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 #:	NDAs 201280, 201281, 208026
Supplement #:	S-27, S-35, S-24
Drug Name:	Tradjenta (linagliptin), Jentadueto (linagliptin + metformin), Jentadueto XR (linagliptin + metformin extended release)
Indication(s):	No proposed indication
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc (BIPI)
Date(s):	Receipt date:
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Type 2 diabetes, pediatric study, DPP4-inhibitor, master protocol, shared control, analysis of covariance, placebo washout imputation, shrinkage analysis, Bayesian hierarchical modelling

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1 EXECUTIVE SUMMARY

On December 20, 2022, the Sponsor, BIPI, submitted NDA 201280 S-027 for Tradjenta (linagliptin, or lina) and NDA 204629 S-042 for Jardiance (empagliflozin, or empa), in support of product label updates for Section 8.4: Pediatric Use. The label updates of both products were based on a single Phase 3 pediatric trial titled "DIabetes Study of LiNAgliptin and eMpagliflozin in children and adOlescents" (DINAMO). The study was conducted to satisfy the pediatric Post Marketing Requirement (PMR)-3300-1, which applies to all drug products containing empa and lina, and the pediatric written request amended on August 11, 2022, which applies to all drug products containing lina.

On January 31, 2023, BIPI submitted NDA 201281 S-035 for Jentadueto (the FDC of lina and metformin, or lina + met), and NDA 206111 S-038 for Synjardy (the fixed dose combination product [FDC] of empa and metformin, or empa + met). On April 25, 2023, BIPI submitted NDA 208026 S-024 for Jentadueto XR (lina + met extended release [XR]), and NDA 208658 S-26 for Synjardy XR (empa + met XR). All four NDA supplements referred to the study DINAMO for label updates on Section 8.4. To facilitate the review, the Agency decided to combine the internal review timelines of all the aforementioned NDA supplements concerning empa and lina. This statistical review focuses on lina, its FDC with metformin and its FDC with metformin XR under NDA201280, NDA 201281 and NDA 208026, respectively. Refer to a separate review for empa and its FDC with metformin under NDA204629, NDA206111 and NDA 208658.

The three drug products containing lina are currently indicated for treatment of adult patients with type 2 diabetes mellitus (T2DM) as adjuncts to diet and exercise. In the current submissions, the Sponsor proposed to update Section 8.4 of both product labels with the study result from DINAMO. The study failed to demonstrate a significant treatment effect of linagliptin in comparison to placebo with respect to the primary endpoint. Specifically, the placebo-adjusted HbA1c change from baseline was -0.34% with a 95% confidence interval (-0.99, 0.30). The analysis borrowing from literature data on other DPP-4 inhibitors was robust to the prior weight assigned to the informative prior, and is considered more reliable than the results from the analysis based on the pharmacometric simulation. Bayesian supplementary analyses confirmed that the study DINAMO did not demonstrate the treatment effectiveness of linagliptin compared to placebo.

1.1 Brief overview of Clinical Study

The Study DINAMO was a multi-center, randomized, parallel-group, placebo-controlled study intended to evaluate the efficacy and safety of lina 5 mg and an empa dosing regimen vs. placebo after 26 weeks of treatment in children and adolescents with T2DM. It consisted of 1-week Screening Period, a 2-week Run-in Period, a 26-week Main Treatment Period, a 26-week Extended Treatment Period, and a 3-week safety Follow-up Period. At Week 1 of the Main Treatment Period, a total of 158 subjects were randomized in a 1:1:1 ratio to one of the three treatment arms: lina 5mg, empa 10 mg, or placebo. Subjects randomized to lina 5mg and placebo continued with their initially assigned treatments throughout the entire Main Treatment Period.

The primary endpoint HbA1c change from baseline was assessed at Week 26 of the Main Treatment Period.

1.2 Major Statistical Issues

Overall, there were no statistical issues with missing data and statistical methods. The missing rate of the primary endpoint measurement was 5.7% for lina, and 5.7% for placebo. Missing endpoints were multiply imputed based on placebo washout. For primary efficacy analyses, the applicant applied an ANCOVA adjusted for treatment, baseline HbA1c and age stratum at baseline (< 15 years vs 15 to <18 years).

The study was underpowered for the comparison of lina vs. placebo (See Section 3.2.1). As requested by the Agency to address the concern about a potentially undersized study, the submission package also included the results of the supplementary Bayesian borrowing analyses, which leverage information from the previously fitted pharmacokinetic and exposure-response models for linagliptin and based on available historical data in adult and pediatric patients with T2DM[1] . The choice of prior distribution had a consequential effect on the strength of evidence associated with a determination of superior efficacy and provided contradictory results. The exposure-response based prior resulted in superior efficacy for linagliptin whereas borrowing information from other historical DPP-4 inhibitor failed to reach agreed decision threshold.

1.3 Collective Evidence

The primary efficacy results are summarized in Table 1. Sensitivity analyses that inspected the impact of untestable missing data assumptions demonstrated a similar estimated treatment effect to the primary efficacy analysis (Section 3.2.4). Subgroup analyses on the primary efficacy endpoint demonstrated consistent findings in subgroup levels defined by age, sex, race, region, and background medication (Section 4). An increased risk of hypoglycemia was found in subjects treated with linagliptin compared to those treated with placebo (Section 3.3). The exposure response-based Bayesian borrowing analysis provided evidence for superior efficacy for linagliptin, with a point estimate of −0.51% and 95% credible interval (−0.92%, −0.05%). Whereas the Bayesian borrowing from literature data on other DPP-4 inhibitors did not meet the pre-specified criterion for superiority of linagliptin compared to placebo with a point estimate of −0.28% and 95% credible interval (−0.69%, 0.09%). The analysis borrowing from literature data on other DPP-4 inhibitors was robust to the prior weight assigned to the informative prior, and is considered more reliable than the results from the analysis based on the pharmacometric simulation. Bayesian supplementary analyses confirmed that the study DINAMO did not demonstrate the treatment effectiveness of linagliptin compared to placebo.

Table 1: Primary Efficacy Result on HbA1c Change from Baseline at Week 26

	Lina 5 mg N=52	**Placebo N=53**
Baseline, mean (SD)	8.05 (1.11)	8.05 (1.23)

[1] The Bayesian analyses were reviewed by Dr. Satyajit Ghosh. Details about this review can be found in Section 3.2.

Missing primary endpoint, n (%)	3 (5.7)	3 (5.7)
Change from baseline, LSMean[1] (SE)	0.33 (0.23)	0.68 (0.23)
Difference from Placebo, LSMean[1] (CI)		-0.34 (-0.99, 0.30)
Two-sided p-value (unadjusted)		0.29

Abbreviations: CI = confidence interval, SD = standard deviation, SE = standard error. N = sample size of the mITT set, defined as all randomized and treated subjects who had baseline HbA1c measurements, regardless of treatment adherence or rescue medication.
1 The LSMean estimate is based on an ANCOVA model adjusted for baseline HbA1c, baseline age stratum (< 15 years vs 15 to <18 years), and treatment after imputing missing data using placebo washout method
Source Clinical Study Report Table 15.2.1.1 1 (Page 312), verified by the statistical reviewer

1.4 Conclusion and Recommendations

In the DINAMO study, treatment effectiveness of linagliptin 5 mg to placebo regarding HbA1c reduction was not demonstrated. The applicant only sought to add the study information to Section 8.4 of the product label without any efficacy claim for pediatric patients (11 to <18 years) with T2DM. We recommend the proposed label update in Section 8.4 .

2 INTRODUCTION

2.1 Overview

Linagliptin (Tradjenta®), a Dipeptidyl Peptidase-4 (DPP4) inhibitor, and its FDC with metformin (Jentadueto® and Jentadueto® XR) were approved by the FDA in 2011 and 2012, respectively, both as adjuncts to diet and exercise to improve glycemic control among adults with T2DM. In the current NDA supplements, the applicant proposed to update Section 8.4 of both product labels based on the analysis results from the Phase 3 study DINAMO conducted among pediatric patients with T2DM aged 11 to < 18 years. The study started on April 26, 2018, and completed on June 27, 2022. Database lock occurred on August 10, 2022. An overview of the study is presented in Table 2.

Table 2: Overview of Study DINAMO

Trial ID	Design*	Treatment (Sample size)	Endpoint/Analysis
1218.91	MC, R, DB, PG, PC (3-week screening & run-in period + 52-week treatment period + 3-week follow-up period)	Empagliflozin 10 mg and 25 mg† (empa pooled) (N = 52) Linagliptin 5mg (lina) (N = 52) Placebo (pbo) (N = 53)	Primary: Change in HbA1c from baseline at Week 26 Key Secondary: None The primary endpoint was analyzed with an ANCOVA adjusted for treatment, baseline HbA1c, and baseline age category (< 15 years vs 15 to < 18 years). The analysis was based on the mITT population††, with missing data

			multiply imputed using the washout method.

