CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125431Orig1s000

STATISTICAL REVIEW(S)

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

SECONDARY STATISTICAL REVIEW MEMO

CLINICAL STUDIES

BLA Serial Number:	125431/00
Drug Name:	Albiglutide (proposed: Eperzan™) 30 mg and 50 mg for subcutaneous injection
Indication(s):	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Applicant:	Glaxo SmithKline, LLC
Date(s):	1-11-2013 (Received 1-14-2013)
Review Priority:	Standard
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Biometrics Division:	2
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Concurring Reviewers:	Thomas Permutt, Ph.D.
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Keywords: Non-inferiority, Missing Data, Subgroup Analyses, Clinical Studies, BLA Review

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1. EXECUTIVE SUMMARY

This submission is for the use of albiglutide in patients with Type 2 diabetes. The submission consists of results from eight active- and placebo-controlled clinical trials. Collectively, these trials included comparisons to glimepiride, pioglitazone, liraglutide, sitagliptin, insulin, and to placebo. Albiglutide was studied as a monotherapy, in combination with oral antidiabetic agents, and in combination with basal insulin. Trials evaluated the use of albiglutide 30 mg and/or 50mg, with some trials allowing for optional titration of albiglutide from 30 mg to 50mg. The primary endpoint in each trial was HbA1c change from baseline. The timing of the end point varied across studies and included Week 26, Week 32. Week 52, and Week 104.

In addition to these studies, the results were submitted from a bioequivalence study that compared mean HbA1c change from baseline to Week 17 between albiglutide made by Process 2 to albiglutide made by Process 3. The efficacy portion of the aforementioned eight active- and placebo-controlled clinical trials used albiglutide that was made by Process 2. The intended commercial product will be made by Process 3.

The results of the primary endpoint from each study are summarized in Table 1 (which is taken from Dr. Choudhury's review). In Table 1, the limits of the confidence intervals are percents.

For further details on the design and results of these studies see the statistical review by Dr. Choudhury. While I agree with much in the review of Dr. Choudhury's I believe there are three areas where more general discussion are needed. These areas are

1. the justification of the used non-inferiority margins
2. the impact and evaluation of missing data, and
3. the interpretation of subgroup analyses.

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Table 1. Main Results (Primary efficacy at primary time point):

Study	Treatment	n	Vs albiglutide CI (-ve sign indicates albiglutide better)	Vs albiglutide p-value Non-inferiority	Superiority
GLP108486 Week 26	Insulin Glargine in combination with Insulin lispro Albiglutide	278 279	-.32, 00	<.0001	.0533
GLP112753 Week 104	Placebo Sitagliptin Glimepiride Albiglutide	97 297 299 293	-1.16, -.65 -.53, -.17 -.45, -.09	<.0001 .0001 .0033	<.0001
GLP112754 Week 52	Insulin Glargine Albiglutide	238 493	-.04, .27	.0086	.1463
GLP112755 Week 52	Placebo Albiglutide 30mg/W	149 149	-.95, -.56		<.0001
GLP112756 Week 52	Placebo Albiglutide 30mg/W Albiglutide 50mg/W	98 100 97	Vs. Placebo -1.11, -.58 -1.31, -.77	<.0001 <.0001	
GLP112757 Week 52	Placebo Pioglitazone (super) Albiglutide	115 268 265	-1.07, -.68 .1,.4	.2685	<.0001 .0012 (Pio sup)
GLP114179 Week 32	Liraglutide (superio) Albiglutide	402 398	.08, .34	.0846	.0016 (Liraglutid Super., my computation)
GLP114130 Week 26	Sitagliptin Albiglutide	236 242	-.49, -.15	<.0001	.0003
GLP114856 Week 17	Process 2 Process 3	135 141	-.31, .15		.4874

1.1 Conclusions and Recommendations

Based on the results of all studies provided in Table 1 it appears that albiglutide positively affects HbA1c change. Process 3 does appear to be non-inferior to Process 2 in HbA1c change. Collectively, it is also appears that albiglutide may be more efficacious than some products and less efficacious than other products on HbA1c change. Substantial missing data seen in many of the studies make it difficult to estimate treatment differences and interpret the estimated differences in the primary analyses. The primary analyses on HbA1c change used last-observation-carried-forward (LOCF). This means that the primary endpoint is essentially the HbA1c change from baseline to the intended end point or to the last measurement of HbA1c prior to the intended end point. These issues should be considered when making regulatory decisions.

1.2 The Non-inferiority Margins

Studies GLP10846, GLP112753, GLP112754, GLP112757, GLP114179, and GLP11430 each had at least one active comparator for a total of seven active (non-inferiority) comparisons to albiglutide on HbA1c change from baseline. The non-inferiority margin selected for each comparison was 0.3%, regardless of the active control or the time of the

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endpoint (i.e., week 26, week 104, week 52, week 32). Per the draft FDA Guidance for Industry: Diabetes mellitus: developing drugs and therapeutic biologics for treatment and prevention (the underlining is mine):

> "Sample sizes for noninferiority trials should be based on one-sided significance levels of 2.5 percent and at least 80 percent power. Because the calculations depend on the noninferiority margin, <u>the sponsor should provide a rationale for the choice of margin and should be guided by the concept that this margin should not represent a clinically meaningful loss of efficacy relative to the active control</u>. Typically, we accept a noninferiority margin of 0.3 or 0.4 HbA1c percentage units provided this is no greater than a suitably conservative estimate of the magnitude of the treatment effect of the active control in previous placebo-controlled trials. For additional guidance on noninferiority studies, refer to ICH E9 and ICH E10."

To the best of my understanding 0.3% and 0.4% have often been used as the non-inferiority margin for HbA1c change from baseline. Per Dr. Choudhury's review for the comparisons of HbA1c change from baseline to an active treatment a non-inferiority margin of 0.4% was selected for studies GLP108486 and GLP114130 and a non-inferiority margin of 0.3% was selected for studies GLP112753, GLP112754, GLP112757 and GLP114179. No justifications on the choice of the margins were provided in Dr. Choudhury's review. I note that among the seven active comparisons on mean HbA1c change from baseline, based on 95% confidence intervals for the difference in mean HbA1c change from baseline (see Table 1) without considering any adjustment for multiplicity, albiglutide demonstrated superiority three times (to sitagliptin and to glimepiride in study GLP112753 and to sitagliptin in study GLP114130), demonstrated inferiority twice without demonstrating non-inferiority (to pioglitazone in study GLP112757 and to liraglutide in study GLP114179) and demonstrated non-inferiority twice (to insulin lispro in study GLP108486 and to insulin glargine in study GLP112754). Based on the results of all studies provided in Table 1 it appears that albiglutide positively affects HbA1c change. However, it is also appears that albiglutide may be more efficacious than some products and less efficacious than other products on HbA1c change. Related to this, it may not be appropriate to use the same non-inferiority margin universally across products.

The efficacy portion of the eight phase 3 used albiglutide that was made by Process 2. The intended commercial product will be made by Process 3. Study GLP114856 was a bioequivalence/bringing study comparing the use of albiglutide made by Process 3 to the use of albiglutide made by Process 2. Study GLP114856 used a non-inferiority used a non-inferiority margin of 0.3% for HbA1c change from baseline. Through a non-inferiority trial, a new therapy can be deemed efficacious, even when it is less effective than the active control. When the new therapy that is less effective than its comparator is used as an active-control in a future non-inferiority trial, a biocreep is said to have occurred. Unless great care is taken in selecting the non-inferiority margin for future studies, continuing such a series of non-inferiority trials based on less and less effective active-control therapies can lead to deeming an ineffective product is adequately effective. The effect on HbA1c by albiglutide made by Process 2 must be considered when

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justifying the use of any non-inferiority comparison involving Process 2 as the active control.

There were five comparisons on HbA1c change from baseline between albiglutide (made by Process 2) and placebo. Four of these comparisons were primary analyses on HbA1c change from baseline to Week 52, which resulted in 95% confidence intervals in the difference in mean change of (-0.95%, -0.58%), (-1.11%, -0.58%), (-1.31%, -0.77%) and (-1.07%, -0.68%). The other comparison was a primary analysis on HbA1c change from baseline to Week 104, which resulted in a 95% confidence interval in the difference in mean HbA1c change of (-1.16%, -0.65%). These study results support the use of a non-inferiority margin of 0.3% for the difference in mean HbA1c change from baseline to Week 52 or to Week 104. For the study results to support the use of a non-inferiority margin of 0.3% for a shorter duration difference in mean HbA1c change from baseline, further information would be needed. From study GLP114856 the 95% confidence interval in the difference in mean HbA1c change from baseline to Week 17 (Process 3 – Process 2) is (-0.31%, 0.15%). The 95% confidence interval statistically rules out that Process 3 is worse than Process 2 by more than 0.15% on mean HbA1c change from baseline to Week 17. Data on mean HbA1c change from baseline to Week 17 would be needed and/or expert judgment on the behavior of HbA1c change would be needed to determine whether Process 3 is non-inferior to Process 2 on mean HbA1c change from baseline to Week 17.

1.3 Missing Data

Based on Dr. Choudhury's review, I believe there was a fairly substantial amount of missing data for the primary endpoints in the eight active- and placebo-controlled trials. The percent of missing data for the primary endpoint increased at the time of the end point increased, and was larger for placebo arms than for experimental or active arms. When the end point was week 26 or week 32 the percent of missing data ranged from 17% to 31% for experimental or active arms. When the end point was week 52, the percent of missing data ranged from 32% to 42% for experimental or active arms, and ranged from 58% to 70% for placebo arms. For the study having an end point of week 104, the percent of missing data ranged from 46% to 55% for experimental or active arms and was 76% for the placebo arm. For the bioequivalence study, which had an end point of week 17, there were 13% and 12% missing data respectively for the Process 2 and Process 3 arms. All these percents are based on the analysis population that had at least one post-baseline measurement for HbA1c.

All primary analyses were based on last observation carried forward. This means that the primary endpoint is essentially the HbA1c change from baseline to the intended end point or to the last measurement of HbA1c prior to the intended end point. It is not clear whether such an endpoint is meaningful and its meaningfulness may also be influenced by the amount of missing data on HbA1c at the intended end point. The LOCF method is described in the 2008 draft Guidance for Industry: Diabetes Mellitus: developing drugs and therapeutic biologics for treatment and prevention. However, the Division is

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reconsidering this approach to missing data following the publication in 2010 of a report on missing data by the National Academy of Sciences (NAS), The Prevention and Treatment of Missing Data in Clinical Trials. The FDA commissioned this report. The report states "The panel believes that in nearly all cases, there are better alternatives to [LOCF]…which are based on more reasonable assumptions and hence result in more reliable inferences about treatment effects."

There was little information in Dr. Choudhury's review on the potential impact of the missing data. The high amount of missing data for the later endpoints (in particular the week 104 end point) may undermine the reliability and confidence in the results.

For non-inferiority comparisons, such treatment of the missing data (or the amount of missing data in general) may attenuate the treatment difference making it easier to demonstrate non-inferiority. At baseline there is no difference between arms in HbA1c change and there may be little difference shortly after baseline in HbA1c change. If the effect of therapy at such early time points is smaller than the non-inferiority margin, using LOCF may correspond to an imputation that is not consistent with the null hypothesis and may affect the change of concluding that an ineffective product is effective. A high amount of early missingness on both treatment arms may make the difference in mean HbA1c change from baseline to the intended end point or to the last measurement of HbA1c prior to the intended end point close to zero even when one arm is a placebo.

1.4 Subgroup Analyses

Many subgroup analyses and tests for interactions were presented in Dr. Choudhury's review. It is my understanding from Dr. Choudhury that these analyses were performed by the sponsor. The proposed label did not contain any claims on subgroups, claims on interactions, or descriptions of interactions. I believe there were no important subgroup findings provided by the sponsor's subgroup analyses that were presented in Dr. Choudhury's review.

The sponsor included subgroup analyses that pooled data across studies. There were three groupings of studies that were considered – those studies having a placebo control (Group A), those studies having an oral anti-diabetic control (Group B), and those non-placebo studies that had an insulin control (Group C). It appears that these subgroup and interaction tests first pooled results across the studies. It does not seem clear that analyses were stratified by study. When such analyses are not stratified by study, an interaction could be due to study differences and the different distributions for the factor across studies. There were many tests performed on interactions. Some had p-values larger than 0.1, some had p-values smaller than 0.1, and only one (baseline HbA1c within Group A) was smaller than 0.01.

Group B includes two studies, one study where albiglutide showed better HbA1c change than two oral anti-diabetic products and another study where albiglutide showed poorer

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HbA1c change than another oral anti-diabetic product. I believe there is little value in this sort of combining of superior and inferior oral anti-diabetic products together and testing for interactions (or other subgroup analyses). Any interpretation would have to breakdown how the individual oral anti-diabetic products compare with albiglutide in the various subgroups.

In many settings where an interaction p-value was smaller than 0.1, the observed differences in the estimated treatment difference were small. For example, in Group B the treatment by gender interaction p-value was 0.0389, but the estimated treatment differences for females and males were -0.06% and 0.12%, respectively. The confidence intervals about each point estimate were narrow.

The only p-value smaller than 0.01 for an interaction test was for a treatment by baseline HbA1c category (<8%, 8%-9%, >=9%) in Group A. The estimated treatment differences in this sponsor analysis were -0.73%, -0.83% and -1.18% for the <8%, 8%-9%, and >=9% subgroups respectively. Besides that a test for interaction involving three levels only provides a rather general conclusion (does not on its own indicate how the treatment difference compares between any two subgroups), there was substantial missing data in this analysis on the placebo arms, most notably for the 8%-9%, and >=9% subgroups. For the <8% subgroup there were 40% and 21% missing values for the placebo and albiglutide groups, for the 8%-9% subgroup there were 76% and 37% missing values for the placebo and albiglutide groups, and for the 9% subgroup there were 90% and 56% missing values for the placebo and albiglutide groups. This substantial missing undermines the ability to reach a conclusion of a true finding of a treatment by baseline HbA1c category interaction.

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/s/

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10/25/2013

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10/25/2013
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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

BLA Serial Number: 125431/00

Drug Name: Albiglutide (proposed: Eperzan™) 30 mg and 50 mg for subcutaneous injection

Indication(s): Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Applicant: Glaxo SmithKline, LLC

Date(s): 1-11-2013 (Received 1-14-2013)

Review Priority: Standard

Review Due Date: October 17, 2013

Biometrics Division: 2

Statistical Reviewer: Japobrata Choudhury, Ph.D.

Concurring Reviewers: Mark Rothmann, Ph.D., Thomas Permutt, Ph.D.

Medical Division: Metabolic and Endocrine Products

Clinical Team: Kaveeta Vasisht, M.D., Ali Mohamadi, M.D., Amy Egan, M.D.,

Project Manager: Raymond Chiang

Keywords:

Link to DBII key Words: Clinical Studies, BLA Review, Missing data

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1. EXECUTIVE SUMMARY

Note: The primary efficacy variable is the change from baseline in HBA1c. When no efficacy variable is mentioned, the efficacy variable is the primary efficacy variable.

Note: The insulin studies 486 and 754, and the liraglutide comparator Study 179 were open-label.

Note: Process 3 was used in the bioequivalence Study GLP114856 of Process 2 and Process 3 as well as in blinded switching of subjects from Process 2 to Process 3 product in Phase III studies GLP112754 and GLP112756. In these two pivotal trials, patients were randomized to albiglutide process 2 materials until the primary endpoint and then Process 3 (to be marketed product) during the safety extension phases.

Overall Conclusion on the Eight Phase 3 Studies (see table below)**:**

Albiglutide was statistically superior to each of placebo (both 30 mg and 50 mg), sitagliptin, and glimepiride. Based on the datasets provided by the sponsor, this reviewer concludes that albiglutide has shown efficacy.

The claim of non-inferiority of albiglutide to each of preprandial insulin lispro and insulin glargine is acceptable. However, these results are from open-label studies.

Each of liraglutide and pioglitazone were statistically significantly superior to albiglutide.

Conclusion on STUDY GLP114856 (Phase 2 Bioequivalence Study)

Both processes statistically significantly reduced mean HBA1C by Week 17, from baseline, by amount 0.75% for Process 2 and by 0.84% for process 3. Process 3 is non-inferior to Process 2, based on Change from Baseline in HBA1c at Week 17 and a non-inferiority margin of .3 (the 95% confidence interval (-.31, .15)).

Details are in the Section 5.1.

This licensing application is for a 30-mg and a 50-mg single-use prefilled pen, supplied with a 29G 5-mm needle, to be patient self-administered subcutaneously once weekly. The proposed tradename for albiglutide is EPERZAN™.

The sponsor stated, "The mainstay of diabetes therapy is individualization of therapy. Data from the Phase III program show that albiglutide should be considered as an alternative or add-on to

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other antidiabetes therapies, as albiglutide helps patients achieve appropriate glycemic control (or superior glycemic control versus sulfonylurea or dipeptidyl peptidase IV inhibitor), while minimizing some of the tolerability or safety issues associated with other approved antidiabetes therapies. The data from studies such as Study GLP112756 (use as monotherapy vs. placebo), and Study GLP114130 (use in renally impaired patients vs. sitagliptin) – together with the improved gastrointestinal tolerability profile of albiglutide versus approved GLP-1R agonists - fully support albiglutide as first-line therapy in patients (b) (4)

The sponsor claims that, for the BLA, the efficacy and safety of albiglutide are supported by results from 8 well-controlled Phase III studies in adult patients with T2DM. At the time of this submission, five of these Phase III studies are ongoing to 3 years. Program highlights include:

- an adult T2DM population spanning newly diagnosed ("drug naïve") subjects treated with diet and exercise to subjects receiving background oral monotherapy, oral dual therapy, oral triple therapy and/or insulin;
- both placebo and active comparator studies designed to assess the efficacy and safety of albiglutide with commonly used second- and third-line therapies, such as sulfonylureas, thiazolidinediones, DPP-IV inhibitors, another GLP-1R agonist as well as basal and prandial insulin;
- a clinical comparability assessment of Phase III (Process 2) and intended commercial (Process 3) albiglutide with safety, efficacy and PK assessment through a bioequivalence trial (Study GLP 114856) and two Phase III studies (i.e. GLP112754 and GLP112756);
- a cardiovascular (CV) safety profile defined by the absence of a QTc prolongation effect (Study GLP107085), and CV meta-analysis that demonstrated a Hazard Ratio (HR) of 0.93 with the upper bound of the 2-sided Confidence Interval (CI) less than 1.8; and
- an immunogenicity assessment that includes a tiered testing plan, a broad panel of assays and monitoring of antibodies to albiglutide, GLP-1, glucagon and albumin over years of observation for robust characterization.

The sponsor stated, "A total of 2,365 patients with type 2 diabetes were treated with EPERZAN as part of 8 active- and placebo-controlled Phase III clinical trials. The 8 trials included comparisons to glimepiride, pioglitazone, liraglutide (1 trial each), sitagliptin (2 trials, including one in patients with renal impairment), insulin (2 trials, one versus prandial insulin and one versus basal insulin) and to placebo (4 trials). These trials included the use of EPERZAN as monotherapy, in combination with oral antidiabetic agents, and in combination with basal insulin. Trials evaluated the use of EPERZAN 30 mg and 50 mg, with 5 of the 8 trials allowing for optional titration of EPERZAN from 30 mg to 50 mg. For trials that allowed for optional dose uptitration, the glucose levels that triggered uptitration were the same for EPERZAN and oral comparators. All trials included at least a 4-week run-in/stabilization period prior to the start of trial medication (for 2 trials, this period was longer; the add-on to metformin and sulfonylurea trial had a 6-week run-in and the add-on to insulin glargine trial had a 4-week or 8-week run-in depending on whether patients were already on insulin glargine).

Across the 8 clinical trials, patients ranged from 18 to 86 years old (mean 56 years), 52% were male, with a mean body mass index (BMI) of 33 kg/m^2. Sixty seven percent of patients were Caucasian, 15% African American, and 11% Asian; 26% of patients were Hispanic/Latino. The majority of patients (92%) had been previously treated with one or more oral antidiabetic medications or insulin. Trials included a broad spectrum of diabetes patients with respect to duration of disease with equal representation across each of the following categories: <5 years, ≥5 to <10 years, and ≥10 years. Over 60% of patients had mild or moderate renal impairment (eGFR <90 mL/min/1.73 m^2) in Phase III clinical trials (excluding renal impairment trial)."

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Note: The sponsor pre-specified a non-inferiority margin of .3% for the primary efficacy variable, HBA1C, for most studies and .4% for some (e.g., study 486). Non-inferiority margins were not pre-specified for other efficacy variables.

I focused mainly on the primary efficacy variable, though analyzed others too. There were minor differences in numerical results between my various alternative analyses and the sponsor's. If the conclusions differed, I have mentioned those.

Statistically significant interactions are difficult to detect because of lack of power. On the other hand, how much multiple comparison adjustment is needed in this situation is unknown.

I have pointed out inconsistencies in some subgroup results based on confidence intervals (not that convincing because of smaller sample sizes in subgroups of smaller individual studies, but more convincing when the sample sizes are big) and some based on statistically significant interaction p-values, without multiple comparison adjustments. Subgroup results, when not planned to be confirmatory, are not confirmatory. Further evidences are needed to reach the level of confirmation.

When there are more than two subgroups for a factor, a statistically significant result for this interaction test leads to a general conclusion that the treatment difference/effect is not the same across the subgroups. However, the test does not lead to any specific conclusion on how the treatment difference/effect compares across any two subgroups of that factor.

I reviewed studies GLP112753 and GLP114130 in a little more details and analyzed the data for the following nine studies over all time points, by Proc Wilcoxon, Proc TTEST, and Proc Mixed. The sponsor provided many supportive and sensitivity analyses. Slight inconsistency in one or two cases does not nullify the huge amount of other results.

STUDY GLP108486, STUDY GLP112753, STUDY GLP112754, STUDY GLP112755, STUDY GLP112756, STUDY GLP112757, STUDY GLP114179, STUDY GLP114130, and the Phase 2 bioequivalent STUDY GLP114856 (HBA1C only for the last)

Main Results (Primary efficacy at primary time point):

Study	Treatment	n	Vs albiglutide CI (-ve sign indicates albiglutide better)	Vs albiglutide p-value Non-inferiority	Superiority
GLP108486 Week 26	Insulin Glargine in combination with Insulin lispro Albiglutide	 278 279	-.32, 00	<.0001	.0533
GLP112753	Placebo	97	-1.16, -.65		<.0001

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Week 104	Sitagliptin Glimepiride Albiglutide	297 299 293	-.53, -.17 -.45, -.09	<.0001 <.0001	.0001 .0033
GLP112754 Week 52	Insulin Glargine Albiglutide	238 493	-.04, .27	.0086	.1463
GLP112755 Week 52	Placebo Albiglutide 30mg/W	149 149	-.95, -.56		<.0001
GLP112756 Week 52	Placebo Albiglutide 30mg/W Albiglutide 50mg/W	98 100 97	Vs. Placebo -1.11, -.58 -1.31, -.77	<.0001 <.0001	
GLP112757 Week 52	Placebo Pioglitazone (super) Albiglutide	115 268 265	-1.07, -.68 .1,.4	.2685	<.0001 .0012 (Pio sup)
GLP114179 Week 32	Liraglutide (superio) Albiglutide	402 398	.08, .34	.0846	.0016 (Liraglutid Super., my computation)
GLP114130 Week 26	Sitagliptin Albiglutide	236 242	-.49, -.15	<.0001	.0003
GLP114856 Week 17	Process 2 Process 3	135 141	-.31, .15		.4874

2. INTRODUCTION

Note: Tables and Figures presented in this document are referenced by "below" or "above". Those referenced with an extended numbering system, if at all, are in the sponsor-submitted BLA Study Report. Unless mentioned otherwise, the source of all information is the sponsor's submission. The reviewer's interpretations, comments, or conclusions are clearly identified under notes, comments, or separate sections.

2.1 Overview

Sponsor-submitted INDICATIONS AND USAGE:

EPERZAN is a GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. (1, 14)
Important Limitations of Use:

- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise, (b) (4)
- Has not been studied (b) (4) in patients with a history of pancreatitis (b) (4)
- Has not been studied in combination with prandial insulin. (1)
- Not for treatment of type 1 diabetes or diabetic ketoacidosis. (1)

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DOSAGE AND ADMINISTRATION

- Administer 30 mg subcutaneously once weekly. The dose may be increased to 50 mg once weekly based on individual glycemic response. (2.1)
- [redacted] (b) (4)
- May be given at any time of day without regard to meals. (2.1)
- If a dose is missed, administer within 3 days of the missed dose. (2.1)
- Inject subcutaneously in the abdomen, thigh, or upper arm. (2.2)
- See full prescribing information (2.2) and Patient Instructions for Use for reconstitution and administration.

Tables of Summaries of all studies included in Analysis:

Study Identifier/ (Identifier of Study Report)	No. Study Centres; Location(s); Study Start; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria Study Population	Treatment Details (Drug; Formulation (Process); Form, Route; Frequency; Duration)	No. of Subjects by Group: Randomised/Treated/Discontinued /Completed[1]; Gender M/F; Mean Age (Range)	Primary Endpoint (s)	Study Reporting Status (Type of Report) / Location of Report
Efficacy and Safety Studies (5.3.5)								
Controlled Clinical Studies Pertinent to the Claimed Indication (5.3.5.1)								
GLP112753/ A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide When Used in Combination With Metformin Compared With Metformin Plus Sitagliptin, Metformin Plus Glimepiride, and Metformin Plus Placebo in Subjects With Type 2 Diabetes Mellitus	289 Study Centers in Germany, Hong Kong, Mexico, Peru, Philippines, Russia, South Africa, Spain, UK, United States 03-Mar-2009 1049/1000 (Albiglutide-300; Sitagliptin- 300; Glimepiride-300; Matching albiglutide placebo-100)	Evaluate the safety and efficacy of albiglutide administered in combination with metformin as compared with metformin plus sitagliptin, metformin plus glimepiride and metformin plus placebo.	R, DB, PC and AC, PG	Subjects with T2DM (HbA1c ≥7% to ≤10%), ≥18 years of age, currently treated with metformin but who were experiencing inadequate glycemic control	Albiglutide (Process 2) 30 mg weekly with masked up-titration to 50 mg if necessary (disposable pen injector, s.c.) + metformin; sitagliptin + metformin; glimepiride + metformin; metformin + matching albiglutide placebo	Albiglutide: R:315/T:302/D:95/O:207, 135/167, 54.3 y (26-86) Sitagliptin: R:313/T302/D:100/O:202, 139/163, 54.3 y (24-84) Glimepiride: R:317/T:307/D:98/O:209, 158/149, 54.4 y (28-82) Matching albiglutide placebo: R:104/T:101/D:42/O:59, 50/51, 56.1 y (32-79)	Change from baseline HbA1c at Week 104	Complete Report (2-Year TRT data). m5.3.5.1

Reference ID: 3392698

Study Identifier/ (Identifier of Study Report)	No. Study Centres; Location(s); Study Start; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria Study Population	Treatment Details (Drug; Formulation (Process); Form, Route; Frequency; Duration)	No. of Subjects by Group: Randomised/Treated/Discontinued /Completed[1]; Gender M/F; Mean Age (Range)	Primary Endpoint (s)	Study Reporting Status (Type of Report) / Location of Report
GLP112754 A Randomized, Open-Label, Parallel-Group, Multicenter Study to Determine the Efficacy and Long-Term Safety of Albiglutide Compared With Insulin in Subjects With Type 2 Diabetes Mellitus	222 Study Centers in Russia, South Africa, UK, United States 17-Feb-2009 779/750 (Albiglutide:500; Insulin glargine: 250)	Evaluate the safety and efficacy of albiglutide as compared with insulin glargine.	R, OL, PG, AC	Subjects with T2DM (HbA1c ≥7% to ≤10%), ≥18 years of age, currently treated with metformin alone or metformin + SU but who were experiencing inadequate glycemic control	Albiglutide (Process 2 and 3) 30 mg weekly with up-titration to 50 mg if necessary, (disposable pen injector, s.c.); insulin glargine	Albiglutide: R:516/T:504/D:171/C:333; 286/218; 55.8 y (27-81) Insulin glargine: R:263/T:241/D:66/C:175; 132/109; 54.7 y (26-83)	Change from baseline HbA1c at Week 52	Complete Report (2-Year TRT data). m5.3.5.1

Study Identifier/ (Identifier of Study Report)	No. Study Centres; Location(s); Study Start; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria Study Population	Treatment Details (Drug; Formulation (Process); Form, Route; Frequency; Duration)	No. of Subjects by Group: Randomised/Treated/Discontinued /Completed[1]; Gender M/F; Mean Age (Range)	Primary Endpoint (s)	Study Reporting Status (Type of Report) / Location of Report
GLP112755 A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide When Used in Combination With Pioglitazone With or Without Metformin in Subjects with Type 2 Diabetes Mellitus	158 Study Centers in India, Peru, South Africa, United States 26-Jan-2009 310/300 (150/group)	Evaluate the safety and efficacy of albiglutide administered in combination with pioglitazone (with or without metformin) as compared with pioglitazone (with or without metformin).	R, DB, PC, PG	Subjects with T2DM (HbA1c ≥7% to ≤10%), ≥18 years of age currently treated with pioglitazone (with or without metformin), but who were experiencing inadequate glycemic control	Pioglitazone or (metformin + pioglitazone) + albiglutide (Process 2) (30 mg weekly, disposable pen injector, s.c.); pioglitazone or (metformin + pioglitazone) + albiglutide matching placebo	Albiglutide: R:155/T:150/D:34/O:116; 92/58; 55.2 y (29-77) Albiglutide matching placebo: R:155/T:151/D:57/O:94; 88/63; 54.9 y (31-80)	Change from baseline HbA1c at Week 52	Complete Report (2-Year TRT data). m5.3.5.1

Reference ID: 3392698

Study Identifier/ (Identifier of Study Report)	No. Study Centres; Location(s); Study Start; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria Study Population	Treatment Details (Drug; Formulation (Process); Form, Route; Frequency; Duration)	No. of Subjects by Group: Randomised/Treated/Discontinued /Completed[1]; Gender M/F; Mean Age (Range)	Primary Endpoint (s)	Study Reporting Status (Type of Report) / Location of Report
GLP112756 A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Two Dose Levels of Albiglutide Compared With Placebo in Subjects With Type 2 Diabetes Mellitus	143 Study Centers in Mexico, United States 01-Apr-2009 309/315 (target:105/group)	Evaluate safety and efficacy of albiglutide as compared with placebo.	R, DB, PC, PG	Subjects with T2DM (HbA1c ≥7% to ≤10%), ≥18 years of age experiencing inadequate glycemic control and receiving no current antidiabetic therapy	Albiglutide (Process 2 and 3) 30 mg weekly, disposable pen injector, s.c. (I); albiglutide (Process 2 and 3) 30 mg weekly with up-titration to 50 mg weekly after 12 weeks of treatment, disposable pen injector (II); matching albiglutide placebo	Albiglutide: 30 mg: R:102/T:101/D:29/O:72; 58/43; 53.6 y (29-79) Albiglutide: 30 mg with up-titration to 50 mg: R:102/T:99/D:38/O:61; 50/49; 52.0 y (24-78) Matching albiglutide placebo: R:105/T:101/D:40/O:61; 58/43; 53.1 y (20-78)	Change from baseline HbA1c at Week 52	Complete Report (2-Year TRT data). m5.3.5.1

