-marketed formulation linked to the clinical formulation?

The to-be-marketed formulation was used in the pivotal phase 3 study (1002FDC-053) as well as the relative bioavailability study (1002FDC-034) and the food effect study (1002FDC-055).

What are the bioanalytical methods used to measure bempedoic acid and ezetimibe in plasma?

Liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods were developed and validated for quantitation of ETC-1002 (bempedoic acid parent molecule) and ESP15228 (active metabolite) in human plasma, as well as for unconjugated ezetimibe (parent molecule) and ezetimibe-glucuronide (active metabolite). Table 51 and Table 52 highlight the validation summary for bempedoic acid and ezetimibe, respectively.

The Office of Study Integrity and Surveillance (OSIS) inspection was requested for the comparative bioavailability study (1002FDC-034). OSIS concluded that the data from the audited study are reliable to support a regulatory decision. Refer to OSIS Memorandum (DARRTS dated November 26, 2019) for further details.

Table 51. Validation Summary of Bioanalytical Method for Bempedoic Acid

Matrix (Anticoagulant)	Human Plasma (K₂EDTA)
Sample volume	125 µL
Analytical method/detection	Solid phase extraction/LC-MS/MS
Internal standard	ETC-1002-d ₄
Validated range	20 to 20,000 ng/mL
Calibration model	Linear regression
Weighting factor	1/concentration ²
Quantitation method	Peak area ratio
Recovery	95.5% – 101.1%
Intraday accuracy (%deviation)	-0.7% to 1.0%
Intraday precision (%CV)	0.5% to 4.4% (LLOQ)
Interday accuracy (%Bias)	-1.3% to 2.0%
Interday precision (%CV)	1.6% to 4.3%
Freeze-thaw stability	Four cycles at -80°C
Long-term stability	651 days at -80°C in human plasma in the presence of coadministered substances 2,152 days at -80°C in human plasma 1,739 days at -20°C in human plasma 143 days at -20°C and -80°C in the presence of ezetimibe
Ambient matrix stability	48 hours at RT
Study	1002FDC-034, 1002-036, 1002FDC-049, 1002FDC-053, 1002FDC-055

Source: NDA 211617, Module 5.3.1: Report BIO.VR.0033-1092

Abbreviations: FDC, fixed-dose combination; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LLOQ, lower limit of quantification; RT, room temperature

Table 52. Validation Summary of Bioanalytical Method for Ezetimibe

Matrix (Anticoagulant)	Human Plasma (K₂EDTA)
Sample volume	100 µL
Analytical method/detection	Liquid-liquid extraction/LC-MS/MS
Internal standard	Ezetimibe-d ₄
Validated range	0.20 to 200 ng/mL
Calibration model	Quadric regression
Weighting factor	1/concentration ²
Quantitation method	Peak area ratio
Recovery	46.8% – 52.6%
Intraday accuracy (%Bias)	-8.5% to 0.7%
Intraday precision (%CV)	1.2% to 6.6% (LLOQ)
Interday accuracy (%Bias)	-1.3% to .3%
Interday precision (%CV)	1.4% to 10.4%
Freeze-thaw stability	Three cycles at wither -20°C or -80°C
Long-term stability	103 days at -80°C in human plasma
	124 days at -20°C in human plasma
	143 days at -80°C in the presence of bempedoic acid
Ambient matrix stability	24 hr at RT
Study	1002FDC-034, 1002FDC-049, 1002FDC-053, 1002FDC-055

Source: NDA 211617, Module 5.3.1: Report BIO.VR.0033-1666

Abbreviations: FDC, fixed-dose combination; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LLOQ, lower limit of quantification; RT, room temperature

The QC sample results for both bempedoic acid and ezetimibe met the acceptance criteria, i.e., at least 67% of the QC results were within ±15% of the respective nominal values, and at least 50% of QCs at each level were within ±15% of their nominal concentrations. The PK samples were stored and analyzed within the validated storage stability period and conditions.

Pharmacokinetic samples for bempedoic acid and ezetimibe were re-analyzed as part of incurred sample reproducibility assessment. Approximately 10% of the first 1,000 samples and 5% of the remaining samples that met the acceptance criteria of 67% of incurred sample results being within 20% of the original result were re-assessed.

15. Trial Design: Additional Information and Assessment

Title of Study: A Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of Bempedoic Acid 180 mg + Ezetimibe 10 mg Fixed Dose Combination Compared to Bempedoic Acid, Ezetimibe, and Placebo Alone in Patients Treated with Maximally Tolerated Statin Therapy (1002FDC-053) (ClinicalTrials.gov No. NCT03337308)
Indication: (b) (4)
Investigational Product: Bempedoic Acid 180 mg + Ezetimibe 10 mg Fixed Dose Combination (FDC)
Name of Sponsor: Esperion Therapeutics, Inc.
Publications: none
Investigators and Study Sites: This study was conducted at 78 study sites in the United States. Study sites and investigators are listed in Appendix 16.1.4 .
Phase of Development: 3
Study Period: Date first patient enrolled: 23 Oct 2017 Date last patient completed: 03 Jul 2018
Background and Rationale for the Study: This Phase 3, 4-arm study was designed to directly estimate the overall treatment effect of the FDC product by assessing the 12-week efficacy of the bempedoic acid 180 mg + ezetimibe 10 mg FDC vs bempedoic acid 180 mg alone, ezetimibe 10 mg alone, or placebo, in decreasing low-density lipoprotein cholesterol (LDL-C) as added on to maximally tolerated statin therapy (which may include no statins at all). Based on data from an integrated analysis of Phase 2 safety and efficacy, observed values and percent change from baseline in the primary efficacy endpoint, LDL-C, together with a positive safety profile, support the choice of the 180-mg dose for the Phase 3 studies. The target population for this study comprises patients with documented atherosclerotic cardiovascular diseases (ASCVD) and/or heterozygous familial hypercholesterolemia (HeFH) and/or multiple cardiovascular risk factors who required additional LDL-C-lowering therapy despite already being on maximally tolerated statin background therapy. This definition includes patients for whom maximally tolerated statins may mean no statin at all. The treatment duration of 12 weeks and targeted study population of 350 patients were designed to provide efficacy data for LDL-C lowering, safety, and tolerability of bempedoic acid + ezetimibe in patients with high cardiovascular risk requiring additional LDL-lowering therapy despite receiving maximum tolerated statin therapy. A placebo group was included to enable accurate characterization of the magnitude of LDL-C lowering of the FDC, while the active comparator groups of bempedoic acid alone and ezetimibe alone enabled comparison of both individual components to the FDC under well-controlled, realistic conditions. This study provides an assessment of the LDL-C-lowering effect of the fixed combination drug product with concomitant statin use.

Objectives:

Co-primary: To assess LDL-C lowering efficacy in patients receiving maximally tolerated statin therapy and treated for 12 weeks with bempedoic acid 180 mg + ezetimibe 10 mg FDC vs each of the following.

- Placebo
- Bempedoic acid 180 mg
- Ezetimibe 10 mg

Secondary:

- To assess the efficacy of bempedoic acid 180 mg + ezetimibe 10 mg FDC vs placebo alone, bempedoic acid alone, and ezetimibe alone on high-sensitivity C-reactive protein (hsCRP), non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), apolipoprotein B (apo B), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs) after 12 weeks of treatment
- To characterize the safety and tolerability of bempedoic acid 180 mg + ezetimibe 10 mg FDC vs bempedoic acid alone, ezetimibe alone, and placebo alone through 12 weeks of treatment

Methodology: This was a Phase 3, randomized, double-blind, parallel group, multicenter study of bempedoic acid + ezetimibe vs its individual components and placebo. The study consisted of an approximate 2-week screening period and 12 weeks of treatment.

Screening Period

Patients started screening at Week -2 (Visit S1), approximately 2 weeks prior to randomization. Patients with ASCVD or HeFH must have had LDL-C of ≥ 100 mg/dL, while patients with multiple cardiovascular risk factors must have had an LDL-C of ≥ 130 mg/dL.

Treatment Period

Patients were randomized 2:2:2:1 on Day 1 (Visit T1) to receive either bempedoic acid 180 mg + ezetimibe 10 mg FDC (n = 100), bempedoic acid 180 mg (n = 100), ezetimibe 10 mg (n = 100), or placebo (n = 50) for 12 weeks. Randomized patients returned for clinic visits at Week 4 (T2), Week 8 (T3), and Week 12 (T4). Patients who withdrew from investigational medicinal product (IMP) treatment were asked to continue to be followed for safety and efficacy using the protocol-specified visit schedule and procedures.

Number of Patients (Planned and Analyzed):

Planned: 350 patients

Analyzed: 382 patients enrolled and randomized, 381 patients treated

Diagnosis and Main Criteria for Inclusion: Adult men and women (age ≥ 18 years or legal age of majority based on regional law, whichever was greater) who signed the written informed consent document and were on a maximally-tolerated statin therapy at stable dose for at least 4 weeks prior to screening. At screening (Week -2), patients with ASCVD or HeFH must have had a fasting LDL-C of ≥ 100 mg/dL, while patients with multiple cardiovascular risk factors must have had an LDL-C of ≥ 130 mg/dL while on maximally tolerated statin therapy. Patients must have met the definition for ACSVD, HeFH, or multiple cardiovascular risk factors.

Patients could not have had any recent history of documented clinically significant cardiovascular disease, total fasting TG ≥ 500 mg/dL (5.6 mmol/L), estimated glomerular filtration rate (eGFR) of < 30 mL/min/1.73 m² at Week -2 (Visit S1), or uncontrolled hypertension (defined as sitting systolic blood pressure [SBP] ≥ 160 mm Hg and diastolic blood pressure [DBP] ≥ 100 mm Hg after sitting quietly for 5 minutes). Patients also could not have had uncontrolled diabetes including hemoglobin, type A_{1c} (HbA_{1c}) $\geq 10\%$ at Week -2 (Visit S1), uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) $> 1.5 \times$ the upper limit of normal (ULN) at Week -2 (Visit S1), liver disease or

<p>dysfunction, renal dysfunction or glomerulonephritis, hematologic or coagulation disorders (or a hemoglobin level <10.0 g/dL) at Week -2 (Visit S1), or unexplained creatine kinase >3 × ULN at any time prior to randomization. The complete list of eligibility criteria is provided in Protocol Amendment 1, Section 7.</p>
<p>Investigational Product, Non-investigational Product, Dose and Mode of Administration, Batch Number:</p> <p>Each daily allotment of IMP comprised 2 tablets and 1 capsule provided in a blister package.</p> <ul style="list-style-type: none">• The bempedoic acid 180 mg + ezetimibe 10 mg FDC was supplied as a film-coated tablet. The placebo-to-match FDC was a film-coated tablet of identical physical appearance and packaging. The formulation used in this study was the to-be-marketed formulation (also known as the FDC (b)(4) tablet).• Bempedoic acid 180 mg was supplied as a film-coated tablet. The placebo-to-match bempedoic acid was a film-coated tablet of identical physical appearance and packaging.• Ezetimibe 10 mg was supplied as over-encapsulated tablets. The placebo-to-match ezetimibe was a capsule of identical physical appearance and packaging. <p>Lot numbers are provided in Appendix 16.1.6.</p>
<p>Duration of Treatment: Duration of treatment for an individual patient was up to approximately 14 weeks (2 weeks for screening and 12 weeks of treatment).</p>
<p>Study Endpoints:</p> <p>Efficacy</p> <p>The co-primary efficacy endpoints consisted of 3 comparisons of the percent change from baseline to Week 12 in LDL-C: FDC vs placebo, FDC vs ezetimibe, and FDC vs bempedoic acid.</p> <p>The secondary efficacy endpoints were percent change from baseline to Week 12 in hsCRP, non-HDL-C, TC, apo B, HDL-C, and TGs.</p> <p>Safety</p> <p>Safety endpoints were as follows.</p> <ul style="list-style-type: none">• Patient incidence of treatment-emergent adverse events (including adverse events of special interest [AESI])• Clinical safety laboratory (including hematology, blood chemistry, and urinalysis) results• Vital signs, electrocardiograms (ECGs), and physical examination findings
<p>Statistical Methods:</p> <p>Study populations were defined for analysis as follows.</p> <ul style="list-style-type: none">• Full Analysis Set (FAS): also known as the intention-to-treat (ITT) set, was used for all efficacy analyses and was defined as all randomized patients• Treatment Completer Analysis Set: used as a sensitivity analysis for the primary and secondary efficacy analyses, was a subset of the FAS and included patients who completed the 12-week treatment and had non-missing LDL-C data at Week 12• Safety Population: used for all the safety summaries, was defined as all randomized patients who received at least 1 dose of IMP• Pharmacokinetic (PK) Analysis Set: included all patients in the Safety Analysis Set who had at least 1 PK assessment

Primary Efficacy Analysis

An analysis of covariance (ANCOVA) with treatment group and randomization stratification as factors and baseline LDL-C as a covariate were performed to compare treatment groups (LDL-C: FDC vs placebo, FDC vs ezetimibe, and FDC vs bempedoic acid) for the primary endpoint using the FAS. Each of the comparisons within the co-primary endpoint family was conducted at a significance level of 0.05. If all 3 tests within the co-primary endpoint family achieved statistical significance, the hypothesis testing continued to the secondary endpoints; otherwise, all statistical comparisons for secondary endpoints were to be considered descriptive only.