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled
† Subjects from the empa arm received empa 10mg at the beginning of the Treatment Period. At Week 12, an evaluation of HbA1c was performed for these subjects. Subjects achieved HbA1c < 7.0% continued with empa 10mg, whereas those who failed the A1c target were further randomized to empa 10mg or empa 25mg at Week 14. The primary efficacy analysis was conducted based on the empa (10 mg and 25 mg pooled) vs placebo .
†† The mITT population was defined as all subjects who were randomized and received treatment

2.2 Data Sources

The Electronic Document Room (EDR) location for the Tradjenta submission package is \\CDSESUB1\evsprod\NDA201280\0463. Datasets for the study DINAMO (both in ADAM format and SDTM format) and the programming codes for the efficacy analyses can be found under the subdirectory: m5\datasets\1218-0091. The EDR location for the Jentadueto package is \\CDSESUB1\evsprod\NDA201281\0269.

On March 3, 2023, an IR was sent to the Sponsor requesting additional subgroup analyses based on background medication. The Sponsor's response can be found at \\CDSESUB1\evsprod\NDA204629\1494

On March 8, 2023, the Sponsor submitted the list of programs (R codes) for the supplementary Bayesian analysis which can be found at \\CDSESUB1\evsprod\NDA201280\0493 .

On March 14, 2023, an IR was sent to the Sponsor requesting efficacy analyses on FPG change from baseline at Week 26 and BMI Z-score change from baseline. The Sponsor's response can be found at \\CDSESUB1\evsprod\NDA204629\1509.

On April 18, 2023, an IR was sent to the Sponsor requesting model-based analyses on hypoglycemia event counts. The Sponsor's response can be found at \\CDSESUB1\evsprod\NDA204629\1546.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

No issues have been identified with respect to data and analysis quality.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The study DINAMO was a multi-center, randomized, parallel-group, placebo-controlled study intended to evaluate the efficacy and safety of lina 5 mg and an empa dosing regimen vs. placebo after 26 weeks of treatment in children and adolescents with T2DM. As demonstrated in Figure 1, the study consisted of a one-week Screening Period, a two-week Run-in Period, a 26-week

Main Treatment Period, a 26-week Extended Treatment Period, and a three-week safety Follow-up Period. At Week 1 of the Main Treatment Period, a total of 158 subjects were randomized in a 1:1:1 ratio to one of the three treatment arms: empa 10 mg, lina 5mg, or placebo. The randomization was stratified by age (< 15 years vs 15 to < 18 years).

At Week 12, subjects on empa 10 mg were assessed for their HbA1c levels. Those who failed to achieve HbA1c < 7% underwent a second randomization at Week 14, during which subjects were randomized to either empa 10 mg or empa 25 mg in a 1:1 ratio. The primary endpoint HbA1c change from baseline was assessed at the end of the Main Treatment Period (i.e., Week 26). Meanwhile, the Extended Treatment Period started at Week 26. Subjects previously on placebo were randomized to lina 5mg, empa 10mg or empa 25mg in a 1:1:1 ratio, whereas subjects previously on active treatment continued with their treatment. The Extended Treatment Period ended at Week 52, followed by a three-week safety assessment.

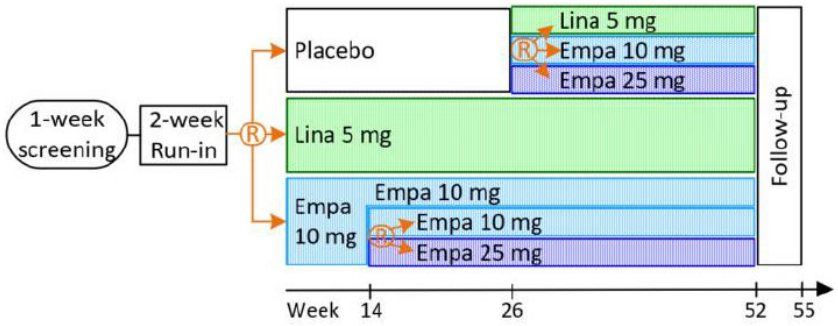


Figure 1: Trial Design for DINAMO
Source Figure 9 1, CSR

The primary objective of the study was to demonstrate both superiority of lina 5 mg to placebo, and superiority of empa (10 mg and 25 mg pooled) to placebo, as assessed by the primary endpoint: HbA1c (%) change from baseline at Week 26. The study did not specify any key secondary endpoint.

Sample Size

The determination of the study sample size, as initially specified in the SAP, is as follows. Assuming a -0.55% treatment effect difference between the active treatment group (lina or empa) and the placebo group and a 0.9% standard deviation (SD), a sample size of 50 subjects per initial randomized treatment arm (150 subjects in total) would provide 85% power at a two-sided 0.05 level.

In the IR Letter issued on November 16, 2021, the Agency expressed concerns that the study might be undersized due to the consideration that the observed SD might be greater than the assumed SD of 0.9%. This concern was raised from recently completed pediatric T2DM trials in which the SDs were generally found larger than adult T2DM trials. In response to this IR, the Sponsor conducted a blinded interim check of the SD. At the time, 157 subjects had started treatment and 141 subjects were included in the SD calculation. The SD observed from the interim check was 1.65%, which confirmed the Agency's concern. The Sponsor, nonetheless, refused to increase the sample size by arguing that the assumed effect size of 0.55% was too

conservative for empa. However, the sponsor did not provide any new assumption for the effect size of lina, or any justification for the previous assumption of -0.55%. The Agency agreed with the Sponsor's decision of no sample size increase, but asked the Sponsor to perform a supplemental Bayesian borrowing analysis as additional supportive evidence to address the sample size concern. The requested analyses were submitted in NDA 204629, S-42, and was reviewed by Dr. Satyajit Ghosh from the Pediatrics and Maternal Health Team at DB II.

In reality, 52 subjects on lina 5mg and 53 subjects on placebo were randomized and treated in the study. The pooled SD for the lina and the placebo groups was 1.69%, and the estimated treatment effect was -0.34% for lina 5mg after placebo adjustment. The study was underpowered for comparing lina vs. placebo with a smaller effect size and a larger SD than the assumptions used in sample size determination. In order to achieve an 85% power for lina vs. placebo, the study should have recruited approximately 3.5 times as many subjects as its current sample size.

Primary Endpoint

- Change from baseline in HbA1c (%) at Week 26

Secondary Endpoints

- Change from baseline in fasting plasma glucose at Week 26
- Change from baseline in body weight at Week 26
- Change from baseline in systolic blood pressure at Week 26
- Change from baseline in diastolic blood pressure at Week 26
- Incidence of HbA1c < 6.5% at Week 26
- Incidence of HbA1c < 7.0% at Week 26

3.2.2 Statistical Methodologies

The Sponsor did not pre-specify an estimand framework for the study in SAP. The key components of an estimand are summarized as follows, based on the pre-specified statistical approaches used for the primary efficacy analysis.

Population & Analysis Set

The target population was the modified ITT population, defined as all randomized and treated subjects who had baseline HbA1c measurements, regardless of treatment adherence or rescue medication.

Handling of Missing Data

Multiple imputation based on placebo washout was applied. Specifically, missing data from the placebo arm were imputed with a sequential linear regression constructed based on observed HbA1c values from the placebo group, measured at baseline, Weeks 4, 12 and 26. Missing data from the treatment arm were imputed with a sequential linear regression constructed based on the observed HbA1c values from the placebo group, measured at baseline and Week 26. 1000 imputed dataset were created, and Rubin's Rule was used to combine the inference results.

Multiplicity Adjustment

The two primary hypotheses concern comparisons of lina 5 mg against placebo and empa pooled against placebo with respect to the primary endpoint: HbA1c change from baseline at Week 26. To control the overall Type I error rate at a two-sided 0.05 level, the Sponsor applied the Hochberg procedure for simultaneous testing of the two primary hypotheses.

Reviewer's note

According to the recently published FDA Guidance on master protocol for oncology product development[2], multiplicity adjustment is considered unnecessary for multiple comparisons of different investigational drugs to the comparator group in an umbrella trial setting. This suggested that the two primary hypothesis tests in this study can be conducted independently, each at a two-sided 0.05 level without Hochberg procedure.

The secondary hypothesis family concerns solely empa vs. placebo, and thus will not be discussed in this review.

Primary Efficacy Analyses

The primary hypothesis test was performed based on an ANCOVA, with HbA1c change from baseline at Week 26 as the response variable, and treatment, baseline HbA1c, and baseline age category (< 15 years vs 15 to < 18 years) as covariates.

Sensitivity Analysis

In the Sponsor's submission package, a mixed model for repeated measure (MMRM) based on the mITT population was used as a sensitivity analysis for the confirmatory tests of the primary hypothesis family. This is considered insufficient from a regulatory perspective, as an MMRM assumes data are missing at random, which is an unlikely scenario for many missing cases in clinical trials. In this review, to study the impact of missing data on the primary analysis result, the primary endpoint was modeled with the same ANCOVA as the Sponsor's, while missing primary endpoints were multiply imputed based on the return-to-baseline approach.