Study Identifier/ (Identifier of Study Report)	No. Study Centres; Location(s); Study Start; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria Study Population	Treatment Details (Drug; Formulation (Process); Form, Route; Frequency; Duration)	No. of Subjects by Group: Randomised/Treated/Discontinued /Completed[1]; Gender M/F; Mean Age (Range)	Primary Endpoint (s)	Study Reporting Status (Type of Report) / Location of Report
GLP112757 A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide Administered in Combination With Metformin and Glimepiride Compared With Metformin Plus Glimepiride and Placebo and With Metformin Plus Glimepiride and Pioglitazone in Subjects With Type 2 Diabetes Mellitus	234 Study Centers in Germany, Hong Kong, India, Peru, Philippines, Russia, Spain, UK, United States 13-Apr-2009 685/600 (Placebo-100; Pioglitazone-250; Albiglutide-250)	To evaluate safety and efficacy of albiglutide administered in combination with metformin and glimepiride compared with metformin plus glimepiride and placebo and with metformin plus glimepiride and pioglitazone.	R, DB, PC and AC, PG	Subjects with T2DM (HbA1c ≥7% to ≤10%), ≥18 years of age currently treated with metformin and an SU but experiencing inadequate glycemic control	Metformin + glimepiride + pioglitazone + albiglutide placebo; metformin + glimepiride + pioglitazone placebo + albiglutide placebo); and metformin + glimepiride + pioglitazone placebo + albiglutide (Process 2) 30 mg weekly (with masked up-titration to 50 mg), (disposable pen injector, s.c.)	Placebo: R:116/T:115D:52/O:63; 70/45; 55.7 y (29-81) Pioglitazone: R:288/T:277/D:97/O:180; 147/129; 55.7 y (28-81) Albiglutide: R:281/T:271/D:105/O:166; 135/136; 54.6 y (25-74)	Change from baseline HbA1c at Week 52	Complete Report (2-Year TRT data). m5.3.5.1

Reference ID: 3392698

Study Identifier/ (Identifier of Study Report)	No. Study Centres; Location(s); Study Start; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria Study Population	Treatment Details (Drug; Formulation (Process); Form, Route; Frequency; Duration)	No. of Subjects by Group: Randomised/Treated/Discontinued /Completed[1]; Gender M/F; Mean Age (Range)	Primary Endpoint (s)	Study Reporting Status (Type of Report) / Location of Report
GLP114130 A Randomized, Double-Blind, Active-Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide as Compared With Sitagliptin in Subjects With Type 2 Diabetes Mellitus With Renal Impairment	Australia, Brazil, Colombia, Germany, India, Israel, Korea, Peru, Philippines, Russian Federation, South Africa, Spain, Taiwan, UK, United States 07-May-2010 Albiglutide:250; Sitaglipitn:250 (n=500)	Evaluate the efficacy and safety of a subcutaneously weekly injected 30 mg dose of albiglutide as compared with sitagliptin.	R, DB, AC, PG	Subjects with T2DM (HbA1c ≥7.0% to ≤10.0%) and renal impairment, BMI ≥20 kg/m2 and ≤45 kg/m2 experiencing inadequate glycemic control on current regimen of diet and exercise or antidiabetic therapy of metformin, TZD, SU, or any combination of these OAD medications	Albiglutide (Process 2) 30 mg weekly (with treatment-masked up-titration to 50 mg weekly, if needed) + sitagliptin matching placebo or albiglutide matching placebo weekly + sitagliptin for 52 weeks	Albiglutide: R:254/T:249/D:51/C:198; 136/113; 63.2 y (41-83) Sitagliptin: R:253/T:246/D:68/C:178; 130/116; 63.5 y (23-82)	HbA1c change from Baseline at Week 26	Complete Report m5.3.5.1

Study Identifier/ (Identifier of Study Report)	No. Study Centres; Location(s); Study Start; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria Study Population	Treatment Details (Drug; Formulation (Process); Form, Route; Frequency; Duration)	No. of Subjects by Group: Randomised/Treated/Discontinued /Completed[1]; Gender M/F; Mean Age (Range)	Primary Endpoint (s)	Study Reporting Status (Type of Report) / Location of Report
GLP108486 A Randomized, Open-Label, Active-Controlled, Parallel-Group, Multicenter Study to Determine the Safety and Efficacy of Albiglutide Administered in Combination With Insulin Glargine as Compared with the Combination of Insulin Glargine and Preprandial Lispro Insulin in Subjects With Type 2 Diabetes Mellitus	159 Study Centers in Brazil, France, Germany, Hong Kong, India, Korea, Mexico, Peru, Philippines, South Africa, Spain, Taiwan, UK, United States 02-Nov-2009; 586/500 (250/group)	Evaluate the safety and efficacy of albiglutide in combination with insulin glargine as compared with the combination of preprandial lispro and insulin glargine.	R, OL, AC, PG	Subjects with T2DM (HbA1c ≥7% to ≤10.5%), 18 to 75 years of age, currently treated with insulin glargine, or other intermediate- or long-acting insulin, with or without OAD medications but who were experiencing inadequate glycemic control	Albiglutide (Process 2) 30 mg weekly with up-titration to 50 mg if necessary (disposable pen injector, s.c.) + insulin glargine; insulin glargine + preprandial lispro insulin	Albiglutide: R:292/T:285/D:42/C:243; 132/153; 54.8 y (18-75) Preprandial lispro insulin: R:294/T:281/D:39/C:242; 136/145; 56.3 y (35-76)	Change from Baseline in HbA1c at Week 26	Complete Report m5.3.5.1

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Study Identifier/ (Identifier of Study Report)	No. Study Centres; Location(s); Study Start; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria Study Population	Treatment Details (Drug; Formulation (Process); Form, Route; Frequency; Duration)	No. of Subjects by Group: Randomised/Treated/Discontinued /Completed[1]; Gender M/F; Mean Age (Range)	Primary Endpoint (s)	Study Reporting Status (Type of Report) / Location of Report
GLP114179 A Randomized, Open-Label, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide as Compared With Liraglutide in Subjects With Type 2 Diabetes Mellitus	162 Study Centers in Australia, Israel, South Korea, Peru, Philippines, Spain, United Kingdom, United States 05-May-2010 841/800 (400/group)	Evaluate the safety and efficacy of albiglutide as compared with liraglutide.	R, OL, PG, AC	Subjects with T2DM (HbA1c ≥7.0% to ≤10.0%), experiencing inadequate glycemic control on current regimen of metformin, TZD, SU, or any combination of these OAD medications	Albiglutide (Process 2) 30 mg weekly (with treatment up-titration to 50 mg weekly at Week 6, disposable pen injector) or liraglutide(0.6 mg daily for the first week followed by an increase in dose to 1.2 mg at Week 1 and an increase in dose to 1.8 mg at Week 2) for 32 weeks	Albiglutide: R:422/T:404/D:58/C:346; 191/213; 55.4 y (25-77); Liraglutide: R:419/T:408/D:68/C:340 218/190; 55.8 y (21-82)	HbA1c change from Baseline at Week 32	Complete Report m5.3.5.1

1. Ongoing (O) Subjects are presented where applicable. With the exception of Randomised Subjects information is displayed for the safety population (subjects who received at least one dose of investigational product).

Abbreviations: Abd = abdomen AC = active control, ALB = Albiglutide, BL = baseline, BMI = body mass index, BW = body weight, C = Completed, CPSR = Clinical Pharmacology Study Report, D = discontinued active treatment, DB = double blind,FDG-PET = [^{18}F]fluoro-2-deoxy-glucose positron emission tomography, FPG = fasting plasma glucose, FSFV = first subject first visit, HbA_{1c} = glycosylated hemoglobin, LEVF = left ventricular ejection fraction, N/A = not applicable, NC = nested crossover, O = ongoing (continuing in study), OAD = oral antidiabetic drug, OL = open label, PC = placebo controlled, PD = pharmacodynamics, PG = parallel group, PK = pharmacokinetics, R = randomized, R & D = research and development, S = safety, SB = single blind, s.c. = subcutaneous, SU = sulfonylurea, T = tolerability, T2DM = type 2 diabetes mellitus, TRT = treatment, TZ = thiazolidinedione, VO_2 max = peak oxygen uptake.

Sponsor-submitted Background Information:

Glucagon-like peptide-1 receptor (GLP-1R) agonists are a new class of incretin-based therapies for type 2 diabetes mellitus (T2DM) designed to replace or supplement endogenous GLP-1, thus regulating postprandial blood glucose concentrations by stimulating glucose-dependent insulin secretion. Albiglutide (GSK716155) is a GLP-1R agonist generated through genetic fusion of two tandem copies of modified human GLP-1to human albumin. The human albumin moiety of the recombinant fusion protein, together with engineered resistance to dipeptidyl peptidase IV (DPP-IV), greatly extends the half-life to 5 days allowing once weekly dosing by subcutaneous injection.

The applicant has sought regulatory advice globally throughout the development program for albiglutide, inclusive of advice from the US Food and Drug Administration (FDA; 7 formal interactions), European Medicines Agency (EMA; 5 rounds of clinical, nonclinical and quality Scientific Advice and Pediatric Implementation Plan), (b) (4) US Investigational New Drug application (IND) 065177 was filed with FDA's Division of Metabolism and Endocrine Products (DMEP) on 15 Dec 2005. The clinical program for albiglutide has been conducted to

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reflect FDA and EMA guidance on development of products for T2DM and to evaluate cardiovascular and other class-specific safety risks.

The clinical program investigating albiglutide for T2DM involves 23 clinical studies including 10 Phase I studies, 5 Phase II studies, and 8 Phase III studies. A further Phase II study has been conducted (b) (4) The efficacy and safety of albiglutide are supported by results from eight well-controlled Phase III studies in patients with T2DM. At the time of this submission, five of these Phase III studies are ongoing (GLP112753, GLP112754, GLP112755, GLP112756 and GLP112757) to 3 years. Both FDA and EMA agreed with registrational filing based upon masked data analyses of the 3-year, Phase III efficacy and safety studies having primary endpoints at 1- and 2-years, if all subjects in the trials had completed a minimum of 2 years treatment. For these five ongoing studies, approximately 70% of the subjects will remain in the long-term extension phase after the submission data cut, to assess durability of efficacy and safety.

The type and number of diabetic background medications required for glycemic control is an important indicator of the stage of disease along the spectrum of T2DM, and therefore the population enrolled in the albiglutide program spanned newly diagnosed subjects treated with diet and exercise alone through to subjects on background oral monotherapy, oral dual therapy, oral triple therapy, and insulin. Importantly, the Phase III program also included a study that evaluated the efficacy and safety of albiglutide in combination with basal insulin (insulin glargine) (Study GLP108486); similar data are not available for the once weekly administered GLP-1R agonist exenatide. A variety of stable background antidiabetic therapies that had been taken prior to study entry were permitted in a number of studies (GLP114130, GLP108486, GLP114179); albiglutide or comparator were then added to background therapy. In all studies, diet and exercise plus any background medications were continued or standardized at maximum tolerated doses for the duration of the Phase III trials. None of the studies incorporated an aggressive treat to HbA1c goal approach, although dose up-titration and hyperglycemia rescue were available in all studies, permitting efficacy and safety to be assessed in a 'real-world' environment.

Albiglutide was administered at an initial dose of 30 mg weekly throughout the Phase III studies; however, optional (in 5 studies) or forced (in 2 studies) up-titration to a dose of 50 mg weekly was allowed. Double-blind monotherapy Study GLP114756 evaluated the comparative efficacy and safety of the 30-mg and 50-mg doses.

Specific active comparator studies (GLP112753, GLP112754, GLP108486, GLP114179, and GLP114130) were designed to compare the efficacy and safety of albiglutide with commonly used second and third line therapies, such as sulfonylureas, thiazolidinediones, DPP-IV inhibitors, other GLP-1R agonists as well as basal and prandial insulin. The range of active comparators in the albiglutide Phase III program allows for a thorough assessment of albiglutide's glycemic effects in a varied population of T2DM subjects.

Experience with albiglutide treatment in T2DM subjects who are early on in the course of their disease comes from Study GLP112756, conducted in drug-naïve subjects who had unsatisfactory glycemic control with diet and exercise, and from the add on to metformin study (GLP112753),

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with sitagliptin and separately glimepiride used as active comparators. The add-on to metformin and sulfonylurea study (GLP112757) allowed comparison of albiglutide versus placebo and pioglitazone in a population with more advanced disease. The head-to-head study versus insulin glargine (GLP112754) and the albiglutide + insulin glargine versus prandial insulin lispro + insulin glargine study (GLP108486) also represent comparative efficacy of albiglutide in subjects at a later stage of their disease. The comparator study versus liraglutide (GLP114179) offers clinicians important information as to the benefit-risk profile of a once daily GLP-1R agonist (liraglutide) compared to once weekly albiglutide used concomitantly with various background oral T2DM medications. The GLP114130 study versus sitagliptin provides essential data in T2DM subjects with mild, moderate, and severe renal impairment who have limited diabetes treatment options. Moreover, >60% of subjects across the integrated Phase III studies had mild or moderate renal impairment at baseline based on the Modification of Diet in Renal Disease (MDRD) equation.

Consistent with FDA's Dec 2008 Guidance: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, GSK conducted a cardiovascular meta-analysis of major adverse cardiac events (MACE+) from the eight Phase III global clinical trials and the Japan Phase IIb clinical trial as adjudicated by a blinded Clinical Endpoint Committee (CEC). The analysis to support registration was conducted in mid-2012. The risk assessment and analysis plan were also developed in accord with EMA draft guidance and consistent with the EMA Guideline on Clinical Investigation of Medicinal Products in the Treatment or Prevention of Diabetes oral dual therapy, oral triple therapy, and insulin. Importantly, the Phase III program also included a study that evaluated the efficacy and safety of albiglutide in combination with basal insulin (insulin glargine) (Study GLP108486); similar data are not available for the once weekly administered GLP-1R agonist exenatide. A variety of stable background antidiabetic therapies that had been taken prior to study entry were permitted in a number of studies (GLP114130, GLP108486, GLP114179); albiglutide or comparator were then added to background therapy. In all studies, diet and exercise plus any background medications were continued or standardized at maximum tolerated doses for the duration of the Phase III trials. None of the studies incorporated an aggressive treat to HbA1c goal approach, although dose up-titration and hyperglycemia rescue were available in all studies, permitting efficacy and safety to be assessed in a 'real-world' environment.

At the pre-BLA meeting with FDA held on 10 Oct 2012, the Review Division noted that meeting a hazard ratio noninferiority margin of 1.8 satisfied the criterion for registration, but more data would be required to rule out excess risk by a margin of 1.3. In addition to this cardiovascular risk assessment, a thorough QT study (GLP107085) was added to the registration program in 2011, in agreement with FDA, although EMA was satisfied that risk of proarrhythmic potential of albiglutide could be assessed using the triplicate electrocardiograms (ECGs) in the Phase III studies.

To evaluate other adverse events (AEs) of special interest for the incretin class, the Phase III studies incorporated assessments and analyses of thyroid disease/tumors, pancreatitis (including blinded review of events and amylase/lipase elevations by the Pancreatitis Adjudication Committee [PAC]), hypoglycemia, hepatic events, systemic allergic reactions, injection site reactions, immunogenicity, and GI events. Module 5.3.5.3 contains integrated reports to address

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the cardiovascular meta-analysis, pancreatitis, immunogenicity, and clinical comparability from the Phase III switch, as well as the Integrated Analysis of Efficacy and Integrated Analysis of Safety.

It is important to note that clinical comparability was specifically assessed for albiglutide, given that manufacturing Process 2 albiglutide was used in Phase III confirmatory efficacy/safety studies and Process 3 albiglutide is intended for commercial product. Comparability assessment has included biochemical/biophysical characterization, followed by clinical assessment for pharmacokinetic (PK) bioequivalence in Study GLP114856 (single-dose bioequivalence [BE] phase) with 12-week repeat dose safety, efficacy, trough PK and immunogenicity phase; and additional efficacy, safety and immunogenicity after blinded switching of subjects from Process 2 to Process 3 product in the extension phase of two ongoing Phase III studies, GLP112754 and GLP112756.

The proposed comparability plan was presented and accepted by FDA, EMA, (b) (4) (b) (4) Results from GLP114856 BE phase demonstrated PK bioequivalence and results from the repeat-dose phase of GLP114856 identified no clinically relevant differences in safety or efficacy parameters between Process 2 and Process 3. In the repeat-dose phase, the PK profiles of the two arms remained virtually identical.

Furthermore, in the Phase III switch Studies GLP112754 and GLP112756, safety and efficacy profiles were comparable among subjects receiving Process 3 albiglutide (after approximately 2 to 3 months of exposure) to those receiving Process 2 albiglutide. The primary packaging container-closure system for albiglutide drug product has been developed during clinical phases (b) (4) to a dual chamber cartridge (DCC) system, composed of a (b) (4) The pen injector is composed of a clear plastic cartridge holder and an opaque plastic pen mechanics sub-assembly. The reconstitution and administration of albiglutide product is performed by patient self-administration. There have been no changes in the materials of construction for either the DCC or the pen injector between the Phase III clinical program and commercial supply. Minor design changes were instituted to address usability issues identified through risk assessment and/or reported during the Phase III studies and to aid in automated pen injector assembly.

Albiglutide has a favorable benefit-risk profile and addresses a number of areas of unmet medical need. The most important favorable effect of albiglutide is the rapid, robust and durable lowering of HbA1c, which can be achieved with a once weekly injection using an easy-to-use pen device. Albiglutide is associated with weight loss compared to many commonly used therapies for T2DM (sulfonylureas, thiazolidinediones, insulin, DPP-IV inhibitor), which is a distinct and important advantage. The benefits of a once weekly subcutaneous injection have been demonstrated as a monotherapy and in combination with other commonly administered antidiabetic therapies, at different stages of the disease, and in patients with non-dialysis-dependent chronic kidney disease. Across all these groups, the dosing regimen is simple – administer albiglutide 30 mg once weekly and if insufficient glycemic control is achieved then up-titrate to 50 mg.

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Albiglutide's safety profile shows the product to be well tolerated with a modest increase in gastrointestinal (GI) AEs over placebo but the GI side effect appears advantageous when compared to the approved GLP-1R agonists. Injection site reactions were reported more commonly with albiglutide than comparators, but for most subjects these were short, mild, and self-limiting AEs that did not require withdrawal from therapy.

Questions around pancreatitis and thyroid cancer for the GLP-1R agonist class remain; GSK considers these important safety concerns and these will be appropriately addressed by postmarketing and risk management activities in addition to precautionary guidance for prescribers in product labeling.

2.2 Data Sources

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3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

It is possible to trace analysis datasets to original data source (e.g., case report form). However, proper conduct of the trials and correctness of CRF's are not guaranteed. Only a limited number of sites are inspected by FDA.

3.2 Evaluation of Efficacy

This subsection contains the sponsor's Tables and Graphs and the reviewer's evaluation based on these and his analyses.

Note: The subsections under each study are: Title, Study center(s), Study period, Phase of development, Objectives, Methodology, Number of subjects, Statistical methods, Patient Disposition, Demographics, Summary of Baseline Diabetes Characteristics.

The main subsection "Results and Conclusions" contains the subsections: Primary Efficacy Endpoints, Forest Plot of Difference of Least Squares Mean Model-Adjusted, and Graphs for the following:

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Mean Change From Baseline in HBA1c through the end of study, Mean Change From Baseline in FPG through the end of study, Mean Change From Baseline in Weight through the end of study, and Cumulative Distributions for HBA1c, FPG, and Weight.

Note: The non-inferiority p-values in the Tables should be neglected. When information from outside the study is brought in to make an inference, a p-value should not be reported. The non-inferiority margin was based on the results from previous placebo controlled studies. Here, comparing the confidence interval with the margin is the test procedure.

STUDY GLP108486

Title: A Randomized, Open-Label, Active-Controlled, Parallel-Group, Multicenter Study to Determine the Safety and Efficacy of Albiglutide Administered in Combination With Insulin Glargine as Compared With the Combination of Insulin Glargine and Preprandial Lispro Insulin in Subjects With Type 2 Diabetes Mellitus

Study center(s): The study was conducted at 159 centers in 14 countries.

Study period: 06 Oct 2009 to 13 Oct 2011

Phase of development: III

Objectives/Endpoints: The primary objective of the study was to evaluate the efficacy of albiglutide in combination with insulin glargine as compared with the combination of insulin glargine and preprandial lispro insulin (lispro) on glycosylated hemoglobin (HbA_{1c}) change from Baseline at Week 26.

Methodology: This was a randomized, open-label, active-controlled, 2-parallel group, multicenter study of 60-64 weeks duration evaluating the safety and efficacy of a once weekly subcutaneous dose of albiglutide in combination with insulin glargine as compared with the combination of insulin glargine and lispro in subjects with type 2 diabetes mellitus (T2DM).

The study had 4 study periods: 2 weeks of Prescreening and Screening; approximately 4 to 8 weeks of Run-in/Stabilization; a 60-week Treatment Period for the assessment of the primary efficacy and safety objectives, including 26 weeks of initial treatment and evaluation for primary safety and efficacy followed by at least an additional 26 weeks of treatment for additional safety and efficacy; and 8 weeks of posttreatment follow-up. Subjects who were not already receiving insulin glargine had a total study duration of approximately 64 weeks that included approximately 8 weeks of Run-in/Stabilization to titrate and stabilize the dose of insulin glargine. Subjects received once per week

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subcutaneous dosing of albiglutide at 30 mg with the option to titrate up to a weekly dose of 50 mg of albiglutide.

Randomization was stratified by HbA1c (≤8.5 or >8.5), history of prior myocardial infarction (MI) and current oral therapy (metformin without thiazolidinedione (TZD), TZD without metformin, both TZD and metformin, or neither TZD nor metformin). Adjudication and review of all major cardiovascular and pancreatitis events took place over the entire Treatment Period.

Subjects not currently taking insulin glargine discontinued their other intermediate- or long-acting insulin and began taking insulin glargine. Otherwise, subjects continued on their current regimen of oral antidiabetic medication for the duration of their participation in the study, with the exception that use of sulfonylureas, glinides, or dipeptidyl peptidase-IV inhibitors were discontinued at Visit 5.

Number of subjects: Approximately 500 subjects were planned for randomization in a ratio of 1:1 albiglutide to lispro. A total of 586 subjects were randomized: 292 albiglutide, 294 lispro.

Statistical methods: The primary analysis of the HbA1c change from Baseline response at Week 26 was applied to the ITT Population using an analysis of covariance (ANCOVA) model with main effects for treatment group, region, history of prior MI, age category, and current oral antidiabetic therapy and with baseline HbA1c as a continuous covariate. The difference in treatment-effect between the albiglutide group and the lispro group was evaluated within this ANCOVA model as least squares means contrast. The contrast was evaluated with a 1-sided *t* test at the 0.025 significance level with a noninferiority margin of 0.4% on the change of HbA1c. With significance on the noninferiority hypothesis, the superiority hypothesis will be tested using a 2-sided, superiority with significance level of 0.05.

Subjects who qualified for hyperglycemia rescue had their primary endpoint value of HbA1c change from Baseline recorded at the time of rescue. Follow-up assessments continued beyond rescue, and postrescue HbA1c assessments were used in supportive efficacy analysis. Subjects who discontinued from active participation in the study (e.g., withdrew consent or were lost to glycemic follow-up) had their last HbA1c observation carried forward for the primary analysis.

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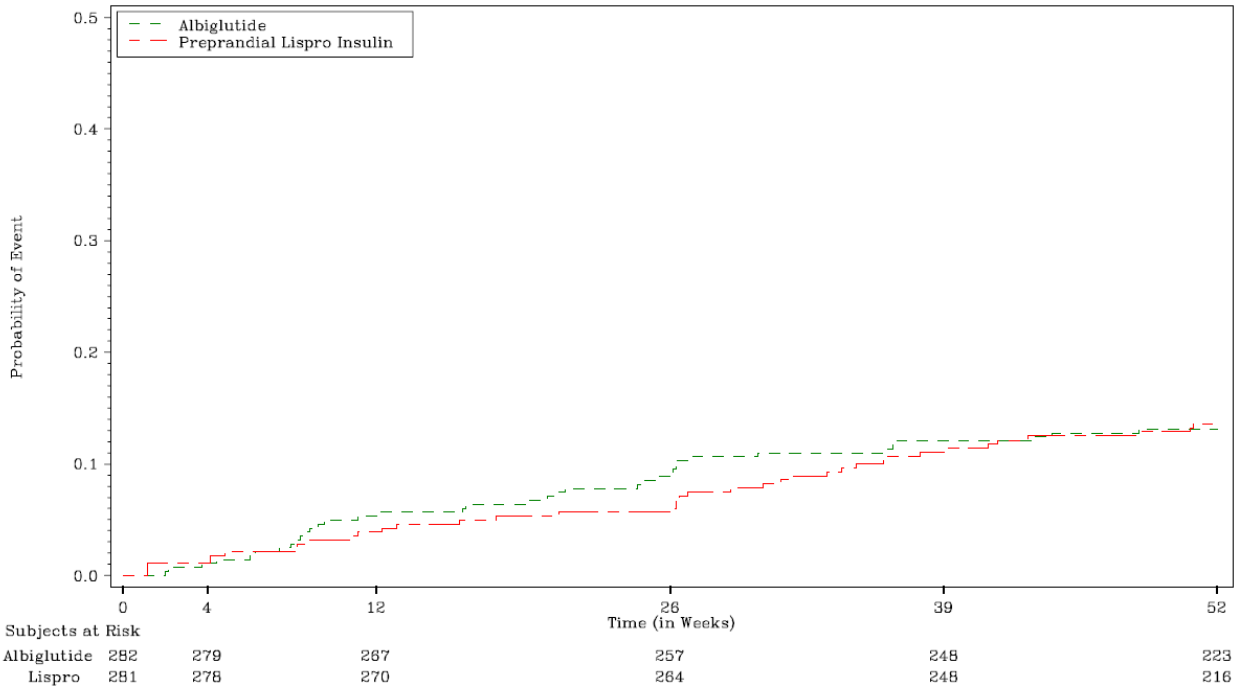
Patient Disposition:

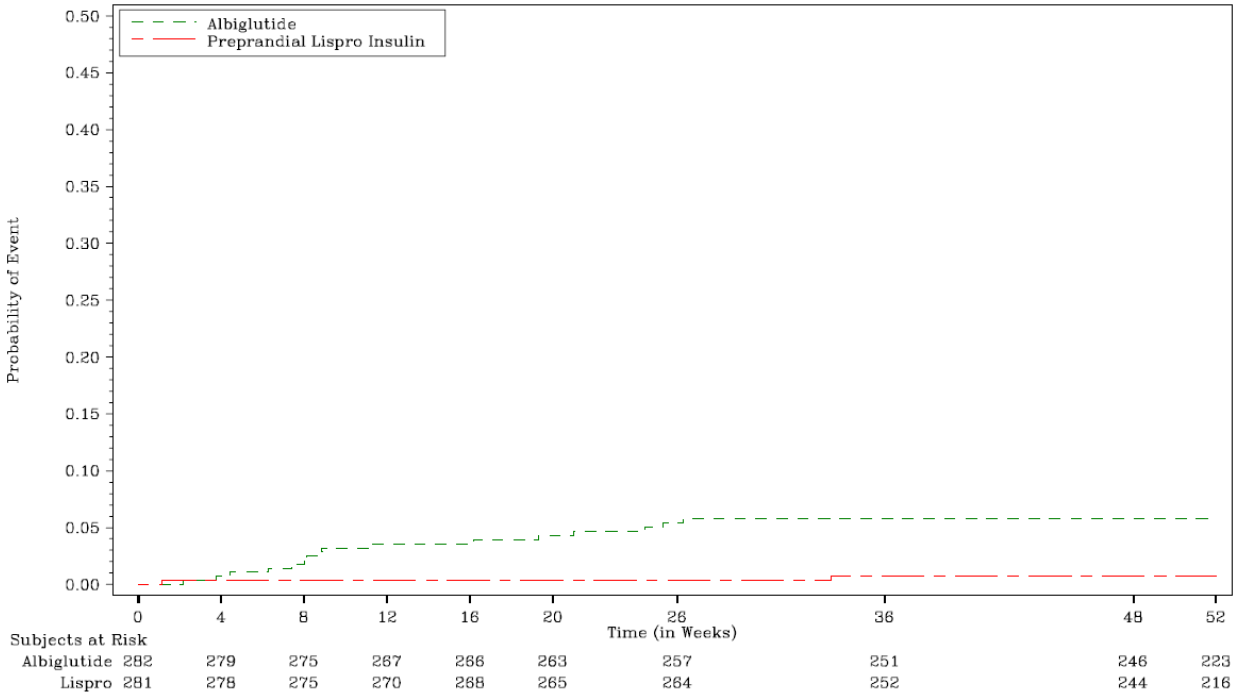
As seen from the following Kaplan-Meier curves, dropouts from the albiglutide group due to adverse events increased up to the middle of the study and remained constant after that; whereas, that rate was low and constant for the preprandial lispro insulin group. This made the overall dropout rate for the albiglutide group more than that in the other group around the middle of the study and, finally, become about equal to the other group. Dropout rate was not unusually high.

Kaplan-Meier Plot of Time to Withdrawal from Treatment
(Intent-to-treat Population)



Kaplan-Meier Plot of Time to Withdrawal from Active Treatment due to Adverse event
(Intent-to-treat Population)

Reference ID: 3392698



Demographic and Baseline Characteristics

As seen in the following Table of demographics, the mean age was 54.8 in the albiglutide group and was 56.3 in the lispro group.

Race was widely represented (details in the Table below), except, in patient number, for Native Hawaiian or other Pacific Islander 2 for albiglutide and 3 for lispro, and White – Arabic/North African heritage - 2 in albiglutide and 3 in lispro.

The percentage of male was 46.3 in the albiglutide group and was 48.4 in the lispro group.
The mean weight (kg) was 92.5 in the albiglutide group and was 91.6 in the lispro group.

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Summary of Demographic Characteristics at Randomization (Safety Population)

	Insulin Glargine in Combination With:		
	Albiglutide (N = 285)	Lispro (N = 281)	Total (N = 566)
Age at randomization (years)			
n	285	281	566
Mean (SD)	54.8 (9.10)	56.3 (8.87)	55.6 (9.01)
Median	55.0	56.0	56.0
Min, max	18, 75	35, 76	18, 76
Age category, n (%)			
n	285	281	566
<65 years	253 (88.8)	228 (81.1)	481 (85.0)
≥65 years	32 (11.2)	53 (18.9)	85 (15.0)
Sex, n (%)			
n	285	281	566
Female	153 (53.7)	145 (51.6)	298 (52.7)
Male	132 (46.3)	136 (48.4)	268 (47.3)
Race[2], n (%)			
n	285	281	566
African American/African heritage	39 (13.7)	34 (12.1)	73 (12.9)
American Indian or Alaskan Native	29 (10.2)	20 (7.1)	49 (8.7)
Asian – Central/South Asian heritage	17 (6.0)	17 (6.0)	34 (6.0)
Asian – East Asian heritage	15 (5.3)	17 (6.0)	32 (5.7)
Asian – South East Asian heritage	16 (5.6)	16 (5.7)	32 (5.7)
Native Hawaiian or Other Pacific Islander	1 (0.4)	3 (1.1)	4 (0.7)
White – Arabic/North African heritage	2 (0.7)	3 (1.1)	5 (0.9)
White – White/Caucasian/European heritage	174 (61.1)	171 (60.9)	345 (61.0)
Other	1 (0.4)	1 (0.4)	2 (0.4)
Ethnicity, n (%)			
n	285	281	566
Hispanic/Latino	75 (26.3)	70 (24.9)	145 (25.6)
Not Hispanic/Latino	210 (73.7)	211 (75.1)	421 (74.4)
Weight (kg)			
n	285	281	566
Mean (SD)	92.50 (21.50)	91.61 (20.96)	92.06 (21.22)
Median	91.50	93.30	92.50
Min, max	45.7, 153.7	51.6, 150.6	45.7, 153.7
Body mass index, kg/m^2			

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n	285	281	566
Mean (SD)	33.15 (6.013)	32.90 (5.812)	33.03 (5.910)
Median	33.00	33.00	33.00
Min, max	21.0, 46.0	21.0, 45.0	21.0, 46.0
Body mass index category			
n	285	281	566

	Insulin Glargine in Combination With:		
	Albiglutide (N = 285)	Lispro (N = 281)	Total (N = 566)
<25 kg/m² n (%)	17 (6.0)	27 (9.6)	44 (7.8)
≥25 kg/m² to <30 kg/m² n (%)	71 (24.9)	55 (19.6)	126 (22.3)
≥30 kg/m² to <35 kg/m² n (%)	79 (27.7)	79 (28.1)	158 (27.9)
≥35 kg/m² n (%)	118 (41.4)	120 (42.7)	238 (42.0)

Max = maximum, Min = minimum, SD = standard deviation.