Secondary Efficacy Analyses

Key secondary efficacy endpoints, which included percent change from baseline to Week 12 in LDL-C, non-HDL-C, TC, and apo B, were analyzed in a manner similar to the primary efficacy endpoint. For hsCRP, a non-parametric (Wilcoxon rank-sum test) analysis with Hodges-Lehmann estimates and confidence intervals (CI) were performed. High-density lipoprotein and TGs were summarized using descriptive statistics for the observed value and the change/percent change from baseline at each protocol-scheduled visit.

Pharmacokinetic Analyses

Descriptive statistics of trough plasma concentrations of bempedoic acid (ETC-1002), its metabolite (ESP15228), ezetimibe (unconjugated), and ezetimibe-glucuronide and/or ezetimibe were provided at Weeks 4, 8, and 12, by treatment group.

Safety Analyses

All safety analyses were performed using the Safety Population. Descriptive summaries were provided for all safety endpoints.

Post Hoc Sensitivity Analyses of Key Study Results

Following database lock and review of the Plasma Bempedoic Concentrations Listing and Plasma Ezetimibe Concentrations Listing, it became apparent that an unusual number of patients who reported routinely ingesting IMP had no detectable IMP in their PK blood samples. Subsequent investigation revealed that of the 78 sites included in this study, most of these patients referenced above were from 3 sites. This led to completion of a detailed Root Cause Analysis (RCA). Based on these findings, strong inferential evidence pointed to the fact that these sites and/or patients may have been perpetuating some level of patient misconduct and therefore data from these sites (1028, 1058, and 1068) were suspect. In response, post hoc sensitivity analyses of key safety, efficacy, and PK study results were completed with all data from these sites removed.

Results:

Patient Disposition

Screened: 821 patients

Randomized: 382 total patients: 108 FDC, 110 bempedoic acid, 109 ezetimibe, 55 placebo

Discontinued IMP: 10 (9.3%) FDC, 14 (12.7%) bempedoic acid, 13 (11.9%) ezetimibe, 6 (10.9%) placebo

Withdrew from study: 5 (4.6%) FDC, 7 (6.4%) bempedoic acid, 5 (4.6%) ezetimibe, 2 (3.6%) placebo

Demographic and Baseline Characteristics

Sex: 180 (47.1%) men, 202 (52.9%) women

Mean (standard deviation [SD]) age: 64.4 (9.68) years

Race: 314 (82.2%) white, 62 (16.2%) black or African American, 4 (1.0%) Asian, 1 (0.3%) Native Hawaiian or other Pacific Islander, and 1 (0.3%) American Indian or Alaskan native

Ethnicity: 117 (30.6%) Hispanic or Latino; 265 (69.4%) not Hispanic or Latino

Mean (SD) LDL-C: 149.17 (38.583) mg/dL

In the post hoc sensitivity analysis, patient characteristics generally are similar except that the percentage of randomized patients of Hispanic and Latino ethnicity decreased from 30.6% to 12.0% of the randomized population (FAS). A large proportion of the patients enrolled at the 3 Miami sites that were removed from the sensitivity analysis were of Hispanic or Latino ethnicity.

Efficacy Results:

In the co-primary efficacy analysis:

- Treatment with the FDC resulted in significantly greater reductions from baseline for least squares (LS) mean LDL-C (-31.5%) compared with placebo (-2.5%). The difference from placebo for LS means (-29.0%) was statistically significant ($p < 0.001$).
- Treatment with the FDC resulted in significantly greater reductions from baseline for LS mean LDL-C (-31.5%) compared with ezetimibe (-21.0%). The difference from ezetimibe for LS means (-10.5%) was statistically significant ($p = 0.001$).
- Treatment with the FDC resulted in significantly greater reductions from baseline for LS mean LDL-C (-31.5%) compared with bempedoic acid (-17.7%). The difference from ezetimibe for LS means (-13.8%) was statistically significant ($p < 0.001$).

Mean absolute changes from baseline to Week 12 in LDL-C were -51.26, -27.44, -33.75, and -5.11 mg/dL for the FDC, bempedoic acid, ezetimibe, and placebo groups, respectively (observed data).

In the key secondary efficacy analyses:

- The location shift comparing the FDC and placebo was statistically significantly different for hsCRP (-37.2%), and the LS mean difference was statistically significantly different for non-HDL-C (-25.4%), TC (-20.6%), and apo B (-21.7%).
- The location shift comparing the FDC and ezetimibe was statistically significantly different for hsCRP (-19.0%), and the LS mean difference was statistically significantly different for non-HDL-C (-10.9%), TC (-9.1%), and apo B (-6.9%).
- The location shift comparing the FDC and bempedoic acid 180 mg was not statistically significantly different for hsCRP (-7.2%, $p = 0.321$); and the LS mean difference was statistically significantly different for non-HDL-C (-12.3%), TC (-9.8%), and apo B (-8.4%).

Primary and secondary efficacy analyses in the FAS population based on the percent change from baseline at Week 12 are summarized below:

Parameter Percent Change From Baseline at Week 12	FDC ^a (N = 108)	Bempedoic Acid 180 mg (N = 110)	Ezetimibe 10 mg (N = 109)	Placebo (N = 55)
LDL-C, n	108	110	109	55
Least squares mean ^b (SE)	-31.5 (2.50)	-17.7 (2.28)	-21.0 (2.04)	-2.5 (3.07)
Non-HDL-C, n	108	110	109	55
Least squares mean ^c (SE)	-27.2 (2.24)	-14.9 (2.01)	-16.3 (2.02)	-1.8 (2.82)
TC, n	108	110	109	55
Least squares mean ^c (SE)	-22.6 (1.89)	-12.8 (1.68)	-13.5 (1.54)	-2.0 (2.17)
apo B, n	104	107	107	52
Least squares mean ^c (SE)	-20.1 (2.28)	-11.7 (2.15)	-13.1 (1.76)	1.6 (2.75)
hsCRP, n	102	101	102	52
Median ^d (IQR)	-34.0 (61.4)	-20.0 (84.4)	-8.5 (64.5)	4.0 (82.2)

ANCOVA = analysis of covariance; apo B = apolipoprotein B; FDC = fixed dose combination; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; non-HDL-C = non-high-density lipoprotein cholesterol; SE = standard error; TC = total cholesterol.

^a Bempedoic acid 180 mg + ezetimibe 10 mg fixed dose combination

^b Percent change from baseline in LDL-C was analyzed using ANCOVA with treatment group and randomization stratification as factors and baseline LDL-C as a covariate. Baseline was defined as the mean of the values from Week -2 (Visit S1) and predose Day 1/Week 0 (Visit T1). For LDL-C, if measured LDL-C value was available, measured LDL-C was used.

^c Analyzed using an ANCOVA with treatment group and randomization stratification as factors and baseline value as a covariate

^d Observed data

Source: Tables 14.2.1.1.1, 14.2.2.1, 14.2.1.2.1, 14.2.1.3.1, 14.2.1.5.1, 14.2.1.4.1, 14.2.2.7, 14.2.2.3, 14.2.2.4, 14.2.2.6

Pharmacokinetic Results:

In the initial analysis, mean and median trough plasma concentrations of ETC-1002 (bempedoic acid parent compound) and ESP15228 (active metabolite) for patients in the FDC group and the bempedoic acid group were similar at Weeks 4, 8, and 12. The same is true in the post hoc sensitivity analysis, but as expected, mean and median trough PK levels were slightly higher in the post hoc analysis.

Safety Results:

- Patients who received active treatment had an incidence of adverse events of 58.9%, 61.8%, and 53.2% for FDC, bempedoic acid, and ezetimibe, respectively, compared with patients in the placebo group (43.6%). The percentage of patients who had IMP-related adverse events was 12.1%, 11.8%, 8.3%, and 7.3% in the FDC, bempedoic acid, ezetimibe, and placebo groups, respectively.
- The percentage of patients who had a serious adverse event was 7.5%, 6.4%, 9.2%, and 1.8% in the FDC, bempedoic acid, ezetimibe, and placebo groups, respectively. There were no IMP-related serious adverse events or deaths. No patient met the criteria for Hy's Law.
- The patient incidence of adverse events leading to discontinuation of IMP was 6.5%, 8.2%, 9.2%, and 3.6% in the FDC, bempedoic acid, ezetimibe, and placebo groups, respectively.
- For the majority of patients who had a treatment-emergent adverse event, the highest severity event that they experienced was mild or moderate. The percentage of patients who had a severe treatment-emergent adverse event was 8.4%, 6.4%, 8.3%, and 1.8% in the FDC, bempedoic acid, ezetimibe, and placebo groups, respectively.

- Mean changes from baseline to Week 4, 8, and 12 in creatine kinase were not clinically meaningful in any of the treatment groups. In the initial analysis, mean increases in creatinine were seen in each treatment group: 2.4% FDC, 7.0 bempedoic acid, 2.6% ezetimibe, and 0.2% for placebo at Week 12.
- Hepatic AESI occurred in 2 patients (1.9%) in the FDC group, 1 patient (0.9%) in the bempedoic acid group, and no patients in the ezetimibe or placebo groups. Muscular AESI occurred in 6 patients (5.6%) in the FDC group, 7 patients (6.4%) in the bempedoic acid group, 7 patients (6.4%) in the ezetimibe group, and 3 patients (5.5%) in the placebo group. New onset or worsening of diabetes AESI occurred in 4 patients (3.7%) in the FDC group, 1 patient (0.9%) in the bempedoic acid group, 2 patients (1.8%) in the ezetimibe group, and no patients in the placebo group. Renal disorder AESI occurred in 4 patients (3.7%) in the FDC group, 2 patients (1.8%) in the bempedoic acid group, and no patients in the ezetimibe and placebo groups. Three patients (2.8%) in the FDC group and 2 patients (1.8%) in the bempedoic acid group had adverse events of blood uric acid increased. No patient in any treatment group reported new onset of gout or exacerbation of gout as an adverse event and no patient discontinued from the study due to an adverse event of uric acid increased.
- At Week 12, treatment with bempedoic acid (either alone in the FDC group) was associated with slightly greater increases than observed in the ezetimibe alone or placebo treatment groups in mean change from baseline for creatinine and uric acid.
- Mean heart rate, SBP and DBP, weight, and body mass index were essentially unchanged from baseline across all treatment groups at all time points.
- One patient each (0.9%) in the FDC and ezetimibe groups went from having a normal ECG at baseline to an “abnormal, clinically significant” ECG at Week 12, and 2 patients (1.8%) in the bempedoic acid group went from having “abnormal, not clinically significant” ECGs at baseline to “abnormal, clinically significant” ECGs at Week 12. No patient in the placebo group had an “abnormal, clinically significant” ECG at Week 12.

