U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA022362-S29
Drug Name:	Welchol® (Colesevelam Hydrochloride)
Indication(s):	T2DM among pediatric patients 10 to 17 years old
Applicant:	Daiichi Sankyo, Inc. (DSI)
Date(s):	Stamp date: 12/23/2020
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Biometrics Division:	Division of Biometrics II
Statistical Reviewer:	Wenda Tu
Concurring Reviewers:	Yun Wang, Team Lead
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Hyon Kwon
	Patrick Archdeacon, Team Lead
Project Manager:	Arati Kamath
Key Words:	Pediatric study, Glycemic Control, T2DM

Table of Contents

LIST OF TABLES

1. EXECUTIVE SUMMARY

The applicant, Daiichi Sankyo, Inc. has submitted this supplemental new drug application (sNDA) to support changes to *Section 8.4: Pediatric Use* in the labels for Welchol® (Colesevelam Hydrochloride). The proposed changes provided additional information on the drug's efficacy and safety for pediatric use. Specifically, the drug was found not effective among the pediatric population based on the results from the pediatric study WEL-A-U307: Colesevelam Oral Suspension as Monotherapy or Add-on to Metformin Therapy in Pediatrics Subjects with T2DM.

1.1 Brief overview of Clinical Study

WEL-A-U307 was a multi-center, randomized, double-blind, parallel group, placebo-controlled trial consisting of a $\leqslant$ 2-week Screening Period, a 2-week Lead-in/Stabilization Period, a 12-month Treatment Period, and a 2-week Follow-up Period. It compared the effect of Welchol high dose (3.75 g/day) against Welchol low dose (0.625g/day) on glycemic control among 236 participants (10 to 17 years old) with T2DM. According to the applicant, the low dose arm was considered the placebo arm for the following two reasons: 1. a placebo with matching organoleptic to the high dose was not available, and 2. the 0.625g/day dose was presumed to have minimal therapeutic effects. The primary efficacy endpoint of the study was "change in HbA1c from baseline over the first 6 months of Treatment Period".

More details about Study Wel-A-U307 can be found in Section 2.1.2.

1.2 Statistical Issues

Two statistical issues were identified during this review. Firstly, the intent-to-treat (ITT) set defined by the applicant, which served as the basis for the primary efficacy analysis, was not in alignment with the division's guideline. In the submitted analysis, the ITT set was defined as "all randomized subjects who have taken at least 1 dose of randomized study medication, have a baseline A1c measurement, and have at least 1 post-baseline A1c measurement prior to any rescue therapy". On the other hand, as recommended by the division, an ITT set should include all randomized and treated patients, *regardless of* the availability of post-baseline measurements.

Secondly, in the primary efficacy analysis, the handling of missing endpoint data was not in alignment with the division's guideline. The applicant imputed missing endpoint data via the method of last observation carried forward (LOCF). However, for a placebo-controlled trial, we recommended multiple imputation based on retrieved dropouts, or the washout method if there are not sufficient retrieved dropouts.

An IR was sent to the applicant on January 15, 2021, requesting the applicant to redo their primary analysis based on our recommended washout method. The applicant rejected this request however, arguing that the statistical analysis was conducted according to the analysis plan, which was created 10 years ago and approved by the Agency at the time. After several rounds of communication, the Agency and the applicant reached an agreement that the FDA statistical

reviewer would redo the primary efficacy analysis for the applicant using the recommended ITT set and the washout method for missing data imputation. More details about the analysis can be found in Section 3.

1.3 Collective Evidence

Efficacy data were re-analyzed by the FDA statistical reviewer. The analysis included data collected from all randomized and treated patients, and utilized the ANCOVA model pre-specified in the study protocol. Missing data were handled based on the washout method and Rubin's Rule for multiple imputation. The result from this analysis follows next.

The change in A1c at Month 6 from baseline in patients treated with Welchol® (N = 141) was estimated to be 0.07% compared to 0.19% in patients treated with placebo (N = 95), resulting in a difference of -0.12% (95% C.I.: -0.55, 0.30). On the other hand, in the analysis submitted by the Applicant, the change in A1c at Month 6 from baseline in patients treated with Welchol® (N = 132) was 0.09% compared to 0.21% in patients treated with placebo (N = 88), resulting in a difference of -0.13% (95% C.I.: -0.54, 0.29). Despite the discrepancies in the analysis method, the outcomes from the two analyses appeared similar. Neither demonstrated superiority of Welchol® regarding A1c reduction when compared to placebo.

