CLINICAL REVIEW/SUMMARY MEMO/ SUMMARY BASIS FOR REGULATORY ACTION

Application Type	NDA
Application Number(s)	22362
Priority or Standard	Standard
Submit Date(s)	December 23, 2020
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Division/Office	DDLO/OCHEN
Reviewer Name(s)	Hyon Kwon
Review Completion Date	See stamped date
Established/Proper Name	Colesevelam hydrochloride
(Proposed) Trade Name	Welchol
Applicant	Daiichi Sankyo, Inc.
Dosage Form(s)	Oral suspension
Applicant Proposed Dosing Regimen(s)	3.75 gram per daily
Applicant Proposed Indication(s)/Population(s)	None proposed
Recommendation on Regulatory Action	Approval with appropriate labeling
Recommended Indication(s)/Population(s) (if applicable)	None

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Glossary

AC	advisory committee
AE	adverse event
ANCOVA	analysis of covariance
ALT	alanine aminotransferase
Apo A-1	apolipoprotein A-1
Apo B	apolipoprotein B
AR	adverse reaction
AST	aspartate aminotransferase
BMI	body mass index
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
FDA	Food and Drug Administration
FPG	fasting plasma glucose
GCP	good clinical practice
GI	gastrointestinal
GRMP	good review management practice
HDL-C	high-density lipoprotein cholesterol
IND	Investigational New Drug Application
ITT	intent to treat
LDL-C	low-density lipoprotein cholesterol
LOCF	last observation carried forward
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities

NDA	new drug application
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PADER	Periodic Adverse Drug Event Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PSUR	Periodic Safety Update report
PT	Preferred Term
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	System Organ Class
TC	total cholesterol
TG	triglyceride
TEAE	treatment emergent adverse event
T2D	type 2 diabetes
T2DM	type 2 diabetes mellitus
ULN	upper limit of normal

1. Executive Summary

1.1. Product Introduction

Welchol (colesevelam hydrochloride [HCl]) is a bile acid sequestrant that was first approved on May 26, 2000 (Welchol tablets, NDA 21176) for lowering low density lipoprotein cholesterol (LDL-C) in adults. The indication for pediatric use in lipid reduction was subsequently approved.

Welchol is a non-absorbed polymer with a high capacity for binding bile acids in the gastrointestinal (GI) tract. These binding blocks reabsorption of bile acids and depletes the bile acid pool causing upregulation of hepatic cholesterol 7-alpha-hydroxylase. This leads to increased conversion of cholesterol to bile acids that increases transcription and activity of 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase and increases hepatic LDL-C receptors, resulting in decreased serum LDL-C.

In addition, Welchol tablet was approved on January 18, 2008 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) (NDA 21176/S-017); the pediatric study requirement was waived at the time of approval. In adult clinical trials, Welchol for glycemic control as an add-on therapy to metformin, sulfonylureas, and insulin showed a mean reduction in HbA1c of ~0.5% compared to placebo.

Welchol for Oral Suspension (NDA 22362) was approved on October 2, 2009, based on bioequivalence to the tablet formulation. Welchol oral suspension provided an alternative formulation that can be mixed with water, fruit juice, or diet soft drink for ease of ingestion, as the large tablet size and the high number of tablets per day (i.e., 6 tablets) can present challenges to ingest in some patients treated with Welchol. To address the Pediatric Research Equity Act (PREA) for the diabetes indication with approval of Welchol for Oral Suspension, the pediatric study requirement for T2DM in children 0 to 9 years of age, inclusive, was waived due to the low prevalence of the disease in children younger than 10 years, and the pediatric study requirement in children 10 to 17 years of age was deferred with the following postmarketing requirement (PMR):

> **PMR 1729-1:** Deferred, 1-year, pediatric efficacy and safety study under PREA for the treatment of type 2 diabetes in pediatric patients ages 10 to 17 years.

The exact mechanism of Welchol's glucose-lowering effect is unknown. Hypothesized mechanisms include decreased hepatic gluconeogenesis by suppressing the farnesoid X receptor, the bile acid dedicated G-protein coupled receptor (TGR5) and mitogen activated protein kinase pathway receptors, lowered insulin resistance through increased mitochondrial activity and oxidate phosphorylation, and increased enteroincretin effect by stimulating

secretion of glucagon-like peptide-1 (GLP-1) from altered bile acid dynamics.

The recommended dosage for Welchol tablets and oral suspension for all approved indications is 3.75 g/day.

1.2. Conclusions on the Substantial Evidence of Effectiveness

To establish the effectiveness of Welchol in pediatric patients with T2DM, we required one trial since we can partly extrapolate the effectiveness of Welchol from adult trials with T2DM. However, the effectiveness of Welchol in pediatric patients with T2DM was not demonstrated in a 6-month, randomized, double-blind, two-group parallel trial (WEL-A-U307).

Trial WEL-A-U307 evaluated Welchol oral suspension in 236 pediatric subjects with T2DM, 10-17 years of age, who were either treatment naïve or on metformin monotherapy with inadequate glycemic control. A low subtherapeutic dose of Welchol (0.625 g daily) was used as a placebo arm for comparison against the active Welchol arm receiving the recommended dose of 3.75 g daily.

The primary efficacy analysis conducted by the FDA Statistical Reviewer, Dr. Wendy Tu, showed that after 6 months, the HbA1c change from baseline was 0.07% for the active Welchol arm (N=141) and 0.19% for the placebo arm (N=95), with treatment difference of -0.12% that did not reach statistical significance (95% confidence interval [CI] of -0.55 to 0.30; p-value=0.56). The estimated treatment effect size of 0.12% reduction in HbA1c does not suggest that Welchol provides a clinically meaningful glycemic effect after 6 months of treatment. A large proportion of subjects in both treatment arms required glycemic rescue therapy during the trial (51.5% in the placebo arm and 45.5% in the active Welchol arm) and about one-third of subjects in both treatment groups had missing HbA1c values by 6 months. The safety profile of Welchol was similar to those seen in adults and no new safety issues were identified.

Trial WEL-A-U307 fulfilled the PREA PMR 1729-1. The Pediatric Review Committee agreed.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The prevalence of pediatric type 2 diabetes mellitus (T2DM) has been increasing in the United States over the past 20 years[1]. Despite this growing number of patients, clinical trial development for therapeutic options has been challenging due to mostly recruiting difficulties in this patient population. Treatment options for pediatric T2DM are limited, and currently include metformin, liraglutide, exenatide extended-release, and insulin.

On December 23, 2020, the Applicant submitted supplemental new drug application for Welchol Oral Suspension with the results of one pediatric trial (WEL-A-U307) conducted to fulfill the PREA PMR 1729-1. Because the trial failed to show superiority in glycemic control with Welchol treatment, the Applicant did not seek a pediatric indication and proposed to update the pediatric use section (8.4) of labeling.

The efficacy and safety of Welchol was evaluated in WEL-A-U307 trial, a randomized, double-blind, two-group parallel trial in pediatric subjects with T2DM with inadequate glycemic control who were either treatment naïve or on metformin monotherapy. The primary efficacy endpoint (HbA1c change from baseline) was evaluated at 6 months, and subjects were followed for an additional 6 months for a total of 12 months of follow-up. A low dose of Welchol (0.625 g daily) was used as a placebo arm for comparison against the active Welchol arm receiving the recommended dose of 3.75 g daily.

The primary efficacy analysis conducted by the FDA Statistical Reviewer, Dr. Wendy Tu, showed that after 6 months, the HbA1c change from baseline was 0.07% for the active Welchol arm (N=141) and 0.19% for the placebo arm (N=95), with treatment difference of -0.12% that did not reach statistical significance (95% CI of -0.55 to 0.30; p-value=0.56). The estimated effect size of 0.12% reduction in HbA1c is also not clinically meaningful.

A large proportion of subjects in both treatment arms required glycemic rescue therapy during the trial (51.5% in the placebo arm and 45.5% in the active Welchol arm) and about one-third of subjects in both treatment groups had missing HbA1c values by 6 months.

Adverse events associated with Welchol in WEL-A-U307 trial were generally similar to those seen in adult trials and were already labeled events. Common adverse reactions included upper respiratory tract infections (17% versus 9.5% in the Welchol versus placebo), vomiting (14.2% versus 11.6% in the Welchol versus placebo), headache (12.8% versus 8.4% in the Welchol versus placebo), and constipation (7.1% versus 1.1% in the Welchol versus placebo). Hypertriglyceridemia occurred in 3.5% of the active Welchol treatment group compared to none

with low dose Welchol treatment group. There was an increase in the percent median triglycerides in both treatment groups from baseline to Month 6, with a larger increase in the active Welchol group compared to the low dose group; the difference in the median percent change was 6.0% (Table 10). No pancreatitis was reported. Unlike some other antidiabetic agents, Welchol was not associated with an increased incidence of hypoglycemia.

Since Welchol was not found to be effective in pediatric patients with T2DM, there is no expected benefit for pediatric patients with T2DM on glycemic control. Pediatric Use section 8.4 of the Prescribing Information will be updated to reflect that the effectiveness of Welchol has not been established in pediatric patients with T2DM. Per labeling guidance, if an important safety issue in pediatric patients was found in the trial, that information should be labeled in section 8.4 as well; however, there were no safety issues found that warrant pediatric-specific labeling.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The prevalence of type 2 diabetes mellitus (T2DM) in youth has been increasing in the U.S. • Type 2 diabetes affects higher number of youths from racial and ethnic minorities. • Type 2 diabetes is characterized by insulin resistance without an autoimmune component, and there is rapid decline in beta cell function. • Youths with T2DM have an accelerated development of diabetes complications and comorbidities.	Type 2 diabetes in youth is increasing and affects a disproportionate number of minority groups. Type 2 diabetes in youth is different than disease in adults due to its rapid decline in beta cell function and rapid onset of diabetes related comorbidities.
Current Treatment Options	• Metformin, insulin, liraglutide, and exenatide extended-release are current therapeutic options for youth with type 2 diabetes.	There are limited treatment options for pediatric patients with type 2 diabetes mellitus.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• After 6 months of treatment, Welchol 3.75 g/daily did not demonstrate superiority over Welchol 0.625 g/daily (considered to be placebo due to subtherapeutic dose given). The change from baseline in HbA1c was 0.07% for the active Welchol arm (N=141) and 0.19% for the placebo arm (N=95), with treatment difference of -0.12% that did not reach statistical significance (95% CI of -0.55 to 0.30; p-value=0.56) • A large proportion of subjects in both treatment arms required glycemic rescue therapy during the trial (51.5% in the placebo arm and 45.5% in the active Welchol arm) and about one-third of subjects in both treatment groups had missing HbA1c values by 6 months.	No benefit to pediatric patients with T2DM is expected. The effectiveness of Welchol to improve glycemic control in pediatric patients with T2DM was not demonstrated.
Risk and Risk Management	• No deaths were reported; one subject delivered a non-viable male infant due to premature labor after receiving the low dose Welchol/placebo. • Slight imbalance in serious adverse events (SAEs) related to psychiatric disorder (depression, suicidal ideation/attempt) was noted, with 5 subjects (3.5%) receiving Welchol and 2 subjects (2.1%) receiving placebo. However, most of these subjects had underlying mental disorder, and the overall incidence of depression and suicidal events (both SAE and non-SAEs) did not show an imbalance between treatment groups. • Hypertriglyceridemia is a labeled adverse reaction for Welchol and occurred in 3.5% with Welchol and none with placebo; there was also a larger increase in the percent median triglycerides with Welchol compared to placebo; the difference in the median percent change was 6%. No pancreatitis was reported. • No new safety issues were identified in the pediatric patients with T2DM.	Overall, treatment with Welchol appeared to be well tolerated in the pediatric patients with T2DM. Unlike some other antidiabetic agents, Welchol was not associated with an increased incidence of hypoglycemia. Common adverse events were similar to those observed in adults and were labeled events.

1.4. Patient Experience Data

This section is not relevant to this application.

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

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

The incidence of pediatric type 2 diabetes mellitus (T2D) has been increasing over the past 20 years, with new cases in the U.S. estimated at around 5,000 per year[1]. The prevalence of pediatric T2D appears to be higher in certain racial and ethnic groups (including Hispanic, American Indian and African American adolescents) and in adolescent girls (with a 60% higher prevalence rate than boys)[2]. Nearly 80 to 90% of youth with T2D have overweight and obesity. The onset of pediatric T2D often coincides with pubertal insulin resistance and it is rarely diagnosed in patients below 10 years of age.

The pathophysiology of pediatric T2D is similar to adults, involving non-autoimmune pancreatic β-cell failure occurring in the background of insulin resistance. However, pediatric T2D has several unique features compared to adult T2D. The degree of insulin resistance in pediatric T2D appears to be more profound than in adults, even at the same degree of adiposity[3,4]. According to the TODAY study, nearly 50% of pediatric patients on metformin monotherapy failed glycemic control over a 4-year follow up with a median time to insulin of 11 months, far greater than the rates of glycemic failure reported in adults on metformin monotherapy[5]. Data from the TODAY study also suggests that some youth with T2D may experience more rapid deterioration of β-cell function as compared to adults[6], while others may exhibit more durable glycemic control on metformin monotherapy. This heterogeneity may indicate two subgroups of pediatric T2D, one that is easily controlled and another with more rapid progression of disease[7]. The predictors of treatment response in pediatric T2D are currently under study, however intrinsic differences in β-cell function may partly account for the heterogeneity in disease progression. TODAY study participants with durable glycemic control had lower HbA1c (<6.3% on metformin) and higher insulinogenic index at baseline[8]. In addition, participants with oral glucose tolerance test response curves characterized by “incessant increase” had greater 6-month decline in C-peptide index and higher rates of glycemic failure, supporting that reduced β-cell function near the time of diagnosis or after a short course of metformin may predict subsequent β-cell function and risk for treatment failure[7,9]. Youth with T2D also appear to have accelerated development of diabetes complications and co-morbidities, including high prevalence of hyperfiltration (predicting rapid GFR decline), diabetic retinopathy, and echocardiographic changes associated with major cardiovascular risk[7].

2.2. Analysis of Current Treatment Options

Compared to adults, there are limited treatment options for youths with T2D. Treatment options include metformin hydrochloride (pediatric approval in 2000), liraglutide (pediatric approval in 2019), exenatide extended release (pediatric approval in 2021), and insulin. Metformin is the only oral antihyperglycemic agent approved for use in pediatric T2D.