A post hoc sensitivity analysis was performed in which all patients from 3 sites were removed. Compared to the initial overview, and with the exception of the number of patients who had at least 1 treatment-emergent adverse event, the numbers of patients who had particular types of events in the post hoc sensitivity analysis are generally the same or similar in all treatment groups, but because the numbers of patients in each treatment group are lower, the percentages are slightly higher.

CONCLUSIONS:

Results from this 12-week, Phase 3, randomized, double-blind, placebo- and active-controlled study of the bempedoic acid + ezetimibe FDC compared with ezetimibe, bempedoic acid, or placebo alone in patients with elevated LDL-C treated with maximally tolerated statin therapy demonstrate the following.

- Treatment with the FDC results in both clinically meaningful and statistically significant greater reductions in LDL-C at Week 12 (LS mean: -31.5% from baseline) compared with ezetimibe (LS mean -21.0%), bempedoic acid (LS mean -17.7%), or placebo (LS mean -2.5%) on a background of maximally tolerated statin use. The LS mean differences from placebo (-29.0%), ezetimibe (-10.5%), and bempedoic acid (-13.8%), were statistically significant ($p \leq 0.001$). The mean absolute change from baseline to Week 12 in the FDC group was -51.26 mg/dL.
- The results in the FDC group are suggestive of an additive effect of its 2 components on a background of maximally tolerated statin use, as there did not seem to be any loss of effect of either component when administered as the combination. This is supported by the known difference in mechanisms of action of the 2 drugs.
- The overall treatment benefit of the FDC on a background of maximally tolerated statin use was also observed across all key secondary endpoints. The treatment difference between the FDC and placebo in LS mean percent change from baseline at Week 12 was -25.4%, -20.6%,

and -21.7% for non-HDL-C, TC, and apo B, respectively ($p < 0.001$ for each). The estimated median difference between the FDC and placebo group for hsCRP was -37.2% ($p < 0.001$). In addition, statistically significant decreases were also observed for non-HDL-C, TC, and apo B when FDC was compared with ezetimibe or bempedoic acid, and the decrease in hsCRP was statistically significant when the FDC was compared with ezetimibe (the estimated median difference was -19.0% [$p = 0.010$]).

- The FDC was safe and well tolerated on a background of maximally tolerated statin use with a favorable safety profile compared with placebo. No deaths occurred during the study and no serious adverse events were deemed related to IMP. The incidence of adverse events and serious adverse events was similar in the FDC group and the other active treatment groups. The patient incidence of adverse events leading to discontinuation of IMP was 6.5%, 8.2%, 9.2%, and 3.6% in the FDC, bempedoic acid, ezetimibe, and placebo groups, respectively. When reviewing both system organ classes and preferred terms, there were no meaningful differences between treatments in the adverse events that led to discontinuation of IMP. No new safety concerns were detected for FDC treatment compared with bempedoic acid, ezetimibe, or placebo.

Conclusions from the post hoc sensitivity analysis are as follows.

- The post hoc sensitivity analysis of the co-primary efficacy endpoints demonstrated that treatment with the FDC results in both clinically meaningful and statistically significant greater reductions in LDL-C at Week 12 (LS mean: -36.2% from baseline) compared with ezetimibe (LS mean -23.2%), bempedoic acid (LS mean -17.2%), or placebo (LS mean +1.8%) on a background of maximally tolerated statin use. The LS mean difference from placebo in the FDC group was -38.0%. Notably, the magnitude of the FDC percentage change from baseline for the primary endpoint and key secondary endpoints is greater in the post hoc sensitivity analysis compared with the initial analysis. This is what would be expected from the removal of data from 3 sites where it is believed, based on PK sampling, that a high percentage of the patients at those sites did not take the IMP.
- Both the initial analysis and the post hoc sensitivity analysis showed that FDC was generally safe and well tolerated. Results were generally similar in both the initial analysis and the sensitivity analysis. Since no new safety events were added but some were removed in the sensitivity analysis, rates of some safety events shifted slightly although the safety profile generally remained the same. By removing patients who did not take IMP from the post hoc sensitivity analysis, slight changes were seen in the descriptive summaries of some laboratory tests that are associated with AESIs. The Sponsor considers the post hoc sensitivity analysis results to better represent the actual safety profile of the FDC.
- The initial ITT analysis demonstrated statistically and clinically significant results for the hypothesis regarding the efficacy of the FDC as compared to placebo, bempedoic acid alone, and ezetimibe alone, and safety data that was similar to other Phase 2 and 3 clinical trials. The post hoc sensitivity analysis with data from Sites 1028, 1058, and 1068 removed also produced results that were statistically and clinically significant and generally recapitulated the safety findings of the original ITT analysis. It is the position of the Sponsor that the findings of the sensitivity analysis more accurately represent the overall efficacy, safety, and PK profile of the FDC.

Date and Version of the Report:

08 January 2019, Final

Source: Applicant

16. Efficacy: Additional Information and Assessment

16.1. Patient Disposition, Demographics, and Baseline Characteristics: Full Analysis Set (Including Sites 1028, 1058, and 1068)

Table 53. Patient Disposition, Full Analysis Set, Trial 053

Parameter	BA 180 mg +			
	EZE 10 mg FDC	BA 180 mg	EZE 10 mg	Placebo
Randomized/full analysis set, n	108	110	109	55
Safety population, ¹ n (%)	107 (99.1)	110 (100.0)	109 (100.0)	55 (100.0)
Completed IMP, n (%)	97 (89.8)	96 (87.3)	96 (88.1)	49 (89.1)
Withdrew from IMP, n (%)	10 (9.3)	14 (12.7)	13 (11.9)	6 (10.9)
Adverse event	7 (6.5)	9 (8.2)	10 (9.2)	2 (3.6)
Withdrawal by patient	3 (2.8)	2 (1.8)	3 (2.8)	2 (3.6)
Protocol violation	0	1 (0.9)	0	1 (1.8)
Lost to follow-up	0	2 (1.8)	0	0
Completed study, n (%)	103 (95.4)	103 (93.6)	104 (95.4)	53 (96.4)
Withdrew from study, n (%)	5 (4.6)	7 (6.4)	5 (4.6)	2 (3.6)
Missed LDL-C at Week 12, n (%)	3 (2.8)	8 (7.3)	6 (5.5)	2 (3.6)
Retrieved dropout, ² n (%)	7 (6.5)	7 (6.4)	8 (7.3)	4 (7.3)

Source: adsl, statistical reviewer's analysis

¹ Safety population consists of all randomized patients who receive at least one dose of blinded IMP

² Patients off-treatment and had LDL-C measurement at Week 12

Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed-dose combination; IMP, investigational medicinal product; LDL-C, low-density lipoprotein cholesterol; n, number of subjects with disposition

NDA 211617

Nexlizet / bempedoic acid and ezetimibe

Table 54. Patient Demographics, Full Analysis Set, Trial 053

Characteristic	BA 180 mg + EZE 10 mg FDC (N=108)	BA 180 mg (N=110)	EZE 10 mg (N=109)	Placebo (N=55)
Age (years)				
Mean (SD)	63.0 (9.97)	65.2 (9.54)	64.4 (8.91)	65.6 (10.74)
Median (Min, Max)	63.5 (30, 85)	65 (38, 89)	66 (42, 87)	65 (39, 86)
Age group (years), n (%)				
18-40	1 (0.90)	1 (0.90)	0	1 (1.80)
41-64	57 (52.8)	50 (45.5)	48 (44.0)	26 (47.3)
65-74	37 (34.3)	40 (36.4)	46 (42.2)	13 (23.6)
≥75	13 (12.0)	19 (17.3)	15 (13.8)	15 (27.3)
Gender, n (%)				
Male	50 (46.3)	45 (40.9)	52 (47.7)	33 (60.0)
Female	58 (53.7)	65 (59.1)	57 (52.3)	22 (40.0)
Race, n (%)				
American Indian or Alaska Native	1 (0.90)	0	0	0
Asian	2 (1.90)	1 (0.90)	1 (0.90)	0
Black or African American	20 (18.5)	19 (17.3)	16 (14.7)	7 (12.7)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.90)	0
White	85 (78.7)	90 (81.8)	91 (83.5)	48 (87.3)
Other	0	0	0	0
Multiple	0	0	0	0
Ethnicity, n (%)				
Hispanic or Latino	32 (29.6)	33 (30.0)	32 (29.4)	20 (36.4)
Not Hispanic or Latino	76 (70.4)	77 (70.0)	77 (70.6)	35 (63.6)
Body mass index group (kg/m ²), n (%)				
<25	13 (12.0)	16 (14.5)	13 (11.9)	6 (10.9)
25 - <30	27 (25.0)	38 (34.5)	37 (33.9)	22 (40.0)
≥30	68 (63.0)	56 (50.9)	59 (54.1)	27 (49.1)
CVD risk, n (%) ¹				
ASCVD and/or HeFH	61 (56.5)	68 (61.8)	60 (55.0)	32 (58.2)
Multiple CV risk factors	47 (43.5)	42 (38.2)	49 (45.0)	23 (41.8)
HeFH, n(%)				
Yes	3 (2.80)	1 (0.90)	2 (1.80)	1 (1.80)
No	105 (97.2)	109 (99.1)	107 (98.2)	54 (98.2)

NDA 211617

Nexlizet / bempedoic acid and ezetimibe

Characteristic	BA 180 mg + EZE 10 mg FDC (N=108)	BA 180 mg (N=110)	EZE 10 mg (N=109)	Placebo (N=55)
Baseline statin intensity, n (%)				
High-intensity statin	42 (38.9)	40 (36.4)	39 (35.8)	21 (38.2)
Other intensity statin	33 (30.6)	43 (39.1)	38 (34.9)	20 (36.4)
None	33 (30.6)	27 (24.5)	32 (29.4)	14 (25.5)

Source: adsl, statistical reviewer's analysis

¹ There is small discrepancy from Applicant's number for CVD risk (Table 14.1.2.1, CSR)

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BA, bempedoic acid; CVD, cardiovascular disease; FDC, fixed-dose combination; EZE, ezetimibe; HeFH, heterozygous familial hypercholesterolemia; N, number of subjects in group; n, number of subjects in subgroup; SD, standard deviation