Bayesian Supplementary Analysis

Bayesian inference was used in this supplementary analysis to leverage information from the previously fitted pharmacokinetic and exposure-response models for linagliptin and based on available historical data in adult and pediatric patients with T2DM. Partial exchangeability of pediatric and adult data was assumed through covariate adjustment. The objective of the Bayesian analysis was to provide supportive evidence for the comparison of the mean change in HbA1c (%) from baseline to the end of 26 weeks between linagliptin and placebo. Throughout the review we will refer to this as the placebo-corrected treatment effect of linagliptin. Bayesian borrowing analyses based on two prior approaches were provided.

1. *Prior based on exposure-response based pharmacometric model*

[2] FDA Guidance for Industry: Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics: https://www fda.gov/media/120721/download

Using the population PK and PK-PD models for linagliptin, 5000 simulations was conducted to generate treatment responses for HbA1c served as prior information for the Bayesian borrowing analysis. The sample means from each of the 5,000 corresponding iterations in the pharmacometric simulation constitute a random sample of the predicted placebo-corrected treatment effect in DINAMO. Due to the nature of the pharmacometric models, it is assumed that the predicted placebo-corrected mean HbA1c change from baseline approximately follows a normal distribution (Figure 2). This approximate normal distribution had a mean of μ_I=−0.64% and a standard deviation of 0.02%.

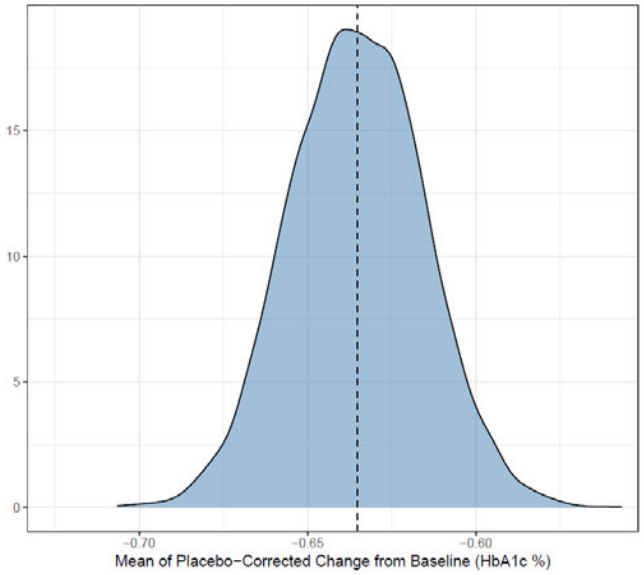


Figure 2: Simulated treatment effects for Linagliptin
Source Excerpted from page 42 of the supplemental analysis report

The unit standard deviation (SD), σ_I, was estimated from the clinical trials in adults and the blinded assessment of the DINAMO study. The estimated SD of empagliflozin, linagliptin, and placebo arm were 1.52, 1.65 and 1.72 respectively. Assuming mutual independence among the treatment arms, the SD corresponding to the linagliptin treatment difference was found to be $\sigma_I = \sqrt{1.65^2 + 1.72^2} = 2.38$. In order to obtain comparisons that correspond to an informative prior weight of at most 100 patients per treatment arm, the applicant replaced the prior variances v_I from the pharmacometrics simulations with

$$v_I^* = \begin{cases} v_I, & \text{if } v_I \geq \sigma_I^2/100 \\ \dfrac{\sigma_I^2}{100}, & else \end{cases}$$

The informative prior was then robustified against potential prior-data conflict. The final prior was a two component normal mixture prior - the informative component with weight w_I= 0.65 (corresponds to prior ESS 51 per treatment arm) and a weakly informative normally distributed

prior with mean μ_I corresponding to the mean placebo corrected treatment effect estimated from the pharmacometric simulation, and standard deviation σ_I. This leads to the following final prior probability densities for the placebo-corrected treatment effect

$$p_I(\theta_I) = w_I Norm(\mu_I, v_I^*) + (1 - w_I) Norm(\mu_I, \sigma_I^2).$$

The weight w_I=0.65 was determined and agreed upon with the Agency (Advice Information letter dated July 28, 2022) to have overall prior ESS of 100 in the linagliptin and placebo arm combined.

2. *Prior based on data from other DPP-4 inhibitors*

A second Bayesian borrowing analysis to leverage prior data in a blinded assessment of DINAMO was performed. In this analysis the placebo-corrected treatment effects reported for pediatric populations with T2DM treated with sitagliptin was considered to be informative for the outcome in DINAMO. Two studies with "Januvia 100 mg" (sitagliptin) were identified for providing prior information in DINAMO (Table 3).

Table 3: HbA1c (%) change in historic placebo-controlled trials of SGLT-2 or DPP-4 inhibitors in pediatric patients with T2DM

	Placebo			Active treatment			Treatment difference[4]
Active treatment / Endpoint	N	Mean	Variabi-lity	N	Mean	Variabi-lity	Adj. mean active – placebo (95% CI)
Farxiga 10mg[1]							
Treated patients	33			39			
HbA1c change at Week 24	23	0.50	SE=0.34	31	-0.25	SE=0.30	-0.75 (-1.65, 0.15)
Januvia 100mg[2]							
HbA1c change at Week 20	95	0.23		95	0.06		-0.17 (-0.62, 0.28)
Januvia 100mg[3]							
HbA1c change at Week 20	113	0.09		107	-0.23		-0.33 (-0.70, 0.05)

[1] Study to Evaluate Safety and Efficacy of Dapagliflozin in Patients with Type 2 Diabetes Mellitus Aged 10-24 Years ClinicalTrials.gov Identifier: NCT02725593
[2] US PI for Januvia, revised 12/2020, Section 8.4 Pediatric use, study 1
[3] US PI for Januvia, revised 12/2020, Section 8.4 Pediatric use, studies 2 and 3
[4] Treatment difference: Least Square Mean difference of active treatment – placebo.
Sources Page 34 of the Statistical Analysis Plan for the Bayesian borrowing Analysis.

Based on the reported standard errors for the placebo-corrected effect and the sample sizes for the sitagliptin and placebo arm, the estimated unit-information SD was σ_I=2.12. The informative component of the prior was derived from the adjusted mean differences for Januvia 100 mg (-0.17 and -0.33) and unit-information SD 2.12 using the meta analytic predictive (MAP) [Schmidli et al, 2014] approach. Further, a moderate prior was used for the between-study

heterogeneity (τ). Modelling $\tau \sim Half - Normal\left(scale = \frac{\sigma_I}{16}\right)$[3], the resulting informative component prior for linagliptin was a two component normal mixture prior. The first component had a weight of 0.47, a mean of −0.25, and a standard deviation of 0.17. The second component had a weight of 0.11, a mean of −0.23, and a standard deviation of 0.32. In order to have overall prior ESS of 100, the combined weight for the two informative components of the prior was determined to be 0.58 (Advice Information letter dated July 28, 2022), with the remaining 0.42 weight allocated to a unit information prior with mean -0.23 to provide robustness in the case of prior-data conflict. This resulted in an effective sample size (ESS) of 51 per treatment arm. The ESS was calculated with the expected local information ratio (ELIR). The final robust MAP prior distribution has the probability density as below

$$p_L(\theta_l) = 0.47Norm(-0.25, 0.17^2) + 0.11Norm(-0.23, 0.32^2) + 0.42Norm(-0.23, 2.12^2)$$

.

Posterior calculation
Posterior distributions were derived from each prior and the observed placebo-corrected treatment effect in the DINAMO trial. The decision rule to determine the efficacy of linagliptin was based on the comparison of the 97.5% quantile of the posterior treatment effect with 0 i.e.

$$\text{Prob}(\theta_l < 0 \mid y) \geq 0.975$$

where:

- y is the observed data.
- θ_l is the placebo-corrected effect of linagliptin.

If these decision criterion was met, then there was evidence of superior efficacy of the treatment in the pediatric population of DINAMO.

A tipping point sensitivity analysis with alternative prior weights for the informative component was performed for weights 0, 0.1, 0.2, …, 0.9, 1. Here a weight of 0 corresponded to a weakly-informative prior, with the resulting estimate being based almost entirely on the DINAMO data. A weight of 1 corresponded to a prior that is entirely based on the pharmacometric model predictions (or the literature data on DPP-4 inhibitors) assuming full exchangeability of the covariate-adjusted predictions (or the literature data on DPP-4 inhibitors) with the DINAMO outcome data without robust component down-weighting.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A summary of subject disposition is presented in Table 4. All randomized subjects received at least one dose of the study drug. No notable difference was observed between the lina and placebo arms with respect to the study disposition. Slightly higher study discontinuation and treatment discontinuation rates were observed in the placebo arm compared to the lina arm.

[3] If $X \sim N(0, \sigma^2)$ then $|X|$ is said to have a Half-Normal distribution with scale=σ.