Metformin is a biguanide used to improve glucose tolerance in patients with T2D. Metformin has several physiologic effects including decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin hydrochloride products with an indication for use in pediatric type 2 diabetes (in children ages 10 years and older) include metformin hydrochloride immediate release tablets, immediate release oral solution and extended-release oral suspension[1]. Pediatric dosing instructions for the immediate-release formulations include a starting dose of 500 mg twice daily with meals, and to increase dosage in increments of 500 mg weekly up to a maximum of 2000 mg per day given in divided doses twice daily. Pediatric dosing instructions for the extended-release oral suspension include a starting dose of 500 mg once daily with evening meal, and to increase dosage in increments of 500 mg weekly up to a maximum of 2000 mg once daily with the evening meal. Efficacy of metformin in children was supported by a double-blind placebo-controlled study in pediatric T2D patients aged 10 to 16 years that showed a significantly greater reduction in fasting plasma glucose (FPG) after 16 weeks of metformin compared to placebo (FPG change of -42.9 mg/dL in metformin group compared to + 21.4 mg/dL in placebo group, $P<0.0001$)[2]. The safety profile of metformin is similar in adults and children. Common adverse reactions include diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort and headache. Labeling for metformin also includes a boxed warning for lactic acidosis, as well as warnings and precautions regarding vitamin B12 deficiency and hypoglycemia with concomitant use with insulin and insulin secretagogues.

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist. Similar to GLP-1, liraglutide increases cyclic AMP leading to insulin release in the presence of elevated glucose concentrations, delays gastric emptying and decreases glucagon secretion in a glucose-dependent manner. Liraglutide is available as an injection for subcutaneous use in pre-filled single patient-use pens delivering doses of 0.6 mg, 1.2 mg or 1.8 mg. Pediatric dosing instructions recommend initiating liraglutide at 0.6 mg daily for at least one week, to increase the dose to 1.2 mg daily if additional glycemic control is required, and to increase to 1.8 mg daily after at least 1 week of treatment with the 1.2 mg dose if additional glycemic control is still required. Efficacy of liraglutide in children was supported by a 26-week, double-blind, placebo-controlled clinical trial and a 26-week open-label extension in 134 pediatric patients 10 to 17 years of age with T2D. All patients were randomized to liraglutide once daily or placebo in combination with metformin, with or without insulin treatment. At 26 weeks, treatment with liraglutide was superior in reducing HbA1c from baseline compared to placebo (estimated treatment difference in HbA1c reduction from baseline between liraglutide and placebo was -1.06% with 95% confidence interval of -1.65% to -0.46%). The safety profile of liraglutide in

[1] Metformin hydrochloride extended-release tablets are labeled only for adult use.
[2] While FPG may have been used in the past, HbA1c is currently the preferred surrogate endpoint to support an indication for the treatment of type 2 diabetes.

children and adults is similar, with the exception of hypoglycemia. In adults, serious hypoglycemia was seen when liraglutide was used with an insulin secretagogue or insulin, however in pediatric patients, the risk of hypoglycemia was higher with liraglutide treatment regardless of concomitant antidiabetic therapies. Labeled adverse reactions include nausea, diarrhea, vomiting, decreased appetite, dyspepsia, constipation, and immunogenicity-related events (including urticaria). The liraglutide label also includes a boxed warning for thyroid C-cell tumors and contraindicated use in patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. Other warnings and precautions include pancreatitis, renal impairment, hypersensitivity, and acute gallbladder disease.

Exenatide is also a GLP-1 receptor agonist, and an extended-release formulation is available for a subcutaneous injection delivering a dose of 2 mg to be administered once weekly. The efficacy of exenatide extended-release in children was supported by a 24-week, double-blind, placebo-controlled trial and a 28-week open-label uncontrolled extension in 82 pediatric patients 10 to 17 years of age with T2D treated with diet or exercise alone or in combination with a stable dose of oral antidiabetic agents and/or insulin. At 24 weeks, treatment with exenatide extended-release was superior in reducing HbA1c from baseline compared to placebo (estimated treatment difference in HbA1c reduction from baseline between exenatide extended-release compared to placebo was -0.71% with 95% confidence interval of -1.42% to 0%). The safety profile of exenatide extended-release product in children and adults is similar.

The following insulin products have an indication "to improve glycemic control in adults and children with diabetes mellitus" and therefore include pediatric patients with T2D:

- Humulin R (insulin human injection)
- Novolin R (insulin human injection)
- Humulin N (isophane insulin human injection)
- Novolin N (isophane insulin human injection)
- Novolin 70/30 (human insulin isophane suspension and human insulin injection)
- Humulin R U-500 (insulin human injection)
- Apidra (insulin glulisine [rDNA origin] injection)
- Fiasp (insulin aspart injection)
- Humalog (insulin lispro injection)
- Levemir (insulin detemir injection)
- Novolog (insulin aspart injection)
- Ryzodeg 70/30 (insulin degludec and insulin aspart injection)[3]
- Toujeo (insulin glargine injection)[4]

[3] Labeled indication for Ryzodeg includes pediatric patients 1 year and older with diabetes mellitus.
[4] Labeled indication for Toujeou includes pediatric patients 6 years and older with diabetes mellitus.

- Tresiba (insulin degludec injection)[5]

In the majority of insulin products, efficacy for the treatment of pediatric T2D was supported by studies of pediatric patients with type 1 diabetes and/or adult patients with diabetes mellitus. None of the insulin product labels listed above include any pediatric T2D efficacy trial data.

Among insulin products that do not include an indication for treatment of pediatric T2D[6], many are commonly used off-label in clinical practice for the treatment of pediatric T2D.

Overall, treatment options for pediatric T2D patients are limited, with only a single oral agent (metformin) and GLP-1 agonists (liraglutide and exenatide extended-release) apart from insulin products. Notably, many antihyperglycemic agents available to adults with T2D (including the commonly used drug classes of sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors and thiazolidinediones) are not approved for use in children with T2D. While some antihyperglycemic agents are used off-label, the safety and efficacy of these products have not been established in pediatric T2D.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Welchol for Oral Suspension was approved October 2, 2009, based on bioequivalence to the Welchol tablet formulation. To address the PREA for the diabetes indication, the Agency waived the requirement for studies in pediatric patients ages 0-9 years, inclusive, due to the low prevalence of the disease in children younger than 10 years. The requirement to study pediatric patients ages 10-17 years was deferred with the following PMR at approval:

PMR 1729-1: Deferred, 1-year, pediatric efficacy and safety study under PREA for the treatment of type 2 diabetes in pediatric patients ages 10 to 17 years.

The timeline for final report (FR) submission was initially November 2015. However, due to difficulty with recruiting pediatric patients with T2DM, a deferral extension was granted on October 14, 2015 to extend the FR submission to November 2019, and again on August 6, 2019 to extend the FR submission to December 2020 due to delays in enrollment.

[5] Labeled indication for Tresiba includes pediatric patients 1 year and older with diabetes mellitus.
[6] Labels that exclude pediatric type 2 diabetes may indicate "treatment of adult and pediatric patients with type 1 diabetes and adults with type 2 diabetes" or may indicate approved treatment only in adults with diabetes.

3.2. Summary of Presubmission/Submission Regulatory Activity

There was none.

3.3. Foreign Regulatory Actions and Marketing History

Colesevelam was approved in the European Union in April 2004, and is also approved for use in Canada, India, and Russia.

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

4.1. Office of Scientific Investigations (OSI)

No efficacy/safety or scientific misconduct concerns were identified during the review that resulted in a request for an OSI review.

4.2. Product Quality

There is no new data regarding chemistry, manufacturing and controls (CMC), sterility, or biopharmaceutics in the submission.

4.3. Clinical Microbiology

There is no new data regarding microbiology information in the submission.

4.4. Nonclinical Pharmacology/Toxicology

There is no new nonclinical pharmacology or toxicology data in the submission.

4.5. Clinical Pharmacology

There is no new clinical pharmacology data in the submission.

4.6. Devices and Companion Diagnostic Issues

There are no devices included in this submission.

4.7. Consumer Study Reviews

This section is not applicable to this submission.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The primary efficacy and safety data for this review was derived from a single pediatric trial:

WEL-A-U307 – Colesevelam Oral Suspension as Monotherapy or Add-on to Metformin Therapy in Pediatric Subjects with Type 2 Diabetes Mellitus.

5.2. Review Strategy

The review strategy focused on the safety and efficacy findings from WEL-A-U307 study, since this is the single pediatric study submitted for this supplement. The clinical reviewer reviewed the protocol, protocol amendments, the statistical analysis plan, and the study report. The clinical reviewer also reviewed the safety data.

Dr. Wendy Tu was the FDA primary statistical reviewer and independently conducted and confirmed the primary efficacy finding and performed subgroup analysis for the primary efficacy endpoint.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. WEL-A-U307

6.1.1. Study Design

Overview and Objective

Trial WEL-A-U307 will also be referred to as "U307 trial" throughout this review.

Trial Sites: The trial was conducted at 29 clinical sites in the U.S.

Primary objective: To demonstrate the effects of Welchol oral suspension as monotherapy or as an add-on therapy to metformin on the change in HbA1c from baseline after 6 months of treatment in pediatric subjects with T2DM.

Secondary objectives:

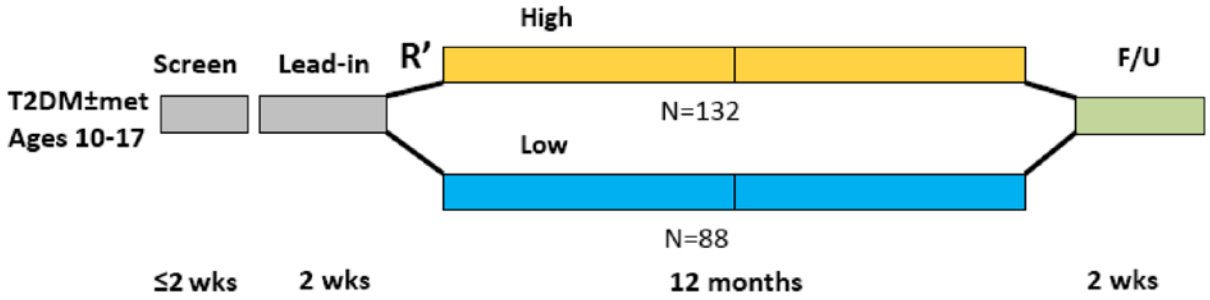
- To demonstrate the safety and tolerability of Welchol oral suspension as an anti-diabetic treatment in pediatric subjects with T2DM;
- To assess the effect of Welchol oral suspension on:

- HbA1c during 12 months of treatment;
- Fasting plasma glucose (FPG) during 12 months of treatment;
- Glycemic response over time (i.e., percentage of subjects with HbA1c <7% and <6.5%, decrease in HbA1c ≥0.7% or ≥0.5% from baseline, or decrease in FPG ≥30 mg/dL from baseline);
- Changes in plasma lipids including total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), triglycerides (TG), apolipoprotein A-1 (apo A-1), and apolipoprotein B (apo B);
- Proportion of subjects requiring rescue and the time from randomization to initiation of rescue.

Trial Design

Trial U307 was a multicenter, randomized, double-blind, controlled 12-month treatment trial in subjects with T2DM (ages 10-17 years) having suboptimal glycemic control with or without metformin. Figure 1 shows the overview of the trial design.

Figure 1: WEL-A-U307 Trial Design



F/U = follow-up; met = metformin; R' = randomization; T2DM = type 2 diabetes mellitus; wks = weeks.
Source: CSR, Figure 6-1

The trial consisted of screening, followed by a 2-week, single-blind, lead-in/stabilization period and a 12-month double-blind treatment period, with a follow-up visit 2 weeks after the end of treatment period. The total duration of participation for each subject was about 58 weeks.

After screening, all eligible subjects entered a 2-week single-blind lead-in/stabilization period. During the 2-week, single-blind lead-in/stabilization period, all subjects received low-dose (0.625 g) Welchol oral suspension mixed in 4-8 ounces of water, fruit juice, or diet soft drink once daily with dinner. Subjects on metformin monotherapy remained on the same dose at the time of screening unless s/he met the glycemic rescue criteria.

At randomization, subjects were assigned in a 3:2 ratio to 12 months of treatment with either high dose Welchol oral suspension (3.75 g, equivalent to 6 tablets) once daily or to low dose Welchol oral suspension (0.625 g, equivalent to one tablet) as placebo once daily, to be mixed in 4 to 8 ounces of water, fruit juice, or diet soft drink with dinner. To maintain blind, both 3.75 g and 0.0625 g of Welchol were provided in identically appearing unbranded packets. The low dose Welchol oral suspension was used instead of a placebo as the control treatment since a placebo oral suspension product with matching organoleptic characteristics to the Welchol oral suspension product was not available.

Reviewer's comment: Using the low dose Welchol oral suspension as a control treatment in this trial is acceptable, as low dose of Welchol (0.625 g daily) would not be expected to have much effect on glycemia. In the discussion sections of the results and throughout this review, the low dose Welchol group will also be referred as a placebo arm.

Randomization was stratified by prior T2DM treatment status (naïve or metformin monotherapy). Subjects who were on metformin monotherapy remained on the same dose during their participation in the trial unless subjects needed glycemic rescue (see below for glycemic rescue criteria).

Diet and exercise were reviewed and reinforced at study visits. In addition, all subjects were provided with home glucose monitoring systems with appropriate instruction to measure glucose levels during the lead-in period and throughout the 12-month treatment period. Subjects were to obtain glucose levels every morning before breakfast, and to monitor a random, non-fasting glucose level once daily, with instruction to call the clinic immediately if fasting glucose level was <50 mg/dL or >240 mg/dL and received appropriate medical advice based on their glucose level. At the Investigator's discretion, a clinic visit was scheduled within 3 days for a follow-up evaluation of fasting glucose if deemed necessary.

Adherence to the study drug was evaluated by counting unused study drug at the next study visit, and subjects were counseled about the importance of adherence if it was not between 80 and 120%, inclusive.

A Data Monitoring Committee was established to ensure safety of study participants.

Glycemic Rescue criteria: To minimize prolonged hyperglycemia, all subjects were monitored for elevated blood glucose at each study visit in addition to monitoring at home. The Investigator was blinded to HbA1c values throughout the study, and laboratory reports alerted the Investigator to abnormal values. If a subject's HbA1c could not be maintained below 8.5% after 3 months or below 7.5% after 6 months of treatment with study drug, as measured by the central laboratory, subjects remained on the trial and received an open-label glycemic rescue with metformin. Metformin therapy was optimized in subjects who were not on the maximally

tolerated dose or initiated in subjects not on metformin by up-titrating to 2g/day or the maximally tolerated dose of metformin.