1 The p-value was for testing the null hypotheses that summary statistics (mean or proportion) are equal among treatment groups. All tests were 2-sided.

2 A subject may have been counted in more than 1 category.

Summary of Baseline Diabetes Characteristics (Safety Population)

As seen in the following Table of baseline characteristics, the mean duration of diabetes in years was 11.3 in the albiglutide group and was 10.8 in the lispro group.

Reference ID: 3392698

	Insulin Glargine in Combination With:		
	Albiglutide (N = 285)	Lispro (N = 281)	Total (N = 566)
Subjects with any conditions, n (%)	238 (83.5)	240 (85.4)	478 (84.5)
Dyslipidaemia	215 (75.4)	200 (71.2)	415 (73.3)
Peripheral neuropathy	83 (29.1)	82 (29.2)	165 (29.2)
Diabetic retinopathy	46 (16.1)	37 (13.2)	83 (14.7)
Impotence	30 (10.5)	30 (10.7)	60 (10.6)
Proteinuria	16 (5.6)	22 (7.8)	38 (6.7)
Microalbuminuria	15 (5.3)	22 (7.8)	37 (6.5)
Nephropathy	19 (6.7)	16 (5.7)	35 (6.2)
Diabetic foot ulcer	8 (2.8)	9 (3.2)	17 (3.0)
Autonomic neuropathy	3 (1.1)	6 (2.1)	9 (1.6)
Chronic renal insufficiency	3 (1.1)	2 (0.7)	5 (0.9)
Other	6 (2.1)	7 (2.5)	13 (2.3)
Duration (years)			
n	285	281	566
Mean (SD)	11.30 (6.691)	10.84 (6.157)	11.07 (6.430)
Median	10.33	10.20	10.25
Min, max	0.6, 37.2	0.7, 35.4	0.6, 37.2
Duration category, n (%)			
n	285	281	566
<8 years	103 (36.1)	107 (38.1)	210 (37.1)
≥8 years to <13 years	92 (32.3)	86 (30.6)	178 (31.4)
>13 years	90 (31.6)	88 (31.3)	178 (31.4)

Reference ID: 3392698

	Insulin Glargine in Combination With:		
	Albiglutide (N = 285)	Lispro (N = 281)	Total (N = 566)
Prior myocardial infarction			
n	285	281	566
Yes	22 (7.7)	27 (9.6)	49 (8.7)
No	263 (92.3)	254 (90.4)	517 (91.3)
Baseline HbA_{1c}, n (%)			
n	285	281	566
Mean (SD)	8.48 (0.923)	8.44 (0.856)	8.46 (0.890)
Median	8.40	8.40	8.40
Min, max	6.5, 11.4	6.7, 10.5	6.5, 11.4
Baseline HbA_{1c} category, n (%)			
n	285	281	566
<8.5%	150 (52.6)	144 (51.2)	294 (51.9)
≥8.5%	135 (47.4)	137 (48.8)	272 (48.1)
Current antihyperglycemia oral therapy, n (%)			
n	285	281	566
Metformin without TZD	196 (68.8)	191 (68.0)	387 (68.4)
Neither TZD nor metformin	64 (22.5)	67 (23.8)	131 (23.1)
Both TZD and metformin	18 (6.3)	19 (6.8)	37 (6.5)
TZD without metformin	7 (2.5)	4 (1.4)	11 (1.9)

TZD = thiazolidinedione.
The p-value was for testing the null hypotheses that summary statistics (mean or proportion) are equal among treatment groups. All tests were 2-sided.

Results and Conclusions

Primary Efficacy Endpoint

HbA_{1c} Change From Baseline at Week 26

Mean Baseline HbA_{1c} values were similar across treatment groups. A decrease in mean HbA_{1c} from Baseline to Week 26 was observed in both the albiglutide and lispro groups with the greatest reduction in the albiglutide group. Baseline HbA_{1c}, history of prior MI, age category, and region, the model-adjusted LS mean change in HbA_{1c} from Baseline to Week 26 was -0.82% in the albiglutide group, -0.66% in the lispro group. The treatment difference for albiglutide – lispro of -0.16% (95% CI: –0.32, 0.00) met the prespecified primary endpoint of noninferiority to lispro ($p < 0.0001$) and nearly met the prespecified primary endpoint of superiority ($p=0.0533$). The separation between the curves was apparent by Week 4 and was maintained through Week 26. At Week 26, the mean HbA_{1c} values were 7.65% and 7.78% in the albiglutide and lispro groups, respectively.

Reference ID: 3392698

Analysis of Change From Baseline in HbA_{1c} (%) at Week 26 (ITT Population – LOCF)

	Insulin Glargine in Combination With:	
	Albiglutide (N = 282)	Lispro (N = 281)
Number of subjects[1]	279	278
Number (%) of values carried forward	82 (29.4)	81 (29.1)
Baseline – mean (SD)	8.47 (0.924)	8.43 (0.858)
Week 26 – mean (SD)	7.65 (1.113)	7.78 (1.120)
Change from Baseline – mean (SD)	-0.82 (1.034)	–0.65 (1.009)
Model-adjusted change from Baseline[2]		
LS mean (SE)	–0.82 (0.058)	–0.66 (0.058)
95% CI	–0.93, –0.70	–0.77, –0.54
Difference from preprandial lispro insulin[2]		
Difference of LS means	–0.16	
95% CI	–0.32, 0.00	
Noninferiority p-value[3]	<0.0001	
Superiority p-value[4]	0.0533	

ANCOVA = analysis of covariance, CI = confidence interval, HbA_{1c} = glycosylated hemoglobin,
LOCF = last observation carried forward, LS = least squares, SD = standard deviation, SE = standard error.
Note: This analysis used the LOCF method for missing postbaseline HbA_{1c} values. The HbA_{1c} values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values.

1 Number of subjects with a value at Baseline and at the specified visit.

2 Based on ANCOVA: Change = treatment + baseline HbA_{1c} + prior myocardial infarction + age category + region + current oral antidiabetic therapy. Difference of least squares means (albiglutide –preprandial lispro insulin) from ANCOVA model.

3 This p-value was from a 1-sided *t* test to test whether the difference of least squares means (albiglutide – preprandial lispro insulin) was equal to the prespecified noninferiority margin of 0.4%.

4 This p-value was from a 2-sided *t* test to test whether the difference in the least squares means (albiglutide –preprandial lispro insulin) was equal to zero.

Note: My analyses provided superiority p-value of .0541by parametric and .0595 by non-parametric methods. Albiglutide arm maintained numerical superiority at all visits. The non-inferiority claim is acceptable.

Forest Plot of the Difference of Least Squares Mean Model-Adjusted Change From Baseline in HbA_{1c} (%) and 95% CI for Albiglutide Versus Lispro at Week 26 by Subgroup Category (ITT Population – LOCF)

Note: Left side represents the numerical superiority of albiglutide.

There was a statistically significant Treatment by Race (Black, white, other non-white) (p= 0.0023) interaction:

As seen below, in the black group, the upper boundary of the confidence interval (-.42,.53) is out of the non-inferiority margin .3; so, does not exclude the possibility of the albiglutide group being inferior. However, subgroup results, when not planned to be confirmatory, are not confirmatory. Further evidences are needed to reach the level of confirmation.

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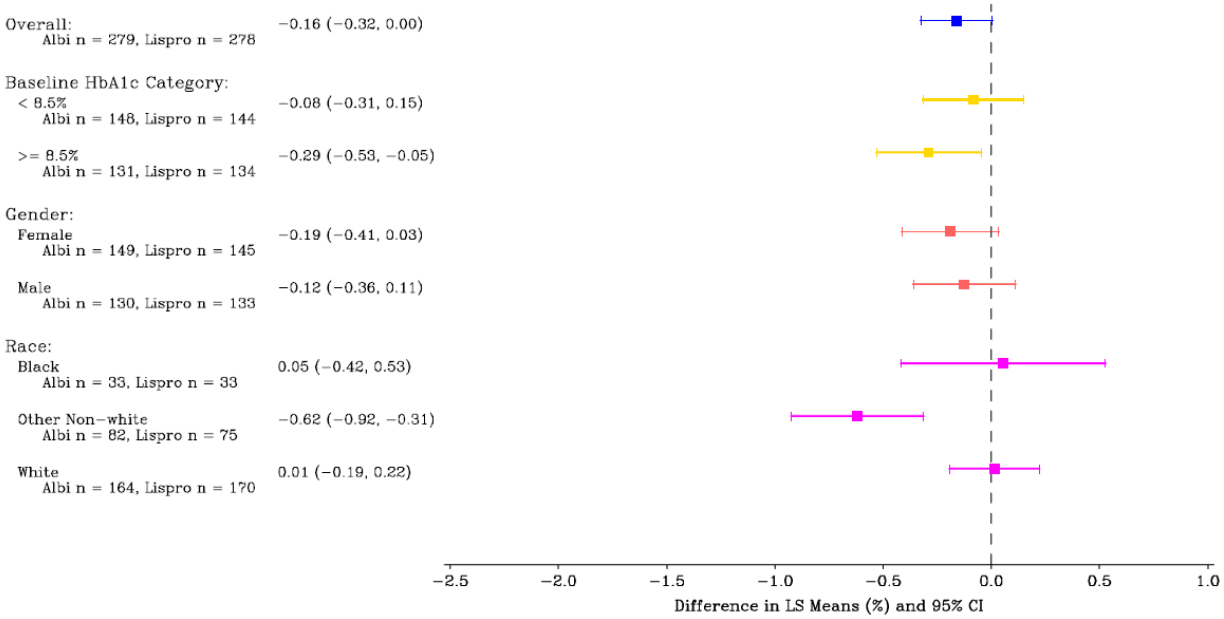
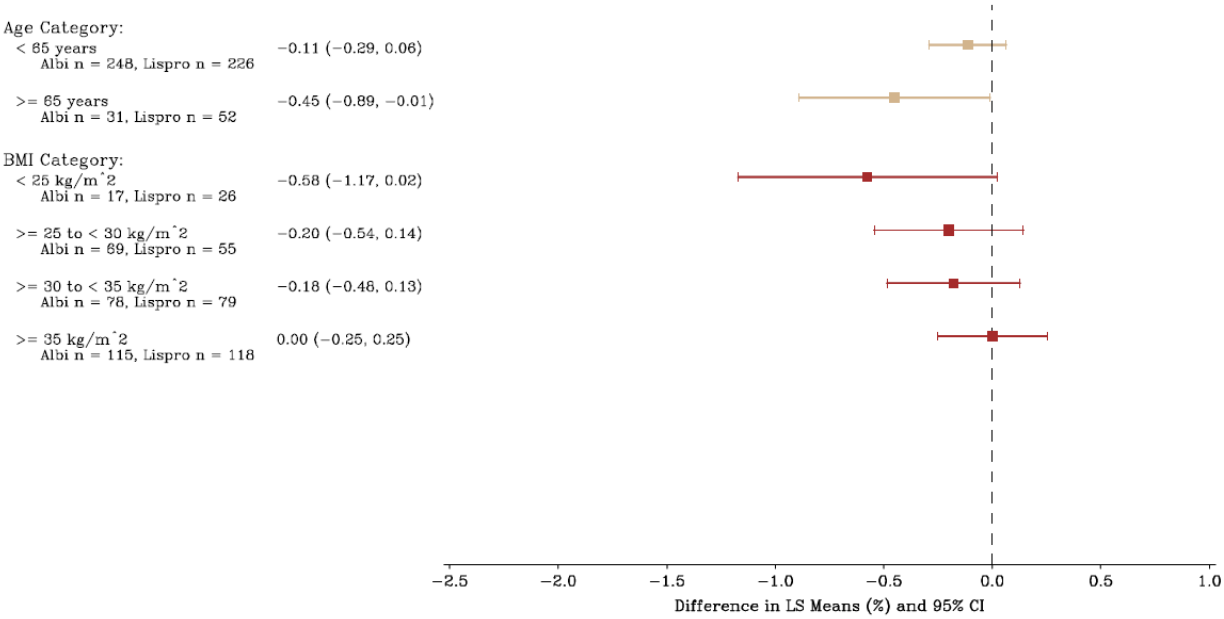
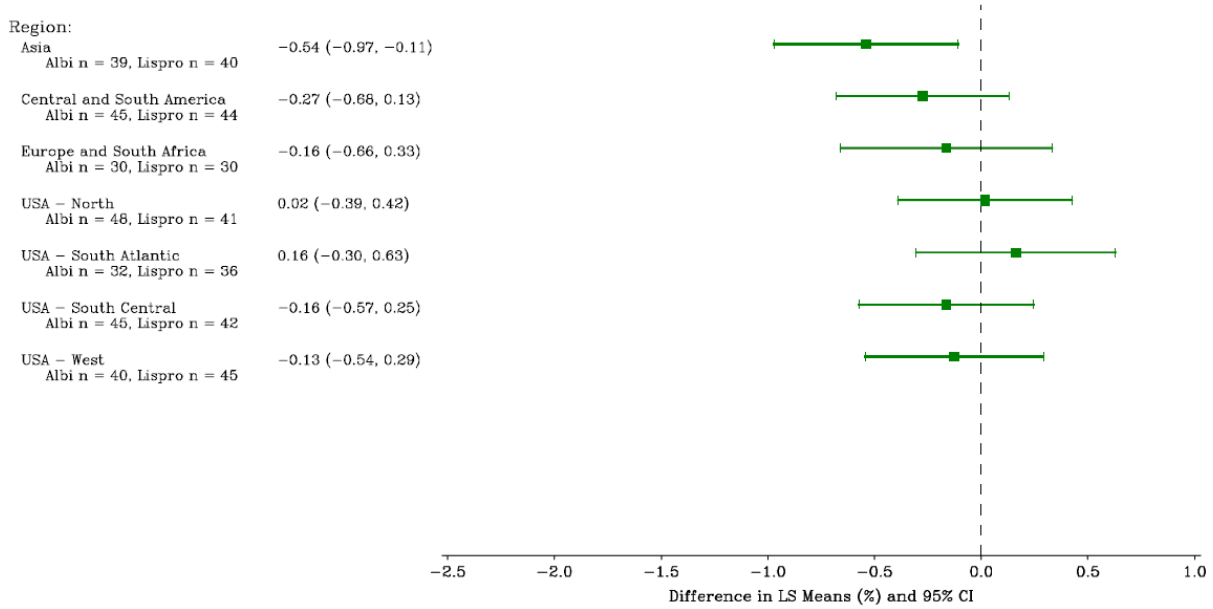




As seen below, in the South Atlantic Region of USA, the upper boundary of the confidence interval (-.3,.63) is out of the non-inferiority margin .3; so, does not exclude the possibility of the

Reference ID: 3392698

albiglutide group being inferior in that region. However, subgroup results, when not planned to be confirmatory, are not confirmatory. Further evidences are needed to reach the level of confirmation.



As seen below, *in the Current Oral Antidiabetic Therapy group, the upper boundary of the confidence interval (-.37,.90) is out of the non-inferiority margin .3; so, does not exclude the possibility of the albiglutide group being inferior in this subgroup. However, subgroup results, when not planned to be confirmatory, are not confirmatory. Further evidences are needed to reach the level of confirmation.*

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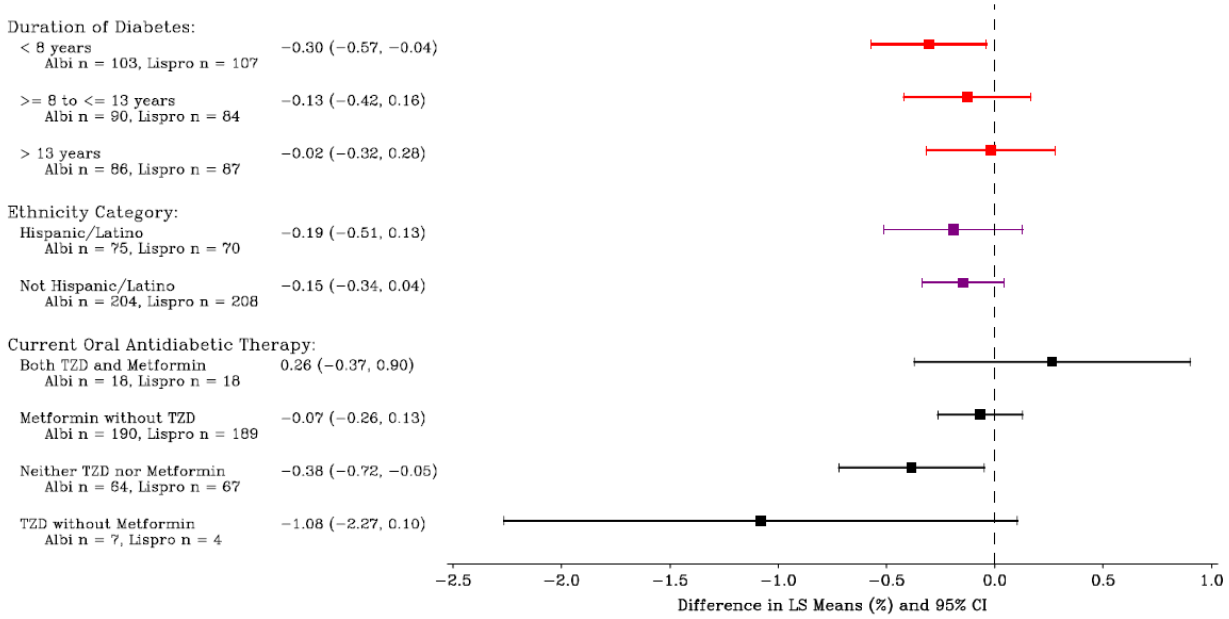

Albi = albiglutide, HbA_{1c} = glycosylated hemoglobin, LOCF = last observation carried forward, LS = least squares, TZD = thiazolidinedione.

There was a statistically significant current antidiabetic therapy by treatment interaction p-value of .0913. The preprandial insulin lispro was numerically superior to albiglutide in the 'Both TZD and Metformin' subgroup. The results of the two subgroups follow:

Analysis of Change from Baseline in HbA1c (%) Through Week 26 by Current Oral Antidiabetic Therapy (Intent-to-treat Population - LOCF)

Reference ID: 3392698

Current Oral Antidiabetic Therapy: TZD without Metformin - Week 26

	Albiglutide (N=282)	Preprandial Lispro Insulin (N=281)
Number of Subjects [1]	7	4
Number (%) of Values Carried Forward	1 (14.3%)	2 (50.0%)
Baseline		
Mean	8.24	8.60
Standard Deviation	1.220	1.517
Week 26		
Mean	7.19	8.48
Standard Deviation	1.499	1.517
Change from Baseline		
Mean	-1.06	-0.13
Standard Deviation	1.614	0.862
Model-Adjusted Change from Baseline [2]		
LS Mean	-1.11	-0.03
Standard Error	0.365	0.482
95% Confidence Interval	(-1.83, -0.40)	(-0.98, 0.92)
Difference from Preprandial Lispro Insulin [2]		
Difference of LS Means	-1.08	
95% Confidence Interval	(-2.27, 0.10)	

Current Oral Antidiabetic Therapy: Both TZD and Metformin - Week 26

	Albiglutide (N=282)	Preprandial Lispro Insulin (N=281)
Number of Subjects [1]	18	18
Number (%) of Values Carried Forward	6 (33.3%)	3 (16.7%)
Baseline		
Mean	8.59	8.41
Standard Deviation	0.916	0.886
Week 26		
Mean	7.90	7.52
Standard Deviation	0.996	0.875
Change from Baseline		
Mean	-0.69	-0.88
Standard Deviation	0.903	0.854
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.67	-0.93
Standard Error	0.231	0.231
95% Confidence Interval	(-1.12, -0.22)	(-1.39, -0.48)
Difference from Preprandial Lispro Insulin [2]		
Difference of LS Means	0.26	
95% Confidence Interval	(-0.37, 0.90)	

Note: This analysis uses the last observation carried forward (LOCF) method for missing post-baseline HbA1c values. HbA1c values obtained after hyperglycemic rescue are treated as missing and replaced with pre-rescue values.
[1] Number of subjects with a value at baseline and at the specified visit.
[2] Based on ANCOVA: Change = trt + baseline HbA1c + prior MI history + age category + region + current oral antidiabetic therapy + ethnicity category + trt*current oral antidiabetic therapy. Difference of least squares means (albiglutide — preprandial lispro insulin) from ANCOVA model. The p-value for the interaction term = 0.0913.

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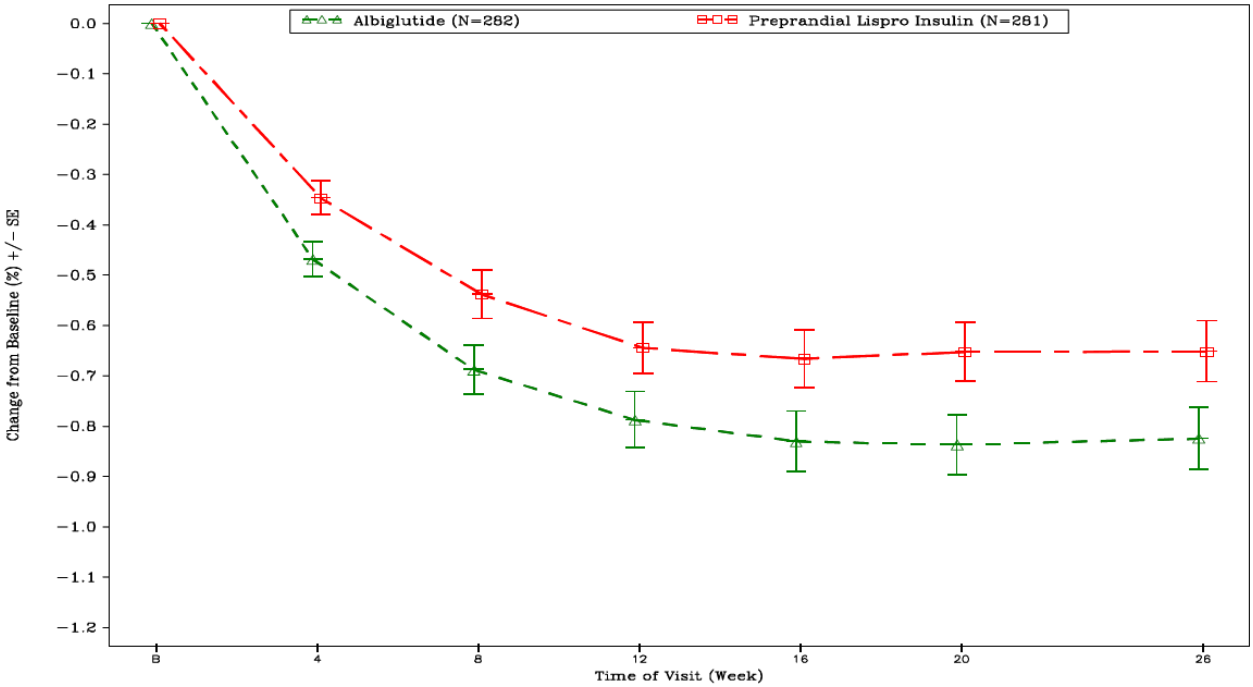
As seen in the following graph, albiglutide was numerically superior to lispro over all time points with respect to change from baseline in HBA1c.

Mean Change From Baseline in HbA_{1c} (%) Through Week 26 (ITT Population – LOCF)



B = Baseline; HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; SE = standard error.

My analyses of FPG, provided superiority p-value of .4395 by parametric and .1771 by non-parametric methods. Both arms had decreases from baseline but albiglutide maintained numerical superiority at all visits. Sponsor's results follow:

Analysis of Change From Baseline in FPG (mmol/L) at Week 26 (ITT Population – LOCF)

Reference ID: 3392698

	Insulin Glargine in Combination With:	
	Albiglutide (N = 282)	Lispro (N = 281)
Number of subjects[1]	282	279
Number (%) of values carried forward	89 (31.6%)	84 (30.1%)
Baseline Mean (SD)	8.46 (3.033)	8.50 (3.107)
Week 26 Mean (SD)	7.48 (2.893)	7.78 (2.949)
Model-adjusted change from Baseline[2]		
Least squares mean	–0.99	–0.71
Standard error	0.164	0.164
95% CI	(–1.31, –0.67)	(–1.04, –0.39)
Difference from lispro[2]		
Difference of least squares means	-0.28	
95% CI	(-0.73, 0.18)	
p-value	0.2366	

CI = confidence interval, FPG = fasting plasma glucose, LOCF = last observation carried forward, SD = standard deviation.
Note: This analysis used the LOCF method for missing postbaseline FPG values. The FPG values obtained after hyperglycemic rescue were treated as missing and replaced with prerescue values.

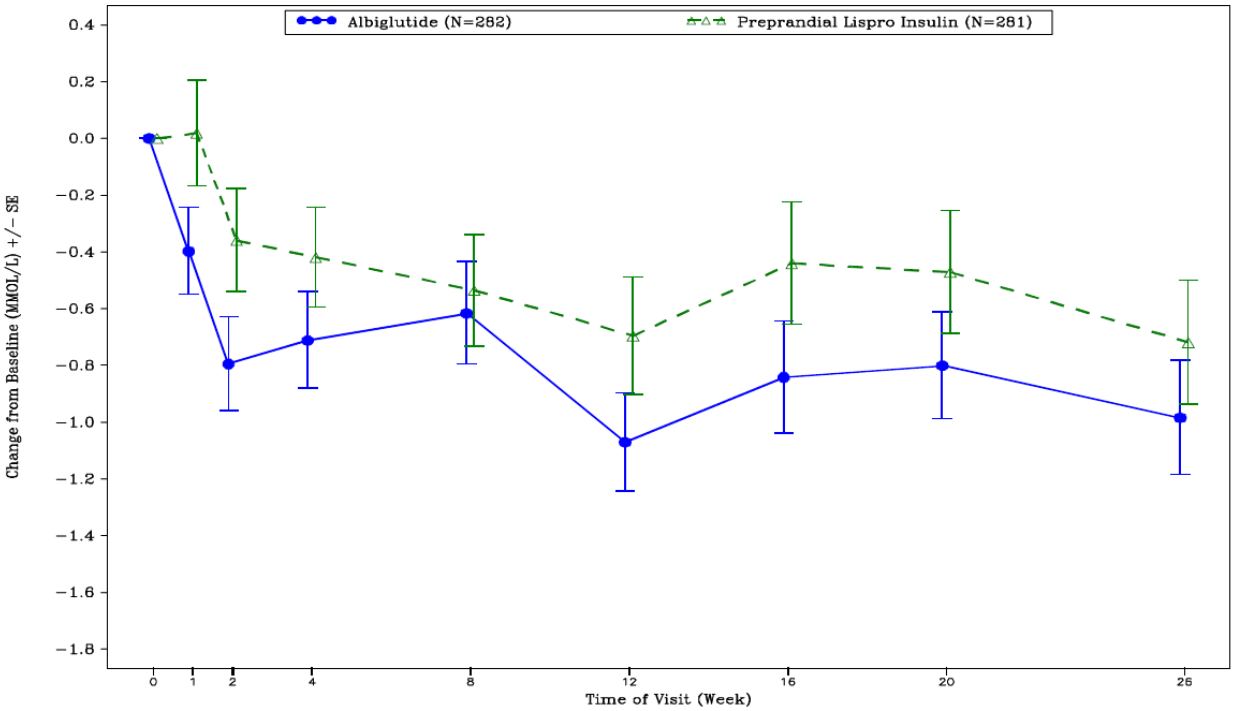
1 Number of subjects with a value at baseline and at the specified visit.

2 Based on analysis of covariance (ANCOVA): Change = treatment + baseline FPG + baseline HbA_{1c} category + prior myocardial infarction history + age category + region + current oral antidiabetic therapy. The difference of least squares means (albiglutide – lispro) is from the ANCOVA model. The p-value is from a 2-sided *t* test for the difference in means.

Mean Change From Baseline for FPG (mmol/L) Through Week 26 (ITT Population – LOCF)

Note: As seen in the following graph, except at Week 8, the responses in the two treatment arms were almost parallel. However, albiglutide was always numerically superior.

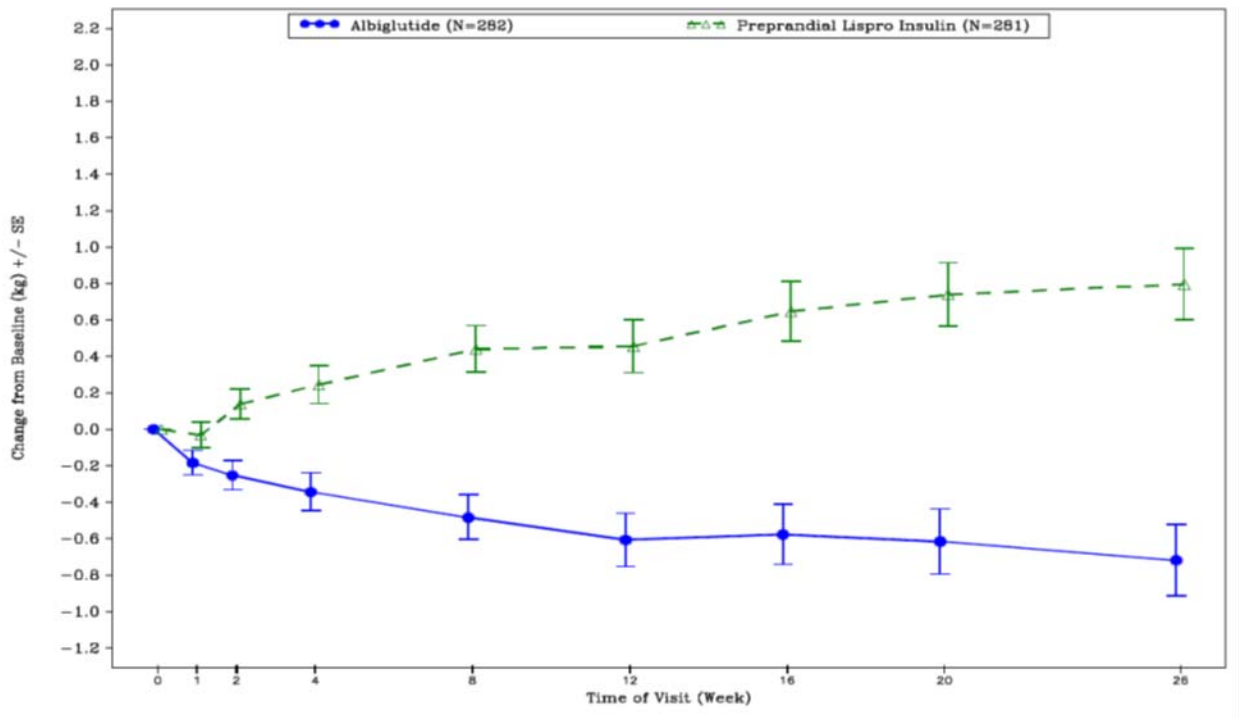
Reference ID: 3392698



Mean (±SE) Percent Change From Baseline in Weight (kg) Through Week 26 (ITT Population – LOCF)

As seen in the following graph, *weight decreased for albiglutide but increased for the other arm. There were statistically significant differences starting from Week 2.*

Reference ID: 3392698



Analysis of Change From Baseline in Weight (kg) at Week 26 (ITT Population – LOCF)

As seen from the following Table, the lispro group gained weight on average up to Week 26, while the albiglutide group continued to lose weight during that period. At Week 26, the model-adjusted LS mean weight change from Baseline for subjects in the albiglutide group averaged -0.73 kg while the corresponding gain in the lispro group was 0.81 kg. The difference in weight change from Baseline to Week 26 was statistically significantly different (p=0.0007 or better) in favor of albiglutide at each time point from Week 2 through Week 26. Percent change from Baseline in weight was less than 1.0% in both treatment groups at Week 26.