Table 55. Baseline Efficacy Parameters, Full Analysis Set, Trial 053

Characteristic	BA 180 mg + EZE 10 mg FDC (N=108)	BA 180 mg (N=110)	EZE 10 mg (N=109)	Placebo (N=55)
LDL-C (mg/dL)				
Mean (SD)	152.02 (38.87)	146.36 (36.35)	147.45 (38.72)	152.63 (42.36)
Median	142.50	139.50	139.50	152.00
Minimum, maximum	83.5, 282.5	84.5, 266.0	83.5, 298.5	88.5, 306.5
Non-HDL-C (mg/dL)				
Mean (SD)	185.85 (44.65)	178.48 (38.54)	179.10 (44.27)	182.24 (45.34)
Median	174.00	173.00	168.00	184.00
Minimum, maximum	113.5, 315.0	113.0, 297.0	105.0, 340.0	107.0, 338.5
TC (mg/dL)				
Mean (SD)	235.01 (46.59)	228.24 (40.75)	230.37 (47.01)	232.28 (45.94)
Median	225.00	225.75	222.50	233.00
Minimum, maximum	152.0, 371.5	156.0, 349.5	153.0, 394.5	156.0, 393.0
Apo-B (mg/dL)				
Mean (SD)	119.38 (29.83)	114.63 (26.36)	115.32 (29.36)	116.25 (29.54)
Median	117.5	114.0	107.0	117.0
Minimum, maximum	61, 215	68, 187	66, 211	62, 197
hsCRP (mg/L)				
Mean (SD)	5.78 (10.35)	4.94 (6.35)	5.51 (5.94)	3.95 (3.77)
Median	3.12	2.95	3.03	3.01
Minimum, maximum	0.2, 91.3	0.1, 37.6	0.4, 32.0	0.2, 15.9
TG				
Mean (SD)	173.99 (87.86)	164.72 (73.08)	166.19 (77.83)	152.27 (58.68)
Median	157.50	149.75	146.00	141.50
Minimum, maximum	61.0, 449.5	49.5, 489.5	63.5, 478.5	50.0, 308.5
HDL-C				
Mean (SD)	49.20 (13.47)	49.78 (12.14)	50.72 (14.78)	50.05 (12.73)
Median	47.50	50.25	48.00	46.00
Minimum, maximum	27.0, 117.0	28.0, 94.0	29.5, 127.0	28.0, 82.0

Source: adsl, statistical reviewer's analysis

Abbreviations: Apo-B, apolipoprotein B; BA, bempedoic acid; EZE, ezetimibe; FDC, fixed-dose combination; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; N, number of subjects in group; SD, standard deviation; TC, total cholesterol; TG, triglycerides

16.2. Primary Endpoint, Additional Analyses

Table 56. Sensitivity Analysis, Percent Change From Baseline to Week 12 in LDL-C,¹ Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053

LDL-C	FDC (N=86)	BA (N=88)	EZE (N=86)	Placebo (N=41)
Baseline mean (mg/dL)	153.8	145.1	148.8	152.8
Percent change from baseline (LS mean ²) (SE)	-36.2 (2.7)	-16.5 (2.8)	-22.1 (2.6)	1.8 (3.6)
FDC vs. placebo (LS mean) (95% CI)	-38.0 (-46.8 to -29.3)			
P-value	<0.001 ³			
FDC vs. BA (LS mean) (95% CI)	-19.7 (-27.2 to -12.1)			
P-value	<0.001 ³			
FDC vs. EZE (LS mean) (95% CI)	-14.1 (-21.4 to -6.7)			
P-value	<0.001 ³			

Source: ad b adsl, statistical reviewer's analysis

¹ For patients with missing data at Week 12, missing LDL-C values were imputed based on placebo completers, regardless of whether they were on active treatment; an ANCOVA model was fit including treatment group, randomization strata, and baseline LDL-C

² LS means adjusted according to distribution of baseline covariates

³ Statistically significant based on prespecified alpha allocation

Abbreviations: BA, bempedoic acid; CI, confidence interval; EZE, ezetimibe; FDC, fixed-dose combination; LDL-C, low-density lipoprotein cholesterol; LS, least square; N, number of subjects in group; SE, standard error

Table 57. LDL-C (mg/dL) Summary Statistics, Observed Values in Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053

Analysis Visit	Planned Treatment	N	Mean	SD	Median	Lower Quartile	Upper Quartile
Baseline							
	BA 180 mg + EZE 10 mg FDC	86	153.80	40.53	144.50	122.00	186.00
	BA 180 mg	88	145.13	38.46	139.00	116.25	171.00
	EZE 10 mg	86	148.80	41.84	137.25	118.00	166.50
	Placebo	41	152.80	46.77	152.00	116.50	180.50
Week 4							
	BA 180 mg + EZE 10 mg FDC	77	84.97	39.77	72.00	57.00	97.00
	BA 180 mg	82	111.72	35.07	103.50	90.00	130.00
	EZE 10 mg	79	113.01	38.36	108.00	85.00	136.00
	Placebo	39	147.74	54.56	142.00	104.00	179.00
Week 8							
	BA 180 mg + EZE 10 mg FDC	75	84.44	31.04	78.00	60.00	104.00
	BA 180 mg	79	117.67	40.44	113.00	89.00	143.00
	EZE 10 mg	74	113.19	35.43	109.50	89.00	137.00
	Placebo	36	147.28	50.06	141.00	109.00	189.00
Week 12							
	BA 180 mg + EZE 10 mg FDC	83	94.41	39.67	85.00	66.00	117.00
	BA 180 mg	82	116.98	39.68	110.00	88.00	140.00
	EZE 10 mg	80	111.90	37.54	104.00	91.50	131.00
	Placebo	40	154.95	58.79	146.00	110.50	189.00

Source: adlb, statistical reviewer's analysis

Baseline is defined as the mean of values from Week -2 (Screening) and predose Day 1/Week 0 in the SAP. If one value is available then the single value will be used as baseline.

Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed-dose combination; LDL-C, low-density lipoprotein cholesterol; N, number of subjects in group; SD, standard deviation

Table 58. Subgroup Analysis on Percent Change in LDL-C From Baseline to Week 12,¹ Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053

Subgroup	N (FDC, BA, EZE, Placebo)	FDC - Placebo (95% CI)	FDC - BA (95% CI)	FDC - EZE (95% CI)
Sex				
Male	42, 40, 43, 24	-37.4 (-49.5, -25.3)	-21.2 (-31.8, -10.6)	-11.6 (-21.9, -1.2)
Female	44, 48, 43, 17	-38.7 (-52.0, -25.3)	-17.1 (-27.0, -7.3)	-15.5 (-25.7, -5.3)
Age				
<65	51, 42, 38, 21	-36.2 (-48.4, -24.0)	-15.6 (-25.4, -5.9)	-4.8 (-14.9, 5.4)
≥65	35, 46, 48, 20	-41.5 (-54.2, -28.7)	-23.8 (-34.2, -13.4)	-22.9 (-33.3, -12.5)
Race				
White	67, 70, 72, 34	-36.8 (-46.7, -27.0)	-16.7 (-24.7, -8.6)	-10.6 (-18.6, -2.6)
Non-White	19, 18, 14, 7	-42.1 (-62.5, -21.8)	-27.1 (-42.6, -11.6)	-26.3 (-43.2, -9.5)
CVD risk				
ASCVD and/or HeFH	53, 57, 53, 27	-38.0 (-49.2, 26.8)	-20.5 (-29.6, -11.4)	-13.9 (-23.2, -4.6)
Multiple CV risk factors	33, 31, 33, 14	-37.6 (-52.4, -22.8)	-16.1 (-28.0, -4.2)	-13.5 (-25.2, -1.8)
Baseline statin				
High-intensity	31, 29, 28, 16	-44.0 (-58.3, -29.8)	-24.1 (-36.3, -11.9)	-15.0 (-27.6, -2.5)
Other intensity	22, 32, 26, 11	-26.7 (-44.1, -9.2)	-11.6 (-25.2, 2.0)	-6.8 (-20.9, 7.4)
None	33, 27, 32, 14	-39.3 (-54.4, -24.2)	-19.4 (-31.3, -7.4)	-17.3 (-28.9, -5.7)

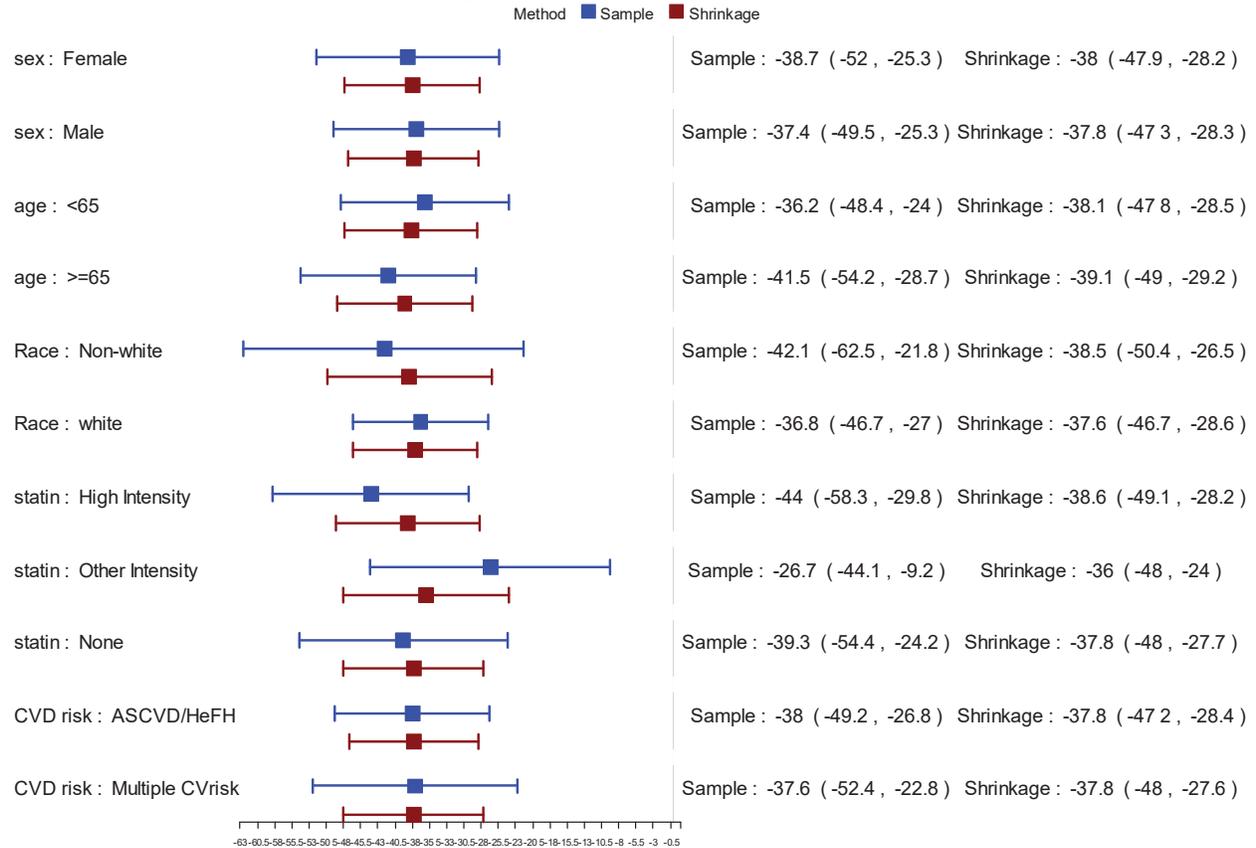
Source: adsl adbl, statistical reviewer's analyses

¹ Missing data were imputed in the same way as the primary efficacy analysis. A similar ANCOVA model was fit including additional factors: subgroup and subgroup-by-treatment interaction

Subgroup analysis by country was not performed, since all subjects are from USA

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BA, bempedoic acid; CI, confidence interval; CVD, cardiovascular; EZE, ezetimibe; FDC, fixed-dose combination; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; N, number of subjects in group

Figure 16. Treatment Difference of FDC vs. Placebo by Subgroup in Percent Change in LDL-C From Baseline to Week 12, Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053