The safety evaluation has shown that Welchol® was generally safe and well-tolerated through a 12-month length of treatment.

1.4 Conclusion and Recommendations

Since superiority of HbA1c reduction was not demonstrated by Study WEL-A-U307, the applicant did not plan to pursue any efficacy claim for Welchol use among pediatric patients (10 to 17 years old) with T2DM. The applicant only sought to add the study information in Section 8.4: Pediatric Use. This proposal would be approvable, (b) (4) efficacy analysis result with the one obtained by the statistical reviewer.

2. INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Colesevelam, as a bile acid-binding resins, is indicated as an adjunct to diet and exercise to reduce elevated low-density lipoprotein cholesterol (LDL-C) in adults and pediatrics (10 to 17 years old) with hyperlipidemia. It is also indicated as an adjunct to diet and exercise to improve glycemia control in adults with T2DM. The drug has three different forms. Welchol tablets (NDA 21776) and Welchol capsules (NDA 21141) were approved in 2000. Welchol Oral solution (NDA 22362) was approved in 2009. The recommended dosage for adults with T2DM is 3.75 g/day.

2.1.2 Studies Reviewed

Study WEL-A-U307[1] was included in this submission. Table 1 provides an overview of this study.

Table 1. Summary of Study WEL-A-U307*

Trial ID	Design*	Treatment (Sample Size)	Primary Efficacy Objective/Hypothesis	Primary Efficacy Endpoint/Analysis
WEL-A-U37	MC, R, DB, PG, PC trial** (⩽ 2-week screening period + 2-week lead-in/stabilization period + 12-month treatment period + 2-week follow-up period)	High-dose (3.75 g/day) colesevelam (N = 141) Low-dose (0.625g/day) colesevelam (N = 95)	**Objective:** Assess the treatment effect of colesevelam compared to placebo on glycemic control in pediatric subjects with T2DM (10 to 17 years old). **Hypothesis**: The addition of colesevelam reduces A1c more than the addition of placebo after 6 months of treatment (H_0: difference = colesevelam - placebo = 0).	**Primary Endpoints**: Change in A1c from baseline at Month 6 **Analysis**: Treatment policy estimand based on the ITT set/MI + washout method (analyzed by ANCOVA***).

* Information from this table was based on the statistical analysis conducted by the statistical reviewer, not the applicant.
** MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled
*** The ANCOVA model included treatment, previous T2DM treatment stratum, and baseline A1c.

[1] The first subject was screened on 1/27/2011, and the last subject completed the study on 4/12/2020.

2.2 Data Sources

The Electronic Document Room (EDR) locations for this NDA submission is listed as follows:

- NDA022362-S29: \\CDSESUB1\evsprod\NDA022362\0093

All the datasets (both in ADAM format and STDM format) and the programming codes for the statistical analyses documented in this NDA submission can be found under the subdirectory: m5/datasets.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

There was no issue on data quality. Regarding the statistical analysis, two issues were identified. Firstly, the analysis set for the primary efficacy analysis violated the ITT principle. As specified in the study protocol, the analysis set was defined as "all subjects who had taken at least 1 dose of randomized study medication, had a baseline A1c measurement, and had at least 1 post-baseline A1c measurement prior to any rescue therapy". Since whether having an on-treatment A1c measurement was post-randomization and might be related to the treatment, this definition violated the ITT principle, which ignores anything that occurs after randomization in order to maintain the prognostic balance created by the original randomization scheme.

Secondly, in this NDA submission, the handling of missing endpoint was not in alignment with the division's guideline. For a placebo-controlled trial, the division advocated multiple imputation for missing endpoint data based on retrieved dropouts (or washout method if there are not enough retrieved dropouts). The applicant, however, utilized a single imputation method based on last observation carried forward (LOCF).

Given the above two issues, data related to the primary efficacy endpoint was reanalyzed by the reviewer. Sections 3.2.2 through 3.2.4 elaborated the details of this new analysis.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study WEL-A-U307 was a multi-center, double-blind, randomized, parallel-group, placebo-controlled trial. It consists of:

- A Screening Visit;
- A 2-week single-blind Lead-in/Stabilization Period;
- A 12-month double-blind Treatment Period; and
- A Follow-up Visit approximately 2 weeks after the End of Treatment.