Three subjects from the lina arm and three subjects from the placebo arm missed their primary endpoint assessments. Due to a limited sample size of the retrieved dropouts, missing data cannot be imputed based on the retrieved dropout group.

Table 4: Subject Disposition

	Lina 5mg (%) N = 53*	**Placebo (%) N = 53**	**Total (%) N = 106**
Treated	52 (100)	53 (100)	105 (100)
Study Discontinuation (up to Week 52)	4 (7.7)	6 (11.3)	10 (9.5)
Lost to follow-up	1 (1.9)	2 (3.8)	3 (2.9)
withdrawal by subject	3 (5.8)	4 (7.5)	7 (6.7)
Other	0	0	0
Treatment Discontinuation (up to Week 52)	8 (15.4)	11 (20.8)	19 (18.1)
Adverse Event	0	2 (3.8)	2 (1.9)
Lost to follow-up	1 (1.9)	1 (1.9)	2 (1.9)
Withdrawal by subjects	5 (9.6)	7 (13.2)	12 (11.4)
Other	2 (3.8)	1 (1.9)	3 (2.9)
Primary Endpoint Missing (up to Week 26)	3 (5.8)	3 (5.7)	6 (5.7)
Retrieved Dropout (up to Week 26)	0	2 (3.8)	2 (1.9)

* One subject randomized to lina were not treated, and was not included in the primary analysis set.
Source Table 10 2, Page 336, CSR

A summary of patient demographics and baseline characteristics is presented in Table 5. Based on the summary, demographics and baseline characteristics are generally balanced between lina and placebo.

Table 5: Subject Baseline and Demographics

	Lina 5mg N=52	**Placebo N=53**	**Total N=105**
Sex , n (%)			
Female	30 (57.7)	34 (64.2)	64 (61.0)
Male	22 (42.3)	19 (35.8)	41 (39.0)
Age , years			
Mean (SD)	14.6 (1.94)	14.6 (1.76)	14.6 (1.84)
Median	14.5	14.0	14.0
Min, Max	10.0, 17.0	11.0, 17.0	10.0, 17.0
Age Category , n (%)			
<15	25 (48.1)	26 (49.1)	51 (48.6)
≥ 15 to <18	27 (51.9)	27 (50.9)	54 (51.4)
Race , n(%)			
American Indian/ Alaska Native	3 (5.8)	1 (1.9)	4 (3.8)
Asian	4 (7.7)	3 (5.7)	7 (6.7)
Black/African American	13 (25.0)	17 (32.1)	30 (28.6)
Native Hawaiian/Other Pacific Islander	2 (3.8)	1 (1.9)	3 (2.9)

White	26 (50.0)	29 (54.7)	55 (52.4)
Multiple	2 (3.8)	1 (1.9)	3 (2.9)
Missing	2 (3.8)	1 (1.9)	3 (2.9)
Region, n (%)			
Asia	3 (5.8)	1 (1.9)	4 (3.8)
Europe	5 (9.6)	7 (13.2)	12 (11.4)
North America	37 (71.2)	34 (64.2)	71 (67.6)
South America	7 (13.5)	11 (20.8)	18 (17.1)
Baseline BMI Z-score, n (%)			
≥ -2 to 1 (Normal)	0	2 (3.8)	2 (1.9)
>1 to 2 (Overweight)	4 (7.7)	7 (13.2)	11 (10.5)
>2 (Obese)	48 (92.3)	44 (83.0)	92 (87.6)
Baseline background medication, n (%)			
Insulin Only	0	2 (3.8)	2 (1.9)
Metformin and Insulin	22 (42.3)	19 (35.8)	41 (39.0)
Metformin Only	26 (50.0)	28 (52.8)	54 (51.4)
None	4 (7.7)	4 (7.5)	8 (7.6)
Baseline HbA1c, %			
Mean (SD)	8.0 (1.11)	8.1 (1.23)	8.0 (1.16)

Source Statistical Reviewer Analysis; adsl.xpt

3.2.4 Results and Conclusions

3.2.4.1 Results from Primary Efficacy Analysis and Sensitivity Analysis

As demonstrated in Table 6, the LSMean difference (95% CI) in HbA1c change from baseline at Week 26 is -0.34 (-0.99, 0.30) for lina 5 mg vs. placebo, with a two-sided p-value 0.29. The study failed to demonstrate superiority of lina to placebo with respect to the primary endpoint.

Table 6: Primary Efficacy Result on HbA1c Change from Baseline at Week 26

	Lina 5 mg N=52	**Placebo N=53**
Baseline, mean (SD)	8.05 (1.11)	8.05 (1.23)
Missing primary endpoint, n (%)	3 (5.7)	3 (5.7)
Change from baseline, LSMean[1] (SE)	0.33 (0.23)	0.68 (0.23)
Difference from Placebo, LSMean[1] (CI)	-0.34 (-0.99, 0.30)	
Two-sided p-value (unadjusted)	0.29	

Abbreviations: CI = confidence interval, SD = standard deviation, SE = standard error.
[1] The LSMean estimate is based on an ANCOVA model adjusted for baseline HbA1c, baseline age stratum (< 15 years vs 15 to <18 years), and treatment
Source Clinical Study Report Table 15.2.1.1 1 (Page 312), verified by reviewer

It is worth noting that a placebo-adjusted treatment effect of 0.34% HbA1c reduction from baseline by itself could be clinically meaningful. However, considering that the average patient after 26 weeks of treatment of lina had a worse-than-baseline glycemic level (i.e., a 0.33% increase from baseline, as opposed to a 0.17% *reduction* from baseline for those treated with

empa), the treatment effect size of lina seems questionable. In fact, a mediocre treatment effect in lack of statistical significance has been observed in pediatric T2DM trials for other DPP4 products such as sitagliptin. This further suggested that the study's failure to demonstrate superiority of lina to placebo is mostly likely a consequence of inadequate drug efficacy (which is an intrinsic trait of the DPP4 drug class), instead of an insufficient trial sample size. This is also confirmed by the Bayesian supplementary analyses, with details elaborated in Section 3.2.4.2.

For sensitivity analysis, missing primary endpoint was multiply imputed based on the return-to-baseline approach. The same ANCOVA model as the primary efficacy analysis was fitted to 500 imputed datasets, and Rubin's Rule was applied to combine the inference results. As shown in Table 7, the placebo-adjusted treatment effect was -0.36 with a 95% confidence interval (-0.99, 0.27) and a two-sided nominal p-value of 0.26. The estimates based on different imputation methods generated similar results, which confirmed the robustness of the primary analysis result.

Table 7: HbA1c Change from Baseline at Week 26, Sensitivity Analysis to Primary Analysis

	Lina 5mg N=52	**Placebo N=53**
Baseline, mean (SD)	8.05 (1.11)	8.05 (1.23)
Change from baseline, LSMean[1] (SE)	0.28 (0.23)	0.66 (0.22)
Difference from Placebo, LSMean[1] (CI)		-0.36 (-0.99, 0.27)
Nominal two-sided p-value (unadjusted)		0.26

Abbreviations: CI = confidence interval, SD = standard deviation, SE = standard error.
[1] The LSMean estimate is based on an ANCOVA model adjusted for baseline HbA1c, baseline age stratum (< 15 years vs 15 to <18 years), and treatment. Missing data was multiply imputed based on the method of the method of return to baseline. Inference results were combined with Rubin's Rule.
Source Reviewer's Analysis; adsl.xpt, adhba1c.xpt

3.2.4.2 Results from the Bayesian Supplementary Analysis

Bayesian borrowing based on exposure-response based pharmacometric model
The prior SD from the pharmacometric simulations (0.02) was less than the threshold for an ESS of 100 ($0.238 = 2.38/\sqrt{100}$). Therefore, the standard deviation of the informative component was set to 0.238. This resulted in the following prior distribution:

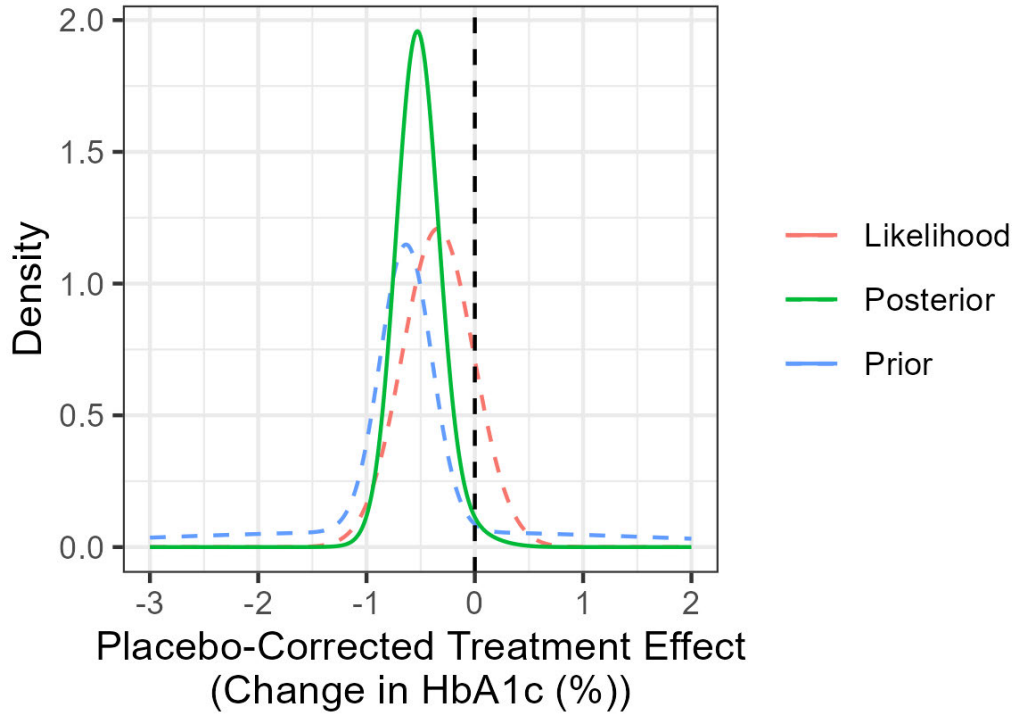
$$p_I(\theta_I) = w_I Norm\left(\mu_I, v_I^*\right) + (1 - w_I) Norm\left(\mu_I, \sigma_I^2\right),$$

where $\mu_I = -0.64$, $v_I^* = 0.238^2$, $\sigma_I^2 = 2.238^2$.

This robust prior distribution had a mean of −0.64% and a standard deviation of 1.42%. The 2.5% quantile (−4.12%) and 97.5% quantile (2.85%) were farther than the approximately 2 standard deviations from the mean as would have been expected in a normal prior; this was a result of the robustification of the prior.

Comparison of the prior, likelihood, and posterior distributions of the mean placebo-corrected treatment effect are provided in Figure 3. There was moderate amount of prior-data conflict as the prior mean deviates from the observed DINAMO mean (likelihood estimate) by 1 standard error.

Figure 3: Linagliptin placebo-corrected treatment effect distributions



Source Statistical Reviewer's Analyses

The posterior mean placebo-corrected treatment effect was −0.51%, with a standard deviation of 0.22%. The 97.5% quantile was −0.05%, which was less than zero corresponding to superior efficacy for linagliptin compared to placebo. The posterior probability of a placebo-corrected treatment effect less than zero was 0.98.

Table 8: Tipping point sensitivity analysis for different prior weights. 0 corresponded to only using the weakly-informative prior and 1 corresponded to only using the pharmacometric simulation results as the prior

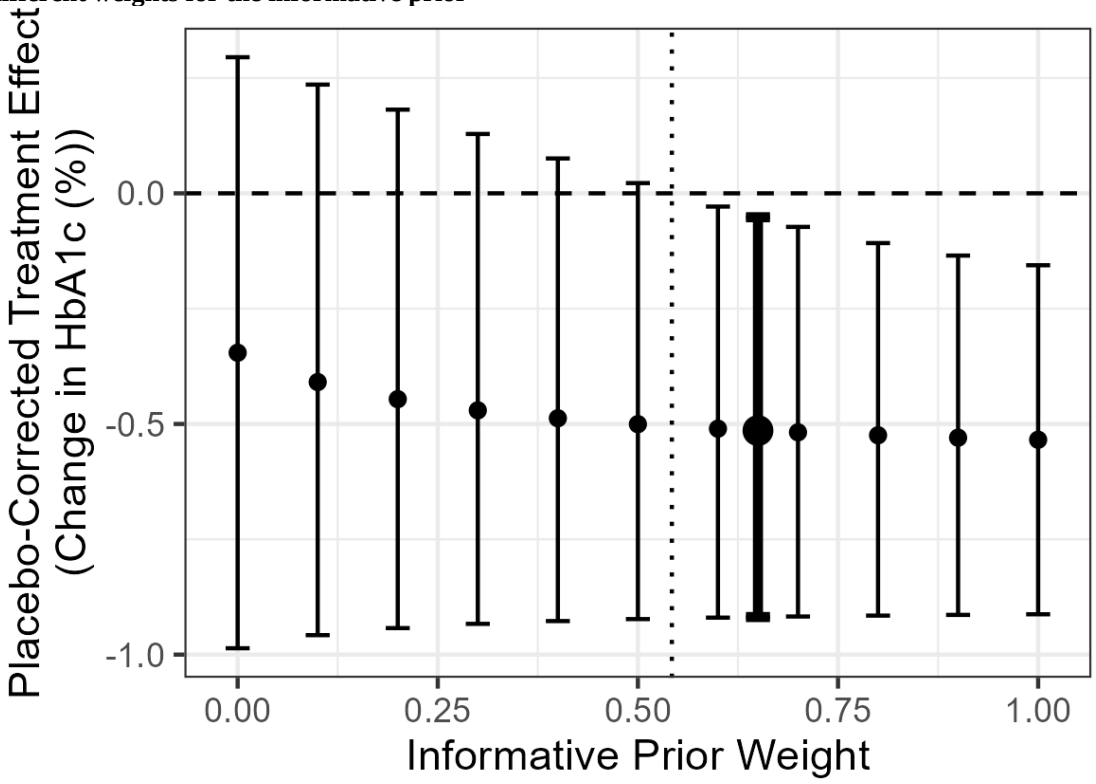
Informative Prior Weight	Prior ESS per Treatment Arm	Posterior Probability of Superior Efficacy	97.5% Decision Rule Met	Posterior Mean Treatment Effect	95% Equal-tailed Credible Interval
0.65	51	0.982	YES	-0.51	(-0.92, -0.05)
0	1*	0.855	NO	-0.35	(-0.99, 0.30)
0.1	4	0.903	NO	-0.41	(-0.96, 0.24)
0.2	9	0.931	NO	-0.45	(-0.94, 0.18)
0.3	16	0.949	NO	-0.47	(-0.93, 0.13)
0.4	25	0.962	NO	-0.49	(-0.93, 0.08)
0.5	35	0.972	NO	-0.50	(-0.92, 0.02)

0.6	45	0.979	YES	-0.51	(-0.92, -0.03)
0.7	56	0.985	YES	-0.52	(-0.92, -0.07)
0.8	69	0.990	YES	-0.52	(-0.92, -0.11)
0.9	83	0.994	YES	-0.53	(-0.91, -0.13)
1	94	0.997	YES	-0.53	(-0.91, -0.16)

[*] : With 0 weight to the informative component, the robust component of the prior contributes 1 patient worth of information.
Source Statistical Reviewer's Analyses

The tipping point sensitivity analyses showed that the informative prior weight of 0.54 (corresponding prior ESS 39 per treatment arm) resulted in 97.5% posterior probability of the placebo-corrected treatment effect being less than zero (Figure 4). Furthermore, as the informative prior weight increased, the width of the credible intervals decreased, and the mean estimate was closer to the prior mean. This reflected the increased information and lower variability in the informative prior compared to the robust prior component.

Figure 4: Linagliptin placebo-corrected treatment effects and 95% equal-tailed credible intervals for different weights for the informative prior

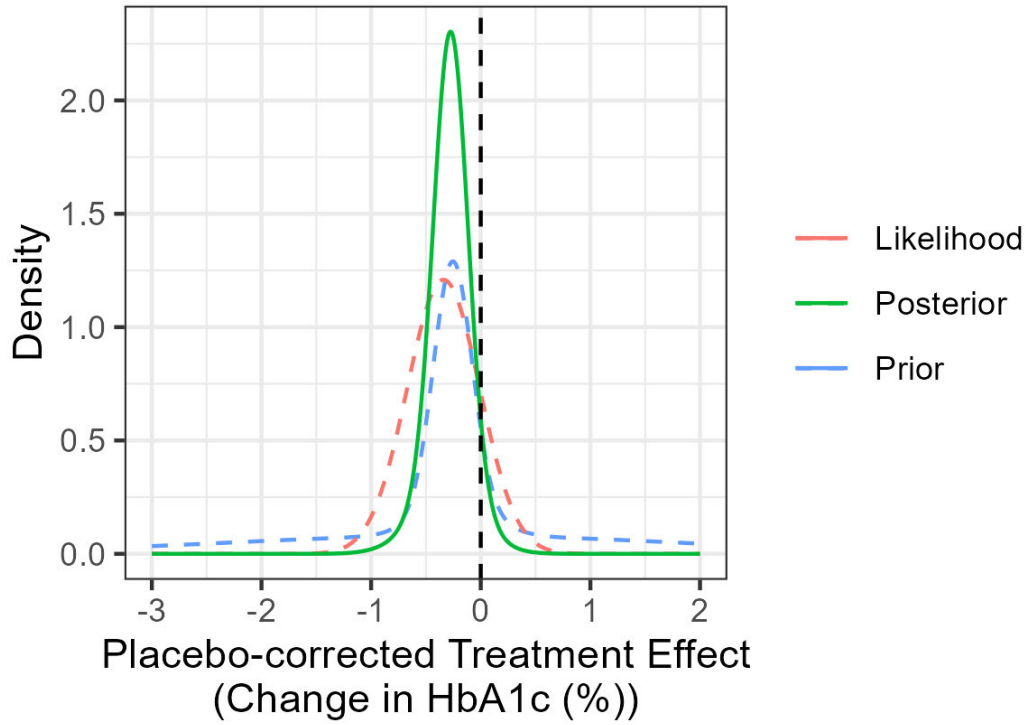


Sensitivity analysis for different prior weights for the informative prior component. A weight of 0 corresponded to only using the weakly-informative prior and 1 corresponded to only using the pharmacometric simulation results as the prior. The horizontal dashed line corresponds to the null value (0). The vertical dashed line is the tipping point (0.54) where there was exactly a 97.5% probability of a placebo-corrected treatment effect less than zero. The bolded interval is the weight used in the primary analysis. Intervals are 95% credible intervals.
Source Statistical Reviewer's Analyses