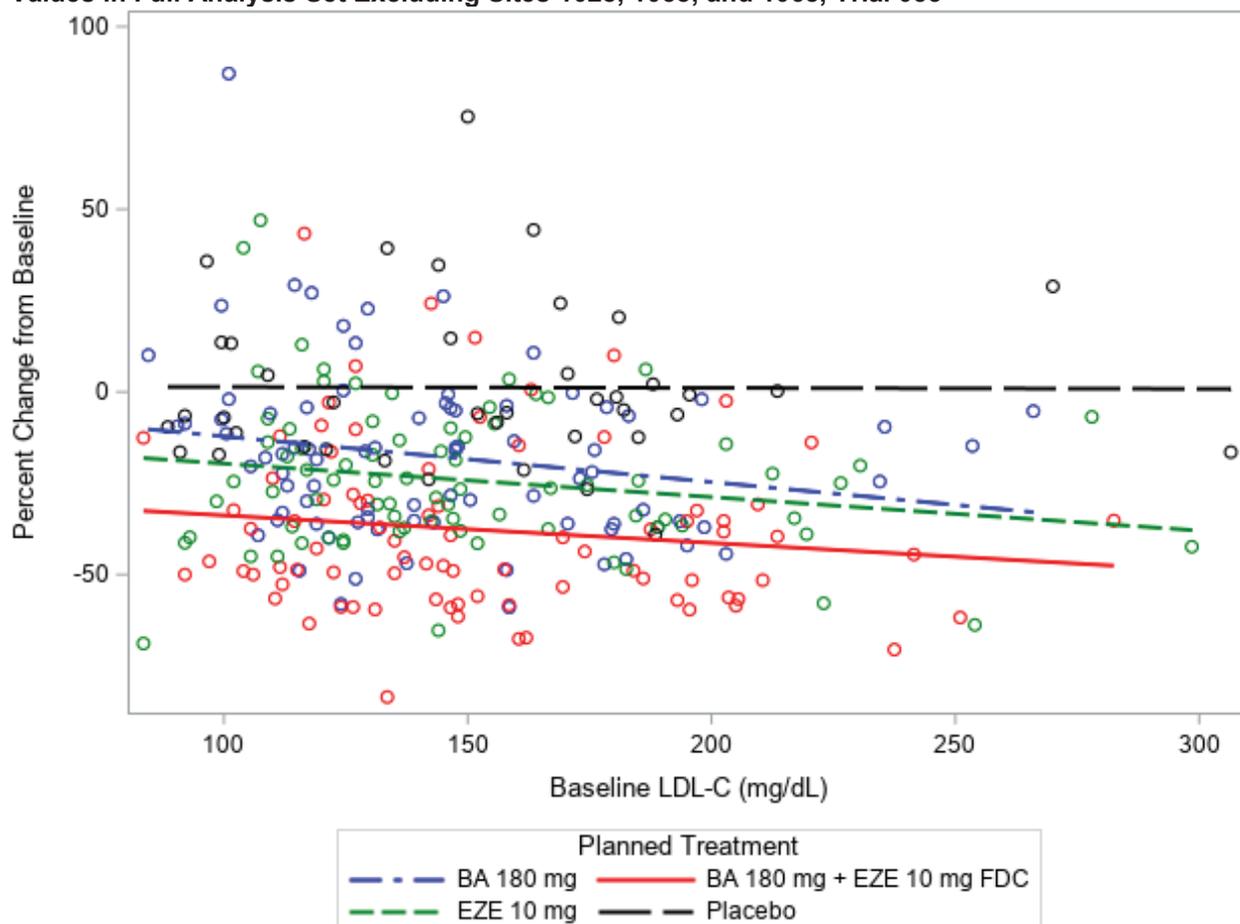
Source: adsl adbl, statistical reviewer's analyses

Sample: estimates from Table 58.

Shrinkage: estimates from Bayesian hierarchical model based on summary sample estimates. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and overall estimate. A flat prior with overall mean following a truncated normal distribution was used for mean treatment effect in each subgroup: $\mu_i \sim N(\mu, \tau^2)$, $\mu \sim N(\text{mean}=0, \text{std}=100, \text{lower limit}=-100)$, $1/\tau^2 \sim \text{Gamma}(0.001, 0.001)$. Note: 100 refers to 100%, since the primary endpoint is expressed as percent change. The patient-level residual standard deviation from the ANCOVA model is around 25%.

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular; FDC, fixed-dose combination; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; N, number of subjects in group

Figure 17. Percent Change in LDL-C From Baseline to Week 12 vs. Baseline LDL-C, Observed Values in Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053



Source: adlb, statistical reviewer's analyses

Note: A linear regression line was fit to each treatment group.

Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed-dose combination; LDL-C, low-density lipoprotein cholesterol

16.3. Secondary and Exploratory Endpoints

Table 59. Exploratory Analysis: Absolute Change From Baseline to Week 12 in hsCRP,¹ Observed Values in Full Analysis Set Excluding Sites 1028, 1058, and 1068,² Trial 053

hsCRP	FDC (N=80)	BA (N=81)	EZE (N=79)	Placebo (N=39)
Baseline median (mg/L)	3.00	3.00	2.80	3.10
Absolute change from baseline (median) (IQR)	-0.82	-0.48	-0.18	0.17
FDC vs. placebo (location shift) (95% CI)	-1.5 (-2.50, -0.64)			
FDC vs. BA (location shift) (95% CI)	-0.22 (-0.88, 0.38)			
FDC vs. EZE (location shift) (95% CI)	-0.69 (-1.38, -0.09)			

Source: ad b adsl, statistical reviewer's analysis

¹ Nonparametric (Wilcoxon rank-sum test) analysis with Hodges-Lehmann estimates and confidence interval was performed

² Only included subjects with both baseline and Week 12 hsCRP measurements; no imputation for missing data was performed

Abbreviations: BA, bempedoic acid; CI, confidence interval; EZE, ezetimibe; FDC, fixed-dose combination; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; N, number of subjects in group

Table 60. Exploratory Analysis: Patients Who Achieved Normal hsCRP¹ at Week 12, Observed Values in Full Analysis Set Excluding Sites 1028, 1058, and 1068,² Trial 053

hsCRP	FDC (N=80)	BA (N=81)	EZE (N=79)	Placebo (N=39)
Elevated baseline ³	41 (51.3)	38 (46.9)	37 (46.8)	20 (51.0)
Normal Week 12 ¹	22 (53.7)	20 (52.6)	10 (27.0)	3 (15.0)

Source: Reviewer's analysis [adlb, adsl]

¹ hsCRP <3.0 mg/dL; percentage calculated among patients who started with baseline hsCRP ≥3.0 mg/dL² Only included subjects with both baseline and Week 12 hsCRP measurements³ hsCRP ≥3.0 mg/dL

Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed-dose combination; hsCRP, high-sensitivity C-reactive protein; N, number of subjects in group

Table 61. Exploratory Secondary Endpoint: Percent Change From Baseline to Week 12 in HDL-C,¹ Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053

HDL-C	FDC (N=86)	BA (N=88)	EZE (N=86)	Placebo (N=41)
Baseline mean (mg/dL)	49.2	49.9	51.2	50.4
Percent change from baseline (LS mean ²) (SE)	-5.4 (1.4)	-5.5 (1.6)	-2.0 (1.4)	-0.5 (2.0)
FDC vs. placebo (LS mean) (95% CI)	-4.9 (-9.6, -0.1)			
FDC vs. BA (LS mean) (95% CI)	0.1 (-4.1, 4.3)			
FDC vs. EZE (LS mean) (95% CI)	-3.4 (-7.2, 0.5)			

Source: adlb adsl, statistical reviewer's analysis

¹ Similar approach as analysis for primary efficacy endpoint² LS means adjusted according to distribution of baseline covariates

Abbreviations: BA, bempedoic acid; CI, confidence interval; EZE, ezetimibe; FDC, fixed-dose combination; HDL-C, high-density lipoprotein cholesterol; LS, least square; N, number of subjects in group; SE, standard error

Table 62. Exploratory Secondary Endpoint: Percent Change From Baseline to Week 12 in TG,¹ Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053

TG	FDC (N=86)	BA (N=88)	EZE (N=86)	Placebo (N=41)
Baseline mean (mg/dL)	177.2	156.7	161.7	144.6
Percent change from baseline (LS mean ²) (SE)	-7.5 (3.0)	8.5 (4.7)	-1.7 (3.8)	4.7 (4.9)
FDC vs. placebo (LS mean) (95% CI)	-12.2 (-23.5, -0.9)			
FDC vs. BA (LS mean) (95% CI)	-16.0 (-26.9, -5.1)			
FDC vs. EZE (LS mean) (95% CI)	-5.8 (-15.2, 3.6)			

Source: adlb adsl, statistical reviewer's analysis

¹ Similar approach as analysis for the primary efficacy endpoint² LS means adjusted according to distribution of baseline covariates

Abbreviations: BA, bempedoic acid; CI, confidence interval; EZE, ezetimibe; FDC, fixed-dose combination; LS, least square; N, number of subjects in group; SE, standard error; TG, triglycerides

Table 63. Sensitivity Analysis Using Analysis Windows Defined by Trial 040 SAP From NDA 211616-Full Analysis Set Excluding Sites 1028, 1058, and 1068, Trial 053

Endpoints	Visit Windows	BA 180 mg + EZE 10 mg FDC vs Placebo		BA 180 mg + EZE 10 mg FDC vs EZE 10 mg		BA 180 mg + EZE 10 mg FDC vs BA 180 mg	
		Difference ((1-alpha)%C.I.)	p-value*	Difference ((1-alpha)%C.I.)	p-value*	Difference ((1-alpha)%C.I.)	p-value*
% change from baseline in LDL-C (mg/dL) at WK12	Study 053 visit window	-38.0 (-46.5, -29.6)	<0.001	-13.1 (-19.7, -6.5)	<0.001	-19.0 (-26.1, -11.9)	<0.001
	Study 040 visit window	-37.9 (-46.4, -29.4)	<0.001	-12.9(-19.5, -6.3)	<0.001	-19.9 (-27.2, -12.6)	<0.001
% change from baseline in hsCRP (mg/dL) at WK12	Study 053 visit window	-46.1 (-78.75, -15.78)	<0.001	-25.6 (-45.0, -7.15)	0.002	-2.6 (-21.35, 16.25)	0.734
	Study 040 visit window	-46.1 (-78.75, -15.78)	<0.001	-25.6 (-45.0, -7.15)	0.002	-2.6 (-21.35, 16.25)	0.734
% change from baseline in Non-HDL-C (mg/dL)at WK12	Study 053 visit window	-33.7 (-43.9, -23.4)	<0.001	-12.1 (-19.1, -5.0)	<0.001	-17.8 (-25.1, -10.5)	<0.001
	Study 040 visit window	-33.5 (-43.7, -23.3)	<0.001	-11.9 (-18.9, -4.8)	<0.001	-18.4 (-25.9, -10.9)	<0.001
% change from baseline in ApoB (mg/dL) at WK12	Study 053 visit window	-30.1(-39.9, -20.3)	<0.001	-9.3 (-16.5, -2.1)	0.003	-12.8 (-20.3, -5.3)	<0.001
	Study 040 visit window	-30.1(-39.9, -20.3)	<0.001	-9.3 (-16.5, -2.1)	0.003	-12.8 (-20.3, -5.3)	<0.001
% change from baseline in Total Cholesterol (mg/dL) at WK12	Study 053 visit window	-27.1 (-35.1, -19.1)	<0.001	-10.4 (-16.1, -4.6)	<0.001	-14.2 (-20.4, -8.1)	<0.001
	Study 040 visit window	-27.0 (-35.0, -19.0)	<0.001	-10.2 (-16.0, -4.5)	<0.001	-14.8 (-21.1, -8.5)	<0.001

Source: Applicant's response to information request, dated April 9, 2019

* For percent change in LDL-C, 95% CI was reported; for percent change in hsCRP, non-HDL-C, Apo-B and total cholesterol, (1- α)% CI were reported; BA 180 mg + EZE 10 mg FDC versus placebo using $\alpha=0.01$; BA 180mg + EZE 10 mg FDC versus EZE 10 mg using $\alpha=0.02$; BA 180 mg + EZE 10 mg FDC versus BA 180 mg using $\alpha=0.02$