For the Screening Visit, subjects had to be either on metformin monotherapy or currently untreated[2] with anti-diabetic agents. After being confirmed as eligible to participate in the study, subjects entered the Lead-in/Stabilization Period. A blinded once-daily medication (low dose colesevelam) was provided to all subjects.

For the 12-month Treatment Period, eligible subjects were randomized in a 3:2 ratio to high dose colesevelam (3.75g/day) or to low dose colesevelam (0.625g/day). Subjects on metformin monotherapy remained on the same dose as at the time of Screening, unless and until subjects met the criteria for glycemic rescue. The investigator was blind to A1c values throughout the study and lab reports alerted the investigator to abnormal values. In the event that a subject's A1c could not be maintained below 8.5% after 3 months or below 7.5% after 6 months of study medication (measured by the central lab), open-label glycemic rescue with metformin was initiated or optimized, and if this was not adequate, with a once-daily insulin preparation (e.g., insulin glargine).

Sample size

A total of 220 to 230 subjects were planned to be randomized in a 3:2 ratio to receive either the high dose or low dose colesevelam. It was assumed that a 0.4% difference between high dose and low dose for the change from baseline in A1c, with a common SD of 1.0%. Using a 2-sided significance level of 0.05, a minimum sample size of 208 subjects (125 for the high dose arm and 83 for low dose arm) provided 80% power to detect the difference.

Primary endpoints for efficacy evaluation

Change in HbA1c from baseline at Month 6.

3.2.2 Statistical Methodologies

Estimand

The reviewer performed the primary efficacy analysis based on the treatment policy estimand, as was recommended by the FDA for anti-diabetic products. The treatment policy estimand for this study was characterized as follows:

- Targeted Study Population:
    - Pediatric patients (10 to 17 years old) with T2DM;
- Endpoint of Interest:

[2] "Untreated" includes subjects who had either never received anti-diabetic therapy; or received anti-diabetic medications for less than 14 days within the 3 months prior to screening but no insulin therapy within 14 days of screening.

    - Change from baseline in A1c at Month 6;
- Handling of Intercurrent Events:
    - Use 6-month A1c regardless of whether study medication or rescue medication was taken up to Month 6;
- Population-Level Summary:
    - Difference in endpoint means comparing the effect of the drug vs placebo.

The applicant failed to follow the treatment policy estimand when handling intercurrent events. Specifically, the applicant discarded all data collected after the initiation of rescue medications and imputed missing endpoints vis a single imputation based on LOCF.

The primary analyses conducted by this reviewer

The endpoint of A1C change from baseline at Month 6 was analyzed using analysis of covariance (ANCOVA). The ANCOVA model adjusted for terms for treatment, previous T2DM treatment stratum, and baseline A1c.

The washout approach was utilized for multiple imputation of the missing endpoint data. Missing endpoints from both treatment arms were imputed based on the observed endpoints from the placebo arm. When imputing missing endpoints in the treatment arm, a regression model with previous T2DM treatment stratum and baseline A1c was utilized, whereas the regression model for imputation of the placebo arm also included intermediate endpoint values (*i.e.,* Month-3 A1c) as an additional covariate. This imputation procedure was repeated 100 times. For each completed dataset, the change from baseline at Month 6 was analyzed using an ANCOVA model with the same set of covariates specified for the primary analysis. Finally, Rubin's rule was adopted to combine the results for statistical inference.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

141 subjects were randomized to the treatment arm, and 95 to the placebo arm. This made a total of 236 subjects for the full analysis set (FAS) under the treatment policy estimand. During the Treatment Period, no notable difference concerning subject disposition was observed between the two arms. The most common reasons for study discontinuation were lost to follow-up (7.2%), withdrawal by subjects (7.2%) and other reasons (7.2%).

105 subjects (44.5%) required rescue medication during the study, of which 37 (15.7%) did not complete the Month 6 Visit prior to rescue.

74 subjects (31.4%) discontinued or rescued before the Month 6 Visit.