If a subject had been on 2g or the maximally tolerated dose of metformin therapy and required rescue, a once-daily insulin such as insulin glargine was to be added. The recommended initial insulin glargine treatment was 0.2 U/kg to 0.4 U/kg each evening and could be increased to 1.0 U/kg/day (maximum 100 U).

Inclusion/Exclusion Criteria:
Inclusion:

- Informed assent and consent from a parent or legal guardian at screening;
- Males and females aged 10-17 years, inclusive, at randomization;
- Diagnosed with T2DM and either on metformin monotherapy or untreated (defined as either treatment naïve, or received anti-diabetic drug for less than 14 days within 3 months before screening but no insulin therapy within 14 days of screening);
- Screening HbA1c 7-10%, inclusive, and fasting C-peptide >0.6 ng/mL.

Key Exclusion:

- FPG >270 mg/dL;
- Diagnosis of type 1 diabetes, or have positive autoantibodies (anti-islet cell antigen [ICA] 512 or anti-glutamic acid decarboxylase [GAD]);
- History of more than 1 episode of ketoacidosis after diagnosis of T2DM;
- Used inhaled glucocorticoids at >1 mg of daily fluticasone equivalent or any oral glucocorticoids within past 60 days or >20 days during past year; insulin ≥14 days past 3 months or within 14 days of screening; medication (except metformin) known to affect insulin sensitivity or secretion past 30 days (except oral contraceptives); medication known to cause weight gain or taken for weight loss within past 30 days; or growth hormone/somatotropin;
- Participate in a formal weight-loss program (current or planned);
- Genetic syndrome or disorder known to affect glucose;
- Abnormal reticulocyte count or HbA1c chromatogram indicating abnormal hemoglobin variants other than heterozygosity for S and C;
- Lactating or pregnant females, or planned to become pregnant within one year of screening;
- Females unwilling to use appropriate contraception during participation; study acceptable methods of birth control were at least single-barrier methods (any one of either systemic hormonal regimens, diaphragm, condom, copper intrauterine device, sponge, or spermicide);
- History of bowel obstruction; other significant organ system illness or condition;
- Systolic blood pressure ≥150 mm Hg or diastolic blood pressure ≥95 mm Hg despite

therapy;
- Have the following laboratory values: ALT or AST >2.5x upper limit of normal (ULN); Creatinine clearance <70 mL/min; TG >500 mg/dL; hematocrit <30% or hemoglobin <10 mg/dL despite therapy.

Reviewer's comment: Overall, the inclusion/exclusion criteria are acceptable. The age of subjects enrolled (10-17 years) is acceptable and is consistent with the majority if not all pediatric type 2 diabetes program.

Subject Withdrawal/Early Discontinuation Criteria: Study drug and trial participation were discontinued if a subject had:
- Persistent HbA1c >11%;
- Inability to discontinue acute temporary use of insulin (non-basal) within 8 weeks without decompensation (ketonuria and symptomatic hyperglycemia);
- Pregnancy;
- Any serious adverse event (SAE), clinically significant adverse event (AE), or severe laboratory abnormality which in the opinion of the Investigator indicated that continued participation in the study was not in the best interest of the subject.

If a subject was withdrawn due to an AE, s/he was followed until the AE had resolved or stabilized.

Study Endpoints

The primary efficacy endpoint was the change in HbA1c from baseline to Month 6.

The secondary efficacy endpoints were:
- The change in HbA1c from baseline to Month 12 at visits where measured (Months 3, 6, 9, and 12);
- The change in FPG from baseline to Month 12 at visits where measured (Months 6 and 12);
- Percentage of subjects achieving a response to therapy at Months 6 and 12, defined as HbA1c <7% or <6.5%, reduction in HbA1c ≥0.7% or ≥0.5% from baseline, and/or reduction in FPG ≥30% mg/dL from baseline;
- The change and percent change in plasma lipids at each scheduled visit (i.e., TC, LDL-C, HDL-C, non-HDL-C, TG, apo A-1, and apo B); and
- Proportion of subjects requiring rescue and time from randomization to initiation of rescue therapy.

Safety assessments included evaluation of adverse events (AEs), vital signs, physical examinations, prior and concomitant medications, vitamin D levels, and laboratory parameters

(hematology, blood chemistry, and urinalysis).

Statistical Analysis Plan

Defined populations: The following datasets were defined:

- Randomized Set – all subjects who gave assent and obtained consent from a parent or a legal guardian and were assigned a randomization number; baseline and demographic characteristics were summarized using Randomized Set;
- Intent-to-Treat (ITT) Set – all randomized subjects who had taken at least one dose of randomized study drug, had a baseline HbA1c measurement, and had at least one post-Month 1 HbA1c measurement before rescue therapy; ITT Set was the population used for the primary efficacy analysis;
- Per-protocol (PP) Set – subjects who met the ITT definition as well as had overall study medication compliance of ≥70%, no major protocol violations, and completed the first 6 months of treatment without needing rescue therapy;
- Safety Set – all randomized subjects who had taken at least one dose of randomized study drug; safety was evaluated using Safety Set.

Same size calculation: A minimum sample size of 208 evaluable subjects (125 for the high dose group and 83 for the low dose group) was estimated to provide 80% power to detect 0.4% treatment difference between high dose and low dose Welchol for the change in HbA1c from baseline with a common SD of 1.0%, using a 2-sided significance level of 0.05. Since 6 to 10% of subjects were estimated to not have evaluable baseline or post-Month 1 HbA1c data, the sample size was calculated as 220 to 230 subjects.

Analysis methods:

The Applicant conducted the primary efficacy analysis by comparing the high dose (3.75 g/day) to low dose (0.625 g/day) Welchol oral suspension for change in HbA1c from baseline to Month 6 with last observation carried forward (LOCF) method using the ITT Set.

If a subject discontinued the treatment or received rescue before Month 6, the HbA1c value of the last observed post-Month 1 value before discontinuation or rescue was carried forward to impute the missing or dropout data. The post-Month 1 value was chosen because changes in HbA1c after 1 month of therapy were expected to be negligible, since it typically takes about 2-3 months to achieve a stable HbA1c level after initiating a new therapy.

The treatment difference was tested at a 2-sided significance level of 0.05, using an analysis of covariance (ANCOVA) model with treatment group and previous T2DM treatment stratum as fixed effects and baseline HbA1c as a covariate. P-value from between-treatment comparison

was shown. The least squares (LS) mean, corresponding standard error (SE), and 2-sided 95% confidence interval (CI) for each treatment and for treatment difference between high and low dose Welchol treatment groups were estimated.

Reviewer's comment: There were two main statistical issues with the primary efficacy analysis, as discussed in Dr. Wendy Tu's Statistical Review[7]. First, the ITT Set defined by the Applicant did not meet the ITT principle, as it should have included all randomized and treated patients regardless of the availability of post-baseline measurements. Second, we no longer use the LOCF method for handling missing data in placebo-controlled trial, and instead use multiple imputation based on retried dropouts for missing endpoints (or the washout method if there are not enough retrieved dropouts).

These issues were communicated with the Applicant, but since the statistical analysis plan was created and agreed on almost a decade ago, the FDA Statistical Reviewer, Dr. Wendy Tu, re-analyzed the primary efficacy analysis using appropriate ITT population with correct method for imputing missing data. Thus, Dr. Tu re-analyzed the primary efficacy data from all randomized and treated patients (i.e., equivalent to Applicant's Randomized Set) and used the ANCOVA method pre-specified in the study protocol with the washout method for missing data. I presented both the Applicant's analysis as well as Dr. Tu's analysis of primary efficacy data in Section 7.1.1.

The analyses of the continuous secondary efficacy variables were carried out using the same method as the primary efficacy variable. The between-treatment comparison for change in triglycerides was done using a non-parametric ANCOVA. The glycemic control rates were compared between treatments using Cochran-Mantel-Haenszel test adjusted for the previous T2DM treatment stratum.

No multiplicity adjustment was needed since the study only had one primary efficacy variable to be compared once at a 2-sided 5% level. There was no plan to control for the overall alpha for any secondary efficacy analyses.

Safety analyses were descriptive and presented in tabular format.

Protocol Amendments

There was one amendment to the original protocol which led to Protocol version 2.0, dated August 30, 2011, to implement changes that we advised in our advice letter dated May 9, 2011. The following notable changes were implemented in the Protocol version 2.0:

[7] Statistical Review by Wendy Tu; NDA 22362-S29, dated August 27, 2021.

- The primary analysis was changed from intra-group to between group comparison;
- The study design was amended for all subjects to maintain the same assigned blinded treatment until the end of study (i.e., 12 months) or until rescued: in the original protocol, subjects randomized to receive the low dose Welchol were to switch to receive the high dose Welchol after the initial 6 months of treatment:
    - To mitigate the increased hyperglycemia risk to subjects, changes were made to the rescue criteria;
    - Statistical analyses were revised to compare the high dose group to the low dose group for the change in HbA1c from baseline to Month 6, with LOCF;
- The inclusion criteria were modified to enroll subjects who had received either no oral anti-diabetic drug or less than 14 days of therapy for 3 months before screening as naïve or not currently treated.

Reviewer's comment: Two subjects who were randomized to receive the low dose Welchol completed Month 6 and were switched to receive the high dose Welchol before approval of Protocol version 2.0 and its informed consent, and these two subjects continued the high dose Welchol to the end of the study according to the original protocol. This did not impact the overall efficacy or safety results.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant affirms that the study was conducted in accordance with good clinical practice (GCP) and in accordance with the Declaration of Helsinki.

Financial Disclosure

The Applicant adequately disclosed financial interests of investigators. No investigators reported significant payment.

Overall, the investigator financial disclosures do not raise concerns about the data integrity since the study was blinded and the primary efficacy endpoint was an objective laboratory measurement (HbA1c).

Patient Disposition

Of 483 screened subjects, 226 subjects (47%) failed screening. The reasons for failing screening included the following:

- Did not satisfy inclusion/exclusion criteria (214 subjects [44%]):
    - HbA1c <7% (91 subjects [19%]);
    - ALT >2.5x ULN (69 subjects [14%]);

  - Other (35 subjects [7%]);
  - HbA1c >10% (29 subjects [6%]);
  - AST >2.5x ULN (29 subjects [6%]);
  - Positive autoimmune markers (24 subjects (5%]);
- Withdrawal by subject (6 subjects [1%]);
- Lost to follow-up (5 subjects [1%]);
- Physician decision (1 subject).

Of 257 subjects who entered the lead-in period, 236 subjects (92%) were randomized, and 21 subjects (8%) were not randomized. The reasons for not being randomized included: hyperglycemia meeting protocol-specific discontinuation criteria (9 subjects), withdrawal by subject (5 subjects), other (4 subjects), and adverse event (3 subjects).

A total of 236 subjects were randomized. Similar proportion of subjects in treatment groups completed 6 months of trial (~80%) but a slightly larger proportion of subjects received rescue therapy before 6 months in the Welchol low dose group (17.9%) compared to the Welchol high dose group (14.2%). Not surprisingly, a slightly large proportion of subjects in the low dose group (47.5%) compared to the high dose group (42.6%) received glycemic rescue during the trial. A slightly larger proportion of subjects in the Welchol low dose group completed the trial (75.8%) compared to the Welchol high dose group (70.2%). The most common reason for not completing the trial was due to being lost to follow-up or withdrawal by subject.

Reviewer's comment: There was no notable difference in subject disposition between treatment arms.

Of note, the Randomized Set is the same as the Safety Set in U307 trial. See Table 1 for a summary of subject disposition in U307 trial.

Table 1: Subject Disposition in U307 Trial

	Welchol High Dose N (%)	Welchol Low Dose N (%)	Total N (%)
Screened patients			483
Screen failures			226
Withdrew before randomization			21
Randomized Set[a]	**141 (100)**	**95 (100)**	**236 (100)**
Safety Set[b]	141	95	236
ITT Set[c]	132	88	220
Per-Protocol Set[d]	49	76	125
Completed 6 month	112 (79.4)	76 (80)	188 (79.7)
Received glycemic rescue therapy	60 (42.6)	45 (47.5)	105 (44.5)
Completed 6 months without rescue	40 (28.4)	28 (29.5)	68 (28.8)
Did not complete 6 months before rescue	20 (14.2)	17 (17.9)	37 (15.7)
Discontinued or rescued before 6 months	41 (29.1)	33 (34.7)	74 (31.4)
Completed the trial	99 (70.2)	72 (75.8)	171 (72.5)
Did not complete the trial	42 (29.8)	23 (24.2)	65 (27.5)
Adverse event	8 (5.7)	3 (3.2)	11 (4.7)
Lost to follow-up	11 (7.8)	6 (6.3)	17 (7.2)
Withdrawal by subject	10 (7.1)	7 (7.4)	17 (7.2)
Hyperglycemia	1 (0.7)	2 (2.1)	3 (1.3)
Other	12 (8.5)	5 (5.3)	17 (7.2)

N=number of subjects
[a]Randomized Set included all subjects who gave assent and obtained consent from a parent or a legal guardian and were assigned a randomization number.
[b]Safety Set included all randomized subjects who took at least one dose of randomized study drug.
[c]ITT Set as defined by the Applicant, subjects who took at least one dose of randomized study drug, had a baseline HbA1c measure, and had at least one post-Month 1 HbA1c measurement before any rescue therapy.
[d]Per-Protocol Set included all ITT Set subjects who had overall medication compliance ≥70%, had no major protocol violations, and completed the first 6-month treatment without needing rescue.
Source: Reviewer generated from CSR Tables 7-1, 7-2, and 7-3

Protocol Deviations

The Applicant summarized protocol deviations under categories as shown in Table 2 and provided listing of protocol deviation by subject level (Appendix Data Listing 16.2.2). Review of these deviations did not reveal any differences between treatment arms that would potentially invalidate the trial results.

The most frequent protocol deviations fell under study procedure and were similarly affected in both treatment groups (46.3% in the Welchol low dose group versus 46.1% in the Welchol high dose group). Most of these were related to subjects failing to report FPG >240 mg/dL to the site, did not record FPG for >4 weeks, or did not bring their home glucometer to study visits.

Protocol deviations related to compliance with the investigational product occurred slightly more in the Welchol high dose group (44.7%) compared to the Welchol low dose group (35.8%). Protocol deviations related to this included not taking the study drug for 5 or more consecutive days between study visits, or not returning the study drug to the site.