Bayesian borrowing based on data from other DPP-4 inhibitors

The robust prior distribution, derived from the meta-analysis of DPP-4 inhibitors, had a mean of −0.25% and a standard deviation of 1.38%. This prior had a smaller treatment effect and larger standard deviation than the one based on pharmacometric simulations for linagliptin. The posterior mean placebo-corrected treatment effect was −0.28%, with a standard deviation of 0.20%. The 97.5% quantile was 0.09%, which was greater than zero, and did not meet the pre-specified criterion for superiority of linagliptin compared to placebo. The posterior probability was 0.94 for superior efficacy compared with placebo. The corresponding prior, likelihood and the posterior density plots are given in Figure 5.

Figure 5: Linagliptin placebo-corrected treatment effect distributions



Source Statistical Reviewer's Analyses

The results of the tipping point sensitivity analyses are shown in Table 9 and Figure 6. Even using an informative component weight of 1 and pooling the previous pediatric study results for sitagliptin, the 97.5% decision rule was not met. As the informative prior weight increased, the width of the credible intervals decreased, and the mean estimate was closer to the prior mean.

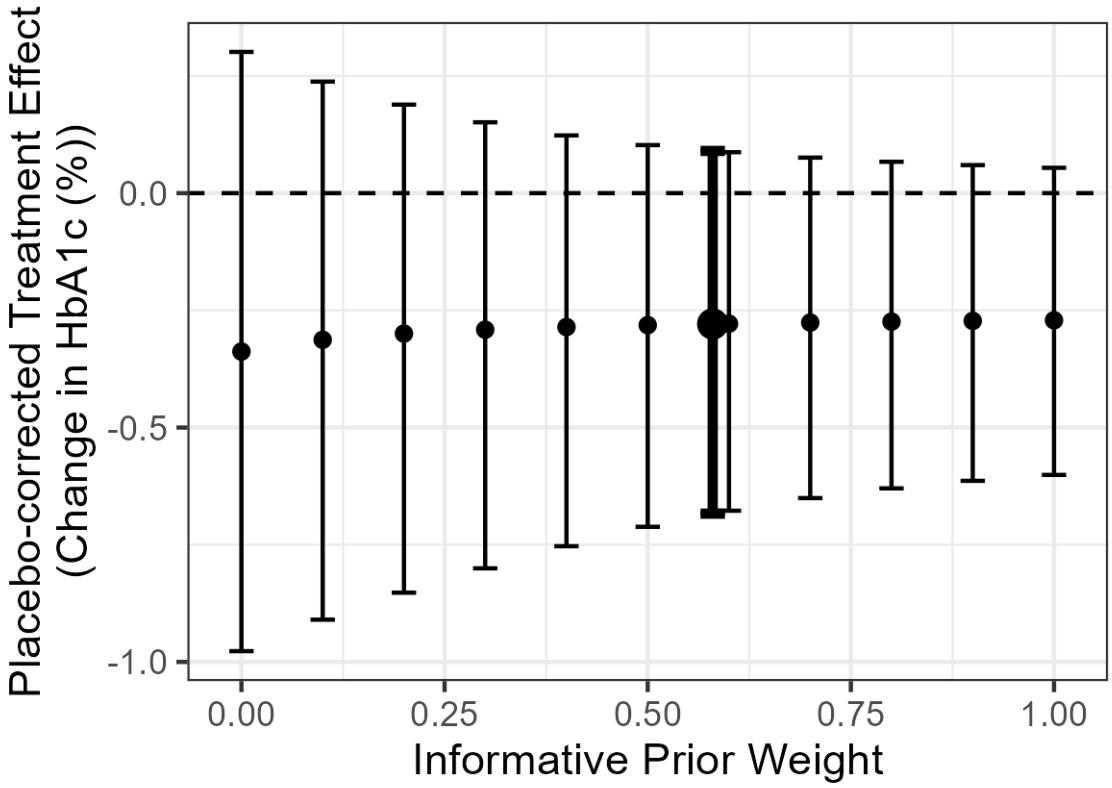
Table 9: Sensitivity analysis for linagliptin (based on sitagliptin). 0 corresponded to only using the weakly-informative prior and 1 corresponded to only using the sitagliptin data as the prior.

Informative Prior Weight	Prior ESS per Treatment Arm	Posterior Probability of Superior Efficacy	97.5% Decision Rule Met	Posterior Mean Treatment Effect	95% Equal-tailed Credible Interval
0.58	51	0.939	NO	-0.28	(-0.68, 0.09)

0	1*	0.850	NO	-0.34	(-0.98, 0.30)
0.1	4	0.888	NO	-0.31	(-0.91, 0.24)
0.2	11	0.908	NO	-0.30	(-0.85, 0.19)
0.3	19	0.921	NO	-0.29	(-0.80, 0.15)
0.4	30	0.929	NO	-0.29	(-0.75, 0.12)
0.5	41	0.935	NO	-0.28	(-0.71, 0.10)
0.6	53	0.940	NO	-0.28	(-0.68, 0.09)
0.7	66	0.944	NO	-0.28	(-0.65, 0.08)
0.8	79	0.947	NO	-0.27	(-0.63, 0.07)
0.9	94	0.949	NO	-0.27	(-0.61, 0.06)
1	110	0.951	NO	-0.27	(-0.60, 0.05)

*: With 0 weight to the informative component, the robust component of the prior contributes 1 patient worth of information.
Source Statistical Reviewer's Analyses.

Figure 6: Linagliptin placebo-corrected treatment effects and 95% equal-tailed credible intervals for different weights



Sensitivity analysis for different prior weights for the informative prior component. A weight of 0 corresponded to only using the weakly-informative prior and 1 corresponded to only using the pediatric trial results from sitagliptin as the prior. The horizontal dashed line corresponds to the null value (0). The bolded interval is the weight used in the primary analysis. Intervals are 95% credible intervals.
Source Statistical Reviewer's Analyses

3.2.4.3 Conclusion

The primary efficacy analysis failed to demonstrate a statistically significant difference between linagliptin 5 mg and placebo with respect to glycemic control. The Bayesian supplementary analysis to address the underpowered study based on pharmacometric simulation demonstrated superior efficacy of linagliptin compared to placebo.

However, a sizable difference between the mean placebo-corrected treatment effect (-0.64%) from the pharmacometric simulation and that from the observed DINAMO study (-0.34%) raised concerns about the validity of the PK-PD model. Besides, the significance of the efficacy result is also sensitive to the prior weight assigned to the informative prior.

On the other hand, the Bayesian supplementary analysis based on previous studies on DPP4 drug class did not establish superior efficacy. Consistent with the primary analysis, the sensitivity analysis also showed that superior efficacy of linagliptin could not have been established for any choice of prior weight. The analysis only used knowledge of the class of the drug to inform the prior and the prior was based on the assumption of a typical response for a drug of its class and is considered more reliable than the results from the analysis based on the pharmacometric simulation.

Besides the primary efficacy analysis and Bayesian supplementary analyses, secondary analyses including the analysis on FPG change from baseline and the analysis on BMI Z-score change from baseline did not demonstrate the treatment efficacy of linagliptin compared to placebo. The placebo-adjusted FPG change from baseline (mg/dL) was -5.64, with a 95% CI (-30.08, 18.81) and a two-sided nominal p-value 0.65. The placebo-adjusted BMI Z-score change from baseline was 0.02, with a 95% CI (-0.06, 0.10) and a two-sided nominal p-value 0.64.[4]

In conclusion, the benefit of linagliptin in treating T2DM among the target pediatric population is not established in the study DINAMO.