Abbreviations: Apo-B, apolipoprotein B; BA, bempedoic acid; CI, confidence interval; EZE, ezetimibe; FDC, fixed-dose combination; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; NDA, new drug application; SAP, statistical analysis protocol

17. Clinical Safety: Additional Information and Assessment

17.1. Vital Signs

17.1.1. Trial 053, Excluding Sites 1028, 1058, and 1068

Table 64. Vital Signs Mean Change From Baseline Over Time, Safety Population, Trial 053, Excluding Sites 1028, 1058, and 1068

Vital Signs Time	FDC N=85	BA N=88	EZE N=86	Placebo N=41
Systolic blood pressure				
Week 4	-2.8 (13.3)	-4.0 (12.5)	-2.0 (13.8)	-0.4 (9.1)
Week 8	-2.5 (13.8)	-3.7 (15.4)	-0.2 (15.4)	-0.8 (13.5)
Week 12	-3.5 (13.6)	-3.3 (14.2)	-2.7 (14.3)	-1.8 (15.7)
Diastolic blood pressure (mmHg)				
Week 4	-1.0 (7.9)	-2.7 (8.4)	-0.8 (7.5)	1.0 (7.1)
Week 8	-1.7 (9.9)	-2.7 (8.7)	-2.0 (9.7)	-3.2 (7.8)
Week 12	-1.6 (9.6)	-3.3 (10.2)	-1.8 (8.5)	-1.2 (9.2)
Heart rate (beats/min)				
Week 4	1.6 (8.9)	0.5 (10.8)	-0.1 (8.7)	0.5 (8.7)
Week 8	-0.9 (7.7)	-1.2 (9.8)	-1.5 (10.9)	0.5 (8.0)
Week 12	-0.9 (10.3)	-0.9 (11.1)	-1.8 (12.3)	-0.1 (8.1)
Weight (kg)				
Week 4	-0.2 (16.5)	0.1 (1.8)	0.1 (1.3)	0.6 (2.1)
Week 8	-1.6 (12.2)	-0.3 (2.0)	0.0 (1.7)	0.7 (1.9)
Week 12	0.0 (15.9)	0.2 (3.2)	-0.2 (2.0)	0.4 (3.0)

Source: advs.xpt; Software: JMP
 Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed-dose combination

17.1.2. Trial 053, Full Analysis Set

Table 65. Vital Signs Mean (SD) Change From Baseline Over Time, Safety Population, Trial 053

Vital Signs Time	FDC N=107	BA N=110	EZE N=109	Placebo N=55
Systolic blood pressure (mmhg)				
Week 4	-1.1 (13.2)	-1.9 (13.9)	-0.4 (15.0)	0.6 (10.3)
Week 8	-0.5 (15.0)	-1.3 (16.3)	0.9 (16.0)	-1.2 (12.6)
Week 12	-1.6 (15.5)	-1.6 (14.8)	-1.5 (15.3)	-2.5 (14.8)
Diastolic blood pressure (mmhg)				
Week 4	-0.9 (8.9)	-1.6 (8.8)	-0.3 (8.4)	0.8 (6.8)
Week 8	-1.2 (10.3)	-1.3 (9.3)	-1.2 (10.3)	-3.5 (8.4)
Week 12	-1.6 (10.1)	-2.4 (10.2)	-1.6 (9.1)	-2.2 (9.5)
Heart rate (beats/min)				
Week 4	1.1 (8.6)	-0.3 (10.5)	-1.1 (9.2)	-0.5 (8.8)
Week 8	-0.7 (9.0)	-1.1 (9.7)	-1.6 (11.2)	-0.3 (8.7)
Week 12	-1.5 (10.6)	-1.5 (11.0)	-2.0 (12.3)	-0.5 (8.6)
Weight (kg)				
Week 4	-0.2 (14.6)	0.1 (1.7)	0.0 (1.2)	0.5 (1.9)
Week 8	-1.3 (10.9)	-0.3 (1.9)	-0.1 (1.5)	0.6 (1.7)
Week 12	-0.1 (14.3)	0.1 (3.0)	-0.2 (1.9)	0.4 (2.7)

Source: advs.xpt; Software: JMP
 Abbreviations: BA, bempedoic acid; EZE, ezetimibe; FDC, fixed-dose combination; SD, standard deviation

17.2. ECGs

17.2.1. Trial 053, Excluding Sites 1028, 1058, and 1068

Table 66. Patients Meeting ECG Abnormality Criteria, From Baseline Through Week 12, Safety Population, Trial 053, Excluding Sites 1028, 1058, and 1068

	FDC N=85 n (%)	BA N=88 n (%)	Ezetimibe N=86 n (%)	Placebo N=41 n (%)
ECG Analysis¹				
Normal to abnormal				
Clinically significant (CS)	1 (1.2)	0 (0.0)	1 (1.2)	0 (0.0)
Not clinically significant (NCS)	12 (14.1)	4 (4.5)	12 (14.0)	5 (12.2)
Abnormal NCS to abnormal CS	0 (0.0)	2 (2.3)	0 (0.0)	0 (0.0)

Source: adeg.xpt; Software: JMP

¹ Investigator interpretation

Abbreviations: BA, bempedoic acid; ECG, electrocardiogram; FDC, fixed-dose combination; N, number of subjects in group; n, number of subjects with ECG result

Table 67. Clinically Significant ECG Abnormalities, From Baseline Through Week 12, Safety Population, Trial 053, Excluding Sites 1028, 1058, and 1068

	FDC N=85 n (%)	BA N=88 n (%)	Ezetimibe N=86 n (%)	Placebo N=41 n (%)
ECG Analysis¹				
Number of patients	1 (1.2)	2 (2.3)	1 (1.2)	0 (0.0)
Number of ECG abnormalities ²	1	2	3	0
Arrhythmias	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tachycardia	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)
Atrial flutter	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)
Conduction abnormalities	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bundle branch block ³	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)
AV block (degree unspecified)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)
ST-T wave changes	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infarct, age undetermined	1 (100.0)	0 (0.0)	1 (33.3)	0 (0.0)

Source: adeg.xpt; Software: JMP

¹ Investigator interpretation

² Includes all ECG abnormalities reported by investigator, may be >1 per patient

³ LBBB, RBBB, LAFB

Abbreviations: AV, atrioventricular; BA, bempedoic acid; ECG, electrocardiogram; FDC, fixed-dose combination; N, number of subjects in group; n, number of subjects with ECG result

17.2.2. Trial 053, Full Analysis Set

Table 68. Patients Meeting ECG Abnormality Criteria, From Baseline Through Week 12, Safety Population, Trial 053

	FDC N=107 n (%)	BA N=110 n (%)	Ezetimibe N=109 n (%)	Placebo N=55 n (%)
ECG Analysis¹				
Normal to abnormal				
Clinically significant (CS)	1 (0.90)	0 (0.0)	1 (0.90)	0 (0.0)
Not clinically significant (NCS)	14 (13.1)	7 (6.4)	14 (12.8)	8 (14.5)
Abnormal NCS to abnormal CS	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)

Source: adeg.xpt; Software: JMP

¹ Investigator interpretation

Abbreviations: BA, bempedoic acid; ECG, electrocardiogram; FDC, fixed-dose combination; N, number of subjects in group; n, number of subjects with ECG result

Table 69. Clinically Significant ECG Abnormalities, From Baseline Through Week 12, Safety Population, Trial 053

ECG Analysis¹	FDC N=107 n (%)	BA N=110 n (%)	Ezetimibe N=109 n (%)	Placebo N=55 n (%)
Number of patients	1 (0.9)	2 (1.8)	1 (0.9)	0 (0.0)
Number of ECG abnormalities ²	1	2	3	0
Arrhythmias	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tachycardia	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)
Atrial flutter	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)
Conduction abnormalities	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bundle branch block ³	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)
AV block (degree unspecified)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)
ST-T wave changes	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infarct, age undetermined	1 (100.0)	0 (0.0)	1 (33.3)	0 (0.0)

Source: adeg.xpt; Software: JMP

¹ Investigator interpretation

² Includes all ECG abnormalities reported by investigator, may be >1 per patient

³ LBBB, RBBB, LAFB

Abbreviations: AV, atrioventricular; BA, bempedoic acid; ECG, electrocardiogram; FDC, fixed-dose combination; N, number of subjects in group; n, number of subjects with ECG result

17.3. Adverse Events

17.3.1. Recoded Adverse Events

Table 70. Recoded Adverse Events

Verbatim Term	Coded As (AEDECOD)	Recoded to (AEDECOD)
Bacteria in urine	Bacterial test positive	Bacteriuria

NDA 211617

Nexlizet / bempedoic acid and ezetimibe

17.3.2. Adverse Events for Trial 053, Full Analysis Set

Table 71. Overview of Adverse Events,¹ Controlled Trial Safety Population, Trial 053, Week 12

Event	FDC N=107 n (%)	Bempedoic Acid N=110 n (%)	Ezetimibe N=109 n (%)	Placebo N=55 n (%)	Risk Difference (95% CI)³
Any AE	63 (58.9)	68 (61.8)	58 (53.2)	24 (43.6)	15.2 (-0.8, 31.3)
Moderate or severe AEs ²	32 (29.9)	27 (24.5)	23 (21.1)	8 (14.5)	15.4 (2.6, 28.1)
SAE	9 (8.4)	8 (7.3)	10 (9.2)	1 (1.8)	6.6 (0.3, 12.9)
SAEs with fatal outcome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
AE leading to discontinuation of study drug	7 (6.5)	9 (8.2)	10 (9.2)	2 (3.6)	2.9 (-3.9, 9.7)
AE leading to interruption of study drug	10 (9.3)	5 (4.5)	4 (3.7)	0 (0.0)	9.4 (3.8, 14.9)

Source: Reviewer's analysis [adae.expt; Software: JMP]

¹ Includes treatment-emergent AE defined as any adverse event that occurred after first dose of drug

² Moderate: events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities; severe: events interrupt the patient's usual daily activity, are incapacitating with inability to do usual activities, or significantly affect clinical status and warrant intervention and/or close follow-up

³ FDC versus placebo

Abbreviations: AE, adverse event; CI, confidence interval; FDC, fixed-dose combination; N, number of subjects in group; n, number of subjects with at least one event; SAE, serious adverse event

NDA 211617

Nexlizet / bempedoic acid and ezetimibe

Table 72. Serious Adverse Events by Descending Difference Order, Safety Population, Trial 053

Adverse Event¹	FDC N=107 n (%)	Bempedoic Acid N=110 n (%)	Ezetimibe N=109 n (%)	Placebo N=55 n (%)	Risk Difference (95% CI)³
Patients with at least one SAE	9 (8.4)	8 (7.3)	10 (9.2)	1 (1.8)	6.6 (0.3, 12.9)
Myocardial infarction ²	1 (0.9)	3 (2.7)	3 (2.8)	1 (1.8)	-0.9 (-4.9, 3.1)
Angina unstable	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Diverticulitis	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Angina pectoris	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Atrial fibrillation	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Coronary artery disease	1 (0.9)	0 (0.0)	0 (0.0)	1 (1.8)	-0.9 (-4.9, 3.1)
Myocardial ischemia	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Hemiparesis	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Non-cardiac chest pain	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Rhinovirus infection	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Cardiac failure	0 (0.0)	1 (0.9)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Chronic obstruction pulmonary disease	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Pneumonia	0 (0.0)	1 (0.9)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Confusional state	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Supraventricular tachycardia	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Coronary vascular graft stenosis	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Deep vein thrombosis	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Chronic respiratory failure	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Limb injury	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Ovarian cancer	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Renal artery occlusion	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Respiratory failure	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)