Table 2: Summary of Protocol Deviations - Randomized Set

Category	Welchol low-dose n (%)	Welchol high-dose n (%)	Total n (%)
N	95	141	236
Study procedures	44 (46.3)	65 (46.1)	109 (46.2)
Investigational product compliance	34 (35.8)	63 (44.7)	97 (41.1)
Laboratory assessments	10 (10.5)	17 (12.1)	27 (11.4)
Concomitant medication	11 (11.6)	15 (10.6)	26 (11.0)
Visit schedule	13 (13.7)	12 (8.5)	25 (10.6)
Informed consent process	7 (7.4)	14 (9.9)	21 (8.9)
Visit window	3 (3.2)	13 (9.2)	16 (6.8)
Eligibility criteria	2 (2.1)	5 (3.5)	7 (3.0)
Safety/SAEs	1 (1.1)	1 (0.7)	2 (0.8)
Inclusion/exclusion	0	1 (0.7)	1 (0.4)

Source: CSR, Table 7-13

As the Applicant noted, the Coronavirus Disease 2019 (COVID-19) pandemic impacted clinical trials worldwide due to quarantine, site closures, travel limitations, and/or other interruptions in study-related procedures. Due to COVID-19 pandemic, 7 study visits for 5 subjects were conducted virtually, by phone, or outside the recommended window. It is unlikely that this small number of deviations from the protocol would have an impact on the result of the trial.

Reviewer's comment: Review of protocol deviations did not raise concerns about the data quality or integrity of the trial.

Demographics and Baseline Characteristics

The demographic and baseline characteristics for all randomized subjects in U307 trial are summarized in Table 3. The mean age of trial population was ~14 years, and the proportion of pediatric subjects in 10-13 years of age group (~36%) and 14-17 years of age group (~64%) were not notably different between treatment groups. The majority of subjects were females (77%), either White (~50%) or African American (~37%) in race, and about 44% of subjects were Hispanic or Latino in ethnicity. At baseline, the majority of subjects reached Tanner stage 4 (23%) or Tanner stage 5 (63%). The mean BMI was 34.91 kg/m^2, the mean BMI z-score was about 2.2 with about 72% of subjects having BMI z-score of ≥2, indicating that on average, enrolled subjects were overweight. The mean weight was slightly higher in the lower dose group (98.6 kg) compared to the high dose group (92.3 kg).

The mean duration of type 2 diabetes was about 14 months and similar between treatment groups, with about 53% of subjects having had T2DM diagnosis for <9 months. Approximately 34% of subjects were treatment naïve while 66% of enrolled subjects were receiving metformin monotherapy.

It should be noted that the mean HbA1c at screening (8.15%) decreased to a mean of 7.78% at randomization (i.e., baseline). At baseline/randomization, the mean HbA1c value was slightly higher in subjects randomized to the low dose Welchol (7.87%) compared to subjects randomized to the high dose Welchol (7.72%), and a slightly larger proportion of subjects randomized to Welchol high dose had HbA1c <7% compared to subjects randomized to Welchol low dose (24.8% versus 13.7%), which is outside of the range specified in the study inclusion criterion[8]. Discussion regarding the HbA1c reduction from screening to baseline is further discussed in the Efficacy Results – Primary Endpoint section below.

Reviewer's comment: Overall, the baseline characteristics were generally comparable between two treatment arms. The small difference in the mean HbA1c value between treatment arms at baseline should not impact the overall results, as the primary efficacy analysis statistical model adjusted for baseline HbA1c value.

[8] All subjects at screening had HbA1c between 7 and 10%, inclusive, per study inclusion criterion.

Table 3: Demographic and Baseline Characteristics in U307 Trial – Randomized Set

Characteristics	Welchol Low Dose (N=95)	Welchol High Dose (N=141)	Total (N=236)
Sex, n (%)			
Male	28 (29.5)	27 (19.1)	55 (23.3)
Female	67 (70.5)	114 (80.9)	181 (76.7)
Age, years			
Mean years (SD)	14.2 (2.02)	14.1 (2.09)	14.2 (2.06)
Median (years)	15.0	14.0	15.0
Age Group, n (%)			
10-13 years	33 (34.7)	51 (36.2)	84 (35.6)
14-17 years	62 (65.3)	90 (63.8)	12 (64.4)
Race, n (%)			
White	46 (48.4)	71 (50.4)	117 (49.6)
Black or African American	38 (40.0)	49 (34.8)	87 (36.9)
Asian	3 (3.2)	4 (2.8)	7 (3.0)
American Indian or Alaska Native	1 (1.1)	0	0
Native Hawaiian or Other Pacific Islander	1 (1.1)	0	0
Other	1 (1.1)	2 (1.4)	3 (1.3)
Ethnicity, n (%)			
Hispanic or Latino	39 (41.1)	65 (46.1)	104 (44.1)
Not Hispanic or Latino	56 (58.9)	76 (53.9)	132 (55.9)
Previous anti-diabetic therapy, n (%)			
Treatment naïve	32 (33.7)	48 (34.0)	80 (33.9)
On metformin monotherapy	63 (66.3)	93 (66.0)	156 (66.1)
Duration of T2D diagnosis, months			
Mean (SD)	14.38 (16.4)	14.16 (17.4)	14.25 (17.0)
Median (min, max)	8.87 (1.1, 85.7)	5.68 (1.0, 96.8)	7.46 (1.0, 96.8)
Tanner stage, n (%)			
I	3 (3.2)	3 (2.1)	6 (2.5)
II	1 (1.1)	2 (1.4)	3 (1.3)
III	6 (6.3)	16 (11.3)	22 (9.3)
IV	24 (25.3)	31 (22.0)	55 (23.3)
V	60 (63.2)	89 (63.1)	149 (63.1)
Height, cm			
Mean (SD)	165.7 (8.83)	163.6 (9.17)	164.4 (9.08)
Median (min, max)	165.0 (145, 190)	163 (141, 186)	164.0 (141, 190)
Weight, kg			
Mean (SD)	98.59 (26.24)	92.89 (23.11)	95.19 (24.52)
Median (min, max)	94.60 (54.9, 199.3)	91.00 (33.8, 165.6)	92.35 (33.8, 199.3)

BMI, kg/m^2			
Mean (SD)	35.65 (7.95)	34.41 (6.91)	34.91 (7.36)
Median (min, max)	34.26 (22.3, 69.8)	33.48 (15.2, 55.3)	33.74 (15.2, 69.8)
BMI category, n (%)			
<30 kg/m^2	25 (26.3)	34.41 (6.91)	34.91 (7.36)
≥30 kg/m^2	34.26 (22.3, 69.8)	33.48 (15.2, 55.3)	33.74 (15.2, 69.8)
BMI z-score*			
Mean (SD)	2.22 (0.45)	2.14 (0.54)	2.17 (0.50)
Median (min, max)	2.26 (0.54, 3.04)	2.20 (-1.51, 3.05)	2.22 (-1.51, 3.05)
BMI z-score category, n (%)			
<2	25 (26.3)	41 (29.1)	66 (28.0)
≥2	70 (73.7)	100 (70.9)	170 (72.0)
HbA1c at screening, %			
Mean (SD)	8.18 (0.83)	8.14 (0.82)	8.15 (0.82)
Median (min, max)	8.10 (7.0, 10.0)	7.90 (7.0, 10.0)	8.00 (7.0, 10.0)
HbA1c category at screening, n %			
<8.5%	60 (63.2)	92 (65.2)	152 (64.4)
≥8.5%	35 (36.8)	48 (34.0)	83 (35.2)
HbA1c at randomization, %			
Mean (SD)	7.87 (0.93)	7.72 (0.92)	7.78 (0.93)
Median (min, max)	7.80 (6.3, 12.2)	7.60 (6.1, 10.2)	7.70 (6.1, 12.2)
HbA1c category at randomization, n %			
<7%	13 (13.7)	35 (24.8)	48 (20.3)
<8.5%	74 (77.9)	110 (78.0)	184 (78.0)
≥8.5%	21 (22.1)	31 (22.0)	52 (22.0)
Fasting plasma glucose, mg/dL			
Mean (SD)	151.4 (55.98)	143.5 (41.57)	146.7 (47.94)
Median (min, max)	136.0 (88, 411)	138.0 (73, 311)	137.5 (73, 411)
LDL-C, mg/dL			
Mean (SD)	95.7 (25.68)	101.2 (29.33)	99.0 (27.98)
Median (min, max)	97.0 (22, 169)	98.5 (37, 185)	97.8 (22, 185)
Non-HDL-C, mg/dL			
Mean (SD)	123.1 (32.11)	129.3 (34.57)	126.8 (33.67)
Median (min, max)	124.5 (29, 196)	126.0 (51, 221)	125.8 (29, 221)
TG, mg/dL			
Mean (SD)	138.6 (73.30)	143.8 (83.47)	141.7 (79.41)
Median (min, max)	123.5 (31, 392)	123.0 (31, 548)	123.3 (31, 548)
Total cholesterol, mg/dL			
Mean (SD)	163.9 (32.55)	170.4 (34.44)	167.8 (33.77)
Median (min, max)	166.0 (61, 239)	167.5 (94, 266)	166.3 (61, 266)
HDL-C, mg/dL			
Mean (SD)	40.8 (9.87)	41.1 (9.20)	41.0 (9.46)
Median (min, max)	39.5 (20, 77)	40.5 (23, 78)	40.5 (20, 78)

Apo A-1, mg/dL			
Mean (SD)	127.6 (19.96)	129.6 (16.39)	128.8 (17.90)
Median (min, max)	125.5 (71, 188)	128.0 (92, 178)	127.5 (71, 188)
Apo B, mg/dL			
Mean (SD)	84.8 (21.67)	88.1 (22.16)	86.8 (21.97)
Median (min, max)	87.0 (23, 138)	87.5 (37, 157)	87.3 (23, 157)
Systolic blood pressure, mmHg			
Mean (SD)	120.9 (10.46)	119.3 (11.15)	119.9 (10.89)
Median (min, max)	120.0 (81, 145)	119.0 (92, 150)	119.5 (81, 150)
Diastolic blood pressure, mmHg			
Mean (SD)	69.8 (9.05)	69.1 (9.28)	69.4 (9.17)
Median (min, max)	69.0 (47, 92)	69.0 (44, 94)	69.0 (44, 94)

Apo A-1=apolipoprotein A-1; apo B=apolipoprotein B; BMI=body mass index; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; TG=triglycerides; SD=standard deviation; T2D=type 2 diabetes; BMI=body mass index.
*BMI z-score was calculated using BMI=M x $(1 + LSz)^{1/L}$, where z is the corresponding BMI z-score, and parameters M, L, and S are from CDC website for each sex and month of age.
Source: CSR, modified from Tables 7-4 and 7-5

Treatment Adherence, Concomitant Medications, and Rescue Medication Use

Treatment Adherence

Adherence to the study drug during treatment period was evaluated by counting unused packets at each study visit. The mean percent adherence with the study drug was calculated as 100 x (total number of packets taken/total presumed number of packets taken). The mean percent adherence was 82.23% for the low dose group and 75.57% for the high dose group. About 72.6% of subjects in the low dose group and 68.8% of subjects in the high dose group had ≥70% treatment adherence.

The number of percentage of subjects with study drug interruptions during treatment period was also evaluated. About 30.5% of subjects in the overall study population had study drug interruptions, and the percentage of subjects with drug interruptions were similar in both treatment groups (28.4% [27 subjects] in the low dose versus 31.9% [45 subjects] in the high dose group). The mean duration of drug interruptions was slightly longer in the low dose group (~50 days) compared to the high dose group (~41 days). Four subjects (4.2%) in the low dose group and 7 subjects (5%) in the high dose group interrupted study drug due to an adverse event.

Reviewer's comment: For unclear reason(s), subjects receiving the high dose Welchol oral suspension seemed to have adhered to the study treatment slightly less than subjects receiving the low dose, but it is unlikely that this small difference had a significant impact on the overall study results.

Concomitant Medications

During the treatment period of the trial, the most commonly reported concomitant medication that subjects received were metformin (84% in the low dose versus 89% in the high dose group), vitamin D and analogues (88% in the low dose versus 89% in the high dose group), and insulin glargine (28% in the low dose versus 23% in the high dose group).

A slightly larger percentage of subjects in the low dose group (25.3% [24 subjects]) compared to the high dose group (17.7% [25 subjects]) started metformin within 8 weeks before screening. During the period between screening and randomization, more subjects in the high dose group (9.9% [14 subjects]) compared to the low dose group (5.3% [5 subjects]) started metformin (see Table 4).

During the treatment period of the trial, a similar proportion of subjects in both treatment groups (86.3% [82 subjects] in the low dose group and 90.1% [127 subjects] in the high dose group) started at least one anti-diabetic drug. Consistent with glycemic rescue specified in the protocol, the most common anti-diabetic drug was metformin, as 84.2% (80 subjects) in the low dose and 89.4% (126 subjects) in the high dose group were taking metformin.

Approximately 34.7% (33 subjects) in the low dose and 26.2% (37 subjects) in the high dose group were taking insulin and insulin analogues, mostly long-acting insulins and analogues for injection and most commonly insulin glargine (28.4% [27 subjects] in the low dose and 22.7% [32 subjects] in the high dose group). The majority of these insulins and analogues were initiated as rescue therapy (33% [31 subjects] in low dose and 22% [31 subjects] in the high dose).

A summary of subjects taking concomitant anti-diabetic medications is provided in Table 4.