3.3 Evaluation of Safety

Hypoglycemic event counts were evaluated among the safety set, defined as all subjects who received at least one dose of the treatment. Subjects were analyzed according to their assigned treatments: lina 5mg, vs. placebo, from Week 0 to Week 26. No severe hypoglycemia events were observed in the study. The results for hypoglycemia events with Plasma Glucose < 54 mg/dL (Level 2 hypoglycemia) and for hypoglycemia events with PG ≤ 70 mg/dL (any hypoglycemia) are presented in Tables 10 and 11, respectively[5]. Compared to the placebo, subjects treated with lina showed an elevated risk for both Level 2 hypoglycemia (risk ratio =

[4] The analysis results on FPG and BMI Z-score are based on the IR response dated March 28, 2023.

[5] Results in Tables 10 and 11 were based on Sponsor's IR response dated April 27, 2023. In the original submission, hypoglycemia events were analyzed descriptively. On April 18, 2023, we requested analyses of hypoglycemia event counts with negative binomial regression models, adjusted for relevant covariates and offset by exposure time.

3.65, two-sided p-value = 0.07) and for any hypoglycemia event (risk ratio = 2.20, two-sided p-value = 0.19).

Table 10: Analysis of hypoglycemia (PG < 54 mg/dL) up to Week 26, Treated Set

	Lina 5mg (N = 52)	**Placebo (N = 53)**
Incidence (%)	8 (15.4)	4 (7.5)
Number of events	30	8
Total time at risk, patient year	24.76	25.08
Unadjusted event rate, events per patient year	1.21	0.32
Adjusted event rate[1], events per patient year (95% CI)	1.15 (0.47, 2.82)	0.31 (0.11, 0.91)
Comparison vs. placebo Adjusted event rate ratio[1] (95% CI)		3.65 (0.91, 14.69)
p-value (two-sided)		0.07

Abbreviations: CI = confidence interval

[1] The adjusted event rate and rate ratio were based on a negative binomial regression, adjusted for treatment and age stratum (< 15 years vs 15 to <18 years), and offset by time of exposure to treatment.

Source Sponsor's analysis; adsl.xpt, adae.xpt, and adhypo.xpt

Table 11: Analysis of hypoglycemia (PG ≤ 70 mg/dL) up to Week 26, Treated Set

	Lina 5mg (N = 52)	**Placebo (N = 53)**
Incidence (%)	15 (28.8)	7 (13.2)
Number of events	89	42
Total time at risk (patient year)	24.76	25.08
Unadjusted event rate	3.59	1.67
Adjusted event rate[1], events per patient year (95% CI)	3.32 (1.46, 7.56)	1.51 (0.64, 3.53)
Comparison vs. placebo Adjusted event rate ratio[1] (95% CI)		2.20 (0.68, 7.17)
p-value (two-sided)		0.19

Abbreviations: CI = confidence interval

[1] The adjusted event rate and rate ratio were based on a negative binomial regression, adjusted for treatment and age stratum (< 15 years vs 15 to <18 years), and offset by time of exposure to treatment.

Source Sponsor's analysis; adsl.xpt, adae.xpt, and adhypo.xpt

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses on HbA1c (%) change from baseline at Week 26 were conducted with respect to the baseline characteristics: sex, race, age (< 15 years, and 15 to < 18 years), and region[6] (US vs outside of US). Each analysis modeled the primary endpoint with an ANCOVA adjusted for baseline HbA1c, treatment, age stratum at randomization (except for the subgroup analysis on age), subgroup and subgroup-by-treatment interaction. Similar to the primary efficacy analysis, missing data were multiply imputed based on placebo washout and the inference results were combined via Rubin's Rule.

[6] The variable "region" was derived based on countries' names.

Additionally, the Bayesian shrinkage analyses based on the sample estimates were performed. For a given baseline characteristic (e.g., sex), when estimating the treatment effect within a subgroup (e.g., the male subgroup), the shrinkage method borrows information from the other subgroup(s) (the female subgroup), and thus is considered a "weighted" average of the sample estimate and the overall estimate. The weights are based on the ratio of the between-subgroup variability to the within-subgroup variability. A small ratio indicates a small between-subgroup variability relative to the within-subgroup variability. Consequently, more weight is put on the overall estimate, and more shrinkage is applied.

For a given baseline characteristic with *k* subgroups, let Y_i (i = 1, ... k) be the observed sample estimate of the treatment effect in subgroup *i*. The shrinkage analysis in this review assumes the following:

- $Y_i \sim N(\mu_i, \sigma_i^2)$, where μ_i is the expected treatment effect for subgroup *i*, and σ_i^2 is the within-subgroup variance
- σ_i^2 is set to the variance for the sample estimate
- $\mu_i \sim N(\mu, \tau^2)$, where $\mu \sim N(0, (6.8)^2)$, and $1/\tau^2 \sim$ Gamma (0.001, 0.001)

The last assumption stated that the expected treatment effect for all *k* subgroups share a common normal distribution centered at μ and with variance τ^2. A non-informative prior, as specified above, was applied to this normal distribution. A standard deviation of 6.8 was chosen for the centrality parameter μ, so that its standard deviation was approximately four times the subject-level standard deviation, which was estimated to be around 1.7 based on the primary analysis results.

4.1 Sex, Race, Age, and Geographic Region

The sample estimates and the shrinkage estimates of the treatment difference with respect to HbA1c change from baseline at Week 26 are presented in Figure 7. The point estimates for all subgroup levels are covered by the 95% confidence interval of the treatment effect estimate of the overall population, suggesting consistent findings on A1c change across different subpopulations.

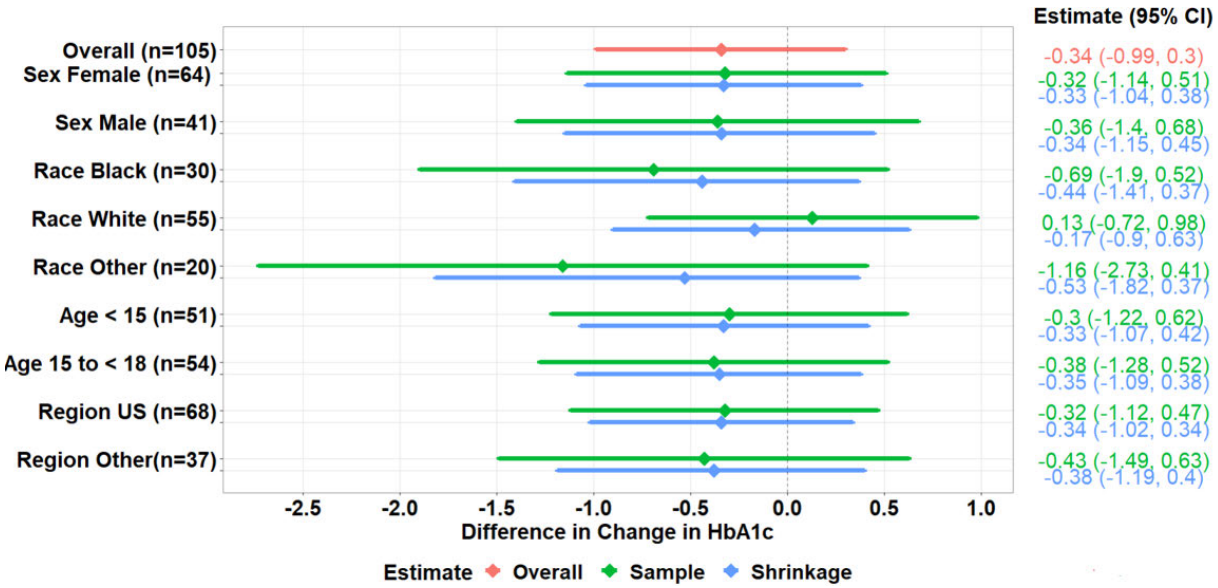


Figure 7: Placebo-Adjusted HbA1c Change from Baseline, Subgroup Analyses

Source reviewer's analysis; adsl.xpt, adhba1c.xpt

When performing the subgroup analysis on race, the race categories American Indian/Alaska Native (n = 3), Asian (n = 7), Multiple (n = 3), Native Hawaiian/ Other Pacific Islander (n = 3), as well as three subjects with missing race information, were combined into the race category "Other", due to insufficient sample sizes. Compared to the race categories Black and White, an uncommonly large treatment effect difference was observed in this "Other" category. Figure 8 displayed the treatment effect for each subject from the "Other" category. Specifically, the dots colored by race and separated by treatment arms represent the observed primary endpoint values (i.e., HbA1c change from baseline at Week 26) for individuals from the "Other" category. The two vertical grey bars are the 95% confidence intervals of the treatment effect for the two treatment arms estimated based on the primary efficacy model. The uncommonly large treatment effect in the "Other" category seems to be driven by outliers both on the low end from the lina arm, and on the high end from the placebo arm.