Reference ID: 3392698

	Insulin Glargine in Combination With:	
	Albiglutide (N = 282)	Lispro (N = 281)
Number of subjects[1]	282	280
Number (%) of values carried forward	86 (30.5)	83 (29.6)
Baseline Mean (SD)	92.54 (21.472)	91.59 (20.991)
Week 26		
Mean (SD)	91.82 (21.463)	92.39 (20.954)
Change from Baseline mean (SD)	–0.72 (3.262)	0.80 (3.292)
Model-adjusted change from Baseline[2]		
Least squares mean (SE)	–0.73 (0.194)	0.81 (0.195)
95% CI	(–1.11, –0.35)	(0.43, 1.19)
Difference from preprandial lispro insulin[2]		
Difference of least squares means	–1.54	
95% CI	(–2.09, –1.00)	
p-value	<0.0001	

CI = confidence interval, Hba_{1c} = glycosylated hemoglobin, LOCF = last observation carried forward.
Note: This analysis used the LOCF method for missing postbaseline weight values. Weight values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values.
1 Number of subjects with a value at Baseline and at the specified visit.
2 Based on analysis of covariance (ANCOVA): Change = treatment + baseline weight + baseline HbA_{1c} category + prior myocardial infarction history + age category + region + current oral antidiabetic therapy. Difference of least squares means (albiglutide – preprandial lispro insulin) from ANCOVA model. The p-value was from a 2-sided *t* test for the difference in means.

Graphs of cumulative distribution functions by treatment groups for the primary efficacy variable (change from baseline in HbA1c) at the study endpoint are provided below. From these, the percent of patients (y-axis value) with a value of percent change from baseline in HbA1c at endpoint, smaller than or equal to a value on the x-axis, can be read.

Cumulative Distribution of HbA1c (%) Change from Baseline at Week 26 (Intent-to-treat Population- LOCF)

Note: As seen below, at any point on the Y-axis, the X-axis value, i.e. any percentile, was smaller for albiglutide than for lispro.

Reference ID: 3392698

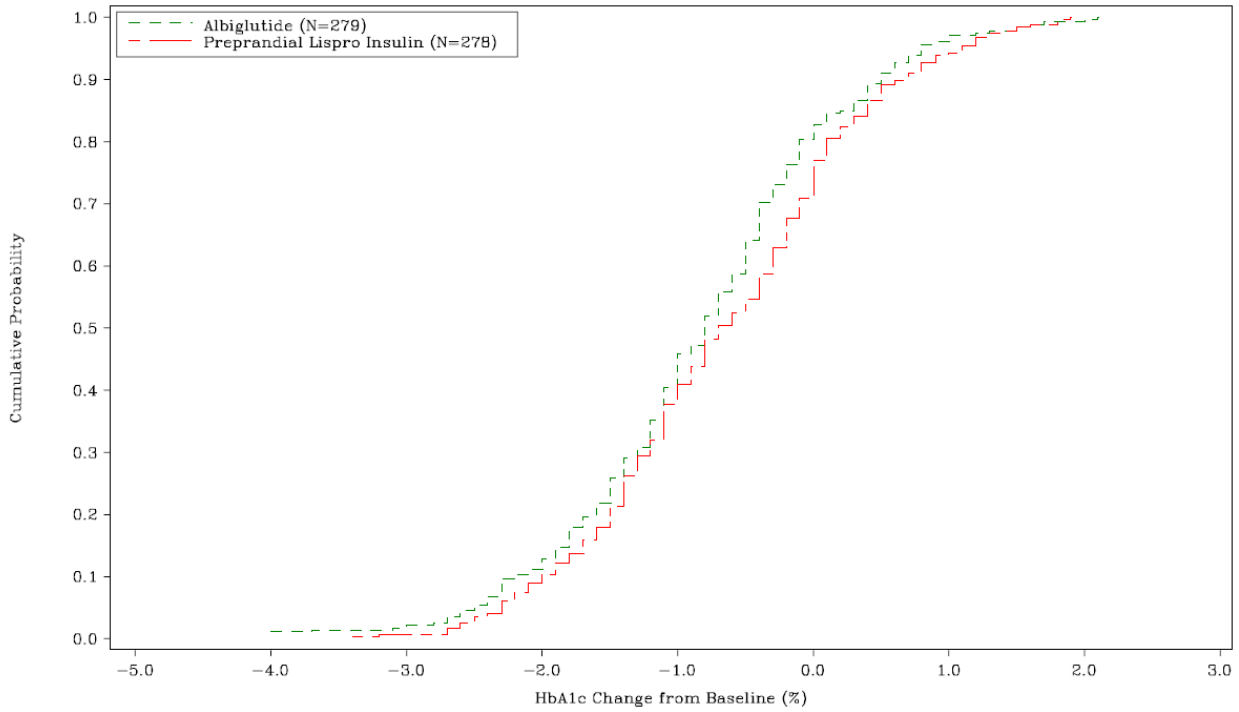


Table of Cumulative Distribution of HbA1c (%) Change from Baseline at Week 26 (Intent-to-treat Population - LOCF)

Percentile	Albiglutide (N=282)	Preprandial Lispro Insulin (N=281)
Number of subjects [1]	279	278
Min	-4.0	-3.4
1%	-4.00	-2.70
5%	-2.50	-2.30
10%	-2.20	-2.00
20%	-1.60	-1.50
30%	-1.30	-1.20
40%	-1.10	-1.00
50%	-0.80	-0.70
60%	-0.50	-0.30
70%	-0.40	-0.10
80%	-0.10	0.10
90%	0.50	0.70
95%	0.80	1.10
99%	1.70	1.80
Max	2.1	1.9

Note: This summary uses the last observation carried forward (LOCF) method for missing post-baseline HbA1c values. HbA1c values obtained after hyperglycemia rescue are treated as missing and replaced with pre-rescue values.
[1] Number of subjects with a value at Week 26.

Cumulative Distribution of Fasting Plasma Glucose (mg/dL) Change from Baseline at Week 26 (Intent-to-treat Population-LOCF)

Reference ID: 3392698

Note: As seen below, the percentiles were not always smaller for albiglutide than for lispro.

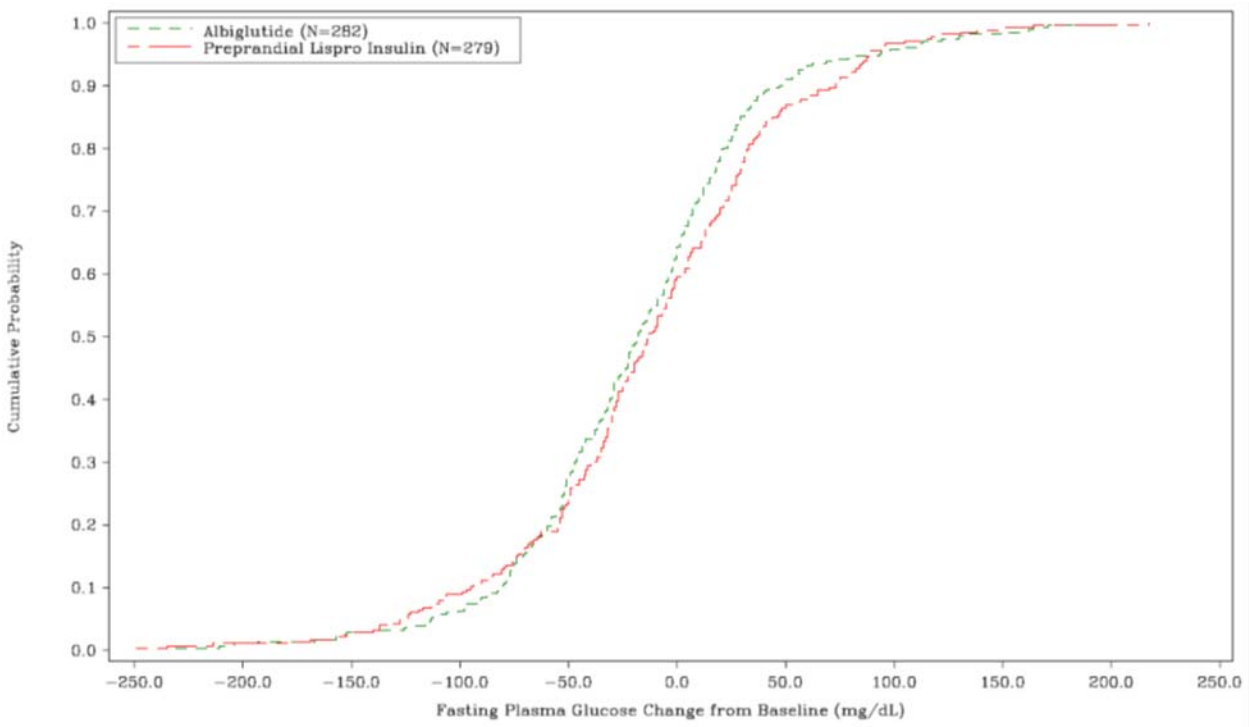


Table of Cumulative Distribution of Fasting Plasma Glucose (mg/dL) Change from Baseline at Week 26
(Intent-to-treat Population - LOCF)

Percentile	Albiglutide (N=282)	Preprandial Lispro Insulin (N=281)
Number of subjects [1]	282	279
Min	-231	-249
1%	-204.0	-214.0
5%	-113.0	-128.0
10%	-81.0	-95.0
20%	-58.0	-55.0
30%	-47.0	-38.0
40%	-31.0	-27.0
50%	-18.0	-13.0
60%	-3.0	2.0
70%	7.0	20.0
80%	21.0	33.0
90%	47.0	73.0
95%	93.0	88.0
99%	164.0	149.0
Max	204	217

Note: This summary uses the last observation carried forward (LOCF) method for missing post-baseline fasting plasma glucose (FPG) values. FPG values obtained after hyperglycemia rescue are treated as missing and replaced with pre-rescue values.
[1] Number of subjects with a value at Week 26.

Reference ID: 3392698

Cumulative Distribution of Weight (kg) Change from Baseline at Week 26 (Intent-to-treat Population- LOCF)

Note: As seen below, at any point on the Y-axis, the X-axis value, i.e. any percentile of weight, was smaller for albiglutide than for lispro.

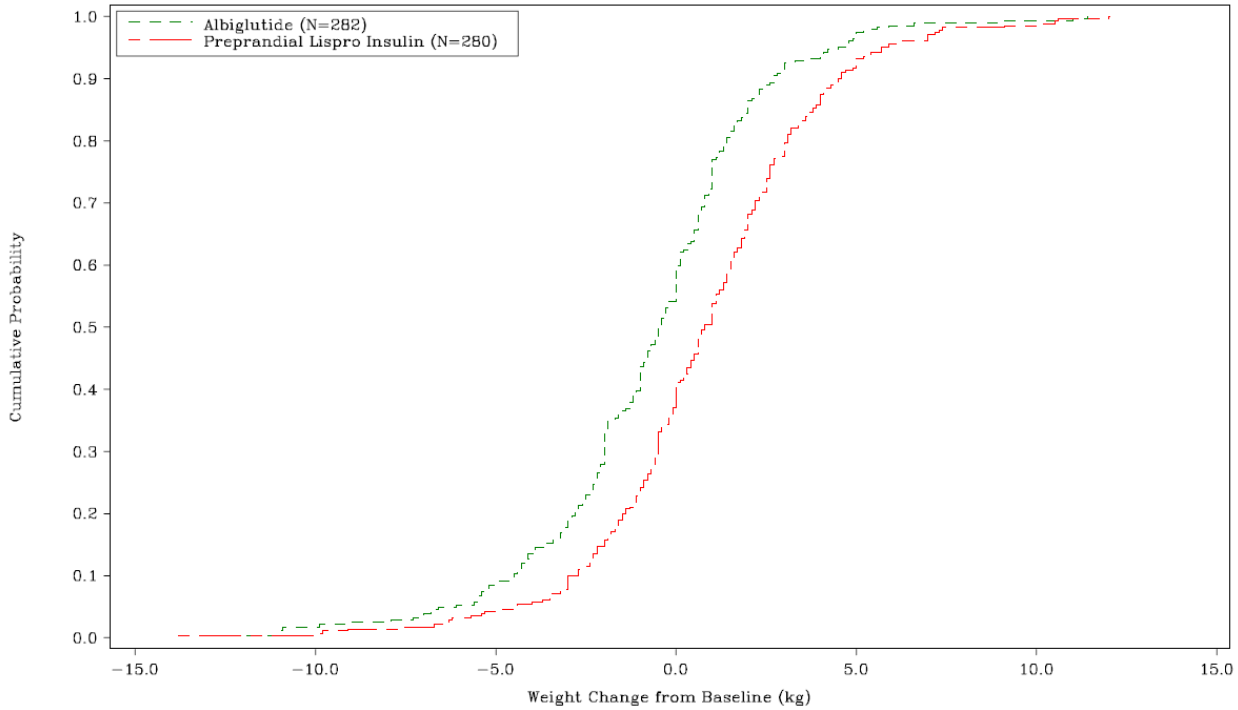


Table of Cumulative Distribution of Weight (kg) Change from Baseline at Week 26 (Intent-to-treat Population - LOCF)

Reference ID: 3392698

Percentile	Albiglutide (N=282)	Preprandial Lispro Insulin (N=281)
Number of subjects [1]	282	280
Min	-11.9	-13.8
1%	-11.00	-9.80
5%	-6.10	-4.45
10%	-4.50	-2.85
20%	-2.80	-1.45
30%	-2.00	-0.50
40%	-1.00	0.00
50%	-0.50	0.80
60%	0.10	1.50
70%	0.80	2.20
80%	1.40	3.10
90%	2.70	4.55
95%	4.50	5.80
99%	9.00	10.50
Max	11.4	12.0

Note: This summary uses the last observation carried forward (LOCF) method for missing post-baseline weight values. Weight values obtained after hyperglycemia rescue are treated as missing and replaced with pre-rescue values.
[1] Number of subjects with a value at Week 26.

STUDY GLP112753

Title: A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide When Used in Combination With Metformin Compared With Metformin Plus Sitagliptin, Metformin Plus Glimepiride, and Metformin Plus Placebo in Subjects With Type 2 Diabetes Mellitus

Study center(s): This study was conducted at 289 study centers.

Study Period: 03-MAR-2009 to 13-JAN-2012

Phase of Development: III

Objectives:

The primary efficacy objective of the study was to evaluate the efficacy of albiglutide administered in combination with metformin as compared with metformin plus sitagliptin, metformin plus glimepiride and metformin plus placebo on HbA_{1c} change from Baseline at Week 104.

Secondary efficacy objectives included evaluations of treatment with the same dosing regimens in terms of:

- HbA1c change from Baseline over time

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- Change from Baseline in fasting plasma glucose (FPG) at Week 104
- Change from Baseline in FPG over time
- Time to hyperglycemia rescue
- Proportion of subjects at an HbA_{1c} treatment goal of <6.5%, <7.0%, and < 7.5%)
- Change from Baseline in body weight

Methodology: This was a phase III, randomized, double-blind, placebo- and active-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of a weekly subcutaneously injected dose of albiglutide in combination with metformin as compared with metformin plus sitagliptin, metformin plus glimepiride and metformin plus placebo in subjects with type 2 diabetes mellitus (T2DM) whose glycemia was not adequately controlled on their current regimen of metformin.

The study comprised 4 study periods: 2 weeks of Pre-screening/Screening, 4 weeks of Run-in/Stabilization, a 156 week Treatment Period, followed by 8 weeks of Posttherapy Follow-up. The total duration of a subject's participation was approximately 170 weeks. Subjects completed a minimum of 2 years of treatment, at which time the formal analysis for submission of regulatory marketing applications was completed. The study is continuing as a blinded study for up to 3 years. This Synopsis is concerned with the 2- year data.

Eligible subjects were stratified by HbA_{1c} based on the value obtained at Visit 5 (<8.0% versus ≥8.0%), prior myocardial infarction (MI) (yes versus no) and age (<65 years versus ≥65 years). Adjudication and review of all major cardiovascular and pancreatitis events took place over the entire treatment period.

Subjects must have been receiving at least 1500 mg of immediate release metformin daily, unless documentation was available to show a lower dose was the subject's maximum tolerated dose for at least 3 months before Screening. Subjects continued on their current dose of metformin for the duration of their study participation.

Number of subjects: Approximately 1000 subjects were randomly assigned in a 3:3:3:1 ratio to albiglutide, sitagliptin, glimepiride and placebo groups.

Diagnosis and main criteria for inclusion: Male and female subjects aged ≥ 18 years, with a historical diagnosis of T2DM currently treated with metformin but experiencing inadequate glycemic control. The subject should not have received >7 contiguous days of any antidiabetic agents other than metformin within the 3 months before Screening. The subject's HbA_{1c} had to be between 7.0% and 10.0% inclusive.

Treatment administration: The dosing and administration for each group is:

Treatment Group (All With	Metformin[1]	Albiglutide[2]	Sitagliptin	Glimepiride[3]
Albiglutide plus	≥1500 mg	30 mg with ↑ 50	Matching placebo	Matching placebo
Sitagliptin plus	≥1500 mg	Matching placebo	100 mg	Matching placebo

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Glimepiride plus	≥1500 mg	Matching placebo	Matching placebo	2 mg with ↑ 4 mg
Metformin plus Placebo	≥1500 mg	Matching placebo	Matching placebo	Matching placebo

1. Metformin prescribed by the investigator was open label. The dose was 1500 mg daily unless there was documented intolerance and the maximum tolerated dose was <1500 mg daily.
2. Albiglutide could be increased from 30 mg weekly to 50 mg weekly, if needed
3. Glimepiride could be increased from 2 mg daily to 4 mg daily, if needed

Albiglutide and matching placebo were supplied as a fixed-dose, fully disposable pen injector system for delivery of the investigational product from a prefilled dual-chamber glass cartridge. It was intended for single use by the subject and designed to work with standard pen needles. Albiglutide/matching placebo was injected subcutaneously into the abdomen, alternating right and left sides of the body. When the injector pen product was reconstituted by the subject (via rotation of the pen housing parts), a neutral, isotonic solution was produced. The pen delivered either 30 mg or 50 mg of investigational product in a 0.5-mL injection volume.

The sitagliptin product was supplied as commercially available 100 mg Januvia tablets overcoated to achieve blinding. Matching sitagliptin placebo was supplied identical in appearance and packaging to sitagliptin.

The glimepiride product was sourced as commercially available 2 mg and 4 mg Amaryl tablets overencapsulated to achieve blinding. Matching glimepiride placebo was supplied identical in appearance and packaging to glimepiride.

In addition to the randomized study medication and background diabetic medications, the addition of nonrandomized diabetic rescue medications was allowed in the study if hyperglycemic rescue criteria were met. The subjects remained on randomized study medication after the addition of hyperglycemic rescue medications. Unless otherwise specified, the overall study Safety Population includes all subjects both pre- and post- hyperglycemic rescue.

More details on Study Design and endpoints are in Appendix IV.

Statistical methods: The primary analysis of HbA_{1c} change from Baseline at Week 104 was applied to the intent to treat (ITT) Population, using an analysis of covariance (ANCOVA) model that incorporated treatment group, region, age category, and history of prior MI as covariates with Baseline HbA_{1c} as a continuous covariate. The difference in treatment effect on HbA_{1c} was evaluated as a contrast of the albiglutide add-on group versus the placebo add-on group. With significance for this contrast, the noninferiority of the albiglutide add-on group relative to the sitagliptin and glimepiride add-on group was evaluated inferentially with a 1-sided t test at the 0.025 significance level. If significant, the superiority of the albiglutide add-on group relative to the sitagliptin and glimepiride add-on group was evaluated using a 2-sided t test at the 0.05 significance level.

Subjects who were rescued for hyperglycemia before Week 104 had their HbA_{1c} recorded at the time of rescue and carried forward for the primary analyses. Subjects who discontinued from

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active treatment in the study before Week 104 had their last HbA_{1c} observation carried forward for the primary analysis.

Using a 2-sided, 2-sample *t* test and a test-wise significance level of 0.05 with 255 subjects in the albiglutide group and 85 subjects in the placebo group, the albiglutide add- on versus placebo add-on comparison had at least a 97% power to reject the null hypotheses of no treatment benefit if the actual albiglutide superiority treatment effect was no smaller than 0.6% and the standard deviation for HbA_{1c} change from Baseline was no larger than 1.2%. Using a noninferiority margin of 0.3% and a 1-sided, 2-sample *t* test and a test-wise significance level of 0.0125, with 255 subjects per group, the albiglutide add-on versus sitagliptin add-on or glimepiride add-on comparison had at least a 93% power to reject the null hypotheses of albiglutide inferiority if the actual albiglutide add-on treatment superiority was no smaller than 0.4%. With significance on either noninferiority hypothesis, the corresponding superiority hypothesis had at least 93% power if the actual albiglutide treatment superiority was no smaller than 0.4%, again using a 2-sided, 2-sample *t* test and a test-wise significance level of 0.025 (Bonferroni adjustment for 2 comparisons). Therefore, the study-wise power through the superiority hypotheses for the active comparators was expected to have at least 0.97 × 0.9348 × 0.9348 or 85.5% statistical power.

More details on the Statistical Analysis Plan are in Appendix I.

Patient Disposition

Sites Closed During the Study

Two centers in USA (site numbers 3636, and 3525) and 1 center in Mexico (site number 5464) were closed, reported to the FDA and discontinued from the trial because of repeated noncompliance with GCP/ICH guidelines. These sites had 19 subjects whose data are questionable; none of these 19 subjects were transferred to other sites.

In addition, nine centers in the USA were closed for a number of reasons.

Duplicate Enrolled Subjects

Across the albiglutide phase III program, in five of the eight studies (GLP112753, GLP112754, GLP112756, GLP112757 and GLP114130), there were 16 unique subjects that enrolled themselves in the same study at multiple sites or, in some instances, in different studies at multiple sites. In total this represents 39 unique instances across the program. In GLP112753, there were 19 unique instances of this that were discovered by either the site staff, the (b) (4) CRA, or the (b) (4) IVRS through site by site comparisons of subject information, including initials, DOB, and demography. At the time of discovery, all subjects were immediately withdrawn from treatment and then assigned to one study site and for those who enrolled in multiple studies, to a single site in one study for annual follow-up. In study GLP112753 1 subject remained assigned. These duplicate subjects have been included in the primary analysis for each study in which they were enrolled.

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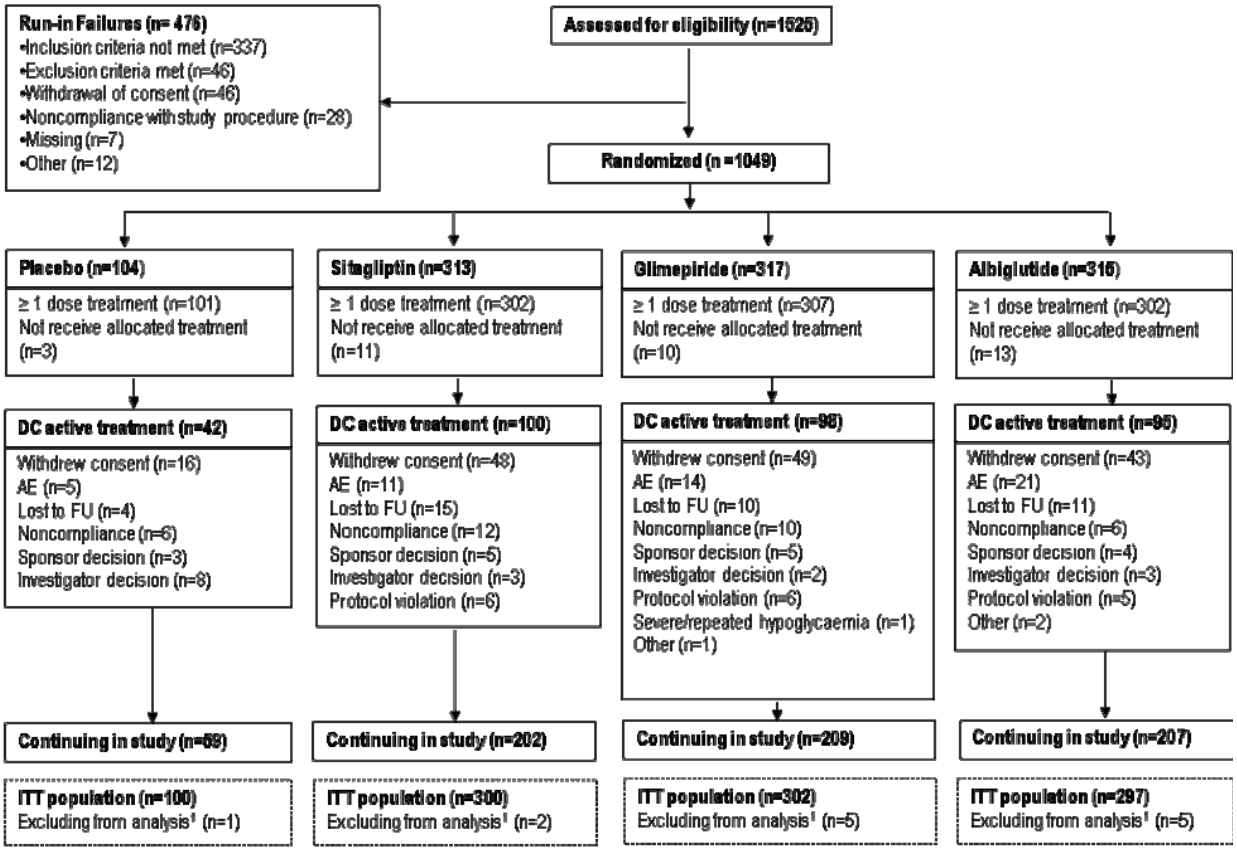
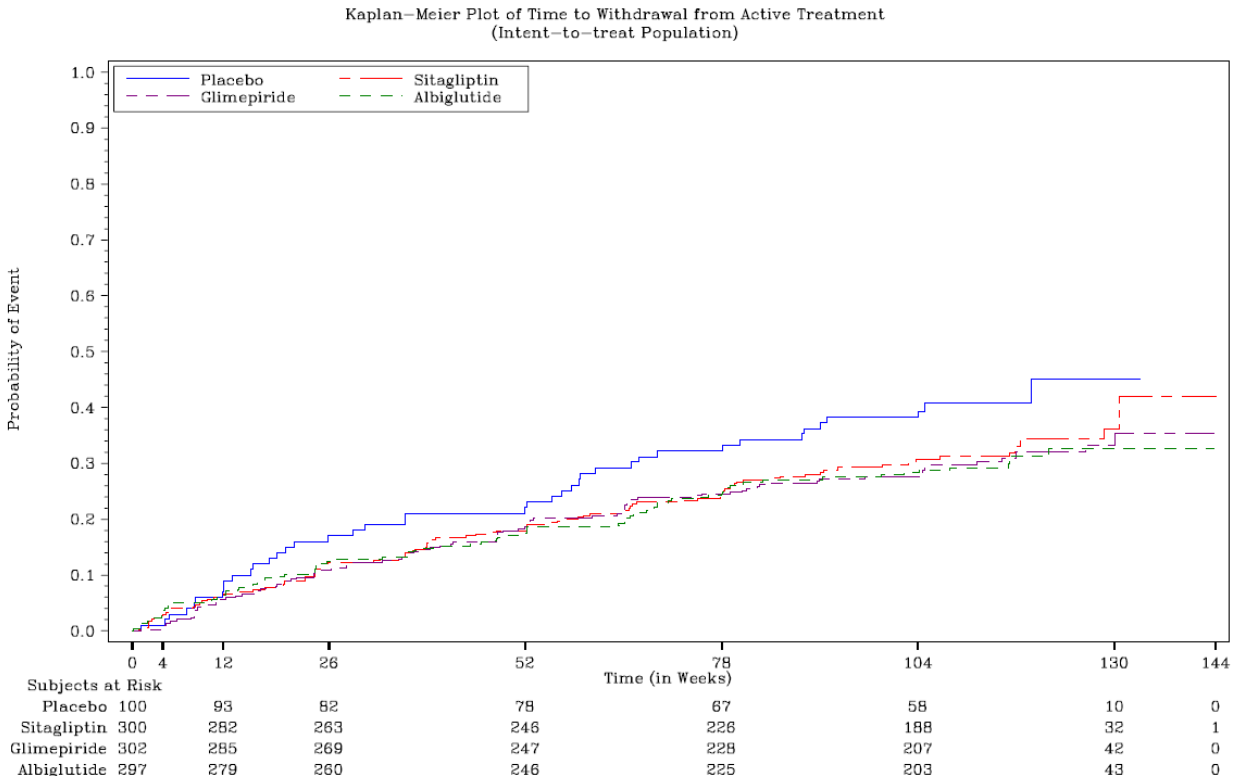
Chart for Patient Disposition:



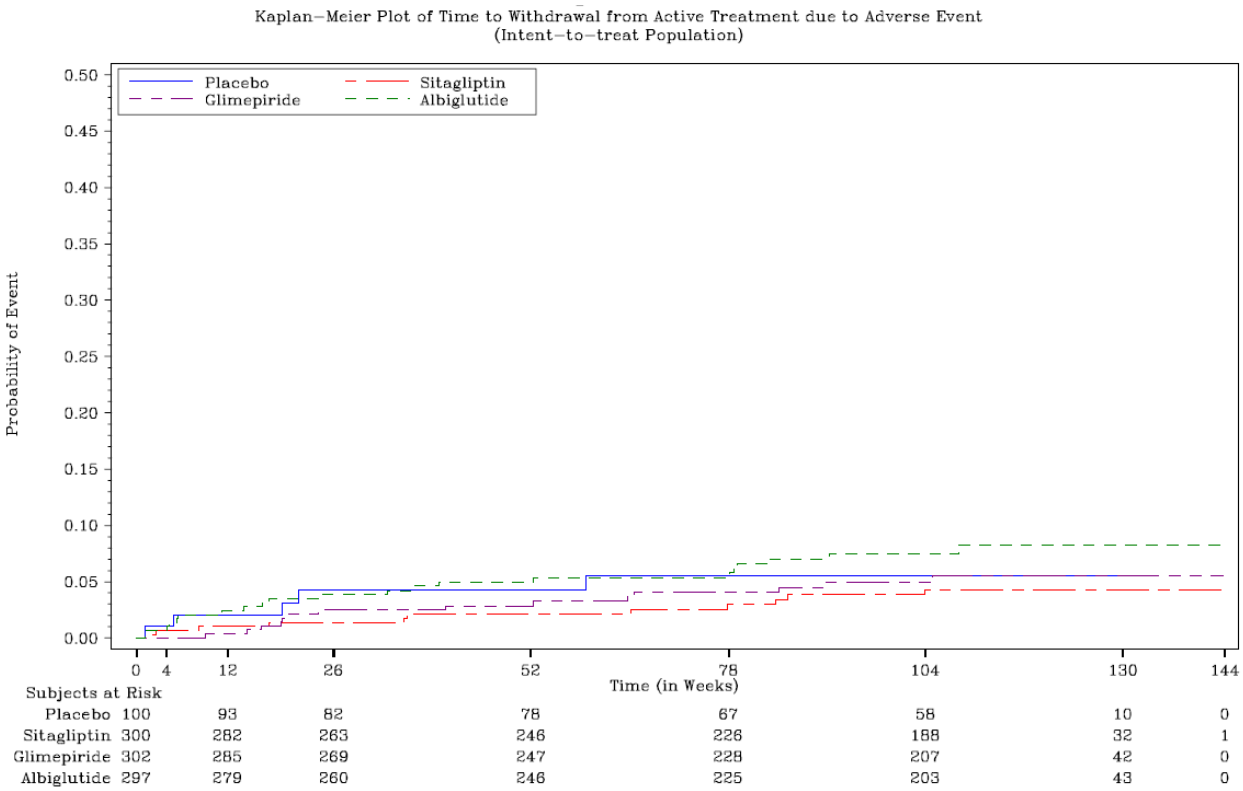
Note: As seen from the following graph, dropout was the highest for placebo and about the same for other treatment arms up to Week 130.