Table 4: Summary of Subjects (N [%]) with Anti-Diabetic Concomitant Medication – Safety Set

	Welchol low dose (N=95)	Welchol high dose (N=141)	Total (N=236)
Subjects initiating metformin within 8 weeks before Screening Visit	**24 (25.3)**	**25 (17.7)**	**49 (20.8)**
Subjects initiating metformin between screening visit and first dose of study drug at randomization	**5 (5.3)**	**14 (9.9)**	**19 (8.1)**
Subjects taking at least one anti-diabetic drug during treatment period	**82 (86.3)**	**127 (90.1)**	**209 (88.6)**
Metformin	**80 (84.2)**	**126 (89.4)**	**206 (87.3)**
Insulin and analogues	**33 (34.7)**	**37 (26.2)**	**70 (29.7)**
Long-acting insulins and analogues	32 (33.7)	35 (24.8)	67 (28.4)
Insulin glargine	27 (28.4)	32 (22.7)	59 (25.0)
Insulin detemir	3 (3.2)	3 (2.1)	6 (2.5)
Insulin and analogues, long-acting	3 (3.2)	1 (0.7)	4 (1.7)
Fast-acting insulins and analogues	9 (9.5)	9 (6.4)	18 (7.6)

Note: Although a subject may have taken 2 or more medications, the subject was counted only once within a category. The same subject may appear in different categories.
Source: CSR, modified from Tables 7-9, 7-10, 7-11, and 7-12

Rescue Therapy

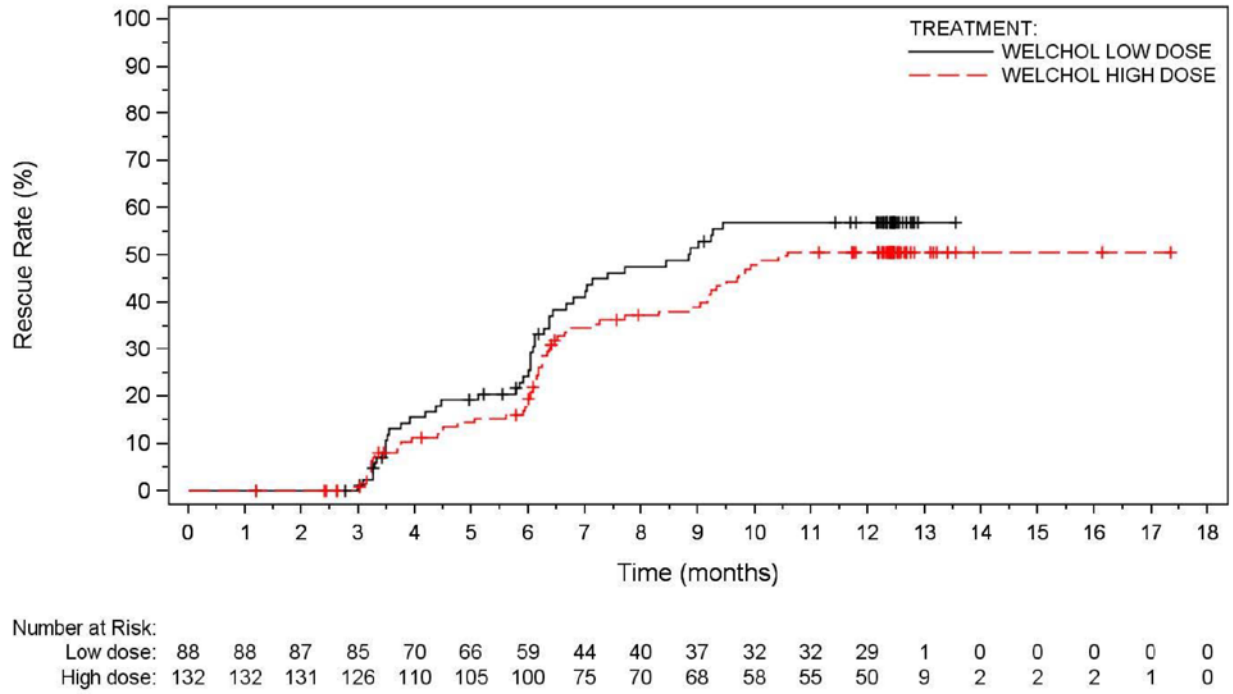
Subjects receiving glycemic rescue therapy are summarized in Table 5. A larger proportion of subjects in the low dose group required a glycemic rescue therapy during the trial compared to the high dose group (51.1% versus 45.5%), and a larger proportion of subjects in the low dose group initiated insulin compared to the high dose group (25% versus 16.2%). The mean time to rescue therapy was slightly shorter in the low dose group (5.8 months) compared to the high dose group (6.3 months). A Kaplan-Meier plot of time to rescue is shown in Figure 2, where the curves appear to separate between treatment groups at ~3.5 months.

Table 5: Subjects Receiving Glycemic Rescue Therapy – ITT Set

	Welchol low dose (N=95)	Welchol high dose (N=141)	Total (N=236)
Subjects who took rescue, N (%)	**45 (51.1)**	**60 (45.5)**	**105 (47.7)**
Subjects who initially met rescue criteria, N (%)			
Month 3 to <6	19 (21.6)	25 (18.9)	44 (20.0)
Month 6 to <9	29 (33.0)	41 (31.1)	70 (31.8)
Month 9 to <12	6 (6.8)	9 (6.8)	15 (6.8)
Month 12 and later	4 (4.5)	9 (6.8)	13 (5.9)
Time to rescue, months			
Mean (SD)	5.8 (1.96)	6.3 (2.27)	6.1 (2.15)
Median (min, max)	6.0 (3, 9)	6.2 (3, 11)	6.1 (3, 11)
Subjects up-titrating metformin dose, N (%)	13 (14.8)	19 (14.4)	32 (14.5)
Subjects initiating metformin, N (%)	24 (27.3)	39 (29.5)	63 (28.6)
Subjects initiating insulin, N (%)	22 (25.0)	22 (16.7)	44 (20.0)

Source: CSR, Table 8-20

Figure 2: Kaplan-Meier Time to Rescue (Months) – ITT Set



Source: CSR, Figure 8-14

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the change in HbA1c from baseline to 6 months.

Dr. Wendy Tu reviewed the primary efficacy data in detail[9]. As discussed in her review and discussed above in Section 6.1.1 under the Statistical Analysis Plan, there were two Statistical issues with the Applicant's primary efficacy analysis:

1. The ITT set defined by the Applicant that was used as the basis for the primary efficacy analysis was not in accordance with the division's guidance. Instead of defining an ITT set that should include all randomized and treated patients regardless of the availability of post-baseline measurements, the Applicant defined the ITT set as "all randomized subjects who have taken at least 1 dose of randomized study medication, have a baseline HbA1c measurement, and have at least 1 post-baseline HbA1c measurement prior to any rescue therapy". The Applicant's definition of ITT violates the ITT principle, as having an on-treatment HbA1c measurement after randomization may be related to the treatment.

2. The Applicant's handling of missing data was not in accordance with the division's guidance. We recommend multiple imputation based on retrieved dropouts (or the washout method if there's insufficient retrieved dropouts) for handling missing endpoint data for a placebo-controlled trials, but the Applicant imputed missing endpoint data using a single imputation method based on the LOCF method.

As a result, Dr. Tu re-analyzed the primary efficacy data using the appropriate ITT set (i.e., all randomized and treated subjects), utilizing the ANCOVA model that was pre-specified in the protocol (i.e., adjusted for terms for treatment, previous T2DM treatment, and baseline HbA1c). Dr. Tu used the washout method for multiple imputation of the missing endpoint data and Rubin's Rule for multiple imputation. Her analysis is summarized in Table 6, and the high dose Welchol group is noted as 'active' arm and the low dose Welchol group is noted as 'placebo' arm.

At baseline, the HbA1c value was numerically higher for the placebo arm compared to the active arm (7.87% versus 7.72% in Dr. Tu's ITT set). Both treatment groups showed an increase in HbA1c from baseline to Month 6, as shown in Table 6. In Dr. Tu's analysis, after 6 months of treatment, the adjusted mean changes from baseline in HbA1c in patients treated with active Welchol (N=141) was 0.07% compared to 0.19% in patients treated with placebo (N=95). The adjusted mean difference between active versus placebo was -0.12% and a 95% confidence interval (CI) of (-0.55, 0.30%) with p-value of 0.56. Since the 95% CI included 0, treatment with Welchol was not superior to placebo.

[9] Statistical Review by Wendy Tu; NDA 22362-S29, dated August 27, 2021.

Table 6 also shows the Applicant's primary efficacy analysis. Although there are small differences between Dr. Tu's and the Applicant's analysis due to different method as discussed above, the findings from two analyses are similar, and the Applicant's analysis also did not demonstrate superiority after 6 months of treatment with Welchol compared to placebo.

Table 6: Primary Efficacy Analysis of the Change in HbA1c (%) from Baseline at Month 6 – Dr. Tu and Applicant's Results

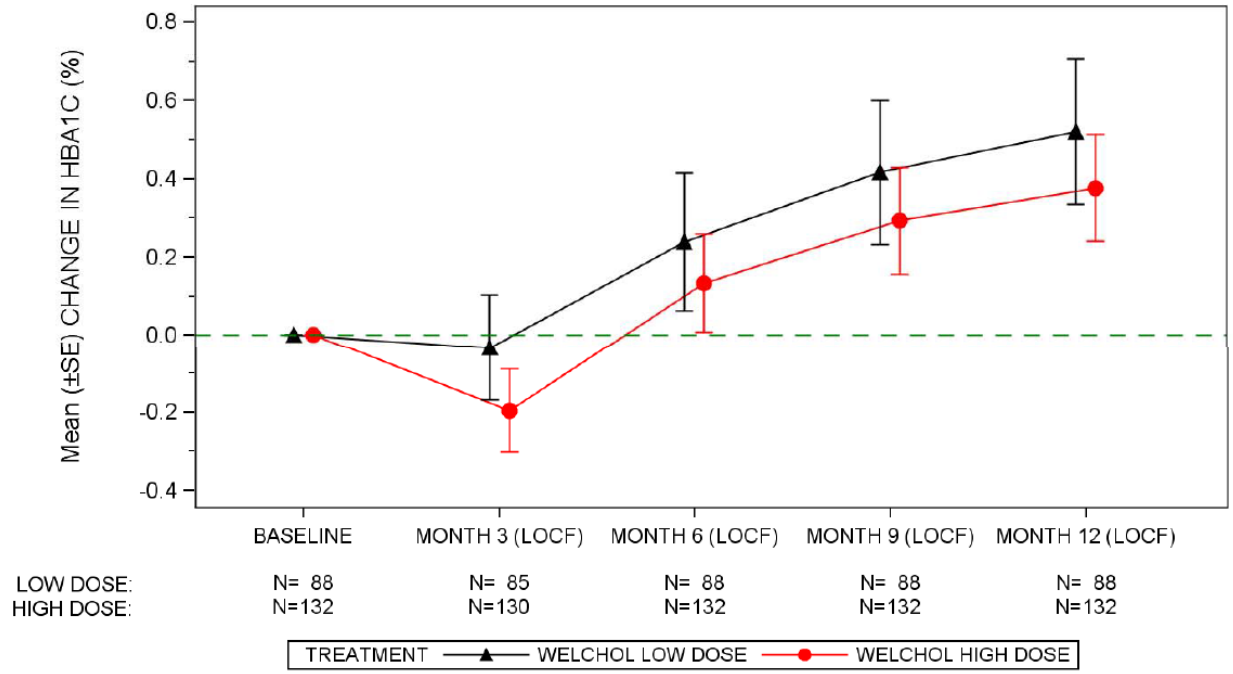
Arm	N	Baseline Mean (SD)	Change from Baseline LS Mean (SE)	Treatment Difference		
				LS Mean (SE)	95% CI	P-Value
Placebo	95	7.87 (0.932)	0.19 (0.166)	-0.12 (0.216)	(-0.55, 0.30)	0.56
Active	141	7.72 (0.920)	0.07 (0.135)			
The Applicant's Result						
Placebo	88	7.83 (0.831)	0.21 (0.166)	-0.13 (0.210)	(-0.54, 0.29)	0.55
Active	132	7.74 (0.819)	0.09 (0.137)			

Analyzed using the ANCOVA model which included treatment, previous type 2 diabetes treatment, and baseline HbA1c.
SD=standard deviation; SE=standard error; CI=confidence interval
Source: Wendy Tu's Statistical Review, Table 4

Dr. Tu noted that the study was underpowered. The Applicant calculated the sample size to have an 80% power to detect 0.4% treatment difference in HbA1c with a width of 0.56% for a 95% CI. However, the observed width of the 95% CI was wider (0.85%), and based on Dr. Tu's analysis, she estimated that the trial should have recruited about 2.3 times of current trial sample size to achieve an 80% power to detect treatment difference of 0.4%. Nevertheless, although the 95% CI is wide, it is unclear that having a larger sample size would have led to a larger treatment effect than what was observed in this trial (i.e., -0.12%). Trials with a larger sample size may have sufficient power to show a statistical significance, but the treatment effect may still not show clinically meaningful difference.

Figure 3 shows the mean change in HbA1c from baseline over time in the Applicant's ITT Set using the LOCF method for missing data. There was an initial mean decrease in HbA1c from baseline to Month 3 in the active Welchol arm (high dose), and then the HbA1c level reverted to baseline value by Month 6 and continued to increase during the remaining follow-up period.

Figure 3: Plot of mean (±SE) change in HbA1c (%) from baseline over time with LOCF method for missing data – Applicant's ITT Set



Source: CSR, Figure 15.2.2.1a

It should be noted that at Month 6, there was a large loss of primary endpoint data; about one-third of subjects in both treatment groups had missing HbA1c values, and two-thirds of HbA1c values were missing by Month 12 (Table 7).

Table 7: Number (%) of Subjects with Missing HbA1c Values by Visit – Applicant's ITT Set

Visit	Welchol low dose (N=88)	Welchol high dose (N=132)
Month 3	5 (5.7)	10 (7.6)
Month 6	26 (29.5)	39 (29.5)
Month 9	50 (56.8)	67 (50.8)
Month 12	56 (63.6)	80 (60.6)

Source: CSR, Table 8-4

Subgroup Analyses:

Dr. Tu performed subgroup analyses for the primary endpoint using the same ANCOVA model with missing data multiply imputed based on the washout method. The results of the subgroup analyses are shown in Table 8. Subgroup analyses were not significant, and Dr. Tu concludes that "the treatment arm was generally found to perform better than the control arm across all

subgroups in terms of glycemic control (except for the ">13 years old" group)".

Table 8: Subgroup Analyses- Change in HbA1c from Baseline to Month 6

Subgroup	Treatment	Baseline		Change from Baseline at Month 6	
		N	Mean (SD)	LS Mean (SE)	Difference in LS Mean (95% CI)
Sex	**Male**				
	High Dose	27	7.48 (0.91)	-0.19 (0.33)	-0.08 (-0.97, 0.82)
	Low Dose	28	7.66 (0.79)	-0.11 (0.32)	
	Female				
	High Dose	114	7.78 (0.92)	0.12 (0.15)	-0.14 (-0.16, 0.33)
	Low Dose	67	7.94 (0.98)	0.26 (0.19)	
Race	**White**				
	High Dose	71	7.69 (0.86)	0.18 (0.20)	-0.08 (-0.69, 0.53)
	Low Dose	46	7.67 (0.79)	0.26 (0.23)	
	Other				
	High Dose	70	7.76 (0.98)	-0.03 (0.18)	-0.05 (-0.62, 0.52)
	Low Dose	49	8.05 (1.02)	0.03 (0.22)	
Age	**≤13 years**				
	High Dose	51	7.57 (0.79)	0.13 (0.20)	-0.49 (-1.11, 0.14)
	Low Dose	33	7.81 (0.81)	0.62 (0.25)	
	>13 years				
	High Dose	90	7.81 (0.98)	0.01 (0.18)	0.08 (-0.48, 0.64)
	Low Dose	62	7.90 (1.00)	-0.07 (0.22)	

Source: Dr. Tu's Statistical Review, Table 5

Change in HbA1c from Screening to Randomization/Baseline:

In both treatment groups, there was a numerical decrease in HbA1c from screening to randomization/baseline, which included 2 weeks of lead-in/stabilization period where all subjects received a daily low dose Welchol oral suspension before randomization. The mean decrease in HbA1c was -0.43% in the high dose group compared to -0.35% in the low dose group, as shown in Table 9.