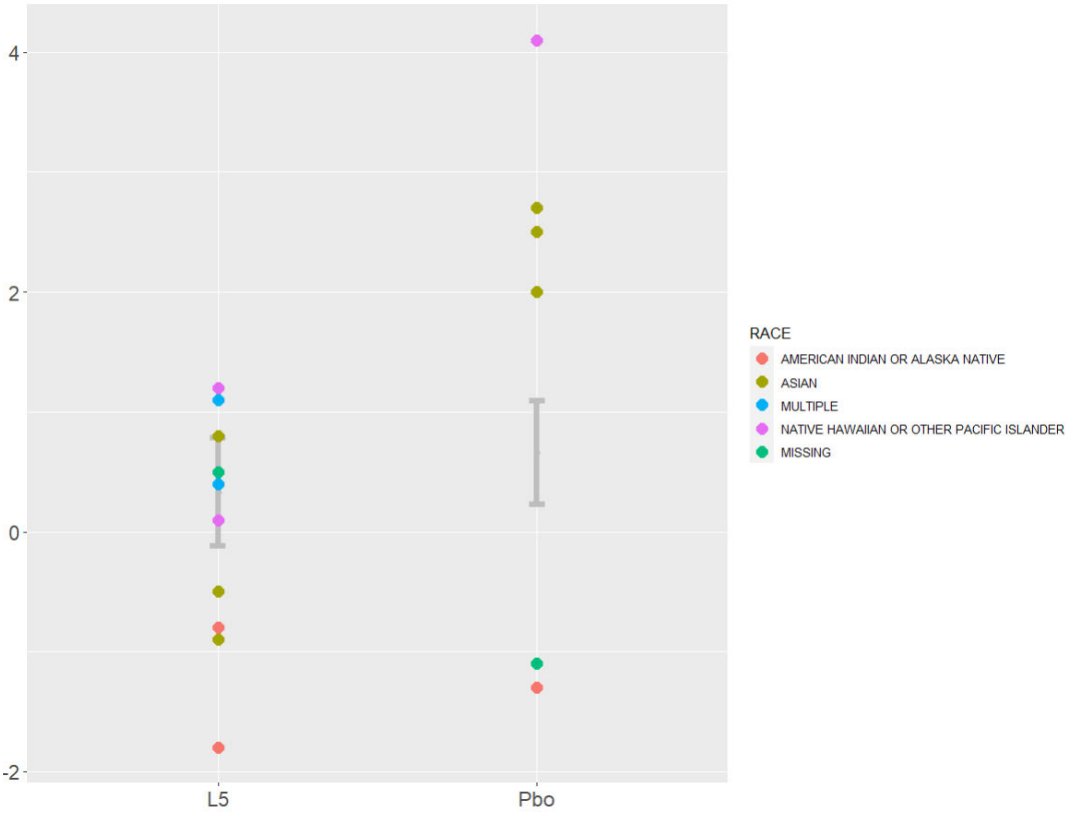


Figure 8: HbA1c Change at Week 26 from Baseline, A Breakdown of the Race Category Other
Source Reviewer's analysis; adsl.xpt, adhba1c.xpt

4.2 Other Special/Subgroup Populations

Subgroup analyses on background medications were performed to examine the treatment effect of lina in combination with metformin. Subjects in this study were on one of the four background therapy regimens (n, %): metformin only [met only] (54, 51.4%), metformin and insulin [met + insulin] (41, 39.0%), insulin only (2, 1.9%), or none (8, 7.6%). Figure 9 presents the results of three analyses, each based on a different grouping of background medications as follows:

- bkgrd1
  - met only
  - met + insulin
  - the other (including "insulin only" and "none")
- bkgrd2
  - met (including "met only" and "met + insulin")
  - the other (including "insulin only" and "none")
- bkgrd3
  - met only
  - the other (including "met + insulin", "insulin only" and "none")

The grouping bkgrd1 intends to compare across all different background regimens. Bkgrd 2 focuses on the comparison of metformin use vs. no metformin use. Bkgrd3 concerns the comparison of metformin as monotherapy vs. the other.

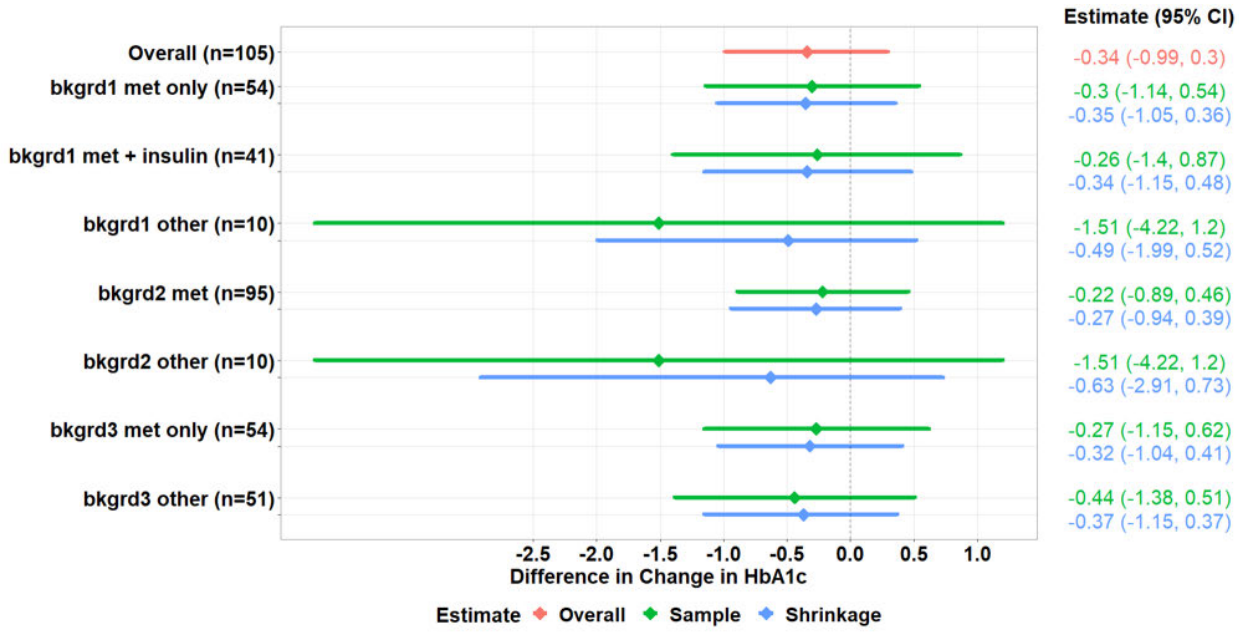


Figure 9: Placebo- Adjusted HbA1c Change from Baseline at Week 26, Subgroup Analysis on Background Therapy
Source: reviewer's analysis; adsl.xpt, adhba1c.xpt

As shown in Figure 9, the estimated treatment effects for all subgroup levels based on different groupings were consistent with the overall population. Further, as the majority of the subjects from the lina or the placebo arms were treated with metformin (95 %), the confidence interval based on the full analysis set considerably overlaps with the confidence interval based on subjects on metformin therapy (i.e., bkgrd2 met).

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Superiority of linagliptin 5mg compared to placebo was not established in DINAMO study. The study was underpowered for the comparison of linagliptin 5 mg vs. placebo due to a smaller effect size and a larger SD than assumptions used in the sample size calculation. The Bayesian supplementary analyses were applied to address the issue of an undersized study.

5.2 Collective Evidence

The placebo-adjusted treatment effect for linagliptin with respect to HbA1change from baseline at Week 26 was -0.34, with a 95% CI (-0.99, 0.30). Sensitivity analyses that inspected the impact of untestable missing data assumptions demonstrated similar findings to the primary analysis result.

The Bayesian analysis that borrowed information from pharmacometric simulations supported superior efficacy of linagliptin compared to placebo. However, the result from this analysis is sensitive to the prior weight assigned to the informative prior. Also, the sizable difference between the pharmacometric model predicted effect (-0.64%) and the observed effect from the study DINAMO (-0.34%) raised concerns about the validity of the pharmacometric model. On the other hand, the Bayesian analysis based on previous clinical trials for other DPP-4 drug products did not establish superiority of linagliptin in comparison to placebo. The result from this analysis was robust to the prior weight assigned to the informative prior, and is considered more reliable than the results from the analysis based on the pharmacometric simulation. In brief, the Bayesian analysis result is in support of the primary efficacy result.

In addition to the primary efficacy analysis, subgroup analyses on the primary efficacy endpoint found consistent results for linagliptin in subgroup levels defined by age, sex, race, region, and background medication. An increased risk of hypoglycemia was found in subjects treated with linagliptin compared to those treated with placebo.

5.3 Conclusions and Recommendations

Since superiority of linagliptin 5 mg to placebo regarding HbA1c reduction was not demonstrated in the study DINAMO, the applicant only sought to add the study information to Section 8.4 of the product label without an efficacy claim for linagliptin use among pediatric patients (11 to < 18 years). We recommend the proposed label updates in Section 8.4. Specific languages in Section 8.4 for description of no established efficacy is still under discussion at the time of this review.

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JAMES E TRAVIS
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I concur

YOONHEE KIM
05/26/2023 12:49:30 PM
I concur.