Source: Reviewer's analysis [adae.xpt; Software: JMP]

¹ Coded as MedDRA preferred terms² Includes acute myocardial infarction and myocardial infarction³ FDC versus placebo

Abbreviations: CI, confidence interval; FDC, fixed-dose combination; N, number of subjects in group; n, number of subjects with adverse event; SAE, serious adverse event

NDA 211617

Nexlizet / bempedoic acid and ezetimibe

Table 73. Adverse Events Leading to Discontinuation, Safety Population, Trial 053

Adverse Event¹	FDC N=107 n (%)	Bempedoic Acid N=110 n (%)	Ezetimibe N=109 n (%)	Placebo N=55 n (%)	Risk Difference (95% CI)²
Patients with at least one AE leading to discontinuation	7 (6.5)	9 (8.2)	10 (9.2)	2 (3.6)	2.9 (-3.9, 9.7)
Oral discomfort	2 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1.9 (-0.7, 4.4)
Fatigue/lethargy ³	1 (0.9)	1 (0.9)	1 (0.9)	0 (0.0)	0.9 (-0.9, 2.8)
Pain in extremity	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Abdominal pain ⁴	1 (0.9)	0 (0.0)	1 (0.9)	0 (0.0)	0.9 (-0.9, 2.8)
Agitation	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Asthenia	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Blood glucose increased	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Dysgeusia	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Hypoglycemia	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Myalgia	0 (0.0)	3 (2.7)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Confusional state	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Diarrhea	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Diverticulitis	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Myocardial infarction ⁵	0 (0.0)	1 (0.9)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Hyperhidrosis	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Chronic respiratory failure	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Constipation	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Joint dislocation	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Musculoskeletal discomfort	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Non-cardiac chest pain	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Renal artery occlusion	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Urticaria	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Wrist fracture	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Muscular weakness	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	-1.8 (-5.3, 1.7)
Weight increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	-1.8 (-5.3, 1.7)

Source: Reviewer's analysis [adae.xpt; Software: JMP]

¹ Coded as MedDRA preferred terms² FDC versus placebo³ Includes fatigue and lethargy⁴ Includes abdominal pain and gastrointestinal pain⁵ Includes acute myocardial infarction and myocardial infarction

Abbreviations: AE, adverse event; CI, confidence interval; FDC, fixed-dose combination; N, number of subjects in group; n, number of subjects with adverse event

NDA 211617

Nexlizet / bempedoic acid and ezetimibe

Table 74. Adverse Events¹ Occurring at 1% Higher Frequency in Treatment Arm Than Comparator Arm,² Phase 3 Safety Population

Adverse Event	FDC	Bempedoic Acid	Ezetimibe	Placebo	Risk Difference ³ (95% CI)
	N=107 n (%)	N=110 n (%)	N=109 n (%)	N=55 n (%)	
Urinary tract infection	8 (7.5)	3 (2.7)	3 (2.8)	2 (3.6)	3.8 (-3.2, 10.9)
Increased uric acid ⁴	4 (3.7)	2 (1.8)	0 (0.0)	0 (0.0)	3.7 (0.1, 7.3)
Constipation	4 (3.7)	0 (0.0)	2 (1.8)	0 (0.0)	3.7 (0.1, 7.3)
Hypertension	3 (2.8)	5 (4.5)	2 (1.8)	0 (0.0)	2.8 (-0.3, 5.9)
Diarrhea ⁵	3 (2.8)	4 (3.6)	2 (1.8)	0 (0.0)	2.8 (-0.3, 5.9)
Blood creatinine increased	3 (2.8)	2 (1.8)	0 (0.0)	0 (0.0)	2.8 (-0.3, 5.9)
Fatigue ⁶	3 (2.8)	2 (1.8)	2 (1.8)	0 (0.0)	2.8 (-0.3, 5.9)
Cough	3 (2.8)	2 (1.8)	1 (0.9)	0 (0.0)	2.8 (-0.3, 5.9)
Nausea	3 (2.8)	1 (0.9)	1 (0.9)	0 (0.0)	2.8 (-0.3, 5.9)
Abdominal pain ⁷	3 (2.8)	1 (0.9)	1 (0.9)	0 (0.0)	2.8 (-0.3, 5.9)
Bronchitis	3 (2.8)	1 (0.9)	4 (3.7)	0 (0.0)	2.8 (-0.3, 5.9)
Upper respiratory tract infection	3 (2.8)	1 (0.9)	0 (0.0)	0 (0.0)	2.8 (-0.3, 5.9)
Nasopharyngitis	4 (3.7)	6 (5.5)	4 (3.7)	1 (1.8)	1.9 (-3.1, 7.0)
Dizziness	2 (1.9)	3 (2.7)	2 (1.8)	0 (0.0)	1.9 (-0.7, 4.4)
Elevated liver enzymes ⁸	2 (1.9)	1 (0.9)	0 (0.0)	0 (0.0)	1.9 (-0.7, 4.4)
Muscle spasms	2 (1.9)	1 (0.9)	4 (3.7)	0 (0.0)	1.9 (-0.7, 4.4)
New/worsening diabetes ⁹	2 (1.9)	1 (0.9)	2 (1.8)	0 (0.0)	1.9 (-0.7, 4.4)
Gastroenteritis viral	2 (1.9)	1 (0.9)	0 (0.0)	0 (0.0)	1.9 (-0.7, 4.4)
Proteinuria ¹⁰	2 (1.9)	0 (0.0)	1 (0.9)	0 (0.0)	1.9 (-0.7, 4.4)
Hypokalemia	2 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1.9 (-0.7, 4.4)
Oral discomfort	2 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1.9 (-0.7, 4.4)
Acute otitis media	2 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1.9 (-0.7, 4.4)
Prostatitis	2 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1.9 (-0.7, 4.4)
Spinal osteoarthritis	2 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1.9 (-0.7, 4.4)
Syncope	2 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	1.9 (-0.7, 4.4)
Sinusitis ¹¹	1 (0.9)	3 (2.7)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Anxiety	1 (0.9)	2 (1.8)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Vomiting	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Angina pectoris	1 (0.9)	1 (0.9)	1 (0.9)	0 (0.0)	0.9 (-0.9, 2.8)
Angina unstable	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Blood triglycerides increased	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Influenza ¹²	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Diverticulitis	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Hypoglycemia	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Restless legs syndrome	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)
Acarodermatitis	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0.9 (-0.9, 2.8)

NDA 211617
Nexlizet / bempedoic acid and ezetimibe

Adverse Event	FDC N=107 n (%)	Bempedoic Acid N=110 n (%)	Ezetimibe N=109 n (%)	Placebo N=55 n (%)	Risk Difference³ (95% CI)
Blood potassium increased	0 (0.0)	2 (1.8)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Headache	0 (0.0)	1 (0.9)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Mean cell volume increased	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Vitamin D deficiency	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Weight increased	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0.0 (0.0, 0.0)
Back pain	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)	0.0 (0.0, 0.0)
Blood lactate dehydrogenase increased	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)	0.0 (0.0, 0.0)
Blood creatine phosphokinase increased	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Cardiac failure congestive	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Palpitations	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Tooth infection	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0.0 (0.0, 0.0)
Hemoglobin decreased ¹³	1 (0.9)	2 (1.8)	0 (0.0)	1 (1.8)	-0.9 (-4.9, 3.1)
Arthralgia	0 (0.0)	0 (0.0)	1 (0.9)	1 (1.8)	-1.8 (-5.3, 1.7)

Source: Reviewer's analysis [adae.xpt; Software: JMP]

¹ Treatment-emergent adverse event defined as any adverse event that occurred after the first dose of drug; coded as MedDRA preferred terms

² Adverse events that occurred only in one placebo-arm patient (and zero active treatment-arm patients) are not displayed

³ FDC versus placebo

⁴ Includes blood uric acid increased and hyperuricemia

⁵ Includes diarrhea and feces soft

⁶ Includes fatigue and insomnia

⁷ Includes abdominal pain, abdominal pain upper, and gastrointestinal pain

⁸ Includes aspartate aminotransferase increased, liver function test abnormal, and liver function test increased

⁹ Includes diabetes mellitus inadequate control and new-onset diabetes mellitus

¹⁰ Includes protein urine present and proteinuria

¹¹ Includes acute sinusitis and sinusitis

¹² Includes influenza and influenza-like illness

¹³ Includes hemoglobin decreased and anemia

Abbreviations: CI, confidence interval; FDC, fixed-dose combination; N, number of subjects; n, number of subjects with adverse event

Table 75. Patients Meeting Laboratory Abnormality Criteria, From Baseline Through Week 12, Safety Population, Trial 053

Laboratory Abnormality	FDC N=107 n (%)	BA N=110 n (%)	Ezetimibe N=109 n (%)	Placebo N=55 n (%)
Creatine kinase (CK) elevations (BL normal to FU high)				
>3x-fold ULN	0 (0.0)	0 (0.0)	2 (1.8)	0 (0.0)
>5x-fold ULN	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
>10x-fold ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic enzyme elevations				
AST >3x-fold ULN	2 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
AST >5x-fold ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ALT >3x-fold ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ALT >5x-fold ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TB >2x-fold ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hemoglobin decrease				
≥2 g/dL from baseline	1 (0.9)	2 (1.8)	2 (1.8)	0 (0.0)
≥3 g/dL from baseline	0 (0.0)	1 (0.9)	1 (0.9)	0 (0.0)
≥5 g/dL from baseline	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)
≥2 g/dL decline and < LLN	1 (0.9)	2 (1.8)	1 (0.9)	0 (0.0)
WBC decrease				
<4×10 ⁹ /L and normal at baseline	2 (1.9)	6 (5.5)	3 (2.8)	1 (1.8)
Creatinine increase				
>30% from baseline anytime	4 (3.7)	14 (12.7)	6 (5.5)	1 (1.8)
>30% from baseline by Week 4	2 (1.9)	2 (1.8)	1 (0.9)	0 (0.0)
>0.5 mg/dL from baseline	1 (0.9)	1 (0.9)	1 (0.9)	0 (0.0)
>1 mg/dL from baseline	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
BUN increase				
Normal baseline to > ULN	23 (21.5)	30 (27.3)	12 (11.0)	3 (5.5)
Normal baseline to >2×-fold increase	5 (4.7)	2 (1.8)	1 (0.9)	1 (1.8)
Normal baseline to >2×-fold increase and > ULN	3 (2.8)	1 (0.9)	0 (0.0)	0 (0.0)

Source: Reviewer's analysis

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BA, bempedoic acid; BL, baseline; BUN, blood urea nitrogen; FU, follow-up; LLN, lower limit of normal; N, number of subjects; n, number of subjects with abnormality; TB, total bilirubin; ULN, upper limit of normal; WBC, white blood cell

Table 76. Mean Change From Baseline in Selected Laboratory Parameters, Safety Population