It is unclear whether this reduction in HbA1c in enrolled subjects during the early part of trial (~4 weeks from screening to randomization) is due in part to diet and exercise counseling that all subjects received after screening. It is unlikely that treatment with subtherapeutic low dose of Welchol (0.625 g/day) that all subjects received during 2 weeks of lead-in period before randomization had much glycemic effect.

However, it is possible that this HbA1c reduction may be attributed to the initiation of anti-diabetic drug before screening/randomization. As discussed above, about 21% of subjects

(n=49) initiated metformin within 8 weeks prior to the screening visit, and an additional 8% of subjects (n=19) initiated metformin between screening and randomization (Table 4). Metformin therapy generally takes 8-12 weeks to maximize its glycemic effect.

Table 9: Change in HbA1c From Screening to Baseline – Applicant's Intent-to-Treat Set

	Welchol low dose	Welchol high dose
N*	87	130
Screening, %		
Mean (SD)	8.18 (0.83)	8.16 (0.82)
Randomization/Baseline, %		
Mean (SD)	7.83 (0.83)	7.73 (0.94)
Mean change from Screening to Baseline, %	-0.35	-0.43

*N is the number of subjects with HbA1c values at both screening and baseline.
SD=standard deviation
Source: CSR, Table 8-1

Data Quality and Integrity

There were no potential issues concerning the submitted data quality or integrity identified during the review of the efficacy results. Dr. Tu, the Statistical Reviewer, also did not identify any issues with data quality.

Efficacy Results – Secondary and other relevant endpoints

Secondary glycemic endpoints that are relevant to the primary endpoint (such as change in HbA1c over 12 months, proportion of subjects requiring rescue) have already been discussed under Efficacy Results – Primary Endpoint section above. Other secondary glycemic endpoints (such as change in FPG, percentage of subjects achieving glycemic response) will not be discussed further as there were no notable findings in these secondary endpoints, which was not surprising given that treatment with Welchol did not demonstrate glycemic effect. This section will only briefly summarize changes in plasma lipids and triglycerides in U307 trial.

As shown in Table 10, active treatment with Welchol led to small numerical decreases in percent change in lipid parameters from baseline to 6 months. The mean total cholesterol reduction was 2.2%, the mean LDL-C reduction was 5.5%, and the mean non-HDL-C reduction was 2.9% in the Welchol arm compared to the placebo.

An increase in the percent median triglycerides (TG) occurred in both treatment groups from baseline to 6 months, and a 6% median increase in TG was observed in the Welchol arm compared to the placebo (Table 10). Six subjects (4.3%) in the Welchol group compared to 4 subjects (4.2%) in the placebo group reported triglycerides >500 mg/dL.

Table 10: Percent Change in Lipid Parameters and Triglycerides (mg/dL) from Baseline to Month 6 with LOCF – Applicant's ITT Set

Treatment Arm*	N[a]	Baseline[b] Mean (SE)	% Change From Baseline[c], LS Mean (SE)	Treatment Difference[d]		
				LS Mean (SE)	95% CI	P-Value
TC						
Placebo	77	160.4 (3.81)	3.2 (1.49)	-2.2 (1.88)	(-5.9, 1.6)	0.2526
Welchol	117	170.2 (3.23)	1.0 (1.20)			
LDL-C						
Placebo	76	93.0 (2.94)	4.4 (2.23)	-5.5 (2.82)	(-11.1, 0)	0.0513
Welchol	115	101.9 (2.80)	-1.1 (1.80)			
HDL-C						
Placebo	77	40.2 (1.16)	2.3 (1.73)	-0.3 (2.17)	(-4.6, 3.9)	0.8777
Welchol	117	40.9 (0.79)	1.9 (1.39)			
Non-HDL-C						
Placebo	77	120.2 (3.72)	4.1 (1.90)	-2.9 (2.39)	(-7.7, 1.8)	0.2209
Welchol	117	129.3 (3.16)	1.2 (1.53)			
Apo A-1						
Placebo	77	126.0 (2.27)	3.1 (1.34)	-0.7 (1.68)	(-4.1, 2.6)	0.6594
Welchol	117	129.2 (1.46)	2.3 (1.07)			
Apo B						
Placebo	77	83.3 (2.54)	2.7 (1.75)	-2.0 (2.20)	(-6.3, 2.4)	0.3749
Welchol	117	88.1 (2.04)	0.8 (1.41)			
Triglycerides		**Baseline[b] Median (IQR)**	**% Change From Baseline[c], Median (IQR)**	**Treatment Difference[d]**		
				Median (IQR)	**95% CI**	**P-value**
Placebo	77	119.0 (75.70)	6.4 (40.66)	6.0 (74.58)	(-5.7, 16.9)	0.2693
Welchol	117	119.5 (88.50)	10.0 (38.77)			

*Placebo arm received Welchol 0.625 g/daily and Welchol arm received 3.75 g/daily.
[a]N is the number of subjects with values at both baseline and during the treatment period.
[b]Baseline was defined as the average of the screening and Day 1 measurements; if one was missing, the available one was used; baseline mean and endpoint mean are arithmetic means.
[c]LS mean, SE, 95% CI and p-value are from a mixed effect ANCOVA model with treatment and previous T2DM treatment stratum as fixed effects and baseline as a covariate.
[d]Treatment difference was high dose versus low dose.
SE=standard error; LS=least squares; CI=confidence interval; TC=total cholesterol; LDL-C=low density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; apo=apolipoprotein; IQR=interquartile range
Source: CSR, Tables 8-16, 8-17

Reviewer's comment: Welchol is approved for the treatment of lipidemia in adults and pediatric patients, so it is not unexpected to see percent reductions in lipid parameters such as LDL-C and TC. There was an increase in the percent median triglycerides with Welchol compared to the placebo arm; increased triglycerides are already a known effect of Welchol that is labeled.

Dose/Dose Response

There is only one recommended dosage of Welchol (3.75 grams daily), and the low dose of Welchol (0.625 grams daily) is considered to be subtherapeutic dose and not expected to have much glycemic effect.

Durability of Response

As shown in Figure 3, the initial glycemic lowering effect with active Welchol treatment seen at around 3 months did not persist during the remaining follow-up time period. It should also be noted that a large proportion of HbA1c values were missing by 6 months of the trial (Table 7).

Persistence of Effect

The effect of Welchol over time after treatment discontinuation was not assessed in this trial. Treatment discontinuation occurred at 12 months after randomization, there was a follow up visit two weeks later, but there was no scheduled assessment for HbA1c at this follow-up visit.

Additional Analyses Conducted on the Individual Trial

None.

7. Integrated Review of Effectiveness

Since there was only one trial submitted for review, subsections were not applicable and have been deleted.

7.1. Integrated Assessment of Effectiveness

Trial U307 was a randomized, double-blind, two-group parallel trial in pediatric subjects with T2DM with suboptimal glycemic control with or without metformin. A low dose of Welchol (0.625 g daily) was used as a placebo arm for comparison against the active Welchol arm with the recommended dose of 3.75 g daily.

The primary efficacy analysis conducted by the FDA Statistical Reviewer, Dr. Wendy Tu, showed

that after 6 months, the HbA1c change from baseline was 0.07% for the active Welchol arm (N=141) and 0.19% for placebo (N=95). The estimated treatment difference in HbA1c reduction from baseline for Welchol compared to placebo was -0.12%, which was not clinically meaningful and not statistically significant with a 95% CI of -0.55 to 0.30 (p-value of 0.56).

A large proportion of subjects in both treatment arms required glycemic rescue therapy during the trial, 51.5% in the placebo arm and 45.5% in the active Welchol arm, with the mean time to rescue at about 6 months. In addition, there was a large loss of primary endpoint data; about one-third of subjects in both treatment groups had missing HbA1c values by 6 months. The trial also may have been underpowered to show statistical significance, as discussed in Section 6.1.2 above, although it is unlikely that a larger trial would have led to a larger treatment effect with Welchol.

In conclusion, trial U307 failed to demonstrate the effectiveness of Welchol to improve glycemic control after 6 months of treatment in children with T2DM.

8. Review of Safety

8.1. Safety Review Approach

Safety Set was used for review of safety, and safety data from the entire 12 months of trial period were reviewed.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The mean exposure to the study drug was slightly lower in the active Welchol arm (9.09 months) compared to the placebo arm (9.83 months). See Table 11.

Table 11: Exposure to Study Drug – Safety Set

	Welchol low dose (N=95)	Welchol high dose (N=141)
Mean exposure (SD), months	9.83 (3.83)	9.09 (4.14)
Exposure category, n (%)		
At least 3 months	85 (89.5)	120 (85.1)
At least 6 months	77 (81.1)	109 (77.3)
At least 9 months	74 (77.9)	97 (68.8)
At least 12 months	12 (12.6)	22 (15.6)

Source: CSR, Table 15.1.5.1

8.2.2. Relevant characteristics of the safety population:

Demographic and baseline characteristics of the trial population have been previously discussed in Section 6.1.2 (Table 3).

8.2.3. Adequacy of the safety database:

Overall, the database was adequate for safety assessments.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

I did not identify critical data qualify issues that had a large impact on the safety review. The submission was organized, and information was not difficulty to find.

8.3.2. Categorization of Adverse Events

All AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 13.1.

AEs were defined as any untoward medical occurrence in a subject administered a product that does not necessarily have a causal relationship to treatment and includes a clinical worsening of a concomitant illness and a laboratory abnormality. The intensity of AEs was assessed as mild, moderate, or severe[10].

An SAE was defined as any untoward medical occurrence that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, was a congenital anomaly/birth defect, or was an important medical event based on medical and scientific judgment.

A procedure was not considered an AE or SAE, but the reason for the procedure might have been an AE. Pre-planned (before informed consent) surgeries or hospitalizations for pre-existing conditions which did not worsen in severity were not SAEs.

Although pregnancy was not technically an AE, all pregnancies were to be reported and followed to conclusion to determine the outcome. If the outcome of the pregnancy met the SAE criteria, it was reported as an SAE.

Treatment emergent AEs (TEAEs) were defined as AEs that had an onset date on or after the first day of exposure to randomized treatment.

[10] Mild - awareness of sign or symptom but easily tolerated; moderate - discomfort enough to cause interference with usual activity; and severe - incapacitating with inability to work or do usual activity.

Reviewer's comment: Overall, the definitions used to categorize AEs were appropriate.

8.3.3. Routine Clinical Tests

Standard blood (hematology, chemistry) and urine tests to assess safety variables were done. Clinical safety assessments included C-peptide at screening as well as vitamin D at screening and at Month 12.

8.4. Safety Results

8.4.1. Deaths

No deaths were reported in subjects during the trial.

One subject became pregnant during the trial and delivered a non-viable male infant after premature labor; this patient received the low dose/placebo, and the narrative for this case can be found in Section 8.8.2.

8.4.2. Serious Adverse Events

Nineteen subjects (8%) in the Welchol low dose group and 10 subjects (7%) in the Welchol high dose group reported SAEs during the trial (Table 12). Two subjects in the Welchol low dose group (one with intentional overdose and one with hyperglycemia) and 2 subjects in the Welchol high dose group (one with diabetic ketoacidosis and one with aggression) also discontinued from the study due to reported SAE.

Table 12: Serious Adverse Events by Preferred Term – Safety Set

Subject Number	Adverse Event Preferred Term
Welchol low dose	
(b) (6)	Affective disorder
	Intentional overdose
	Intra-uterine death, premature labor
	Ankle fracture
	Cellulitis
	Abdominal pain, spontaneous abortion
	Abnormal behavior
	Conversion disorder
*	Hyperglycemia
Welchol high dose	
(b) (6) *	Diabetic ketoacidosis
	Appendicitis
	Suicidal ideation
	Depression
	Headache, blurred vision
	Depression, drug abuse
	Suicide attempt
	Appendicitis
*	Suicide ideation, aggression
	Fall, ankle fracture, fibula fracture, procedural hypertension, tachycardia

*These subjects also discontinued from the study due to SAE.
#These cases are discussed in Section 8.8.2

One case of diabetic ketoacidosis reported with high dose Welchol is briefly summarized:

Subject (b) (6) **Diabetic ketoacidosis** (Welchol high dose): A 14-year-old Black male with T2DM and no other medical history presented with stomach pain on Day 187 with an episode of emesis on the day before. Laboratory testing showed fasting blood glucose of 424 mg/dL and urinalysis showed ketone level of 80 mg/dL. He was taken to the emergency room and laboratory testing showed mild diabetic ketoacidosis (DKA); he was discharged on the same date (the narrative did not specify if he was treated for this DKA). Three days later (Day 190), he experienced vomiting after eating a fruit smoothie and was unable to eat. He was taken to the emergency room and laboratory test showed blood glucose of 505 mg/dL with bicarbonate of 17 mmol/L (normal range: 20 to 40 mmol/L) and he was admitted to the hospital for DKA. He was treated with metformin and insulin glargine. On Day 192, DKA was considered resolved and he was discharged. Study drug was discontinued, and subject discontinued from the study due

to DKA.

Reviewer's comment: This DKA event appear to have been caused initially by emesis episode and worsened after another episode of vomiting.

SAEs related to Psychiatric Disorders:

Five subjects (3.5%) reported SAEs related to psychiatric disorder after receiving Welchol high dose: 2 subjects reported depression, 2 subjects reported suicide ideation (one with aggression), and 1 subject reported suicidal attempt. Three of five subjects reported a previous history of mental disorder before study entry. Two subjects (2.1%) receiving low dose/placebo reported SAEs related to psychiatric disorder (intentional overdose and abnormal behavior); both subjects had a previous history of mental disorder.