Table 2. Subject Disposition by Treatment Group

	Welchol Low Dose (%)	***Welchol High Dose (%)***	***Total (%)***
Randomized	95 (100)	141(100)	236 (100)
Completed the Month 6 Visit	76 (80.0)	112 (79.4)	188 (79.7)
Completed the Month 12 Visit	72 (75.8)	99 (70.2)	171(72.5)
Discontinued Study After Randomization	23 (24.2)	42 (29.8)	65 (27.5)
• Adverse Event	3 (3.2)	8 (5.7)	11 (4.7)
• Lost to Follow-up	6 (6.3)	11 (7.8)	17 (7.2)
• Withdrawal by Subject	7 (7.4)	10 (7.1)	17 (7.2)
• Hyperglycemia Meeting the Protocol-Specified Discontinuation Criteria	2 (2.1)	1 (0.7)	3 (1.3)
• Other	5 (5.3)	12 (8.5)	17 (7.2)
Took Rescue Medication	45 (47.4)	60 (42.6)	105 (44.5)
• Completed Month 6 Prior to Rescue	28 (29.5)	40 (28.4)	68 (28.8)
• Did not Complete Month 6 Visit prior to Rescue	17 (17.9)	20 (14.2)	37 (15.7)
Discontinued or Rescued Before Month 6 Visit	33 (34.7)	41 (29.1)	74 (31.4)
Missing Endpoint at Month 6	19 (20.0)	30 (21.3)	49 (20.8)

Source Table 7-3, CSR. "Missing Endpoint at Month 6" was provided by the reviewer.

Major baseline demographics and disease characteristics for Study Wel-A-U307 were summarized in Table 3. As illustrated in the table, the baseline demographics and disease characteristics were generally comparable between the two trial arms.

Table 3. Demographics and Baseline Characteristics – Randomized Set

	Welchol Low Dose (N=95)	***Welchol High Dose (N = 141)***	***Total (N = 236)***
Age at the Date of Informed Consent			
Mean (SD)	14.2 (2.02)	14.1 (2.09)	14.2 (2.06)
Median (Min, Max)	15.0 (10, 17)	14.0 (10, 17)	15.0 (10, 17)
10 – 13 years (%)	33 (34.7)	51 (36.2)	84 (35.6)
14 – 17 years (%)	62 (65.3)	90 (63.8)	152 (64.4)
Sex (n, %)			
Female	67 (70.5)	114 (80.9)	181 (76.7)
Male	28 (29.5)	27 (19.1)	55 (23.3)
Ethnicity (n, %)			
Hispanic or Latino	39 (41.1)	65 (46.1)	104 (44.1)
Not Hispanic or Latino	56 (59.8)	76 (53.9)	132 (55.9)
Race (n, %)			
White	46 (48.4)	71 (50.4)	117 (49.6)
Black	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 (0.0)	1 (0.4)
Native Hawaiian or Other Pacific			

Islander	1 (1.1)	0 (0.0)	1 (0.4)
Other	1 (1.1)	2 (1.4)	3 (1.3)
Multiple	5 (5.3)	15 (10.6)	20 (8.5)
Previous Anti-Diabetic Medication Status			
Treatment-naïve or untreated	32 (33.7)	48 (34.0)	80 (33.9)
On metformin monotherapy	63 (66.3)	93 (66.0)	156 (66.1)
Duration of T2DM (Months)			
Mean (SD)	14.4 (16.4)	14.2 (17.4)	14.3 (17.0)
Median	8.9	5.7	7.5
(Min, Max)	(1.1, 85.7)	(1.0, 96.8)	(1.0, 96.8)
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)
Body Mass Index (BMI) (kg/m^2)			
Mean (SD)	35.7 (7.95)	34.4 (6.91)	34.9 (7.36)
Median (Min, Max)	34.3 (22.3, 69.8)	33.5 (15.2, 55.3)	33.7 (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)

Source Table 7-3, CSR

3.2.4 Results

Primary Endpoint: Changes in HbA1c (%) from baseline at Month 6

The results for the primary efficacy analysis were presented as follows.

Table 4: Primary Efficacy Analysis Results

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

Source The Statistical reviewer & CSR Table 8-2.

As demonstrated in Table 4, the treatment difference between the two arms was estimated to be -0.12 with the 95% C.I. (-0.55, 0.30). Since the C.I. contains zero, superiority of the treatment was not established. Additionally, the result generated by the applicant provided similar evidence, despite the differences in the analysis method.