Laboratory Abnormality	FDC N=107 Mean (SD)	BA N=110 Mean (SD)	Ezetimibe N=109 Mean (SD)	Placebo N=55 Mean (SD)
Alkaline phosphatase (U/L)				
Week 4	-14.7 (24.2)	-11.4 (12.7)	-1.8 (9.9)	-0.9 (7.7)
Week 8	-16.5 (17.2)	-12.2 (12.2)	-1.7 (10.4)	-2.6 (11.3)
Week 12	-14.2 (22.7)	-13.6 (14.3)	-2.2 (13.2)	-2.1 (9.2)
Fasting plasma glucose (mg/dL)				
Week 4	8.6 (29.8)	-1.3 (22.6)	6.5 (30.2)	3.6 (17.4)
Week 8	8.0 (26.9)	-1.0 (30.4)	4.2 (25.9)	5.1 (15.8)
Week 12	9.1 (31.8)	-4.3 (27.9)	0.1 (28.3)	1.6 (19.8)
Uric acid (mg/dL)				
Week 4	0.6 (1.1)	0.7 (0.2)	-0.2 (0.7)	-0.1 (0.6)
Week 8	0.6 (1.1)	0.8 (1.1)	-0.2 (0.9)	-0.1 (1.1)
Week 12	0.5 (1.2)	0.7 (1.1)	0.0 (0.8)	-0.1 (0.8)
WBC (10⁹/L)				
Week 4	-0.1 (2.0)	-0.3 (1.4)	0.1 (1.3)	-0.2 (1.2)
Week 8	-0.3 (1.7)	-0.3 (1.7)	0.0 (1.4)	-0.3 (1.2)
Week 12	-0.4 (1.4)	-0.4 (1.7)	0.0 (1.4)	-0.2 (1.3)
Platelets (10⁹/L)				
Week 4	22.6 (54.4)	16.5 (45.2)	-1.1 (36.8)	5.4 (35.1)
Week 8	17.9 (45.9)	13.4 (43.4)	-2.7 (37.3)	-6.8 (32.4)
Week 12	11.4 (44.1)	9.3 (46.3)	-5.0 (38.3)	-4.2 (33.6)

Source: Reviewer's analysis

Abbreviations: BA, bempedoic acid; FDC, fixed-dose combination; LLN, lower limit of normal; N, number of subjects; n, number of subjects with abnormality; SD, standard deviation; ULN, upper limit of normal; WBC, white blood cell

18. Mechanism of Action/Drug Resistance: Additional Information and Assessment

N/A

19. Other Drug Development Considerations: Additional Information and Assessment

N/A

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

Clinical Inspection Summary
NDA 211617 bempedoic acid + ezetimibe

Clinical Inspection Summary

Date	12/20/2019
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Anthony Orenca, M.D., Ph.D., Acting Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Laura Higginbotham, M.D., M.P.H., Clinical Reviewer John Sharretts, M.D., Clinical Team Leader Kati Johnson, Senior Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP)
NDA	211617
Applicant	Esperion Therapeutics, Inc.
Drug	Bempedoic acid + ezetimibe
NME	Yes
Therapeutic Classification	(b) (4)
Proposed Indication	(b) (4)
Consultation Request Date	4/17/2019
Summary Goal Date	12/21/2019
Action Goal Date	2/21/2020
PDUFA Date	2/26/2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this new drug application (NDA) consisted of five domestic sites in addition to the sponsor.

In general, based on the inspections of the five clinical sites, the inspectional findings support validity of data as reported by the sponsor under this NDA.

The Esperion Therapeutics, Inc. (sponsor) site inspection included a focus on the lack of any drug product found by the sponsor after database lock in pharmacokinetic (PK) blood samples from certain subjects at certain clinical sites who had reported that they took the investigational drug product. The inspections did not reveal a definitive root cause. The clinical investigators and their staff did not appear to be aware of the PK discrepancies and each site had followed the protocol. The assumption that subjects may have been perpetuating some level of subject misconduct is likely and, therefore, data from these sites (1028, 1058, and 1068) are suspect. We agree with the sponsor's decision to do post hoc sensitivity analyses of key safety, efficacy, and PK study results with all data from Sites 1028, 1058, and 1068 removed. In general, the sponsor handled this issue appropriately, and had proper oversight of Study 1002FDC-053. Data from this sponsor inspection appear acceptable to support this submitted application.

Reference ID: 4538021

1
THE FOLLOWING 11 PAGES HAVE BEEN WITHHELD AS DUPLICATE PAGES.
PLEASE SEE THE CLINICAL INSPECTION SUMMARY DOCUMENT IN THE
OTHER REVIEWS SECTION OF THIS APPROVAL PACKAGE

21. Labeling Summary of Considerations and Key Additional Information

The following major labeling decisions were communicated to the Applicant:

- Alignment of Section 6 (Adverse Reactions) with bempedoic acid and ezetimibe labeling
- Addition of ezetimibe data to Section 8.1 (Pregnancy) and 8.2 (Lactation)
- In Section 14 (Clinical Studies), removal of [REDACTED] (b) (4)
- In Section 14 (Clinical Studies), addition of data from ezetimibe labeling

22. Postmarketing Requirements and Commitments

- 1) Conduct a pharmacokinetic/pharmacodynamic study evaluating bempedoic acid in patients with heterozygous familial hypercholesterolemia (HeFH) aged 10 years to less than 18 years. The Phase 2 study will be a randomized, open-label, 6-week, dose-finding study of bempedoic acid in 36 patients aged 10 years to less than 18 years with HeFH on stable background lipid-modifying therapy with LDL-C \geq 130 mg/dL.

Draft Protocol Submission:	March 2020
Final Protocol Submission:	August 2020
Study Completion:	March 2022
Final Report Submission:	August 2022

- 2) Conduct an efficacy and safety study evaluating bempedoic acid in patients with heterozygous familial hypercholesterolemia (HeFH) aged 10 years to less than 18 years. The Phase 3 study will be a randomized, double-blind, placebo controlled, parallel group, 6-month, multicenter efficacy and safety study in 200 patients (randomized 1:1 to bempedoic acid and placebo), followed by a 6-month open-label extension in at least 100 patients assigned to bempedoic acid in pediatric patients aged 10 years to less than 18 years with HeFH on stable lipid-modifying therapy with LDL-C \geq 130 mg/dL.

Draft Protocol Submission:	August 2022
Final Protocol Submission:	March 2023
Study Completion:	February 2026
Final Report Submission:	August 2026

- 3) Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to Nexlizet (bempedoic acid and ezetimibe) during pregnancy to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The study will collect information for a minimum of 10 years. Results will be analyzed and reported descriptively. Data collected retrospectively will be analyzed separately and reported with the interim and final study reports.

Draft Protocol Submission:	September 2020
Final Protocol Submission:	May 2021
Interim Report Submissions:	April 2022 April 2023 April 2024 April 2025 April 2026 April 2027 April 2028 April 2029 April 2030 April 2031
Study Completion:	May 2032
Final Report Submission:	January 2033

- 4) Perform a lactation study (milk only) in lactating women who have received therapeutic doses of Nexlizet (bempedoic acid and ezetimibe) using a validated assay to assess concentrations of bempedoic acid and ezetimibe in breast milk and the effects on the breastfed infant.

Draft Protocol Submission:	September 2020
Final Protocol Submission:	April 2021
Study Completion:	April 2024
Final Report Submission:	December 2024

- 5) Complete the ongoing randomized, double-blind, placebo-controlled, parallel group, multi-center trial in approximately 14,000 patients (randomized 1:1 to bempedoic acid and placebo) designed to assess the effects of bempedoic acid on the occurrence of major cardiovascular events. The trial will include evaluation of the effects of bempedoic acid on occurrence of tendinopathy, tendon rupture, atrial fibrillation, and renal impairment as adverse events of special interest.

Draft Protocol Submission: June 2020
 Final Protocol Submission: September 2020
 Trial Completion: March 2023
 Final Report Submission: February 2024

23. Financial Disclosure

Table 77. Covered Clinical Studies: FDC-053

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: 359 (Principal and Sub Investigators)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0 Enter text here.		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here.</p> <p>Significant payments of other sorts: Enter text here.</p> <p>Proprietary interest in the product tested held by investigator: Enter text here.</p> <p>Significant equity interest held by investigator: Enter text here.</p> <p>Sponsor of covered study: Enter text here.</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): Enter text here.		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)

24. References

25. Review Team

Table 78. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Kati Johnson
Nonclinical Reviewer	Lydia Haile
Nonclinical Team Leader	Calvin (Lee) Elmore
Office of Clinical Pharmacology Reviewer(s)	Mohammad (Abir) Absar
Office of Clinical Pharmacology Team Leader(s)	Suryanarayana Sista
Clinical Reviewer	Laura Higginbotham
Clinical Team Leader	John Sharretts
Statistical Reviewer	Jiwei He
Statistical Team Leader	Feng Li
Cross-Discipline Team Leader Deputy Division Director (Acting)	John Sharretts

Table 79. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Leeza Rahimi/John Amartey/Parmesa Patel/Muthukumar Ramaswamy/Donna Christner/Christina Capacci-Daniel/Ying Zhang/Kamrun Nahar/Haritha Mandula/Danae Christoulou/James Laurenson
Patient labeling	Sharon Williams/LaShawn Griffiths
OPDP	Charuni Shah
OSI	Cynthia Kleppinger/Anthony Orenca/Kassa Ayalew
OSE/DMEPA	Valerie Vaughn/Sevan Kolejian/Deveonne Hamilton-Stokes
DPMH	Jane Liedka/Miriam Dinatale

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigation; OSE, Office of Surveillance and Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis

Table 80. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Approved ¹
Clinical Pharmacology	Mohammad Absar, PhD	OTS/OCP/DPM	IA,5,6,8,14 <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
Primary Reviewer	Signature: Mohammad Absar -S <small>Digitally signed by Mohammad Absar -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mohammad Absar -S, 0.9.2342.19200300.100.1.1=2001438751 Date: 2020.02.26 12:18:52 -05'00'</small>		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	Suryanarayana Sista, PhD	OTS/OCP/DCEP	IA,5,8,14 <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
Secondary Reviewer	Signature: Suryanarayana M. Sista -S <small>Digitally signed by Suryanarayana M. Sista -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001007118, cn=Suryanarayana M. Sista -S Date: 2020.02.26 12:09:13 -05'00'</small>		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Pharmacology/Toxicology	Lydia Haile, PhD	OND/ODE2/DMEP	IA,5,7,8,13 <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
Primary Reviewer	Signature: Lydia A. Haile -S <small>Digitally signed by Lydia A. Haile -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lydia A. Haile -S, 0.9.2342.19200300.100.1.1=2000470805 Date: 2020.02.26 11:56:00 -05'00'</small>		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Pharmacology/Toxicology	C. Lee Elmore, PhD	OND/ODE2/DMEP	IA,5,7,8,13 <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
Secondary Reviewer	Signature: Calvin L. Elmore -S <small>Digitally signed by Calvin L. Elmore -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000356615, cn=Calvin L. Elmore -S Date: 2020.02.26 12:25:50 -05'00'</small>		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Statistical	Jiwei He, PhD	OTS/OBI/DB2	IA,6,15,16 <input checked="" type="checkbox"/> Authored <input type="checkbox"/> Approved
Primary Reviewer	Signature: Jiwei He -S <small>Digitally signed by Jiwei He -S Date: 2020.02.26 12:02:05 -05'00'</small>		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Approved ¹
Statistical	Feng Li, PhD	OTS/OBI/DB2	IA,6,15,16 <input type="checkbox"/> Authored <input checked="" type="checkbox"/> Approved
Secondary Reviewer	Signature: Feng Li -S <small>Digitally signed by Feng Li -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Feng Li -S, 0.9.2342.19200300.100.1.1=2000332337 Date: 2020.02.26 12:35:31 -05'00'</small>		
Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical	Laura Higginbotham, MD MPH	OND/ODE2/DMEP	ES,IA,3,4,6,7,8,10,15 16,17,21,22 <input checked="" type="checkbox"/> Authored
Primary Reviewer	Signature: Laura B. Higginbotham -S <small>Digitally signed by Laura B. Higginbotham -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002617854, cn=Laura B. Higginbotham -S Date: 2020.02.26 11:50:19 -05'00'</small>		

¹Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

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/

KATI JOHNSON
02/26/2020 02:26:47 PM

JOHN M SHARRETT
02/26/2020 02:28:51 PM

I co-authored the executive summary and approved the integrated assessment. I concur with the conclusions.