Reference ID: 3392698



Note: As seen from the following graph, dropout due to adverse events was the lowest for sitagliptin and highest for albiglutide.

Reference ID: 3392698



Subject Disposition Through Week 104

(Randomized Population)

	Placebo (N=104)	Sitagliptin (N=313)	Glimepiride (N=317)	Albiglutide (N=315)	Total (N=1049)
Randomized Population	104 (100.0%)	313 (100.0%)	317 (100.0%)	315 (100.0%)	1049 (100.0%)
Safety Population	101 (97.1%)	302 (96.5%)	307 (96.8%)	302 (95.9%)	1012 (96.5%)
Intent-to-treat Population	100 (96.2%)	300 (95.8%)	302 (95.3%)	297 (94.3%)	999 (95.2%)
24-hour Ambulatory Blood Pressure Substudy Population	20 (19.2%)	58 (18.5%)	67 (21.1%)	47 (14.9%)	192 (18.3%)
Biomarker and Detailed Lipid Profile Substudy Population	18 (17.3%)	62 (19.8%)	67 (21.1%)	50 (15.9%)	197 (18.8%)
Received at Least One Treatment Dose (Safety Population)	101 (97.1%)	302 (96.5%)	307 (96.8%)	302 (95.9%)	1012 (96.5%)
Completed Active Treatment through Week 104	62 (59.6%)	212 (67.7%)	218 (68.8%)	215 (68.3%)	707 (67.4%)
Discontinued Active Treatment before Week 104	39 (37.5%)	90 (28.8%)	89 (28.1%)	87 (27.6%)	305 (29.1%)
Continuing Follow-up	20 (19.2%)	44 (14.1%)	41 (12.9%)	41 (13.0%)	146 (13.9%)
Lost to Follow-up	19 (18.3%)	46 (14.7%)	48 (15.1%)	46 (14.6%)	159 (15.2%)
Number of Subjects Rescued through Week 104	46 (44.2%)	95 (30.4%)	85 (26.8%)	70 (22.2%)	296 (28.2%)

Note: Percentages are calculated using the number of subjects randomized as the denominator.
[1] Includes termination of the study, and termination of the study site by GSK.

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Subject Disposition Through Week 104
(Randomized Population)

	Placebo (N=104)	Sitagliptin (N=313)	Glimepiride (N=317)	Albiglutide (N=315)	Total (N=1049)
Reason for Discontinuing Active Treatment before Week 104					
Adverse Event	5 (4.8%)	10 (3.2%)	13 (4.1%)	20 (6.3%)	48 (4.6%)
Protocol Violation	0	6 (1.9%)	6 (1.9%)	5 (1.6%)	17 (1.6%)
Noncompliance	6 (5.8%)	11 (3.5%)	10 (3.2%)	6 (1.9%)	33 (3.1%)
Severe or Repeated Occurrences of Hypoglycaemia	0	0	1 (0.3%)	0	1 (0.1%)
Lost to Follow-up	3 (2.9%)	15 (4.8%)	10 (3.2%)	10 (3.2%)	38 (3.6%)
Subject Withdrew Consent from Active Participation	15 (14.4%)	41 (13.1%)	42 (13.2%)	38 (12.1%)	136 (13.0%)
Investigator Decided to Discontinue Study Participation	7 (6.7%)	2 (0.6%)	1 (0.3%)	2 (0.6%)	12 (1.1%)
Termination of Study by GSK [1]	3 (2.9%)	5 (1.6%)	5 (1.6%)	4 (1.3%)	17 (1.6%)
Other	0	0	1 (0.3%)	2 (0.6%)	3 (0.3%)
PT WITHDREW CONSENT - DUE TO LACK OF EFFICACY	0	0	0	1 (0.3%)	1 (0.1%)
SITE CLOSING	0	0	1 (0.3%)	0	1 (0.1%)
SUBJECT IS MOVING OUT OF THE COUNTRY.	0	0	0	1 (0.3%)	1 (0.1%)
Reason for Lost to Follow-up					
Adverse Event	2 (1.9%)	1 (0.3%)	5 (1.6%)	5 (1.6%)	13 (1.2%)
Noncompliance	1 (1.0%)	5 (1.6%)	4 (1.3%)	2 (0.6%)	12 (1.1%)
Subject Lost to Follow-up	4 (3.8%)	21 (6.7%)	14 (4.4%)	16 (5.1%)	55 (5.2%)
Subject Did Not Enter Follow-up Period	3 (2.9%)	5 (1.6%)	7 (2.2%)	5 (1.6%)	20 (1.9%)
Subject Withdrawn from Follow-up Participation	5 (4.8%)	9 (2.9%)	12 (3.8%)	12 (3.8%)	38 (3.6%)
Investigator Decided to Discontinue Study Participation	1 (1.0%)	0	0	1 (0.3%)	2 (0.2%)
Termination of Study by GSK [1]	3 (2.9%)	4 (1.3%)	6 (1.9%)	4 (1.3%)	17 (1.6%)
Other	0	1 (0.3%)	0	1 (0.3%)	2 (0.2%)
INVESTIGATOR STOPPED STUDY AT SITE	0	1 (0.3%)	0	0	1 (0.1%)
SUBJECT DISCONTINUED AS WAS MOVING OUT OF TOWN.	0	0	0	1 (0.3%)	1 (0.1%)

Populations Analyzed

More than of 94% of randomized subjects in each treatment group were included in the safety and ITT populations. In all, 192 subjects (18.3%) and 197 subjects (18.8%) participated in the 24-hour ABP substudy and the biomarker and detailed lipid profile substudy, respectively.

	Placebo (N=104) n (%)	Sitagliptin (N=313) n (%)	Glimepiride (N=317) n (%)	Albiglutide (N=315) n (%)	Total (N=1049) n (%)
Randomized Population	104 (100.0)	313 (100.0)	317 (100.0)	315 (100.0)	1049 (100.0)
Safety Population	101 (97.1)	302 (96.5)	307 (96.8)	302 (95.9)	1012 (96.5)
Intent-to-treat Population	100 (96.2)	300 (95.8)	302 (95.3)	297 (94.3)	999 (95.2)
24-hour Ambulatory Blood Pressure Substudy Population	20 (19.2)	58 (18.5)	67 (21.1)	47 (14.9)	192 (18.3)
Biomarker and Detailed Lipid Profile Substudy Population	18 (17.3)	62 (19.8)	67 (21.1)	50 (15.9)	197 (18.8)

Demographic and Baseline Characteristics

Demographic Characteristics (Safety Population)

Note: As seen in the following Table of demographics, in the four treatment arms - Placebo, Sitagliptin, Glimepiride, and albiglutide, respectively,

the mean age was 56, 54, 54, and 54;
the percentage of male was 49.5, 45.0, 51.5, and 44.7;
the percentage of White was 63.4, 74.5, 71.7, and 70.9;

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the percentage of African was 22.8, 11.6, 12.7, and 17.5;
the mean weight was 91.6, 90.3, 91.8, and 89.6.

	Placebo (N=101)	Sitagliptin (N=302)	Glimepiride (N=307)	Albiglutide (N=302)	Total (N=1012)
Age at randomization (years)					
n	101	302	307	302	1012
Mean (SD)	56.1 (10.01)	54.3 (9.81)	54.4 (9.97)	54.3 (10.12)	54.5 (9.97)
Median	57.0	55.0	55.0	55.0	55.0
Minimum, Maximum	32, 79	24, 84	28, 82	26, 86	24, 86
Age category, n (%)					
n	101	302	307	302	1012
<65 years	84 (83.2)	257 (85.1)	257 (83.7)	255 (84.4)	853 (84.3)
≥65 years	17 (16.8)	45 (14.9)	50 (16.3)	47 (15.6)	159 (15.7)
Sex, n (%)					
n	101	302	307	302	1012
Female	51 (50.5)	163 (54.0)	149 (48.5)	167 (55.3)	530 (52.4)
Male	50 (49.5)	139 (46.0)	158 (51.5)	135 (44.7)	482 (47.6)
Race[2], n (%)	101	302	307	302	1012
African American/African Heritage	23 (22.8)	35 (11.6)	39 (12.7)	53 (17.5)	150 (14.8)
American Indian or Alaskan Native	9 (8.9)	22 (7.3)	25 (8.1)	17 (5.6)	73 (7.2)
Asian - Central/South Asian Heritage	1 (1.0)	7 (2.3)	3 (1.0)	2 (0.7)	13 (1.3)
Asian - East Asian Heritage	0	2 (0.7)	3 (1.0)	5 (1.7)	10 (1.0)
Asian - Japanese Heritage	1 (1.0)	0	1 (0.3)	0	2 (0.2)
Asian - South East Asian Heritage	3 (3.0)	11 (3.6)	9 (2.9)	11 (3.6)	34 (3.4)
Native Hawaiian or Other Pacific Islander	1 (1.0)	0	0	1 (0.3)	2 (0.2)
White - Arabic/North African Heritage	0	1 (0.3)	9 (2.9)	3 (1.0)	13 (1.3)
White - White/Caucasian/ European Heritage	64 (63.4)	225 (74.5)	220 (71.7)	214 (70.9)	723 (71.4)
Ethnicity, n (%)					
n	101	302	307	302	1012
Hispanic/Latino	32 (31.7)	111 (36.8)	107 (34.9)	99 (32.8)	349 (34.5)
Not Hispanic/Latino	69 (68.3)	191 (63.2)	200 (65.1)	203 (67.2)	663 (65.5)
Height (cm)					
n	101	302	307	302	1012
Mean (SD)	166.67 (10.76)	166.35 (10.06)	167.59 (11.32)	165.44 (10.87)	166.49 (10.78)
Median	165.00	166.00	167.00	165.00	166.00

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Minimum, Maximum	141.0, 191.0	144.0, 206.0	142.0, 199.0	141.0, 193.0	141.0, 206.0
Weight (kg)					
n	101	302	307	302	1012
Mean (SD)	91.64 (19.31)	90.31 (19.06)	91.79 (20.42)	89.60 (18.38)	90.68 (19.31)
Median	90.50	88.00	88.90	88.00	88.50
Minimum, Maximum	53.0, 144.5	51.0, 152.4	43.8, 155.6	49.8, 165.9	43.8, 165.9
BMI (kg/m^2)					
n	101	302	307	302	1012
Mean (SD)	32.82 (5.39)	32.50 (5.44)	32.48 (5.45)	32.70 (5.57)	32.58 (5.47)
Median	32.00	32.00	32.00	32.00	32.00
Minimum, Maximum	21.0, 44.0	20.0, 45.0	21.0, 45.0	21.0, 46.0	20.0, 46.0
BMI category, n (%)					
n	101	302	307	302	1012
<25 kg/m^2	5 (5.0)	15 (5.0)	18 (5.9)	14 (4.6)	52 (5.1)
≥25 to <30 kg/m^2	24 (23.8)	82 (27.2)	96 (31.3)	80 (26.5)	282 (27.9)
≥30 to <35 kg/m^2	36 (35.6)	103 (34.1)	84 (27.4)	107 (35.4)	330 (32.6)
≥35 kg/m^2	36 (35.6)	102 (33.8)	109 (35.5)	101 (33.4)	348 (34.4)

BMI = body mass index.
1. The p-value was for testing the null hypothesis that the summary statistics (mean or proportion) were equal among treatment groups. All tests were 2-sided.
2. Subjects could have been counted in more than 1 category.

Baseline Diabetes Characteristics (Safety Population)

As seen in the following Table of Baseline Characteristics, the mean duration of diabetes in years was 6.74, 5.81, 6.03, and5.98, respectively, in the placebo, sitagliptin, glimepiride, and the albiglutide group.

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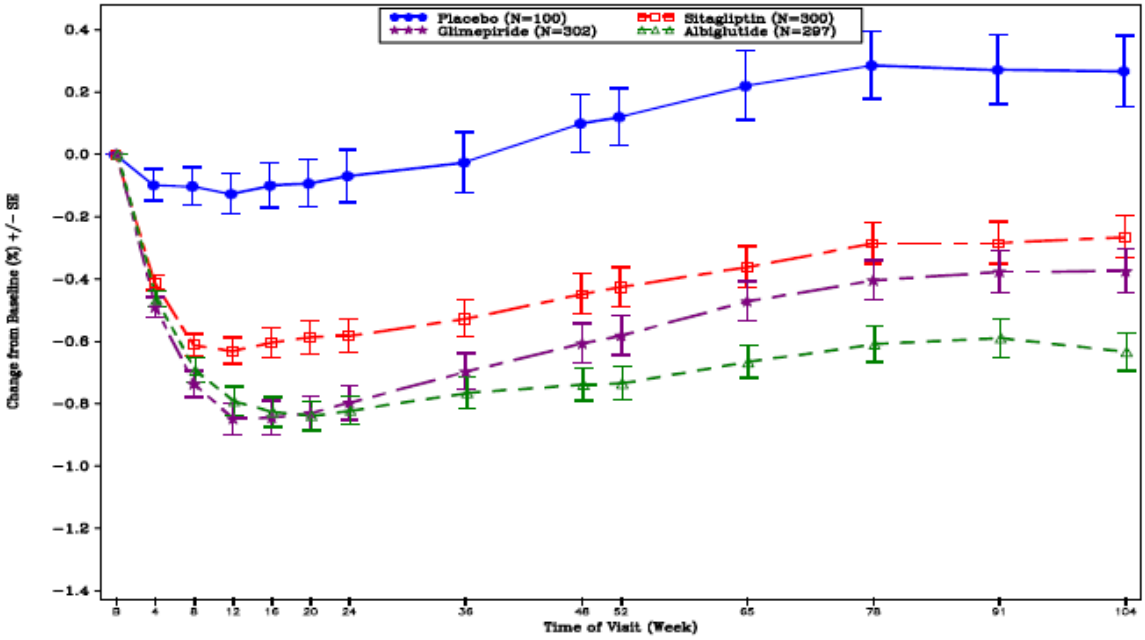
	Placebo (N=101)	Sitagliptin (N=302)	Glimepiride (N=307)	Albiglutide (N=302)	Total (N=1012)
Diabetic condition, n (%)					
Subjects with any conditions	62 (61.4)	187 (61.9)	207 (67.4)	212 (70.2)	
Dyslipidaemia	55 (54.5)	153 (50.7)	175 (57.0)	181 (59.9)	
Peripheral neuropathy	16 (15.8)	41 (13.6)	49 (16.0)	56 (18.5)	
Impotence	11 (10.9)	25 (8.3)	23 (7.5)	21 (7.0)	
Diabetic retinopathy	2 (2.0)	2 (0.7)	8 (2.6)	12 (4.0)	
Microalbuminuria	1 (1.0)	7 (2.3)	8 (2.6)	9 (3.0)	
Proteinuria	3 (3.0)	6 (2.0)	9 (2.9)	7 (2.3)	
Nephropathy	2 (2.0)	5 (1.7)	3 (1.0)	5 (1.7)	
Diabetic foot ulcer	1 (1.0)	1 (0.3)	1 (0.3)	4 (1.3)	
Autonomic neuropathy	0	1 (0.3)	1 (0.3)	4 (1.3)	
Chronic renal insufficiency	0	1 (0.3)	0	2 (0.7)	
Other	3 (3.0)	13 (4.3)	17 (5.5)	14 (4.6)	
Duration of diabetes[2] (years)					
n	101	302	307	302	1012
Mean (SD)	6.74 (6.57)	5.81 (4.75)	6.03 (4.75)	5.98 (4.28)	6.02 (4.83)
Median	5.08	4.53	4.78	5.33	4.89
Minimum, Maximum	0.40, 39.59	0.26, 31.69	0.21, 25.34	0.28, 22.71	0.21, 39.59
Duration category, n (%)					
n	101	302	307	302	1012
<3 years	32 (31.7)	96 (31.8)	99 (32.2)	88 (29.1)	315 (31.1)
≥3 to ≤7 years	35 (34.7)	118 (39.1)	102 (33.2)	111 (36.8)	366 (36.2)
>7 years	34 (33.7)	88 (29.1)	106 (34.5)	103 (34.1)	331 (32.7)
Prior myocardial infarction, n (%)					
n	101	302	307	302	1012
Yes	4 (4.0)	13 (4.3)	13 (4.2)	11 (3.6)	41 (4.1)
No	97 (96.0)	289 (95.7)	294 (95.8)	291 (96.4)	971 (95.9)
Baseline HbA_{1c} (%)					
n	101	302	307	302	1012
Mean (SD)	8.15 (0.90)	8.05 (0.80)	8.12 (0.84)	8.09 (0.80)	8.09 (0.82)
Median	8.00	7.90	8.00	7.90	7.90
Minimum, Maximum	6.7, 10.1	6.5, 10.2	6.6, 10.5	6.8, 10.6	6.5, 10.6
Baseline HbA_{1c} category, n (%)					
n	101	302	307	302	1012
<8.0%	49 (48.5)	160 (53.0)	146 (47.6)	158 (52.3)	513 (50.7)
≥8.0%	52 (51.5)	142 (47.0)	161 (52.4)	144 (47.7)	499 (49.3)

Results and Conclusions

Line Graph of Mean (±SE) Change from Baseline in HbA_{1c} (%) Through Week 104 (Intent-to-treat Population – LOCF)

As seen from the following graph, a decrease in HbA1c from Baseline to Week 104 was observed in the albiglutide, sitagliptin and glimepiride treatment groups. The change from baseline in HBA1c was much worse always for the placebo arm and the best for the albiglutide arm, starting from Week 24.



Analysis of Change from Baseline in HbA_{1c} (%) at Week 104 (Intent-to-treat Population – LOCF)

Note: My analyses corroborate the following sponsor's results (albiglutide's superiority to all other arms).

When adjusted for region, history of prior MI, age category and Baseline HbA1c, the model-adjusted LS mean change in HbA1c from Baseline to Week 104 was -0.63% in the albiglutide group, +0.27% in the placebo group, -0.28% in the sitagliptin group, and -0.36% in the glimepiride group. Albiglutide was statistically superior to placebo (-0.91%; 95% CI: -1.16, -0.65%, p<0.0001). Albiglutide was noninferior compared to sitagliptin (-0.35%; 95% CI -0.53, -0.17%, p<0.0001) and glimepiride (-0.27%; 95% CI -0.45, -0.09, p<0.0001) as measured by change from Baseline in HbA1c at Week 104. In fact, albiglutide was superior compared to both sitagliptin (p=0.001) and glimepiride (p=0.0033) (Table 17 and Figure 4) at Week 104.

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All of the above comparisons achieved the statistical significance as per the multiple comparison procedure.

	Placebo (N=100)	Sitagliptin (N=300)	Glimepiride (N=302)	Albiglutide (N=297)
Number of subjects[1]	97	297	299	293
Number (%) of values carried forward	74 (76.3)	164 (55.2)	153 (51.2)	135 (46.1)
Baseline mean (SD)	8.12 (0.887)	8.06 (0.797)	8.12 (0.843)	8.09 (0.803)
Week 104 mean (SD)	8.38 (1.352)	7.79 (1.317)	7.75 (1.252)	7.46 (1.140)
Model-adjusted change from Baseline[2]				
Least squares mean	0.27	-0.28	-0.36	-0.63
Standard error	0.113	0.065	0.064	0.065
95% confidence interval	(0.05, 0.50)	(-0.41, -0.15)	(-0.49, -0.24)	(-0.76, -0.51)
Difference from albiglutide[2]				
Difference of least squares means	-0.91	-0.35	-0.27	
95% confidence interval	(-1.16, -0.65)	(-0.53, -0.17)	(-0.45, -0.09)	
P-values for sequentially ordered hypotheses				
Superiority over placebo[3]	<0.0001			
Non-inferiority to active control [4]		<0.0001	<0.0001	
Superiority over active control [5]		0.0001	0.0033	

ANCOVA = analysis of covariance; HbA_{1c} = glycosylated hemoglobin; ITT= Intent-to-treat; LOCF = last observation carried forward

Note: This analysis used the LOCF method for missing postbaseline glycosylated hemoglobin (HbA_{1c}) values. The HbA_{1c} values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values. 12 ITT subjects had all postbaseline HbA_{1c} measurements occur more than 14 days after last dose and 1 ITT subject had all postbaseline HbA_{1c} measurements occur after hyperglycemic rescue. These 13 subjects were included in the header ITT population counts but did not contribute to any of the ITT efficacy analyses.

1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on ANCOVA: Change = treatment + Baseline HbA_{1c} + prior myocardial infarction history + age category + region. The difference of least squares means (albiglutide – placebo, albiglutide – sitagliptin, albiglutide – glimepiride) was from ANCOVA model.
3. This p-value was for superiority testing of albiglutide over placebo at 0.05 level. The p-value was from a 2-sided *t* test to test whether the difference of least square means (albiglutide – placebo) was equal to zero.
4. This p-value was for non-inferiority testing of albiglutide versus sitagliptin (or albiglutide versus glimepiride) at 0.0125 level. The p-value was from a one-sided t-test to test whether the difference of least square means (albiglutide – sitagliptin, albiglutide – glimepiride) was equal to the pre-specified non-inferiority margin of 0.3%. If the superiority test (in footnote 3) was not significant, no non-inferiority testing was performed and the p-value was not applicable.
5. This p-value was for superiority testing of albiglutide versus sitagliptin (or albiglutide versus glimepiride) at 0.025 level. The p-value was from a 2-sided t-test to test whether the difference of least square means (albiglutide – sitagliptin, albiglutide – glimepiride) was equal to zero. If one or both of the non-inferiority test(s) (in footnote 4) was/were not significant, then corresponding superiority testing was not performed and the p-value was not applicable.

§ Graphs of cumulative distribution functions by treatment groups for the primary efficacy variable (percent change from baseline in HbA1c) at the study endpoint are provided below. From these, the percent of patients (y-axis value) with a value of percent change from baseline in HbA1c at endpoint, smaller than or equal to a value on the x-axis, can be read.

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Note: As seen from the following cumulative distributions, all the percentiles 10th and higher were the smallest for the albiglutide arm.

Figure for Cumulative Distribution of Weight (kg) Change from Baseline at Week 104 (Intent-to-treat Population-LOCF)

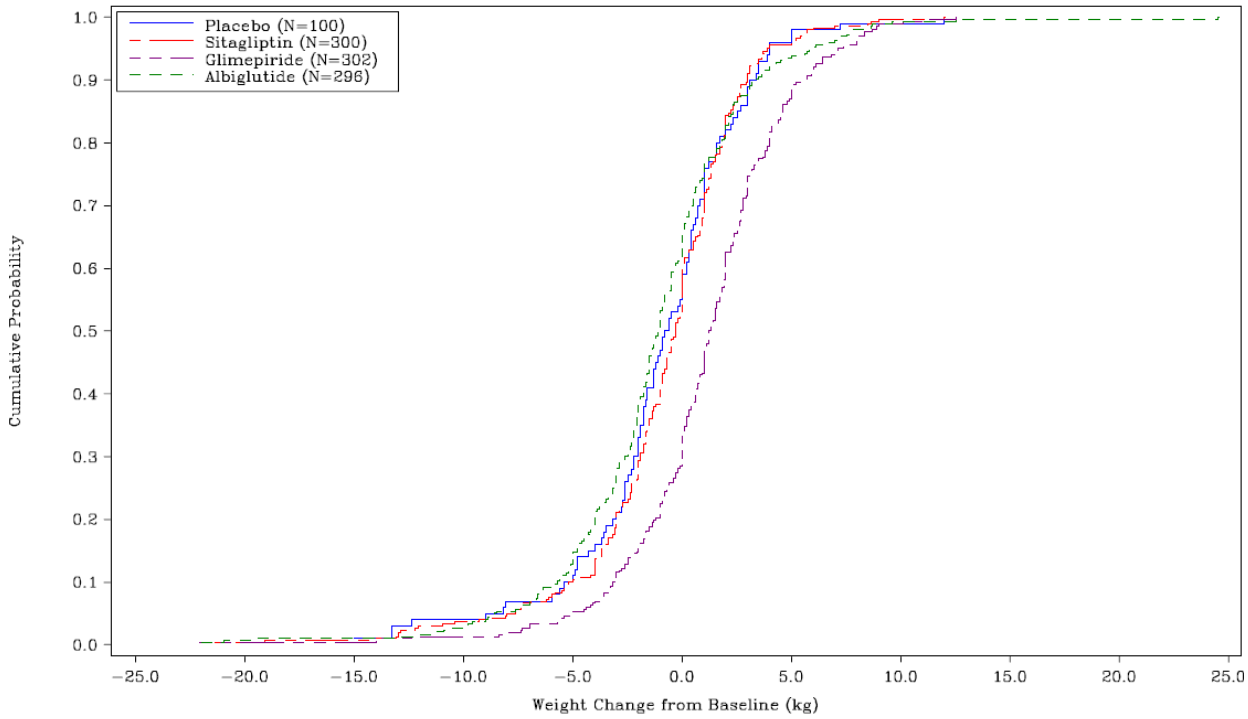

Table for Cumulative Distribution of HbA1c (%) Change from Baseline at Week 104 (Intent-to-treat Population - LOCF)

Percentile	Placebo (N=100)	Sitagliptin (N=300)	Glimepiride (N=302)	Albiglutide (N=297)
Number of subjects [1]	97	297	299	293
Min	-2.4	-4.2	-3.6	-3.3
1%	-2.40	-2.90	-3.20	-3.10
5%	-1.40	-2.00	-2.50	-2.30
10%	-0.80	-1.60	-1.80	-1.90
20%	-0.70	-1.10	-1.20	-1.30
30%	-0.30	-0.70	-0.90	-1.10
40%	-0.10	-0.60	-0.70	-0.90
50%	0.20	-0.30	-0.50	-0.60
60%	0.40	-0.10	-0.30	-0.50
70%	0.70	0.20	0.10	-0.20
80%	1.00	0.50	0.40	0.10
90%	1.40	1.00	1.10	0.50
95%	2.00	1.50	1.80	0.90
99%	4.30	2.90	3.90	2.00
Max	4.3	7.9	4.0	7.0

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Supporting Analyses on Primary Efficacy Endpoint
Supportive analyses on the primary efficacy endpoint did not show any treatment-by-variable interactions of concern for region, age category, history of prior MI, or Baseline HbA_{1c} and were supportive of the use of the main-effects model to evaluate the primary efficacy hypothesis . All the secondary analyses were consistent with the primary analysis and generally supportive of the primary efficacy endpoint analysis.

Sensitivity Analyses on Primary Efficacy Endpoint
Four sensitivity analyses on the primary endpoint were performed.

The first sensitivity analysis was an OC (Observed Cases) analysis that used observed HbA_{1c} values including postrescue values. The effect of the presence of rescue medication and adjustment for the rescue medication effect was further modeled . The OC (Observed Cases) analysis (including rescue value) results are consistent with the model using the LOCF algorithm. In addition, the rescue-modelled LS mean decrease from Baseline in HbA_{1c} was larger for the albiglutide arm compared with placebo, sitagliptin or glimepiride. The analysis produced a treatment difference between albiglutide and placebo of -0.54% (95% CI: -0.77, -0.32%) which was statistically significant ($p<0.0001$). A statistically significant treatment difference between albiglutide and sitagliptin and albiglutide and glimepiride was also demonstrated, -0.37% (95% CI: -0.53, -0.22%, $p<0.0001$), and -0.24% (95% CI: -0.39, -0.09%, $p=0.0020$) respectively.

The results indicated that the rescue medication had a significant effect on HbA1c change from Baseline.

The second sensitivity analysis was an OC (Observed Cases) analysis that used observed HbA1c values with no missing data imputation but excluded postrescue values. Treatment differences at Week 104 were: -0.26% (95% CI: -0.61, 0.10%, $p=0.1594$) for placebo,-0.14% (95% CI: -0.33, 0.05%, $p=0.1458$) for sitagliptin, and -0.15% (95% CI: (-0.33, 0.03%, $p=0.1087$) for glimepiride.

Another sensitivity analysis was performed to evaluate the primary endpoint in the ITT Population using the LOCF algorithm after excluding major protocol violators (Source Data: Post hoc Table 14.2-1.6.22). The model-adjusted LS mean change in HbA1c from Baseline to Week 104 was -0.62% in the albiglutide group, 0.29% in the placebo group, -0.26% in the sitagliptin group, and -0.39% in the glimepiride group. When added to metformin, albiglutide was statistically superior to placebo (-0.91%; 95% CI: -1.20, -0.62%, $p<0.0001$), sitagliptin (-0.36%; 95% CI -0.56, -0.16, $p<0.0006$) and glimepiride (-0.23%; 95% CI -0.44, -0.03, $p<0.0243$) as measured by change from Baseline in HbA1c at Week 104.

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Sensitivity Analysis of Change from Baseline in HbA1c (%) at Week 104 Excluding Subjects with Major Protocol Violations Identified Prior to Database Freeze (Intent-to-treat Population - LOCF)

	Placebo (N=100)	Sitagliptin (N=300)	Glimepiride (N=302)	Albiglutide (N=297)
Number of subjects[1]	77	245	245	237
Number (%) of values carried forward	57 (74.0)	125 (51.0)	114 (46.5)	105 (44.3)
Baseline mean (SD)	8.10 (0.882)	8.03 (0.781)	8.13 (0.846)	8.12 (0.818)
Week 104 mean (SD)	8.38 (1.361)	7.79 (1.342)	7.73 (1.273)	7.49 (1.190)
Model-adjusted change from Baseline[2]				
Least squares mean	0.29	-0.26	-0.39	-0.62
Standard error	0.130	0.073	0.073	0.074
95% confidence interval	(0.03, 0.54)	(-0.41, -0.12)	(-0.53, -0.25)	(-0.77, -0.48)
Difference from comparator[2]				
Difference of least squares means	-0.91	-0.36	-0.23	
95% confidence interval	(-1.20, -0.62)	(-0.56, -0.16)	(-0.44, -0.03)	
P value	<0.0001	0.0006	0.0243	

ANCOVA = analysis of covariance; HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward

Note: This analysis used the LOCF method for missing HbA_{1c} values. HbA_{1c} values obtained after hyperglycemia rescue were treated as missing and replaced with pre-rescue values. Subjects with major protocol violations were excluded from the analysis.

1. Number of subjects with a value at Baseline and at Week 104.
2. Based on ANCOVA: Change = treatment+ Baseline HbA_{1c} + prior MI history + age category + region.

Difference of least squares means (albiglutide – placebo, albiglutide – sitagliptin, albiglutide - glimepiride) from ANCOVA model.

The p-value was from a two-sided t-test for the difference in means.

Change from Baseline in HbA_{1c} by Baseline and Demographic Characteristics

Subgroup analyses for the primary efficacy endpoint did not reveal big concerns.

Forest Plot of Model-Adjusted Difference in Mean Change from Baseline in HbA_{1c} (%)Between Albiglutide and Comparators and 95% CI at Week 104 by Subgroup Category (Intent-to-treat Population – LOCF)

Note: Left side indicates the numerical superiority of albiglutide.