Narratives of these subjects are briefly summarized:

- Subject (b) (6) **Suicidal ideation** and **aggression** (Welchol high dose): A 14-year-old White male with T2DM and history of attention deficit disorder experienced suicidal ideation on Study Day 26 and was hospitalized after threats were made involving a gun. At that time, the study drug was discontinued and was never restarted. On Study Day 33, suicidal ideation was considered resolved and he was discharged from the hospital. On Study Day 58, he was hospitalized following an emergency disorder of detention due to violent behavior and severe aggression towards the school principal and a policy officer. On Study Day 77, aggression was considered to have resolved, he was discharged from the hospital and was withdrawn from the study. ***Reviewer's comment: The second episode occurred about a month after study drug discontinuation.***

- Subject (b) (6) **Suicidal ideation** (Welchol high dose): An 11-year-old mixed race female with T2DM and with history of feeling depression experienced a non-serious AE of worsening depression on Day 350 and was evaluated in the emergency room for a non-serious AE of recurrent suicidal ideation of moderate severity. She was evaluated and started on sertraline therapy. On Day 370, she experienced SAE of suicidal ideation that worsened and was admitted to the hospital. The dose of sertraline was increased, and suicidal ideation was considered resolved by Day 380. She continued on in the study. ***Reviewer's comment: She had a previous history of depression.***

- Subject (b) (6) **Suicide attempt** (Welchol high dose): A 14-year-old Black female with T2DM and a history of bipolar disorder and depression was admitted to the hospital due to a suicide attempt on Day 172. She required 12 sutures to the left forearm after a cutting episode. Two days later, the event was considered recovered and she was discharged from the hospital. She continued on in the study. ***Reviewer's***

comment: She had a previous history of depression and bipolar disorder.

- Subject (b) (6) **Depression** (Welchol high dose): A 15-year-old White female with T2DM and a history of depression was admitted to a mental health facility following a suicide attempt and depression on Day 35. On Day 107, depression was considered to be stable and she was discharged to outpatient therapy. Study drug was interrupted due to the event, and she withdrew her consent and discontinued the study. ***Reviewer's comment: The event should also have been coded as suicide attempt. She had a previous history of depression.***

- Subject (b) (6) **Depression** and **drug abuse** (Welchol high dose): A 15-year-old White female with T2DM with no know history of psychiatric disorder reported drug abuse and depression on Day 255. She was hospitalized due to reported urges of self-harm and concerns from family members of potential misuse of methamphetamines and other illicit drugs. She discontinued the study four days later. The event was reported to be ongoing.

- Subject (b) (6) **Intentional overdose** (Welchol low dose): A 17-year-old Black female with T2DM with a previous history of suicide attempt, self-mutilation, and depression experienced two SAEs of intention overdose, one on Day 46 and another on Day 63 on Zoloft. She was hospitalized after each episode, and she discontinued the study drug after the second event of intentional overdose and discontinued the study. ***Reviewer's comment: This event could also be considered as a suicide attempt. She had a previous history of psychiatric disorder.***

- Subject (b) (6) **abnormal behavior** (Welchol low dose): A 15-year-old White female with T2DM and history of depression and attention deficit hyperactivity disorder became aggressive towards family, broke property, and was admitted to an inpatient behavioral unit on Day 8. On Day 15, her abnormal behavior was considered resolved and she was discharged without any other treatment. She continued the study. ***Reviewer's comment: The event could also have been coded as aggression. She had a previous history of psychiatric disorder.***

Reviewer's comment: Three of 5 subjects in the high dose Welchol group reporting SAEs such as depression and suicidal ideation/attempt had a previous history of mental disorder before study entry. Review of all TEAEs (both SAEs and non-SAEs) showed that the rate of depression and suicidal events are similar between treatment groups: 4.3% versus 4.2% in the high dose versus low dose Welchol group reported depression; 2.1% of suicidal ideation/attempt/ intentional self-injury were reported in both treatment groups (3 subjects in the high dose group and 2 subjects in the low dose group). I do not believe that these events can be attributed to treatment with Welchol, and the small difference in the rate of SAEs related to

psychiatric disorder was likely by chance.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Nine subjects (6.4%) in the Welchol high dose group versus 4 subjects (4.2%) in the Welchol low dose/placebo group discontinued from the trial due to an AE (Table 13).

One subject ((b) (6) receiving Welchol high dose treatment discontinued due to increased triglycerides (unspecified) on Day 1. This 15-year-old female had a previous history of high triglycerides, hyperlipidemia, and non-alcoholic fatty liver (NAFL), and vitamin D deficiency; concomitant medications included metformin, omega 3, and vitamin D2. The study drug was discontinued ~3 weeks later, the event did not resolve, and she was subsequently withdrawn from the study.

Reviewer's comment: It is unlikely that Welchol will lead to increased triglyceride level after one dose of Welchol; it is likely that this event may be natural worsening of her underlying condition (high triglycerides) rather than due to initiation of Welchol. Nevertheless, hypertriglyceridemia is a labeled adverse reaction for Welchol. No further safety labeling updates are recommended.

One subject ((b) (6) receiving Welchol high dose treatment discontinued due to elevated ALT. This 16-year-old Hispanic female had a previous history of NAFL, hyperlipidemia, hypertension, headache, and vitamin D deficiency, and at screening her ALT was 81 U/L (~29 days before Day 1 value). She was also on metformin monotherapy for almost 2 years before study entry and was at 1000 mg twice daily. At Day 1/Randomization, her ALT was elevated at 135 U/L (normal range is 5-35 U/L). The study drug was discontinued one week later, and on Day 8, ALT was 159 U/L, and on Day 15, ALT was 133 U/L. She was subsequently withdrawn from the study.

Reviewer's comment: Elevated ALT on the first day of dosing is not likely due to Welchol; her screening ALT level was 2x upper limit of normal and this increased ALT on Day 1/Randomization may be related to her underlying condition (such as NAFL).

Review of narratives for other cases did not show any new safety concerns associated with Welchol.

Table 13: Listing of Discontinuations Due to Adverse Event – Safety Set

Subject Number	Preferred Term	SAE	Severity	Resolved
Welchol low dose				
(b) (6)	Upper abdominal pain	No	Mild	Yes
	Intentional overdose	Yes	Moderate	Yes
	Hyperglycemia	No	Moderate	No
	Hyperglycemia	Yes	Moderate	Yes
Welchol high dose				
(b) (6)	Diabetic ketoacidosis	Yes	Moderate	Yes
	Constipation	No	Moderate	Yes
	Pregnancy	No	Moderate	Yes
	Pruritus	No	Moderate	No
	Vomiting	No	Moderate	Yes
	ALT increased	No	Moderate	No
	Increased blood triglycerides	No	Moderate	No
	Aggression	Yes	Severe	Yes
	Diarrhea	No	Moderate	Yes

SAE=serious adverse event; ALT=alanine aminotransferase
Source: CSR, Table 10-5

8.4.4. Significant Adverse Events

AEs leading to study drug discontinuation were discussed in Section 8.4.3 and no other significant AEs[11] were noted for discussion here from U307 trial.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Approximately 75.8% (72 subjects) of Welchol low dose group and 80.1% (113 subjects) of Welchol high dose group reported TEAEs during the trial. Table 14 summarizes common TEAEs with ≥2% incidence in the high dose group, organized by System Organ Class (SOC) and Preferred Term (PT).

[11] Significant adverse event refers to the definition in the ICH guideline for industry E3 Structure and Content of Clinical Study Reports that includes: Marked hematological and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to an intervention, including withdrawal of test drug/investigational product treatment, dose reduction, or significant additional concomitant therapy, other than those reported as serious adverse events.

Table 14: Treatment-Emergent Adverse Events (≥2% in Welchol high dose) by System Organ Class and Preferred Term – Safety Set

System Organ Class (SOC) Preferred Term (PT)	Welchol low dose n (%)	Welchol high dose n (%)
N	**95**	**141**
TEAEs	**72 (75.8)**	**113 (80.1)**
Ear and labyrinth disorders	1 (1.1)	3 (2.1)
Ear pain	1 (1.1)	3 (2.1)
Gastrointestinal disorders	29 (30.5)	44 (31.2)
Abdominal discomfort	3 (3.2)	3 (2.1)
Abdominal pain	5 (5.3)	8 (5.7)
Abdominal pain upper	9 (9.5)	12 (8.5)
Constipation	1 (1.1)	10 (7.1)
Diarrhea	10 (10.5)	13 (9.2)
Nausea	7 (7.4)	8 (5.7)
Vomiting	11 (11.6)	20 (14.2)
General disorders and administration site conditions	10 (10.5)	13 (9.2)
Pyrexia	5 (5.3)	7 (5.0)
Infections and infestations	39 (41.1)	57 (40.4)
Bronchitis	1 (1.1)	3 (2.1)
Otitis media	1 (1.1)	7 (5.0)
Gastroenteritis viral	1 (1.1)	3 (2.1)
Influenza	1 (1.1)	4 (2.8)
Nasopharyngitis	8 (8.4)	10 (7.1)
Pharyngitis streptococcal	1 (1.1)	6 (4.3)
Sinusitis	4 (4.2)	4 (2.8)
Upper respiratory tract infection	9 (9.5)	24 (17.0)
Urinary tract infection	6 (6.3)	7 (5.0)
Viral infection	4 (4.2)	3 (2.1)
Injury, poisoning, and procedural complications	18 (18.9)	15 (10.6)
Fall	0	3 (2.1)
Join sprain	6 (6.3)	3 (2.1)
Investigations	19 (20.0)	27 (19.1)
Alanine aminotransferase increased	3 (3.2)	6 (4.3)
Blood creatinine phosphokinase increased	3 (3.2)	5 (3.5)
Blood triglycerides increased	3 (3.2)	7 (5.0)
Glycosylated hemoglobin increased	1 (1.1)	3 (2.1)
High-density lipoprotein increased	1 (1.1)	3 (2.1)
Low-density lipoprotein increased	2 (2.1)	6 (4.3)
Non-high-density lipoprotein cholesterol increased	2 (2.1)	3 (2.1)
Protein urine present	1 (1.1)	4 (2.8)
Metabolism and nutrition disorders	23 (24.2)	32 (22.7)
Hyperglycemia	15 (15.8)	18 (12.8)

Hypertriglyceridemia	0	5 (3.5)
Hypoglycemia	3 (3.2)	3 (2.1)
Vitamin D deficiency	3 (3.2)	4 (2.8)
Musculoskeletal and connective tissue disorders	8 (8.4)	8 (5.7)
Arthralgia	2 (2.1)	3 (2.1)
Pain in extremity	0	3 (2.1)
Nervous system disorders	12 (12.6)	25 (17.7)
Dizziness	3 (3.2)	5 (3.5)
Headache	8 (8.4)	18 (12.8)
Tremor	0	3 (2.1)
Psychiatric disorders	8 (8.4)	9 (6.4)
Depression	4 (4.2)	6 (4.3)
Renal and urinary disorders	1 (1.1)	5 (3.5)
Proteinuria	0	3 (2.1)
Reproductive system and breast disorders	5 (5.3)	8 (5.7)
Dysmenorrhea	1 (1.1)	4 (2.8)
Respiratory, thoracic, and mediastinal disorders	17 (17.9)	32 (22.7)
Asthma	1 (1.1)	3 (2.1)
Cough	6 (6.3)	10 (7.1)
Nasal congestion	4 (4.2)	6 (4.3)
Rhinorrhea	0	6 (4.3)
Skin and subcutaneous tissue disorders	8 (8.4)	16 (11.3)
Rash	2 (2.1)	4 (2.8)

Note: Same subjects may appear in more than one category if s/he had 2 or more AEs.
TEAEs=treatment emergent adverse events
Source: CSR, Table 10-2, 15.3.1.3

Hyperglycemia occurred slightly more often in the lower dose/placebo group (15.8%) compared to the high dose (12.8%), which was not surprising as it likely reflects ineffective therapy with low dose Welchol. Hypoglycemia also appeared more commonly in the lower dose/placebo group (3.2%) compared to the high dose group (2.1%), but this may be attributed to glycemic rescue therapy that subjects in the lower dose group may have received. Hypoglycemia is usually an important AE of interest for diabetes therapy and hypoglycemic events are generally captured using standard definitions established by the American Diabetes Association, with a specific AE form in diabetes trials; however, in this trial, hypoglycemia was captured as adverse events without standard definitions and based on the clinical judgment of the blinded investigators.

Under 'Skin and subcutaneous tissue disorders' SOC, four subjects in each treatment group reported rash-related events[12].

[12] PTs included rash, rash popular, exfoliative rash.

There was a slightly higher rate of 'increased blood triglycerides' and 'hypertriglyceridemia' with Welchol high dose that is likely related to treatment with Welchol due to its compensatory increase in cholesterol biosynthesis in the liver and incorporation of some of that cholesterol into triglyceride-rich lipoproteins secreted into the plasma. Welchol is also known to have constipating effects due to its mechanism of binding intestinal bile acids, and there was a higher incidence of 'constipation' with high dose Welchol compared to low dose/placebo.

Reviewer's comments: Upper respiratory tract infections, headache, constipation, and vomiting are already labeled events for Welchol. Hypertriglyceridemia is also labeled event with Welchol; pancreatitis, which can occur due to elevated triglycerides, was not reported. Unlike many other anti-diabetic agents, hypoglycemia is not a major safety issue with Welchol. Overall, common adverse reactions in U307 trial were similar to the overall common adverse reactions seen in adult trials and TEAEs were labeled events in the Welchol Prescribing Information (PI). I do not recommend any changes to Section 5 of the Common Adverse Reactions in the PI.

8.4.6. Laboratory Findings

Laboratory assessments included hematology and chemistry parameters, urinalysis, and 25-hydroxy-vitamin D levels. Changes in lipid parameters including triglycerides are discussed in Section 6.1.2 under Efficacy Results.

After baseline, complete serum chemistry including liver enzymes and hematology were evaluated during the trial at Month 1, Month 3, Month 6, Month 9, and at Month 12/end of trial. Urinalysis was conducted every 6 months.

Evaluation of hematology, biochemistry and urinalysis central tendencies were similar between treatment arms when comparing by mean change from baseline and mean trends over visit. Overall, the central tendency evaluation remained generally stable for 12 months of treatment period, without clinically relevant differences between treatment arms (Tables 10-6, 15.3.4.1, and 15.3.4.3 in the CSR; data not shown here).