It is worth noting that the study was underpowered for the given sample size. As specified in the study protocol, the study intended to achieve an 80% power for detection of a 0.4% treatment difference in HbA1c. This implied a width of 0.56% for a 95% confidence interval. In reality, however, the width for the observed confidence interval was 0.85% (based on the reviewer's result). This suggested that, during the study planning stage, the applicant understated the residual SD, and likely the amount of missing data. In order to accomplish an 80% power, the study should have recruited approximately 2.3 times as many subjects as its current sample size ($(0.85\% / 0.56\%)^2 \approx 2.3$).

3.2.5 Conclusion

Despite the differences in the analysis method, the analysis results provided by the applicant and the statistical reviewer were highly similar. Both failed to demonstrate efficacy of the investigational product. Given the statistical insignificance in the analysis result, the applicant did not seek any efficacy claim in the label.

3.3 Evaluation of Safety

The safety and tolerability of the investigational product were assessed during the 12-month Treatment Period among the safety set, which consisted of all randomized patients who took at least 1 dose of study medication. Safety assessments included evaluations of adverse events (including nature, frequency, and relationship to treatment), clinical laboratory parameters (including hematology, blood chemistry and urinalysis), vital signs, physical examinations (tanner stage), prior and concomitant medications. The investigational product was found generally well-tolerated and safe over the 12-month Treatment Period. A detailed safety report could be found in *Section 10: Safety Evaluation* in the Clinical Study Report.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses guided by the ITT principle (i.e., an ANCOVA model applied to all randomized subjects who took at least 1 dose of study medication, with missing data multiply imputed based on the washout method) were performed for Study WEL-A-U-307. Subgroups were defined by sex (Female vs Male), race (White vs Others), and age (> 13 vs ≤ 13). The analysis results were presented as follows.

Table 5. A1C(%) Change from Baseline at Month 6 for Different Subgroups

Treatment	Baseline		CHG 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 (-0.61, 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 Old				
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 Old				
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)	

The table was generated based on the subgroup analyses performed by the reviewer.

As demonstrated in the table, 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). The treatment difference between the two arms, however, was not statistically significant. These insignificant results from the subgroup analyses were consistent with the findings based on the entire population.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Two issues regarding the applicant's efficacy analysis were identified during this review. The first issue was with respect to the full analysis set (FAS) for primary analysis. According to the FDA guidelines, all randomized subjects regardless of their post-randomization characteristics should be included in the primary FAS. The applicant failed to follow this guideline by excluding subjects who did not have any post-baseline A1c measurement prior to any rescue therapy. The second issue was with respect to missing data imputation. Instead of multiple imputation based on the washout method as recommended by the division, the applicant imputed missing endpoint data with a single imputation method based on LOCF.

5.2 Collective Evidence

Efficacy analyses were reconducted by the FDA statistical reviewer. Under the treatment-policy estimand, data collected from all randomized and treated patients regardless of post-randomization characteristics were used in the ANCOVA model pre-specified in the study protocols. Missing data were handled based on the washout method and Rubin's Rule for multiple imputation. The conclusion based on this analysis concurred with the one derived from the applicant's analyses. Both were unable to demonstrate superiority of Welchol® (3.75g/day) regarding A1c reduction when compared to placebo (Welchol® 0.625g/day).

Safety evaluation has shown that Welchol® (3.75g/day) was generally well-tolerated through the 12-month length of treatment.

5.3 Conclusions and Recommendations

The statistical findings in this submission failed to demonstrate superiority of Welchol® (3.75g/day) compared to placebo regarding glycemic control in pediatric patients (10 to 17 years old) with T2DM.

5.4 Labeling Recommendations

The applicant proposed the following change to *Section 8.4 Pediatric Use* of the labels for Welchol®:

> *The efficacy of WELCHOL,* (b) (4) *has not been established for the treatment of type 2 diabetes mellitus in pediatric patients.*

In addition, the efficacy analysis results from Study Wel-A-U-307 have been included in Section 8.4. Specifically, the estimated treatment effects regarding HbA1c and fasting plasma glucose (FPG) were reported both in text and in tabular form.

From a statistical perspective, the proposed change in italics is approvable, since it reflected the findings from Study Wel-A-U-307. The analysis result regarding HbA1c, however, needs to be replaced with the one obtained by the statistical reviewer. (b) (4) should be removed from the label.

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