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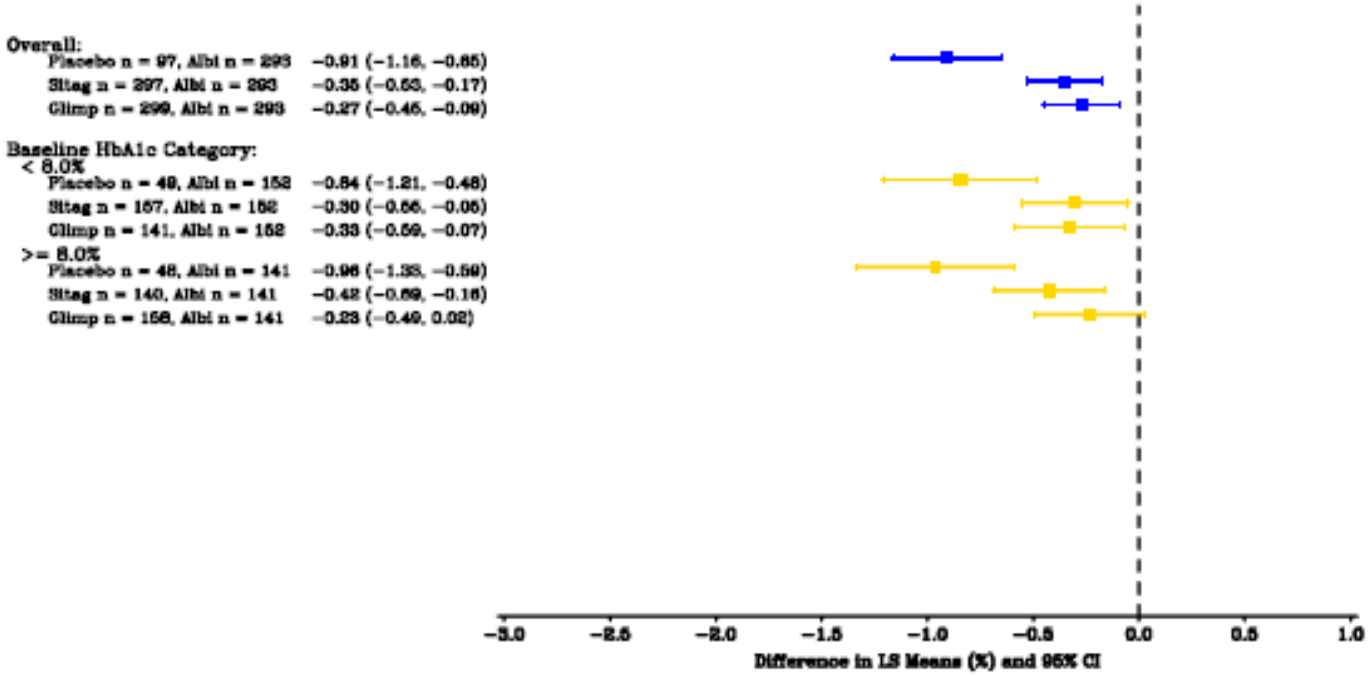

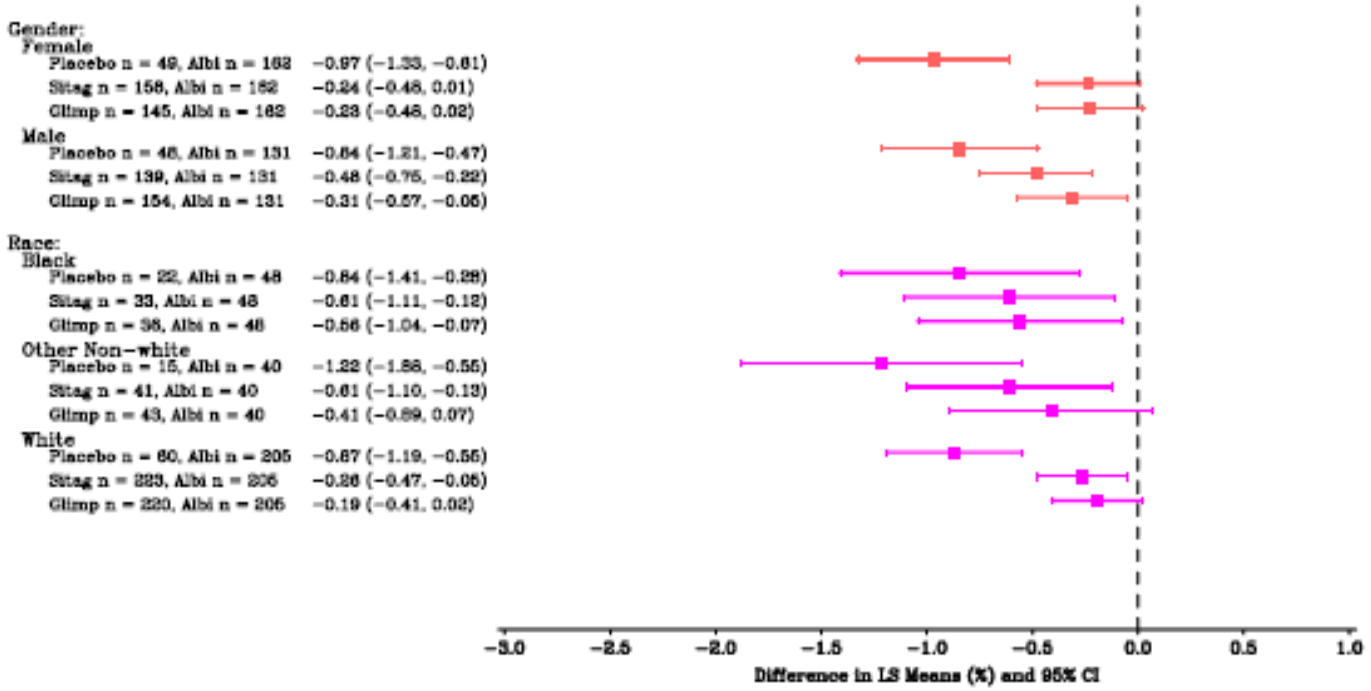

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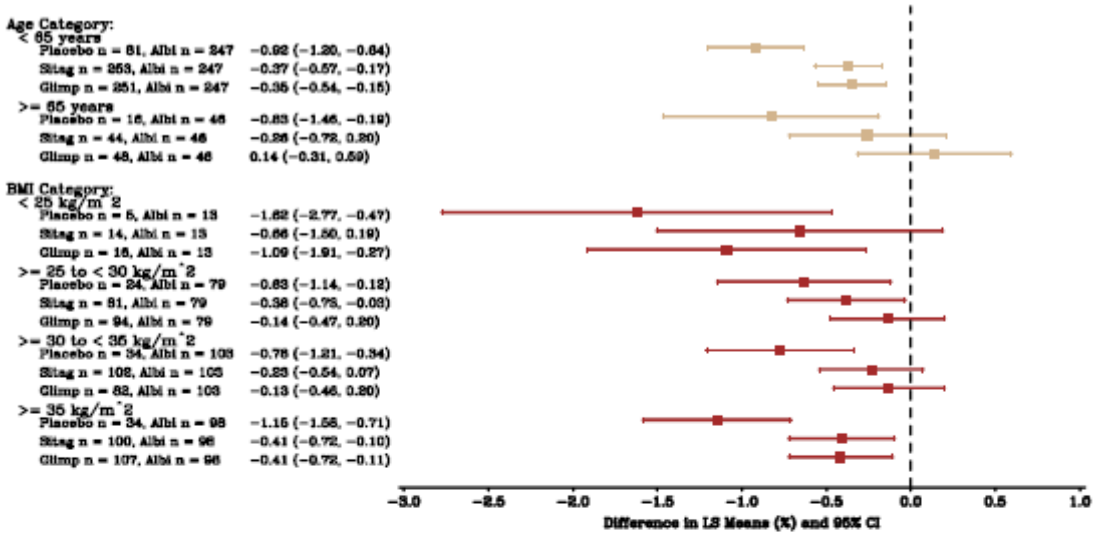

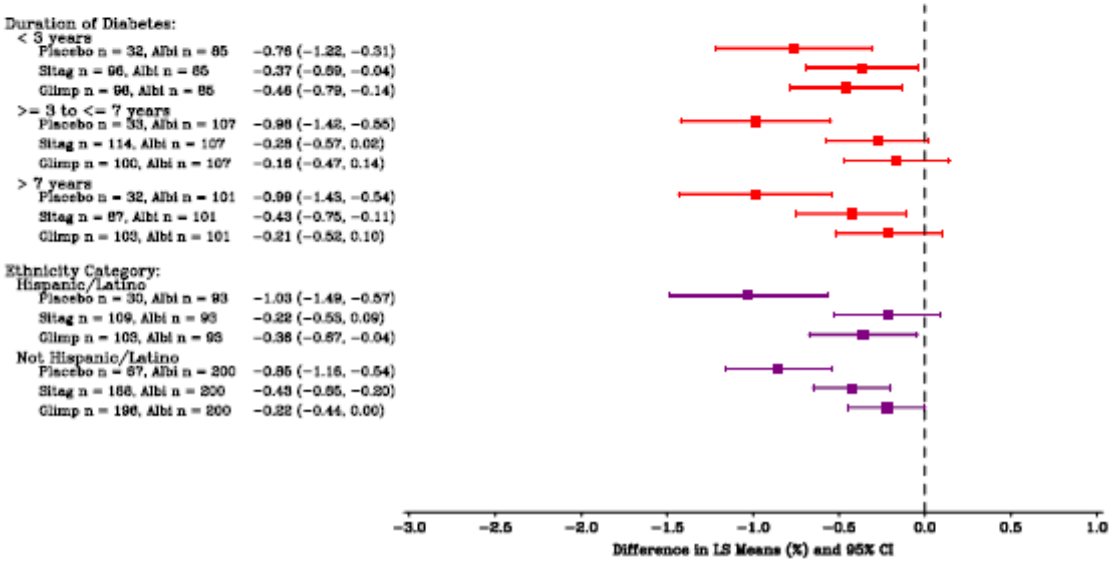

Albi = albiglutide; Glimp = glimepiride; Sitag =sitagliptin; BMI = body mass index; CI = confidence interval; HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; LS = least squares; US/USA = United Sates of America.
Note: The difference on x-axis is the difference in the albiglutide least squares mean change from Baseline minus comparator least squares mean change from Baseline.

Note: In the >65 years age group, the upper boundary of the confidence interval (-.31,.59)for Glimpepiride vs albiglutide is out of the non-inferiority margin .3; so, does not exclude the possibility of the albiglutide group being inferior. However, subgroup results, when not planned

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to be confirmatory, are not confirmatory. Further evidences are needed to reach the level of confirmation.

There was a statistically significant Treatment by Region (Ex-US, USA – North, USA – South Atlantic, USA – South Central, USA – West) (p= 0.0671) interaction, with better Ex-USA and USA-South Atlantic regions favoring albiglutide much more. The subgroup results follow:

Analysis of Change from Baseline in HbA1c (%) Through Week 104 by Region
(Intent-to-treat Population - LOCF)

Region: Ex-US Region - Week 104

	Placebo (N=100)	Sitagliptin (N=300)	Glimepiride (N=302)	Albiglutide (N=297)
Number of Subjects [1]	36	100	101	107
Number (%) of Values Carried Forward	26 (72.2%)	49 (49.0%)	44 (43.6%)	35 (32.7%)
Baseline				
Mean	8.22	8.08	8.13	8.18
Standard Deviation	0.975	0.840	0.822	0.848
Week 104				
Mean	8.71	7.71	7.82	7.30
Standard Deviation	1.385	1.504	1.305	1.222
Change from Baseline				
Mean	0.50	-0.37	-0.31	-0.89
Standard Deviation	1.342	1.325	1.358	1.030
Model-Adjusted Change from Baseline [2]				
LS Mean	0.50	-0.37	-0.29	-0.86
Standard Error	0.185	0.111	0.110	0.107
95% Confidence Interval	(0.14, 0.87)	(-0.59, -0.15)	(-0.51, -0.08)	(-1.07, -0.65)
Difference from Comparator [2]				
Difference of LS Means	-1.36	-0.49	-0.57	
95% Confidence Interval	(-1.78, -0.95)	(-0.79, -0.19)	(-0.87, -0.26)	

Region: USA - North - Week 104

	Placebo (N=100)	Sitagliptin (N=300)	Glimepiride (N=302)	Albiglutide (N=297)
Number of Subjects [1]	10	38	45	35
Number (%) of Values Carried Forward	9 (90.0%)	17 (44.7%)	20 (44.4%)	18 (51.4%)
Baseline				
Mean	8.49	7.95	8.11	8.06
Standard Deviation	1.005	0.712	0.853	0.844
Week 104				
Mean	8.85	7.69	7.52	7.54
Standard Deviation	1.529	1.378	1.066	0.974
Change from Baseline				
Mean	0.36	-0.26	-0.59	-0.52
Standard Deviation	0.715	1.445	0.827	0.905
Model-Adjusted Change from Baseline [2]				
LS Mean	0.59	-0.31	-0.58	-0.49
Standard Error	0.352	0.180	0.165	0.188
95% Confidence Interval	(-0.10, 1.28)	(-0.66, 0.04)	(-0.91, -0.26)	(-0.86, -0.12)
Difference from Comparator [2]				
Difference of LS Means	-1.08	-0.18	0.09	
95% Confidence Interval	(-1.86, -0.30)	(-0.69, 0.33)	(-0.40, 0.58)	

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Region: USA - South Atlantic - Week 104

	Placebo (N=100)	Sitagliptin (N=300)	Glimepiride (N=302)	Albiglutide (N=297)
Number of Subjects [1]	22	55	56	48
Number (%) of Values Carried Forward	19 (86.4%)	36 (65.5%)	34 (60.7%)	29 (60.4%)
Baseline				
Mean	7.88	8.02	7.95	8.04
Standard Deviation	0.749	0.728	0.714	0.770
Week 104				
Mean	8.06	8.02	7.76	7.40
Standard Deviation	1.287	1.205	1.211	0.932
Change from Baseline				
Mean	0.18	0.01	-0.19	-0.64
Standard Deviation	1.091	0.930	1.112	0.906
Model-Adjusted Change from Baseline [2]				
LS Mean	0.09	-0.04	-0.20	-0.67
Standard Error	0.237	0.150	0.148	0.160
95% Confidence Interval	(-0.37, 0.55)	(-0.33, 0.25)	(-0.49, 0.09)	(-0.99, -0.36)
Difference from Comparator [2]				
Difference of LS Means	-0.76	-0.63	-0.47	
95% Confidence Interval	(-1.32, -0.20)	(-1.06, -0.20)	(-0.90, -0.04)	

Region: USA - West - Week 104

	Placebo (N=100)	Sitagliptin (N=300)	Glimepiride (N=302)	Albiglutide (N=297)
Number of Subjects [1]	18	54	48	58
Number (%) of Values Carried Forward	12 (66.7%)	37 (68.5%)	28 (58.3%)	29 (50.0%)
Baseline				
Mean	8.05	8.09	8.24	7.80
Standard Deviation	0.850	0.852	0.869	0.627
Week 104				
Mean	8.08	7.76	7.70	7.59
Standard Deviation	1.248	1.105	1.304	1.326
Change from Baseline				
Mean	0.03	-0.33	-0.54	-0.21
Standard Deviation	1.028	0.875	1.174	1.211
Model-Adjusted Change from Baseline [2]				
LS Mean	0.02	-0.33	-0.52	-0.31
Standard Error	0.261	0.151	0.160	0.146
95% Confidence Interval	(-0.50, 0.53)	(-0.63, -0.04)	(-0.84, -0.21)	(-0.60, -0.02)
Difference from Comparator [2]				
Difference of LS Means	-0.33	0.02	0.21	
95% Confidence Interval	(-0.91, 0.26)	(-0.39, 0.43)	(-0.21, 0.64)	

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Secondary Efficacy Variables

Summary Statistics for Change from Baseline in HbA_{1c} (%) Through Week 104 (Intent-to-treat Population – LOCF)

	Placebo (N=100)	Sitagliptin (N=300)	Glimepiride (N=302)	Albiglutide (N=297)
Week 4 – change from Baseline				
Number of subjects[1]	95	289	294	289
Number (%) of values carried forward	2 (2.1)	8 (2.8)	2 (0.7)	9 (3.1)
Mean (SD)	-0.10 (0.488)	-0.41 (0.403)	-0.49 (0.544)	-0.47 (0.439)
Median	-0.10	-0.40	-0.40	-0.40
Minimum, Maximum	-1.2, 2.6	-1.5, 0.7	-1.9, 4.1	-3.3, 1.1
Week 8 – change from Baseline				
Number of subjects[1]	97	297	299	292
Number (%) of values carried forward	6 (6.2)	11 (3.7)	10 (3.3)	18 (6.2)
Mean (SD)	-0.10 (0.588)	-0.61 (0.596)	-0.74 (0.733)	-0.69 (0.678)
Median	-0.20	-0.60	-0.70	-0.70
Minimum, Maximum	-1.3, 2.2	-2.8, 1.0	-2.8, 2.9	-3.4, 1.5
Week 12 – change from Baseline				
Number of subjects[1]	97	297	299	293
Number (%) of values carried forward	6 (6.2)	17 (5.7)	19 (6.4)	18 (6.1)
Mean (SD)	-0.13 (0.636)	-0.63 (0.739)	-0.85 (0.866)	-0.79 (0.792)
Median	-0.20	-0.60	-0.80	-0.70
Minimum, Maximum	-2.1, 1.6	-3.6, 1.6	-3.4, 2.9	-3.7, 2.1
Week 16 – change from Baseline				
Number of subjects[1]	97	297	299	293
Number (%) of values carried forward	9 (9.3)	24 (8.1)	20 (6.7)	28 (9.6)
Mean (SD)	-0.10 (0.715)	-0.61 (0.831)	-0.85 (0.943)	-0.83 (0.820)
Median	-0.20	-0.60	-0.80	-0.70
Minimum, Maximum	-2.1, 2.0	-3.9, 2.2	-3.4, 3.2	-3.7, 2.1
Week 20 – change from Baseline				
Number of subjects[1]	97	297	299	293
Number (%) of values carried forward	13 (13.4)	26 (8.8)	23 (7.7)	30 (10.2)
Mean (SD)	-0.09 (0.749)	-0.59 (0.901)	-0.83 (0.954)	-0.84 (0.793)
Median	-0.10	-0.60	-0.80	-0.70
Minimum, Maximum	-1.8, 2.0	-3.9, 2.6	-3.4, 3.9	-3.6, 1.8
Week 24 – change from Baseline				
Number of subjects[1]	97	297	299	293
Number (%) of values carried forward	24 (24.7)	44 (14.8)	34 (11.4)	38 (13.0)
Mean (SD)	-0.07 (0.824)	-0.58 (0.931)	-0.80 (0.961)	-0.82 (0.786)
Median	0.00	-0.60	-0.80	-0.70
Minimum, Maximum	-2.2, 2.0	-3.8, 2.6	-3.4, 3.9	-3.6, 1.3
Week 36 – change from Baseline				
Number of subjects[1]	97	297	299	293
Number (%) of values carried forward	35 (36.1)	70 (23.6)	61 (20.4)	55 (18.8)
Mean (SD)	-0.03 (0.966)	-0.53 (1.014)	-0.70 (1.014)	-0.77 (0.863)
Median	-0.10	-0.60	-0.70	-0.70
Minimum, Maximum	-2.1, 3.2	-3.8, 3.0	-3.2, 3.9	-3.7, 2.5
Week 48 – change from Baseline				

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Number of subjects[1]	97	297	299	293
Number (%) of values carried forward	44 (45.4)	93 (31.3)	76 (25.4)	76 (25.9)
Mean (SD)	0.10 (0.918)	-0.45 (1.118)	-0.61 (1.093)	-0.74 (0.886)
Median	0.10	-0.50	-0.70	-0.70
Minimum, Maximum	-1.9, 3.2	-4.1, 7.9	-3.4, 4.0	-4.0, 2.7
Week 52 – change from Baseline				
Number of subjects[1]	97	297	299	293
	Placebo (N=100)	**Sitagliptin (N=300)**	**Glimepiride (N=302)**	**Albiglutide (N=297)**
Number (%) of values carried forward	50 (51.5)	101 (34.0)	92 (30.8)	86 (29.4)
Mean (SD)	0.12 (0.903)	-0.43 (1.099)	-0.58 (1.092)	-0.73 (0.906)
Median	0.10	-0.50	-0.60	-0.70
Minimum, Maximum	-2.2, 3.2	-4.2, 7.9	-3.0, 4.0	-4.1, 2.1
Week 65 – change from Baseline				
Number of subjects[1]	97	297	299	293
Number (%) of values carried forward	57 (58.8)	116 (39.1)	104 (34.8)	100 (34.1)
Mean (SD)	0.22 (1.100)	-0.36 (1.125)	-0.47 (1.089)	-0.67 (0.909)
Median	0.00	-0.40	-0.50	-0.60
Minimum, Maximum	-1.7, 4.3	-4.5, 7.9	-3.5, 4.0	-3.5, 3.8
Week 78 – change from Baseline				
Number of subjects[1]	97	297	299	293
Number (%) of values carried forward	66 (68.0)	136 (45.8)	129 (43.1)	115 (39.2)
Mean (SD)	0.29 (1.061)	-0.29 (1.150)	-0.40 (1.110)	-0.61 (0.996)
Median	0.20	-0.40	-0.50	-0.60
Minimum, Maximum	-1.7, 4.3	-4.2, 7.9	-2.8, 4.0	-3.1, 7.0
Week 91 – change from Baseline				
Number of subjects[1]	97	297	299	293
Number (%) of values carried forward	67 (69.1)	155 (52.2)	140 (46.8)	128 (43.7)
Mean (SD)	0.27 (1.094)	-0.29 (1.161)	-0.38 (1.155)	-0.59 (1.054)
Median	0.20	-0.30	-0.50	-0.60
Minimum, Maximum	-1.8, 4.3	-4.2, 7.9	-3.4, 4.0	-3.1, 7.0
Week 104 – change from Baseline				
Number of subjects[1]	97	297	299	293
Number (%) of values carried forward	74 (76.3)	164 (55.2)	153 (51.2)	135 (46.1)
Mean (SD)	0.27 (1.117)	-0.27 (1.181)	-0.38 (1.227)	-0.63 (1.036)
Median	0.20	-0.30	-0.50	-0.60
Minimum, Maximum	-2.4, 4.3	-4.2, 7.9	-3.6, 4.0	-3.3, 7.0

HbA_{1c} = glycosylated hemoglobin; ITT = Intent-to-treat; LOCF = last observation carried forward; SD = standard deviation
Note: This analysis used the LOCF method for missing postbaseline HbA_{1c}) values. The HbA_{1c} values obtained after hyperglycemia rescue were treated as missing and replaced with pre-rescue values. One ITT subject had all postbaseline HbA_{1c} measurements occur after hyperglycemic rescue. This subject was included in the header ITT population counts but did not contribute to this analysis.

1. Number of subjects with a value at Baseline and at the specified visit.

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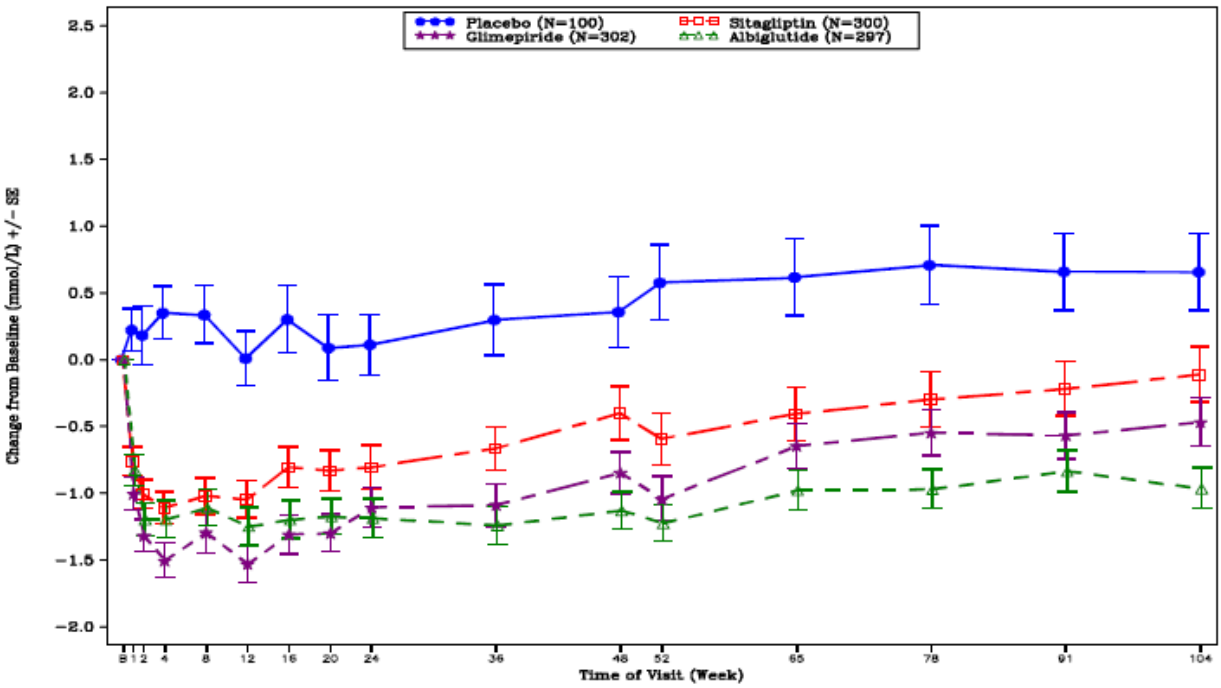
Fasting Plasma Glucose Change from Baseline at Week 104

Note: My analyses corroborate the following results of the sponsor.

The magnitude of change from Baseline in FPG was greater in the albiglutide group than the sitagliptin group and was apparent from Week 2. Similarly, from Week 24 the magnitude of change from Baseline was greater in the albiglutide group than the glimepiride group. These were maintained in the albiglutide group through Week 104.

Albiglutide was statistically superior to placebo, sitagliptin, and glimepiride as measured by change from Baseline in FPG at Week 104.

Line Graph of Mean (±SE) Change from Baseline in Fasting Plasma Glucose (mmol/L) Through Week 104 (Intent-to-treat Population – LOCF)



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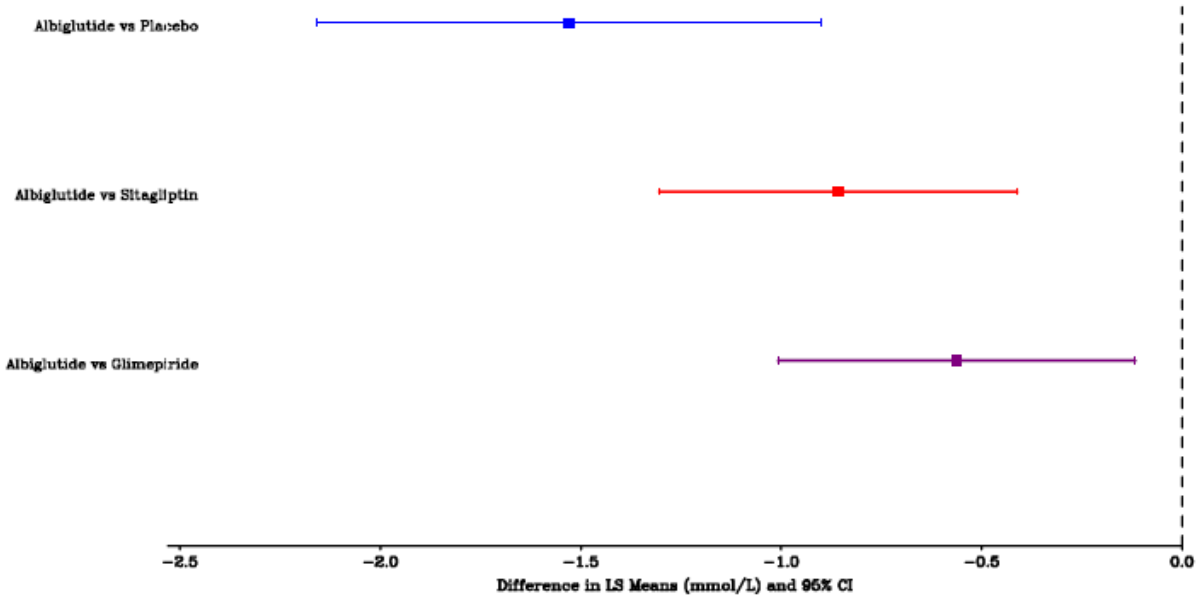
Model-adjusted Difference in Mean Change from Baseline in Fasting Plasma Glucose (mmol/L) Between Albiglutide and Comparators and 95% CI at Week 104 (Intent-to-treat Population - LOCF)



LOCF = last observation carried forward

Analysis of Change from Baseline in Fasting Plasma Glucose (mmol/L) at Week 104 (Intent-to-treat Population – LOCF)

	Placebo (N=100)	Sitagliptin (N=300)	Glimepiride (N=302)	Albiglutide (N=297)
Number of subjects[1]	100	299	302	296
Number (%) of values carried forward	77 (77.0)	166 (55.5)	158 (52.3)	141 (47.6)
Baseline mean (SD)	9.01 (2.341)	9.16 (2.593)	9.30 (2.547)	9.14 (2.767)
Week 104 mean (SD)	9.67 (3.217)	9.05 (3.402)	8.83 (3.011)	8.17 (2.578)
Model-adjusted change from Baseline[2]				
Least squares mean	0.55	-0.12	-0.41	-0.98
Standard error	0.277	0.160	0.159	0.161
95% confidence interval	(0.01, 1.10)	(-0.43, 0.20)	(-0.73, -0.10)	(-1.29, -0.66)
Difference from albiglutide[2]				
Difference of least squares means	-1.53	-0.86	-0.56	
95% confidence interval	(-2.16, -0.90)	(-1.30, -0.41)	(-1.01, -0.12)	
p-value: sequentially ordered hypotheses				
Superiority over placebo[3]	<0.0001			
Superiority over active control[4]		0.0002	0.0133	

ANCOVA = analysis of variance; FPG = fasting plasma glucose; ITT = Intent-to-treat; LOCF = last observation carried forward; SD = standard deviation

Note: This analysis used the LOCF method for missing postbaseline FPG values. The FPG values obtained after hyperglycemia rescue were treated as missing and replaced with pre-rescue values. Two ITT subjects had all post-Baseline FPG

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measurements occur more than 14 days after last dose. These subjects were included in the header ITT population counts but did not contribute to any of the ITT efficacy analyses.

1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on ANCOVA: Change = treatment + Baseline FPG + Baseline HbA1c category + prior myocardial infarction history + age category + region. Difference of least squares means (albiglutide – placebo, albiglutide – sitagliptin, albiglutide – glimepiride) from ANCOVA model.
3. This p-value was for superiority testing of albiglutide over placebo at 0.05 level. P-value was from a two-sided t-test to test whether the FPG difference of least square means (albiglutide – placebo) was equal to zero. If the superiority test for the HbA_{1c} treatment comparison of (albiglutide – placebo) was not significant, then no superiority test was performed and the p-value was not applicable.
4. This p-value was for superiority testing of albiglutide vs. sitagliptin (or albiglutide vs. glimepiride) at 0.025 level. P-value was from a two-sided t-test to test whether the FPG difference of least square means (albiglutide – sitagliptin, albiglutide - glimepiride) was equal to zero. If one or both of the non-inferiority test(s) for the HbA_{1c} treatment comparison of (albiglutide – sitagliptin, albiglutide - glimepiride) was/were not significant, then corresponding superiority testing was not performed and the p-value was not applicable.

Proportion of Subjects who Achieved Clinically Meaningful HbA_{1c} Response Levels

Overall, 17.1%, 38.6% and 58.7% of subjects in the albiglutide treatment group achieved the treatment goal of HbA_{1c} <6.5%, <7.0% and <7.5% at Week 104, respectively (Source Data: Table 14.2-4.1.1, Table 14.2-4.2.1, and Table 14.2-4.3.1, respectively) (Table 28). The proportion of subjects reaching treatment goals at Week 104 for the 3 active treatment groups was higher than the placebo group (Table 28). The difference between albiglutide and placebo was statistically significant for all treatment goals. A higher percentage of subjects in the albiglutide group (58.7%) achieved the treatment goal of HbA_{1c} <7.5% at Week 104 compared with the sitagliptin (44.4%) or glimepiride (49.2%) treatment groups; the differences between albiglutide and each active comparator were statistically significant.