The following small imbalances were noted with elevations in liver enzymes:

- ALT >3x ULN occurred in 7.8% (11 subjects) versus 4.2% (4 subjects) with Welchol high dose versus low dose group (identified using adlb dataset);
    - Two subjects in the high dose group (b) (6)) reported elevated ALT level on Day 1/randomization visit, and it is unlikely that these liver enzyme elevations at randomization are related to the study drug;
    - All of these subjects in both high and low dose group had elevated screening/baseline ALT values (normal range: 5-35 U/L); of note, the baseline mean ALT was 32 U/L in the high dose and 35 U/L in the low dose group;

- Two subjects with high dose Welchol reported concurrent AST >3x ULN versus none with low dose; in one subject ([(b) (6)]), the ALT and AST elevations were noted at the end of treatment visit (Month 12) that returned to baseline level at the follow-up; in another subject [(b) (6)]), ALT and AST elevations were transient and returned to baseline at the subsequent visit while still on study drug (negative rechallenge);
- ALT elevations in four other subjects with high dose were also transient and returned to baseline at follow-up ([(b) (6)]);
- Of these, ALT elevation was >5x ULN in 2 subjects with high dose and 2 subjects with low dose; in one subject with high dose ([(b) (6)]), ALT >5x ULN occurred about 5.5 months after study drug was discontinued and thus unlikely to be related to the study drug; in the other subject with high dose [(b) (6)]), ALT level was continuing to decrease when the subject was discontinued from the study due to non-compliance at Month 6.

In looking at the central tendency analyses, there was a minor increase in serum transaminases from baseline with high dose Welchol versus small decreases in serum transaminases with low dose Welchol, but these small changes would not be expected to be clinically relevant (Table 15).

Table 15: Mean (Median) Changes from Baseline in Serum Transaminases

		Welchol Low Dose (N=95)	n[1]	Welchol High Dose (N=141)	n[1]
ALT (U/L)	Month 1	-3.8 (-1.0)	92	1.5 (2.0)	135
	Month 3	-4.2 (-3.0)	84	2.1 (0)	122
	Month 6	-5.1 (-2.0)	76	1.7 (0)	108
	Mont 12	-0.6 (-3.0)	71	1.1 (0)	99
AST (U/L)	Month 1	-3.1 (-2.0)	92	1.0 (0)	135
	Month 3	-2.2 (-1.0)	84	0.5 (0)	122
	Month 6	-3.4 (-1.5)	76	2.2 (0)	108
	Month 12	-0.4 (-1.0)	71	0 (-1.0)	99

ALT=alanine transferase; AST=aspartate aminotransferase
[1]n is the number of subjects with values at both baseline and during treatment period.
Source: CSR, Table 15.3.4.1 and 15.3.4.2

During the safety review of clinical trials in adults with T2DM[13], Dr. Joffe noted that in 3 of 4 placebo-controlled trials, there was a minor mean increase in serum transaminases from baseline to end of treatment with Welchol compared to placebo (Table 16), but he considered these changes not to be clinically relevant:

[13] NDA 21176/S-017; Clinical Review by Hylton Joffe dated December 5, 2007.

Table 16: Mean (Median) changes from baseline in liver tests across four placebo-controlled trials

	WEL-301		WEL-302		WEL-303		WEL-401	
	WelChol	Placebo	WelChol	Placebo	WelChol	Placebo	WelChol	Placebo
ALT (U/L)	-0.9 [1]	1.1 [0]	2.4 [1]	0.7 [0]	2.9 [1]	-0.5 [0]	3.9	1.8
AST (U/L)	-0.4 [1]	0.9 [0]	1.5 [1]	0.5 [1]	1.8 [1]	-0.3 [0]	2.3	1.4

Source: NDA 21176/S-017; Table 19 in Clinical Review by Hylton Joffe dated December 5, 2007

Welchol-treated patients were also noted to have a higher incidence of newly occurring/worsening[14] serum transaminases in the adult clinical trials with T2DM (Table 17). Dr. Joffe noted that a similar pattern of newly occurring/worsening liver tests was noted in the original Welchol NDA (ALT 15% with Welchol 3.8-4.5 g/day versus 6.4% with placebo).

Table 17: Newly occurring/worsening laboratory abnormalities occurring more frequently with Welchol than placebo in at least two pivotal trials and occurring ≥1% more frequently in the overall Welchol group compared to the overall placebo group

	WEL-301		WEL-302		WEL-303		All (301,302,303)	
	WelChol (N=159) n (%)	Placebo (N=157) n (%)	WelChol (N=147) n (%)	Placebo (N=140) n (%)	WelChol (N=229) n (%)	Placebo (N=231) n (%)	WelChol (N=535) n (%)	Placebo (N=528) n (%)
N*	142	145	141	135	212	210	495	490
Tbili – high	5 (3.5)	3 (2.1)	5 (3.5)	1 (0.7)	4 (1.9)	2 (1.0)	14 (2.8)	6 (1.2)
Alk phos – high	17 (12)	19 (13)	24 (17)	21 (16)	42 (20)	31 (15)	83 (16.8)	71 (14.5)
ALT – high	20 (14)	19 (13)	20 (14)	11 (8.1)	38 (18)	19 (9.0)	78 (15.8)	49 (10.0)
AST – high	18 (13)	16 (11)	25 (18)	13 (9.6)	41 (19)	12 (5.7)	84 (17.0)	41 (8.4)
Hct – low	21 (15)	14 (9.7)	25 (18)	10 (7.4)	24 (11)	24 (12)	70 (14.1)	48 (9.8)
RBC – low	19 (13)	14 (9.7)	22 (16)	10 (7.4)	0	2 (1.0)	41 (8.3)	26 (5.3)
Lymph – low	19 (13)	14 (9.7)	29 (21)	25 (19)	30 (14)	33 (16)	78 (15.8)	72 (14.7)
Tbili = total bilirubin; Alk phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Hct = hematocrit; RBC = red blood cell count; WBC = white blood cell count; Lymph = lymphocytes								

Source: NDA 21176/S-017; Table 20 in Clinical Review by Hylton Joffe dated December 5, 2007

However, none of the Welchol treated adult patients in the phase 3 diabetes trials had two consecutive serum transaminases >3x ULN (or one serum transaminase >3x ULN before early termination).

Reviewer's comment: Although a slightly higher rate of ALT elevations >3x ULN was observed

[14] Newly occurring abnormalities were values that were in the normal range at baseline and outside the normal range post-baseline, or were outside the normal range post-baseline in the opposite direction of baseline abnormal values. Worsening abnormalities were defined as values outside the normal range at baseline that worsened by ≥15%.

with the high dose Welchol compared to the low dose, most elevations with the high dose Welchol were transient or appear to be not related to the study drug. A minor mean increase in serum transaminases from baseline was observed with the high dose Welchol compared to the low dose, but these changes did not appear to be clinically relevant and appear to be consistent with previous studies of Welchol in adult diabetes trials. Therefore, review of liver enzyme data from this pediatric trial does not change the known safety profile of Welchol or suggest a new pediatric safety concern.

Changes in vitamin D level was also evaluated, since bile acid sequestrants such as Welchol could decrease absorption of fat-soluble vitamins including vitamin D. About 87% of subjects in both treatment groups were receiving vitamin D and analogues as concomitant medication. From baseline to Month 12, there were no clinically meaningful differences between the treatment groups in the change in 25-hydroxy-vitamin D levels (Table 10-7 in the CSR; data not shown here), and analysis of shifts in vitamin D categories also did not show meaningful differences between treatment groups (Table 10-8 in the CSR; data not shown here).

8.4.7. Vital Signs

The mean changes in diastolic blood pressure, systolic blood pressure, and heart rate were similar between treatment groups (Table 15.3.5.1 in CSR; not shown here).

8.4.8. Electrocardiograms (ECGs)

ECGs were not performed in this trial. There are no known adverse effects of Welchol on cardiac repolarization, or other cardiac related safety issues.

8.4.9. QT

No QT studies were performed as part of the evaluation in the U307 trial. See above comment.

8.4.10. Immunogenicity

Welchol is a small molecule and does not require immunogenicity assessment.

8.5. Analysis of Submission-Specific Safety Issues

None as there were no submission-specific safety issues.

8.6. Safety Analyses by Demographic Subgroups

Safety analyses by demographic subgroups were not done as there was no significant safety findings in this trial.

8.7. Specific Safety Studies/Clinical Trials

There were no specific studies/clinical trials conducted to evaluate a specific safety concern in this submission.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

There is no information relevant to this section of the review in this submission.

8.8.2. Human Reproduction and Pregnancy

A formal assessment of Welchol use during pregnancy and lactation was not included in this submission.

Five subjects became pregnant while receiving study drug during the trial, two in the Welchol low dose group and three in the Welchol high dose group.

One pregnancy in the low dose group resulted in spontaneous abortion. Another pregnancy in the low dose group reported premature labor and intrauterine death:

One case of premature labor with delivery of a non-viable male infant was reported in a 15-year-old White female with T2DM after receiving a low dose Welchol. Concomitant medications included metformin and cholecalciferol. After completing about 6 months of treatment with the study drug, she was brought into clinic for an unscheduled visit and reported being sexually active. Urine pregnancy test was positive, and she discontinued the study drug due to pregnancy. On Day 271, she experienced premature labor and reported intra-uterine death at 22 weeks of gestation with an hour history of abdominal pain. Physical exam showed preterm labor, and she delivered a non-viable male infant with an Apgar score of 1.

Reviewer's comment: Per Welchol labeling, maternal use is not expected to result in fetal exposure to drug as it is not absorbed systemically after oral administration. It is unlikely that the outcome of this pregnancy is related to the low dose Welchol treatment.

Three subjects in the high dose group became pregnant and withdrew from the trial. Two subjects had a normal delivery of health infant at full term. One subject had an induced abortion at 8 weeks of gestation.

8.8.3. Pediatrics and Assessment of Effects on Growth

There was no assessment of effects on growth.

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

A formal assessment of overdose, drug abuse potential, withdrawal and rebound was not included in this submission which is acceptable as Welchol is not expected to be associated with these risks. Intentional overdose occurred in 2 subjects receiving low dose Welchol, and one was considered an SAE and discussed in Section 8.4.2.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

As part of the evaluation in the postmarketing setting, the clinical reviewer reviewed the Applicant's most recent PADER submitted to NDA 22362 on November 30, 2020, which covered October 2, 2019 through October 1, 2020. There were 28 cases of safety reports during this reporting period from the U.S. The Applicant also noted that about (b) (4) prescriptions were written in the U.S. during this reporting period, compared to (b) (4) prescriptions written during the previous year; this usage data indicates that the use of Welchol is decreasing.

We agree with the Applicant's conclusion that no new safety concerns have been identified that are not already described in the product labeling for Welchol.

8.9.2. Expectations on Safety in the Postmarket Setting

This section is not relevant since a pediatric indication is not being granted.

8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues were identified from other disciplines.

8.10. Integrated Assessment of Safety

The safety of Welchol oral suspension in pediatric patients with T2DM was assessed in 141 subjects who were treated with active Welchol treatment (3.75 g/day) for 12 months and compared to 95 subjects who were treated with low dose Welchol (0.625 g/day) as a placebo.

No deaths occurred in subjects after receiving Welchol. No serious adverse events were likely to be drug related.

There was a small observed increased frequency of elevated ALT above the screening value with the high dose Welchol compared to the low dose (as a reminder, patients were excluded if ALT/AST were >2.5x ULN). Most ALT elevations with the high dose Welchol were transient or appear to be not related to the study drug. In four adult diabetes trials, there were no pre-defined limits for outlier ALT/AST values >3x ULN. A minor increase in serum transaminases

from baseline was observed with Welchol in Trial U307 as well as in adult diabetes trials, but this small change did not appear to be clinically relevant. Therefore, there is no new liver safety signal.

With respect to non-serious, common adverse reactions, 'hypertriglyceridemia' and 'Increased blood triglycerides' as a TEAE occurred at a higher rate in the active Welchol group compared to the low dose group. In addition, there was an increase in the percent median triglycerides in both treatment groups from baseline to Month 6, with a higher increase in the active Welchol group compared to the low dose group; the difference in the median percent change was 6.0% (Table 10). No pancreatitis was reported in U307 trial. Hypertriglyceridemia is a labeled adverse reaction for Welchol, and these results do not change the overall known risk related to elevated serum triglycerides due to use of Welchol. Since Welchol is known to have constipating effects due to its mechanism of binding intestinal bile acids, there was a higher incidence of 'constipation' with high dose Welchol compared to low dose/placebo.

There were no other adverse reactions thought to be drug-related. Unlike many other antidiabetic agents, Welchol was not associated with an increased incidence of hypoglycemia.

In conclusion, AEs observed in U307 trial were similar to the known AEs in adult trials and are already labeled events.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee meeting was not convened for this efficacy supplement as no safety or efficacy issue rose to the level of requiring external input.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

We recommend the following changes to Welchol based on the results of U307 trial:

In Prescribing Information, Section 8.4, Pediatric Use:

- Create a 'type 2 diabetes mellitus' section and specify that the safety and effectiveness of Welchol to improve glycemic control in pediatric patients with type 2 diabetes mellitus have not been established.
- Since the trial has failed, do not include details or results of the trial, but a high-level statement about trial can be included as following: Effectiveness was not

demonstrated in a 6-month, adequate and well-controlled study conducted in 141 WELCHOL-treated pediatric patients aged 10 to 17 years with type 2 diabetes mellitus.

Also, consistent with labeling guidelines to avoid an implication of a pediatric indication, given that no new safety signals were identified in the pediatric population compared to the adults, no specific discussion of pediatric safety information is recommended either in Section 8.4 or Section 6.1.

The Office of Prescription Drug Promotion (OPDP) did not have any additional comments to our recommendation to the labeling after their review[15].

10.2. Nonprescription Drug Labeling

This section is not applicable to this application.

11. Risk Evaluation and Mitigation Strategies (REMS)

REMS are not recommended; there were no new safety issues identified.

12. Postmarketing Requirements and Commitments

No new postmarketing requirement (PMR) or commitment is recommended.

The following PMR is considered fulfilled:

PMR 1729-1: Deferred, 1-year, pediatric efficacy and safety study under PREA for the treatment of type 2 diabetes in pediatric patients ages 10 to 17 years.

13. Appendices

13.1. References

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): WEL-A-U307

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 29		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

APPEARS THIS WAY ON ORIGINAL

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/

HYON J KWON
10/13/2021 01:49:06 PM

LISA B YANOFF
10/13/2021 02:27:39 PM
I was involved with the drafting of this memo and agree with its conclusions