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Analysis of Proportion of Subjects Achieving Clinically Meaningful HbA_{1c} Response Levels (<6.5%, <7.0%, and <7.5%) at Week 104 (Intent-to-treat Population – LOCF)

	Placebo (N=100)	Sitagliptin (N=300)	Glimepiride (N=302)	Albiglutide (N=297)
HbA_{1c} Level: <6.5%				
Number of subjects[1] at Week 104	97	297	299	293
Number (%) of values carried forward	74 (76.3)	164 (55.2)	153 (51.2)	135 (46.1)
Number (%) of subjects achieving HbA_{1c} response – Week 104	7 (7.2)	45 (15.2)	40 (13.4)	50 (17.1)
Difference from albiglutide[2]				
Odds Ratio (95% confidence interval)	NA	1.160 (0.720, 1.871)	1.257 (0.742, 2.128)	
p-value	0.0149	0.5856	0.2228	
Difference from albiglutide[3]				
Odds Ratio (95% confidence interval)	2.700 (1.167, 6.249)	1.148 (0.731, 1.803)	1.272 (0.800, 2.022)	
p-value	0.0203	0.5496	0.3094	
HbA_{1c} Level: <7.0%				
Number of subjects[1] at Week 104	97	297	299	293
Number (%) of values carried forward	74 (76.3)	164 (55.2)	153 (51.2)	135 (46.1)
Number (%) of subjects achieving HbA_{1c} response – Week 104	15 (15.5)	94 (31.6)	94 (31.4)	113 (38.6)
Difference from albiglutide[2]				
Odds Ratio (95% confidence interval)	2.413 (1.273, 4.575)	1.307 (0.888, 1.926)	1.275 (0.858, 1.896)	
p-value	<0.0001	0.1490	0.1546	
Difference from albiglutide[3]				
Odds Ratio (95% confidence interval)	3.779 (2.023, 7.059)	1.384 (0.963, 1.989)	1.285 (0.894, 1.847)	
p-value	<0.0001	0.0791	0.1761	
HbA_{1c} Level: <7.5%				
Number of subjects[1] at Week 104	97	297	299	293
Number (%) of values carried forward	74 (76.3)	164 (55.2)	153 (51.2)	135 (46.1)
Number (%) of subjects achieving HbA_{1c} response – Week 104	27 (27.8)	132 (44.4)	147 (49.2)	172 (58.7)
Difference from albiglutide[2]				
Odds Ratio (95% confidence interval)	4.278 (2.411, 7.589)	1.904 (1.291, 2.808)	1.495 (1.022, 2.186)	
p-value	<0.0001	0.0002	0.0189	
Difference from albiglutide[3]				
Odds Ratio (95% confidence interval)	4.574 (2.650, 7.894)	1.992 (1.392, 2.850)	1.452 (1.017, 2.071)	
p-value	<0.0001	0.0002	0.0399	

HbA1c = glycosylated hemoglobin; LOCF = last observation carried forward; MI = myocardial infarction

Note: This analysis used the LOCF method for missing post-Baseline. The HbA_{1c} values. Hb1Ac values obtained after hyperglycemia rescue were treated as missing and replaced with pre-rescue values.

1. Number of subjects with a Baseline value at the specified visit.
2. Based on non-parametric Mantel-Haenszel test after adjusting for Baseline HbA_{1c} category, prior MI history, age category and region.
3. Based on logistic regression: Logit (Proportion of Response) = treatment+ Baseline HbA_{1c} category + prior MI history + age category + region.

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The proportion of subjects reaching the treatment goal at Week 104 of improvement in HbA_{1c} by at least 1.0%, 1.5% or 2.0% was higher in the 3 active treatment groups than that observed for subjects in the placebo treatment group. Statistically significant differences in favor of albiglutide were observed for all 3 treatment goals of improvement in HbA_{1c} versus placebo. A higher percentage of subjects in the albiglutide group (35.2%) achieved the treatment goal of improvement in HbA_{1c} by at least 1.0% compared with the sitagliptin (24.6%) or glimepiride (27.1%) treatment groups. The treatment difference between albiglutide and each active comparator was statistically significant for the at least 1.0% improvement in HbA_{1c} but not for the improvement in HbA_{1c} of at least 1.5% or 2.0%.

Body Weight Change from Baseline over Time

At Week 104, weight loss was apparent in subjects treated with albiglutide, placebo and sitagliptin, whereas weight gain occurred in the glimepiride subjects. At Week 104, albiglutide-, placebo- and sitagliptin-treated subjects had mean weight decrease from Baseline of 1.18 kg, 1.02 kg and 0.86 kg, respectively. Glimepiride subjects had a mean weight increase from Baseline of 1.15 kg and differed statistically significantly from that for albiglutide.

Note: My analyses corroborate the sponsor's results.

Note: Although, I also performed some analyses on the percent change from baseline, that variable was not mentioned in the Statistical Analysis Plan.

Mean percentage change from Baseline in weight at Week 104 was -1.24% in subjects treated with albiglutide compared with -0.94% in placebo treated subjects, -0.84% in sitagliptin treated subjects and 1.35% in glimepiride treated subjects (Source Data: Table 14.2-5.5). The difference between albiglutide and glimepiride was statistically significant ($p<0.0001$) whereas there was no statistical difference in weight change from Baseline to Week 104 for albiglutide compared to placebo or albiglutide compared to sitagliptin .

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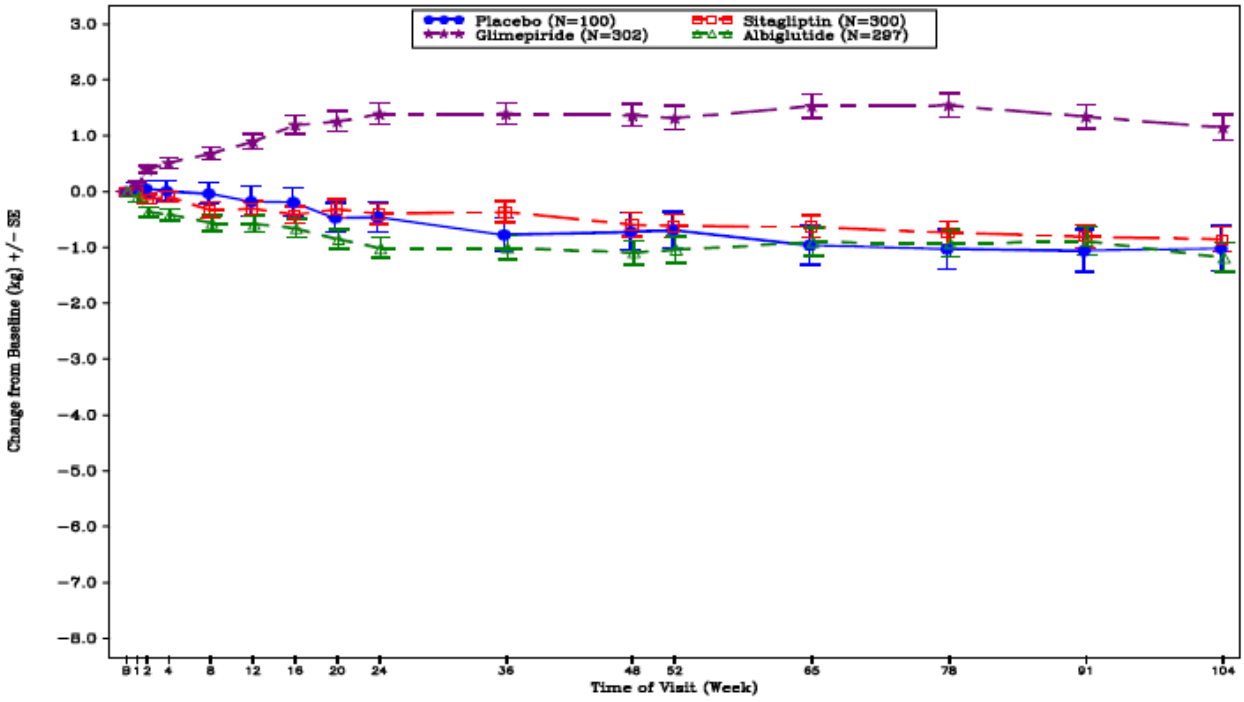
Line Graph of Mean (±SE) Change from Baseline in Weight (kg) Through Week 104 (Intent-to-treat Population – LOCF)



B = Baseline; LOCF = last observation carried forward; SE = standard error.

Analysis of Change from Baseline in Weight (kg) at Week 104 (Intent-to-treat Population – LOCF)

	Placebo (N=100)	Sitagliptin (N=300)	Glimepiride (N=302)	Albiglutide (N=297)
Number of subjects[1]	100	300	302	296
Number (%) of values carried forward	77 (77.0)	167 (55.7)	155 (51.3)	138 (46.6)
Baseline mean (SD)	91.73 (19.385)	90.40 (19.046)	91.88 (20.512)	89.61 (18.384)
Week 104 mean (SD)	90.71 (18.843)	89.54 (18.811)	93.03 (20.774)	88.43 (18.473)
Change from Baseline mean (SD)	-1.02 (4.076)	-0.86 (3.953)	1.15 (3.902)	-1.18 (4.543)
Model-adjusted change from Baseline[2]				
Least squares mean	-1.00	-0.86	1.17	-1.21
Standard error	0.411	0.237	0.237	0.239
95% confidence interval	(-1.81, -0.20)	(-1.32, -0.39)	(0.70, 1.63)	(-1.68, -0.74)
Difference from albiglutide[2]				
Difference of least squares means	-0.20	-0.35	-2.37	
95% confidence interval	(-1.14, 0.73)	(-1.01, 0.31)	(-3.03, -1.71)	
p-value	0.6677	0.2991	<0.0001	

ANCOVA = analysis of covariance; LOCF = last observation carried forward; SD = standard deviation
Note: This analysis used the LOCF method for missing postbaseline weight values as well as for weight values obtained after hyperglycemia rescue

1. Number of subjects with a value at Baseline and at the specified visit.

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2. Based on ANCOVA: Change = treatment + Baseline weight + Baseline HbA1c category + prior MI history + age category + region. Difference of least squares means (albiglutide – placebo, albiglutide – sitagliptin, albiglutide – glimepiride) from ANCOVA model. The p-value is from a 2-sided t-test for the difference in least squares means.

Note: Glimepiride increased weight statistically significantly; all other groups lowered weight statistically significantly from baseline.

STUDY GLP112754

Title: A Randomized, Open-Label, Parallel-Group, Multicenter Study to Determine the Efficacy and Long-Term Safety of Albiglutide Compared With Insulin in Subjects With Type 2 Diabetes Mellitus

Study centers: This study was conducted at 222 study centers.

Study Period: 17-Feb-2009 to 30-Nov-2011 (2-year database)

Phase of Development: III

Objectives: The primary objective of the study was to evaluate the efficacy of albiglutide as compared with insulin glargine on glycosylated hemoglobin (HbA_{1c}) change from Baseline at Week 52.

Methodology: This was a Phase III, randomized, open-label, 2 parallel-group, multicenter study of 3 years (approximately 170 weeks) duration, to evaluate the efficacy and safety of a weekly subcutaneously injected dose of 30 mg (with uptitration to 50 mg, if required) of albiglutide as compared with insulin glargine administered daily in subjects with type 2 diabetes mellitus (T2DM) whose glycemia was not adequately controlled on their current regimen of metformin (± sulfonylurea [SU]). The study comprised 4 study periods: approximately 2 weeks of Prescreening and Screening, 4 weeks of Run-in, 156-week Treatment Period, and 8 weeks of Posttreatment Follow-up. Subjects completed a minimum of 2 years of treatment, at which time the formal analysis for submission of regulatory marketing applications was completed. The study is continuing for up to 3 years. This synopsis is concerned with the 2-year data. Eligible subjects were stratified based on the HbA1c value obtained at Visit 5 (<8.0% versus ≥8.0%), history of prior myocardial infarction (MI) (yes versus no), age (<65 years versus ≥65 years), and current antidiabetic therapy (metformin alone versus metformin + SU). Adjudication and review of all major cardiovascular and pancreatitis events took place over the entire Treatment Period.

The subjects had to have received metformin (± SU) for at least 3 months before Screening, and been on a stable dose for at least 8 weeks before randomization. The dose of metformin should have been ≥1500 mg of metformin unless a lower dose had been documented as the maximum tolerated dose. The subject should not have received

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>7 contiguous days of any antidiabetic agents other than metformin (± SU) within the 3 months before Screening. Subjects continued on their current dose of metformin (± SU) for the duration of their study participation.

Number of subjects: Approximately 750 subjects were planned for randomization in a ratio of 2:1 albiglutide to insulin glargine. A total of 779 subjects were randomly assigned: 516 to albiglutide and 263 to insulin glargine.
Diagnosis and main criteria for inclusion: Male and nonpregnant, nonlactating female subjects aged ≥18 years, with an historical diagnosis of T2DM who were experiencing inadequate glycemic control on their current regimen of metformin alone or metformin + SU.

Statistical methods:
The primary analysis of the HbA1c change from Baseline at Week 52 was applied to the Intent-to-Treat Population, using an analysis of covariance model with main effects for region, history of prior MI, age category, current antidiabetic therapy, and treatment group, and with baseline HbA1c as a continuous covariate. The treatment-effect estimate for the albiglutide group (and associated hypothesis tests) was evaluated within this analysis of covariance model as least squares (LS) mean contrasts relative to the insulin glargine group. The contrast of the albiglutide versus insulin glargine group was evaluated inferentially using a noninferiority hypothesis (2-sample, 1-sided *t* test) with a noninferiority margin of 0.3% and a test-wise criterion significance level of 0.025. With significance on the noninferiority hypothesis, the albiglutide group versus insulin glargine group superiority hypothesis was evaluated at the test-wise criterion significanc level of 0.05.

Subjects who were rescued for hyperglycemia before Week 52 had their HbA_{1c} recorded at the time of rescue and carried forward for primary analyses. Subjects who discontinued from active treatment due to any reason before Week 52 also had their last postbaseline HbA_{1c} observation carried forward for the analyses.

Patient Disposition

The following Kaplan-Meier plots of Time to Withdrawal show that dropout rate due to adverse events was small in the insulin glargine group but was continuing in the albiglutide group up to the end of the study and exceeded 10%. Overall dropout rate exceeded 20% and 30%, respectively, in these two groups.

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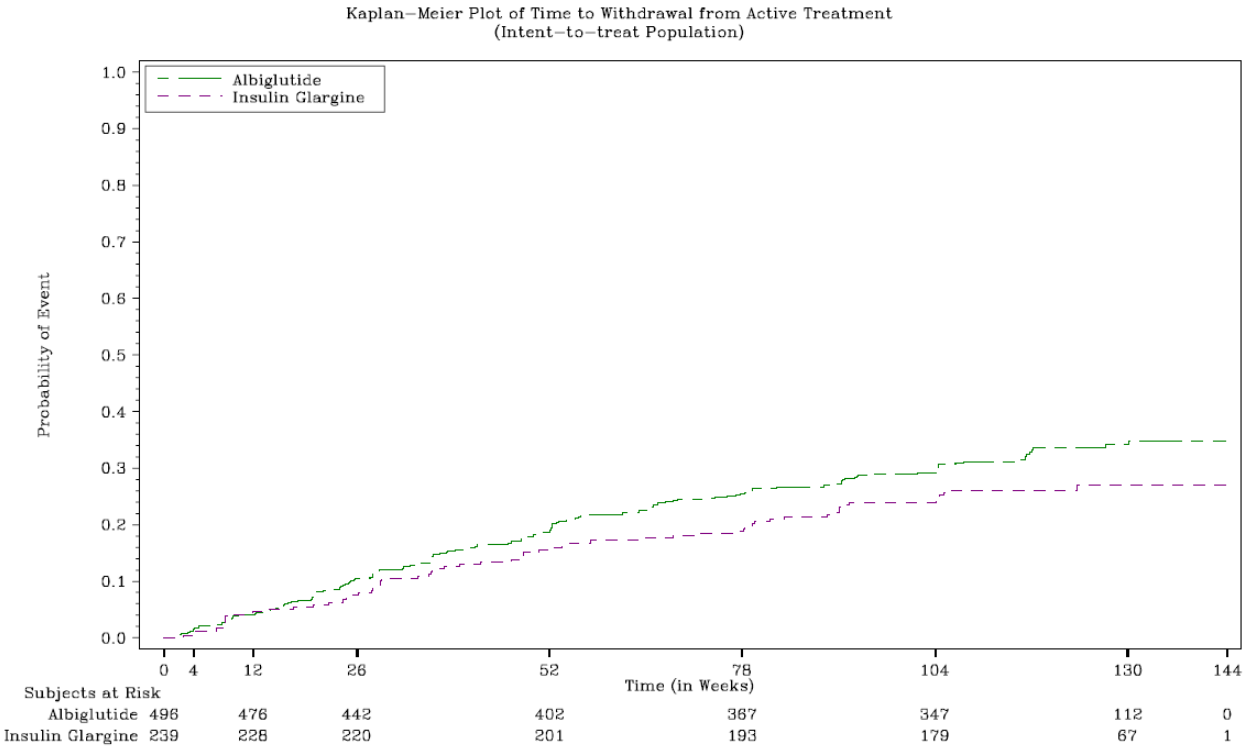

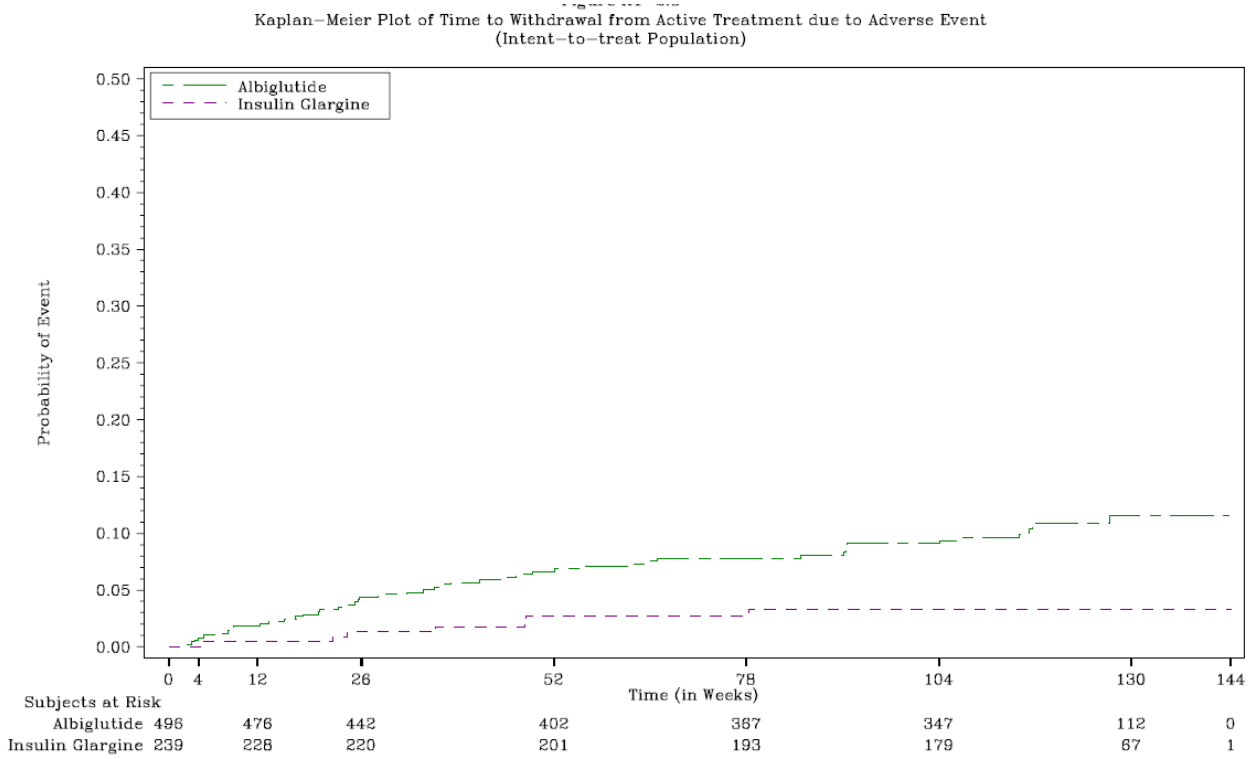

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Demographic and Baseline Characteristics

Demographic Characteristics (Safety Population)

As seen from the following Table of demographics,
The mean age was 55.8 in the albiglutide group and was 54.7 in the glargine group.
The percentage of White was 67.9 in the albiglutide group and was 65.6 in the glargine group.
The percentage of African was 25.8, in the albiglutide group and was 26.6 in the glargine group.
The percentage of male was 56.7 in the albiglutide group and was 54.8 in the glargine group.
The mean weight was 95.1 in the albiglutide group and was 94.6 in the glargine group.

	Albiglutide (N=504)	Insulin Glargine (N=241)	Total (N=745)
Age at randomization (years)			
N	504	241	745
Mean (SD)	55.8 (9.33)	54.7 (9.75)	55.5 (9.48)
Median	56.0	55.0	56.0
Minimum, Maximum	27, 81	26, 83	26, 83
Age category, n (%)			
N	504	241	745
<65 years	424 (84.1)	202 (83.8)	626 (84.0)
≥65 years	80 (15.9)	39 (16.2)	119 (16.0)
Sex, n (%)			
N	504	241	745
Female	218 (43.3)	109 (45.2)	327 (43.9)
Male	286 (56.7)	132 (54.8)	418 (56.1)
Race[2], n (%)			
N	504	241	745
African American/African Heritage	130 (25.8)	64 (26.6)	194 (26.0)
American Indian or Alaskan Native	3 (0.6)	1 (0.4)	4 (0.5)
Asian - Central/South Asian Heritage	7 (1.4)	5 (2.1)	12 (1.6)
Asian - East Asian Heritage	2 (0.4)	1 (0.4)	3 (0.4)
Asian - Japanese Heritage	0	1 (0.4)	1 (0.1)
Asian - South East Asian Heritage	16 (3.2)	8 (3.3)	24 (3.2)
Native Hawaiian or Other Pacific Islander	1 (0.2)	0	1 (0.1)
White - Arabic/North African Heritage	7 (1.4)	2 (0.8)	9 (1.2)
White - White/Caucasian/European Heritage	342 (67.9)	158 (65.6)	500 (67.1)
Other	2 (0.4)	1 (0.4)	3 (0.4)
Ethnicity, n (%)			
N	504	241	745
Hispanic/Latino	81 (16.1)	38 (15.8)	119 (16.0)
Not Hispanic/Latino	423 (83.9)	203 (84.2)	626 (84.0)
Weight (kg)			
N	504	241	745
Mean (SD)	95.08 (19.66)	94.55 (19.08)	94.91 (19.46)
Median	93.10	91.00	92.80
Minimum, Maximum	46.1, 151.5	57.4, 151.4	46.1, 151.5

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	Albiglutide (N=504)	Insulin Glargine (N=241)	Total (N=745)
BMI (kg/m^2)			
N	504	241	745
Mean (SD)	33.18 (5.56)	32.98 (5.44)	33.12 (5.5)
Median	33.00	32.00	33.00
Minimum, Maximum	20.0, 46.0	20.0, 45.0	20.0, 46.0
BMI category, n (%)			
n	504	241	745
<25 kg/m^2	26 (5.2)	8 (3.3)	34 (4.6)
≥25 to <30 kg/m^2	116 (23.0)	63 (26.1)	179 (24.0)
≥30 to <35 kg/m^2	155 (30.8)	83 (34.4)	238 (31.9)
≥35 kg/m^2	207 (41.1)	87 (36.1)	294 (39.5)

BMI = body mass index; n = number; SD = standard deviation.

1. The p-value was for testing the null hypothesis that the summary statistics (mean or proportion) were equal among treatment groups. All tests were 2-sided.
2. Subjects could be counted in more than 1 category.

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Baseline Diabetes Characteristics (Safety Population)

As seen from the following Table of Baseline Characteristics, the mean duration of diabetes in years was 8.9 in the albiglutide group and was 8.4 in the glargine group.

	Albiglutide (N=504)	Insulin Glargine (N=241)	Total (N=745)
Diabetic condition, n (%)			
Subjects with any diabetic condition	379 (75.2)	191 (79.3)	
Dyslipidaemia	313 (62.1)	159 (66.0)	
Peripheral neuropathy	117 (23.2)	58 (24.1)	
Impotence	90 (17.9)	40 (16.6)	
Proteinuria	26 (5.2)	13 (5.4)	
Diabetic retinopathy	16 (3.2)	10 (4.1)	
Microalbuminuria	13 (2.6)	6 (2.5)	
Nephropathy	12 (2.4)	3 (1.2)	
Other	10 (2.0)	5 (2.1)	
Autonomic neuropathy	9 (1.8)	3 (1.2)	
Diabetic foot ulcer	8 (1.6)	3 (1.2)	
Chronic renal insufficiency	3 (0.6)	0	
Duration of diabetes[2] (years)			
n	504	241	745
Mean (SD)	8.93 (6.51)	8.44 (5.69)	8.77 (6.25)
Median	7.51	7.42	7.49
Minimum, Maximum	0.3, 35.3	0.4, 34.6	0.3, 35.3
Duration category, n (%)			
n	504	241	745
<5 years	156 (31.0)	81 (33.6)	237 (31.8)
≥5 to ≤10 years	182 (36.1)	77 (32.0)	259 (34.8)
>10 years	166 (32.9)	83 (34.4)	249 (33.4)
Prior myocardial infarction, n (%)			
n	504	241	745
Yes	26 (5.2)	11 (4.6)	37 (5.0)
No	478 (94.8)	230 (95.4)	708 (95.0)
Current antidiabetic therapy, n (%)			
n	504	240	744
Metformin alone	91 (18.1)	44 (18.3)	135 (18.1)
Metformin + sulfonylurea	413 (81.9)	196 (81.7)	609 (81.9)
Baseline HbA_{1c} (%)			
n	504	241	745
Mean (SD)	8.28 (0.900)	8.37 (0.956)	8.31 (0.919)
Median	8.20	8.30	8.20
Minimum, Maximum	6.5, 11.0	6.7, 10.5	6.5, 11.0
Baseline HbA_{1c} category, n (%)			
n	504	241	745
<8.0%	210 (41.7)	98 (40.7)	308 (41.3)
≥8.0%	294 (58.3)	143 (59.3)	437 (58.7)

HbA_{1c} = glycosylated hemoglobin; SD = standard deviation.

Reference ID: 3392698

1. The p-value was for testing the null hypothesis that the summary statistics (mean or proportion) were equal among treatment groups. All tests were 2-sided.
2. To calculate duration from a partial diagnosis date, a missing month was imputed as January and a missing day was imputed as the first of the month.

Results and Conclusions

Primary Efficacy Endpoint

HbA_{1c} Change From Baseline at Week 52

Mean Baseline HbA_{1c} values were similar across treatment groups. A decrease in HbA_{1c} from Baseline to Week 52 was observed in both the albiglutide and the insulin glargine treatment groups. When adjusted region, history of prior MI, age category, current antidiabetic therapy, and baseline HbA_{1c}, the model-adjusted LS mean change in HbA_{1c} from Baseline to Week 52 was -0.67% in the albiglutide group and -0.79% in the insulin glargine group. The treatment difference (albiglutide - insulin glargine) was 0.11% (95% CI: -0.04%, 0.27%). The upper bound of the confidence interval was below the prespecified noninferiority margin of 0.3%, indicating noninferiority of albiglutide to insulin glargine. A test of the treatment difference showed that there was no statistically significant difference between the albiglutide group and insulin glargine group (p=0.1463).

Analysis of Change From Baseline in HbA_{1c} (%) at Week 52 (ITT Population – LOCF)

	Albiglutide (N=496)	Insulin Glargine (N=239)
Number of subjects[1]	493	238
Number (%) of values carried forward	202 (41.0)	86 (36.1)
Baseline – mean (SD)	8.28 (0.900)	8.36 (0.954)
Week 52 – mean (SD)	7.62 (1.122)	7.55 (1.040)
Change from Baseline – mean (SD)	-0.66 (1.067)	-0.81 (1.103)
Model-adjusted change from Baseline[2]		
LS mean (SE)	-0.67 (0.044)	-0.79 (0.064)
95% CI	-0.76, -0.58	-0.91, -0.66
Difference from insulin glargine[2]		
Difference of LS means	0.11	
95% CI	-0.04, 0.27	
Noninferiority p-value[3]	0.0086	
Superiority p-value[4]	0.1463	

ANCOVA = analysis of covariance; CI = confidence interval; HbA_{1c} = glycosylated hemoglobin; ITT = intent to treat; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; SE = standard error.

Note: This analysis used the LOCF method for missing postbaseline HbA_{1c} values. The HbA_{1c} values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values. Four ITT subjects had all postbaseline HbA_{1c} measurements occurring more than 14 days after the last dose. These 4 subjects are included in the header ITT Population counts but do not contribute to any of the ITT efficacy summaries.

1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on ANCOVA: Change = treatment + baseline HbA_{1c} + prior myocardial infarction history + age category + region + current antidiabetic therapy. Difference of LS means (albiglutide – insulin glargine) from ANCOVA model.

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3. This p-value was from a 1-sided *t* test to test whether the difference of LS means (albiglutide – insulin glargine) was equal to the prespecified noninferiority margin of 0.3%.
4. This p-value was from a 2-sided *t* test to test whether the difference in the LS means (albiglutide – insulin glargine) was equal to zero.

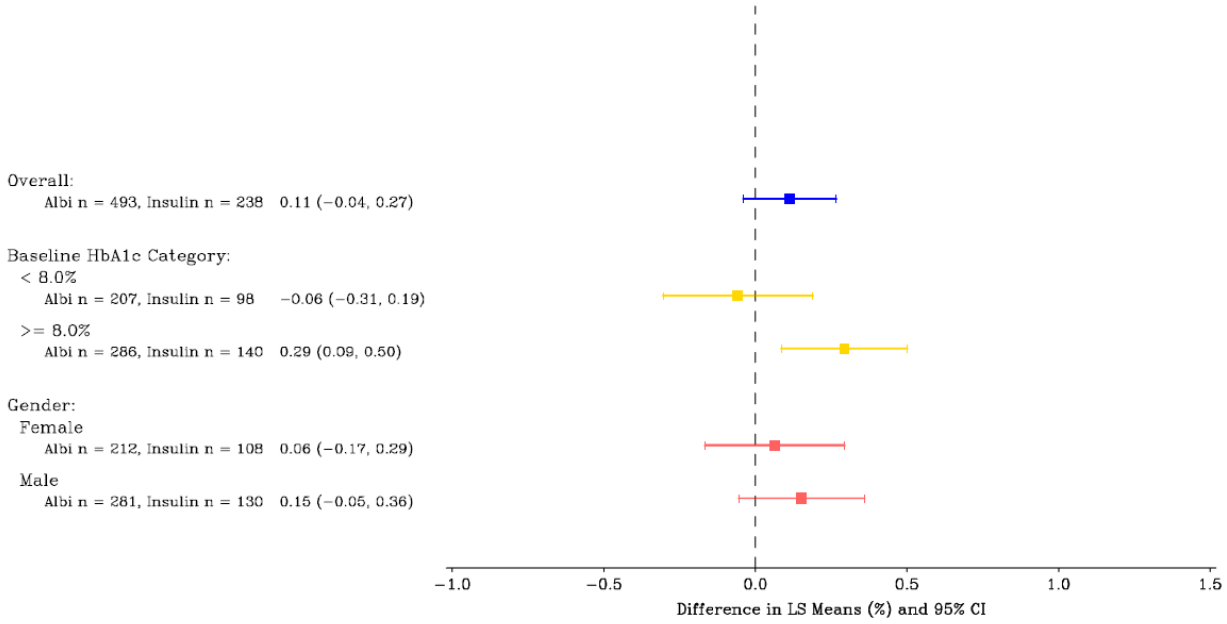
Reviewer's Conclusion: My confidence interval and the above confidence interval are the same and, therefore, non-inferiority of albiglutide to insulin glargine with respect to HBA1C has been shown by the sponsor-submitted data. Nevertheless, insulin glargine was numerically superior.

In the following forest plots, left side represents the numerical superiority of albiglutide.

There were statistically significant Treatment by Baseline HbA1c (<8.0, >=8.0) (p= 0.0328) and by Age at randomization category (<65, >=65) (p=0.0503) interactions, albiglutide being numerically superior in the <8 HBA1c category and in the >=65 age category.

Note: In many subgroups in the following forest plots, the upper boundaries of the confidence intervals are out of the non-inferiority margin .3; so, does not exclude the possibility of the albiglutide group being inferior. However, subgroup results, when not planned to be confirmatory, are not confirmatory. Further evidences are needed to reach the level of confirmation.

Difference of LS Mean Model-Adjusted Change From Baseline in HbA_{1c} (%) and 95% CI for Albiglutide Versus Insulin Glargine at Week 52 by Subgroup Category (ITT Population – LOCF)



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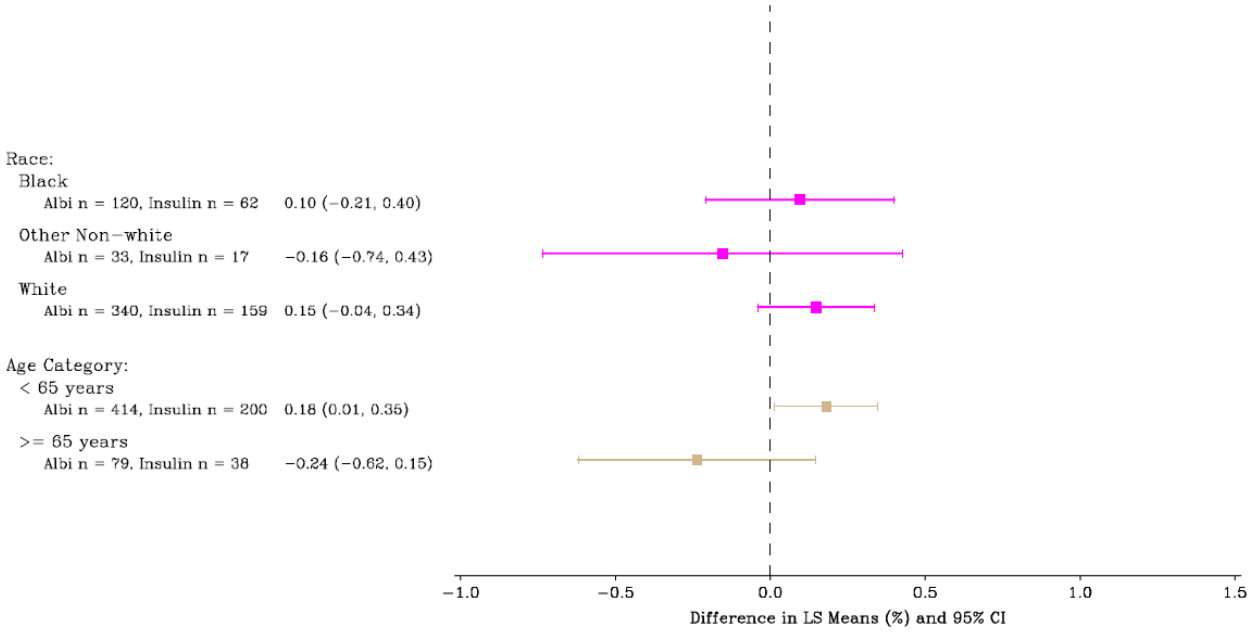
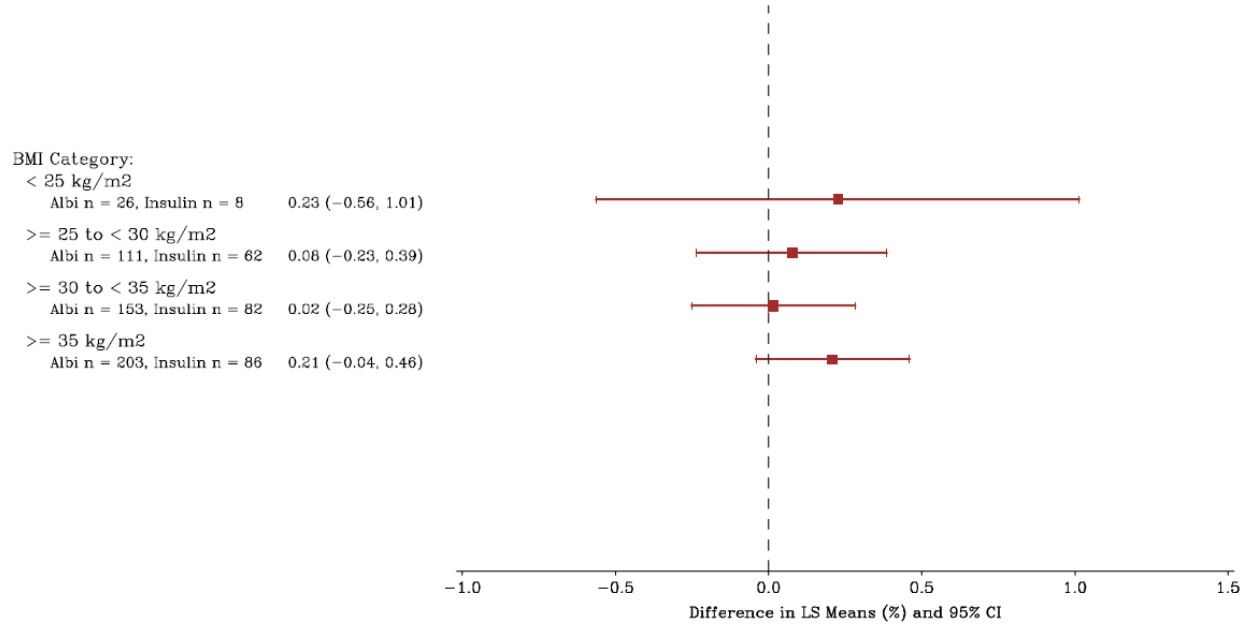
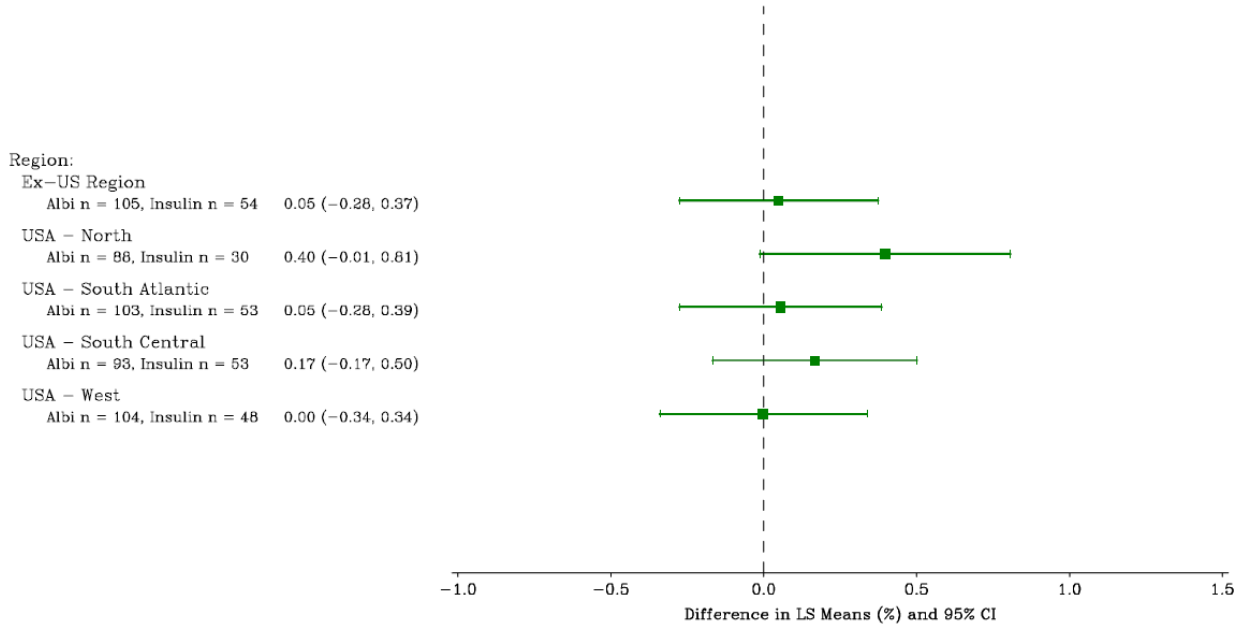
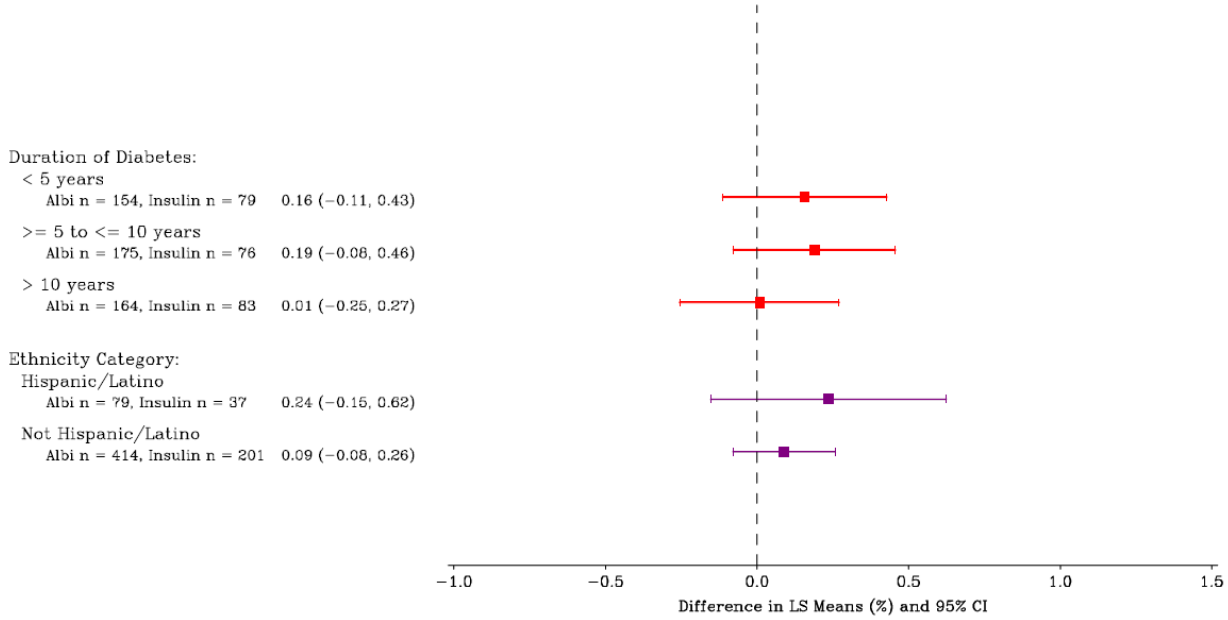


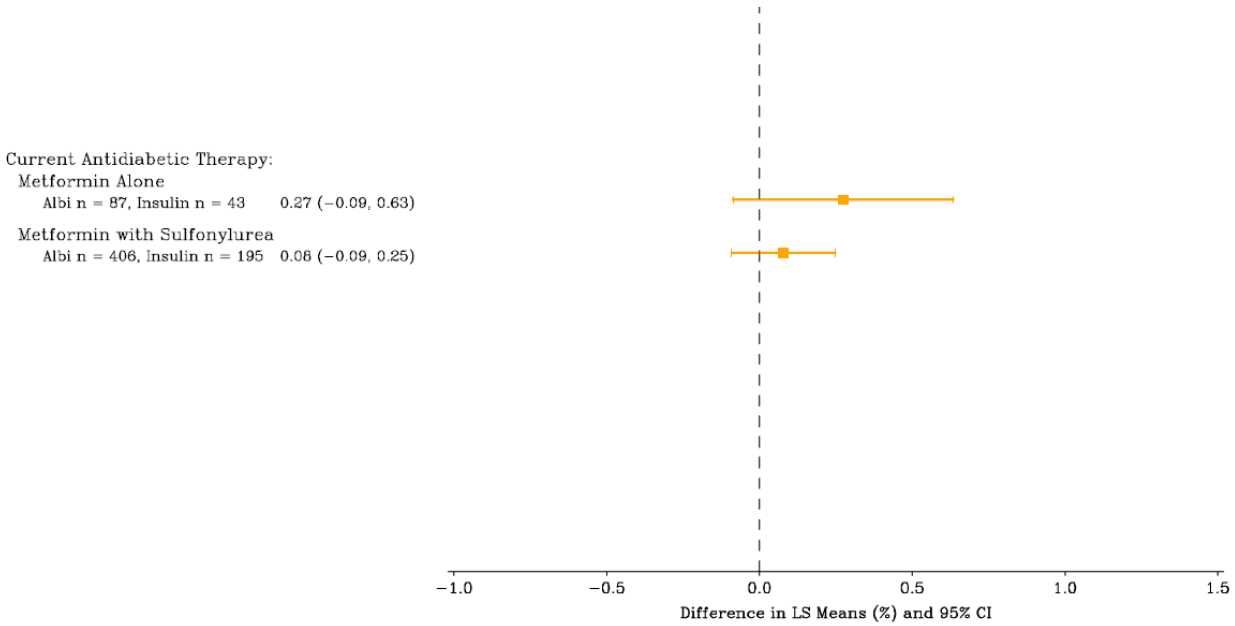


Reference ID: 3392698





Reference ID: 3392698

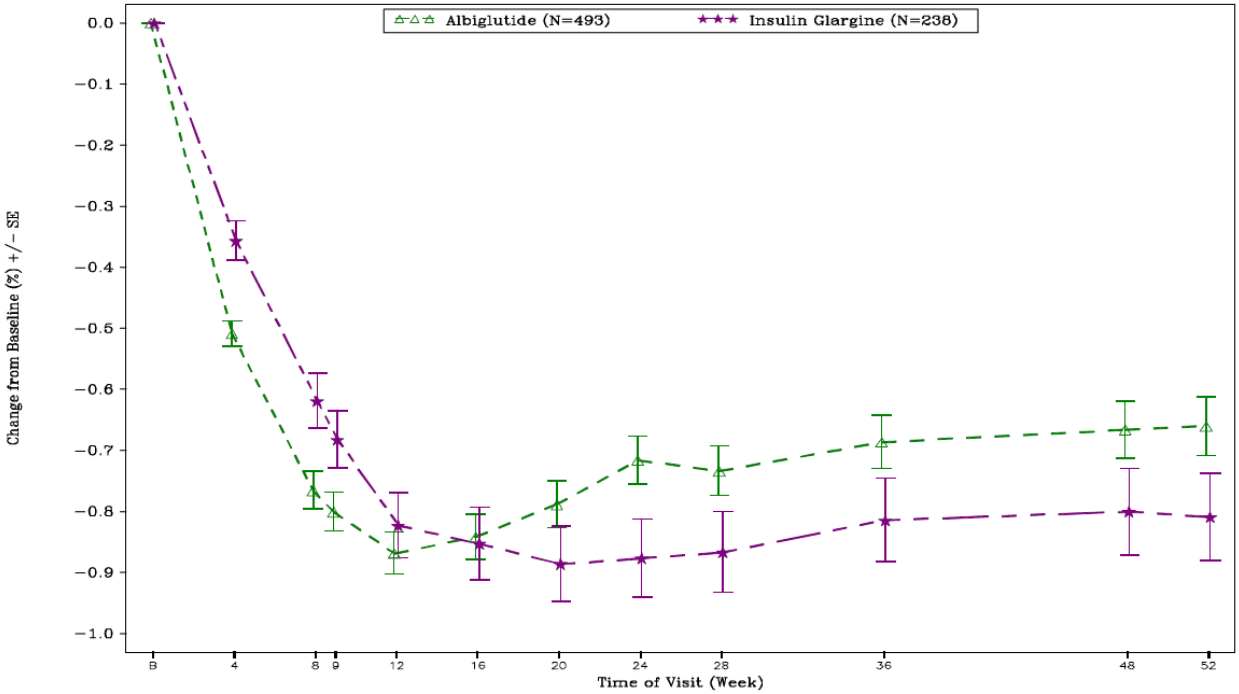


Albi = albiglutide; BMI = body mass index; CI = confidence interval; HbA_{1c} = glycosylated hemoglobin; ITT = intent to treat; LOCF = last observation carried forward; LS = least squares; USA = United States of America.
Note: The difference on the X-axis is the difference in the albiglutide LS mean change from Baseline minus the insulin glargine LS mean change from Baseline.

Reference ID: 3392698

Mean Change From Baseline in HbA_{1c} (%) Through Week 52 (ITT Population – LOCF)

Albiglutide was numerically superior to insulin glargine up to Week 15 and then became much inferior numerically after Week 19.



B = Baseline; HbA_{1c} = glycosylated hemoglobin; ITT = intent to treat; LOCF = last observation carried forward; SE = standard error.

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Analysis of Change From Baseline in FPG (mmol/L) at Week 52 (ITT Population – LOCF)

Reviewer's Comment: As seen in the following Table, Insulin Glargine was statistically superior to albiglutide with respect to FPG at Week 52.

	Albiglutide (N=496)	**Insulin Glargine (N=239)**
Number of subjects[1]	494	238
Number (%) of values carried forward	206 (41.7%)	86 (36.1%)
Baseline Mean (SD)	9.40 (2.826)	9.72 (2.967)
Week 52 Mean (SD)	8.59 (2.999)	7.53 (2.958)
Model-adjusted change from Baseline[2]		
LS mean	-0.87	-2.06
Standard error	0.127	0.184
95% confidence interval	(-1.12, -0.62)	(-2.42, -1.70)
Difference from insulin glargine[2]		
Difference of LS means	1.19	
95% confidence interval	(0.75, 1.63)	
p-value	<0.0001	

ANCOVA = analysis of covariance; FPG = fasting plasma glucose, HbA_{1c} = glycosylated hemoglobin; ITT = intent to treat; LOCF = last observation carried forward; LS = least squares; SD = standard deviation.

Note: This analysis used the LOCF method for missing postbaseline FPG values. The FPG values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values.

1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on ANCOVA: Change = treatment + baseline FPG + baseline HbA1c category + prior myocardial infarction history + age category + region + current antidiabetic therapy. The difference of LS means (albiglutide – insulin glargine) is from the ANCOVA model. The p-value is from a 2-sided t test for the difference in means.

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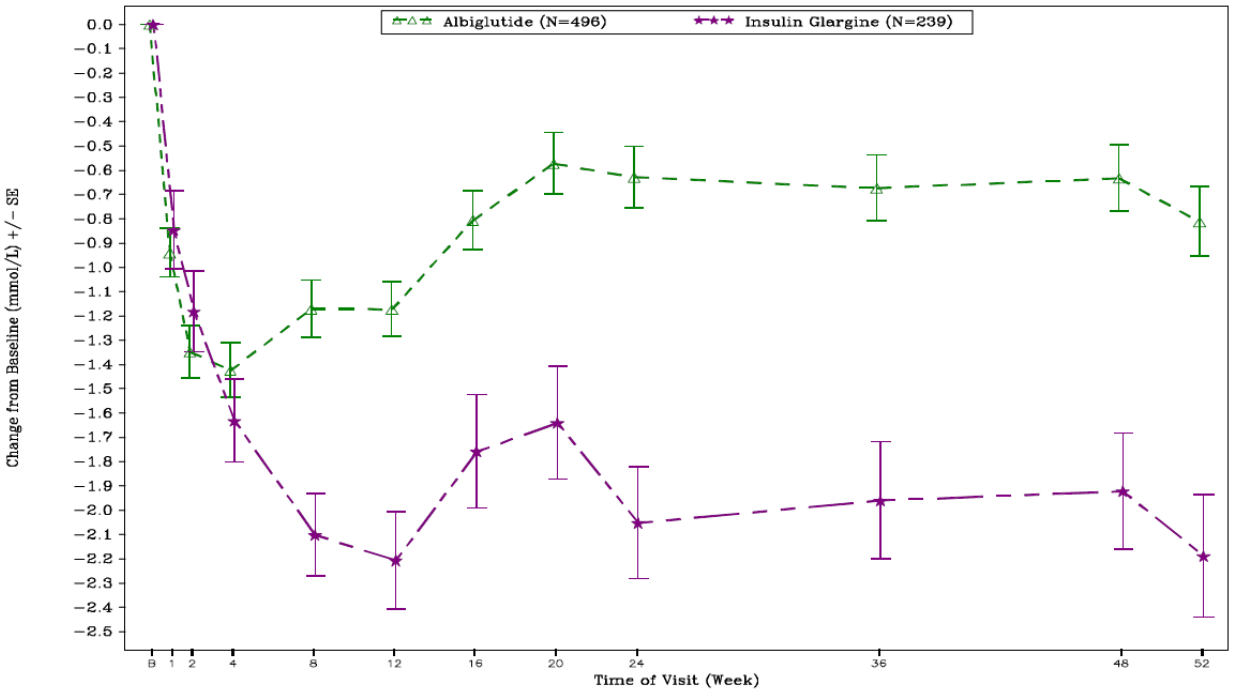
Figure for Mean Change From Baseline in FPG (mmol/L) Through Week 52 (ITT Population – LOCF)

As seen from the following graph, insulin glargine was far superior to albiglutide with respect to FPG after Week 7.



B = baseline; FPG = fasting plasma glucose; ITT = intent to treat; LOCF = last observation carried forward; SE = standard error.

Analysis of Change From Baseline in Weight (kg) at Week 52 (ITT Population – LOCF)

As seen from the following Table of results on change from baseline in weight, Insulin Glargine had a statistically significant weight increase from baseline and albiglutide had a statistically significant decrease in weight. The difference between the two arms, naturally, was statistically significant.

In the albiglutide treatment group, there was a small and continual body weight loss through Week 52 while the insulin glargine group had a mean increase in body weight (Figure 12). At Week 52, the model-adjusted LS mean weight change from Baseline for albiglutide subjects was -1.05 kg while the corresponding gain in the insulin glargine group was 1.56 kg (Table 29). The difference in weight change from Baseline to Week 52 was statistically significant (p=0.0301 or better) in favor of albiglutide at each time point from Week 1 through Week 52 (Source Data: Table 14.2-5.5). The percent change from Baseline in body weight was -1.01% in the albiglutide group and 1.67% in the insulin glargine group at Week 52.

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Analysis of Change From Baseline in Weight (kg) at Week 52 (ITT Population – LOCF)

	Albiglutide (N=496)	**Insulin Glargine (N=239)**
Number of subjects[1]	495	238
Number (%) of values carried forward	205 (41.4)	86 (36.1)
Baseline mean (SD)	95.23 (19.571)	94.64 (19.091)
Week 52 mean (SD)	94.18 (19.288)	96.21 (19.711)
Change from Baseline - mean (SD)	-1.06 (3.803)	1.57 (3.806)
Model-adjusted change from Baseline[2]		
LS mean	-1.05	1.56
Standard error	0.171	0.247
95% confidence interval	(-1.39, -0.72)	(1.07, 2.04)
Difference from insulin glargine[2]		
Difference of LS means	-2.61	
95% confidence interval	(-3.20, -2.02)	
p-value	<0.0001	

ANCOVA = analysis of covariance; HbA_{1c} = glycosylated hemoglobin; ITT = intent to treat; LOCF = last observation carried forward;
LS = least squares; SD = standard deviation.

Note: This analysis used the LOCF method for missing postbaseline weight values. Weight values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values.

1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on ANCOVA: Change = treatment + baseline weight + baseline HbA_{1c} category + prior myocardial infarction history + age category + region + current antidiabetic therapy. The difference of LS means (albiglutide – insulin glargine) was from the ANCOVA model. The p-value was from a 2-sided *t* test for the difference in means.

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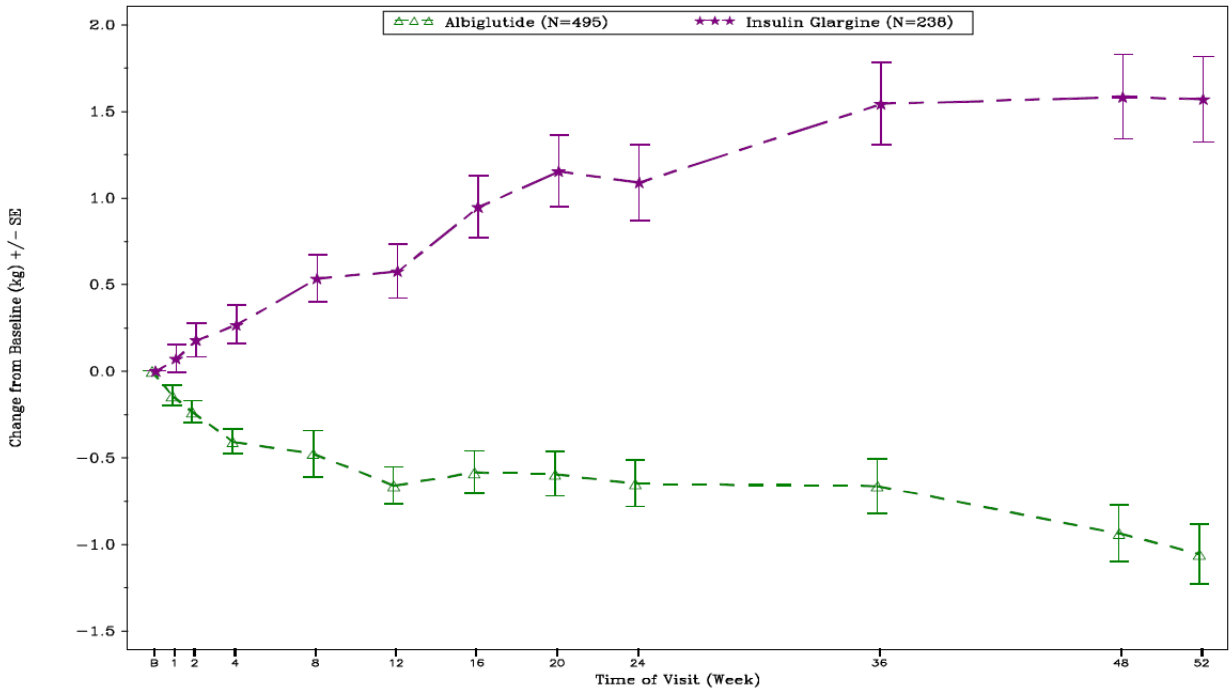
Mean Change From Baseline in Weight (kg) Through Week 52 (ITT Population – LOCF)

A seen from the following graph, the weigh increase in insulin glargine and weight decrese in albiglutide started from the beginning.



B = baseline; ITT = intent to treat; LOCF = last observation carried forward; SE = standard error.

§ Graphs of cumulative distribution functions by treatment groups for the primary efficacy variable (percent change from baseline in HbA1c) at the study endpoint are provided below. From these, the percent of patients (y-axis value) with a value of percent change from baseline in HbA1c at endpoint, smaller than or equal to a value on the x-axis, can be read.

Note: As seen from the following cumulative distribution functions, almost all the percentiles of each of HBA1c and FPG are smaller for insulin glargine than for albiglutide and those for Weight are the opposite (greater for insulin glargine).

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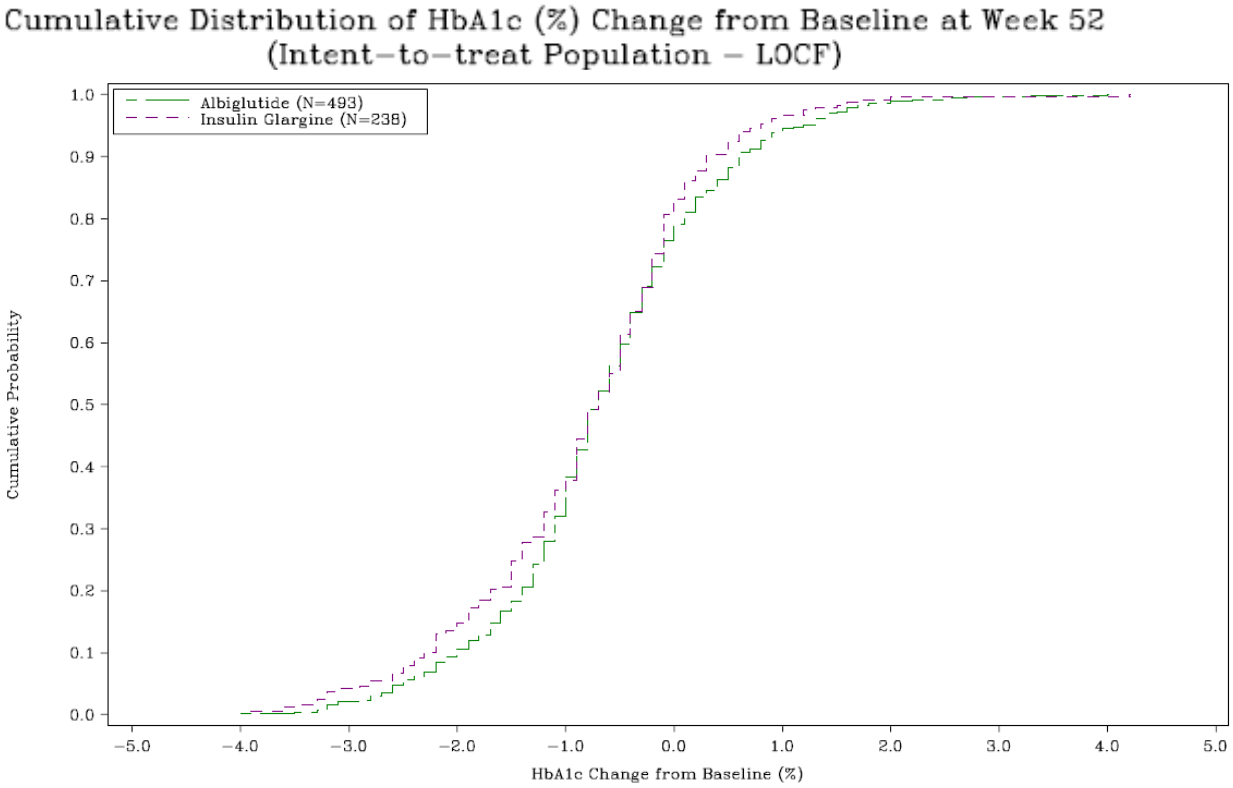

Table of Cumulative Distribution of HbA1c (%) Change from Baseline at Week 52 (Intent-to-treat Population - LOCF)

Percentile	Albiglutide (N=496)	Insulin Glargine (N=239)
Number of subjects [1]	493	238
Min	-4.0	-3.9
1%	-3.20	-3.60
5%	-2.50	-2.80
10%	-2.00	-2.30
20%	-1.40	-1.70
30%	-1.10	-1.20
40%	-0.90	-0.90
50%	-0.70	-0.70
60%	-0.40	-0.50
70%	-0.20	-0.20
80%	0.10	-0.10
90%	0.60	0.30
95%	1.20	0.80
99%	2.20	1.70
Max	4.0	4.2

Note: This summary uses the last observation carried forward (LOCF) method for missing post-baseline HbA1c values. HbA1c values obtained after hyperglycemia rescue are treated as missing and replaced with pre-rescue values.
[1] Number of subjects with a value at Week 52.

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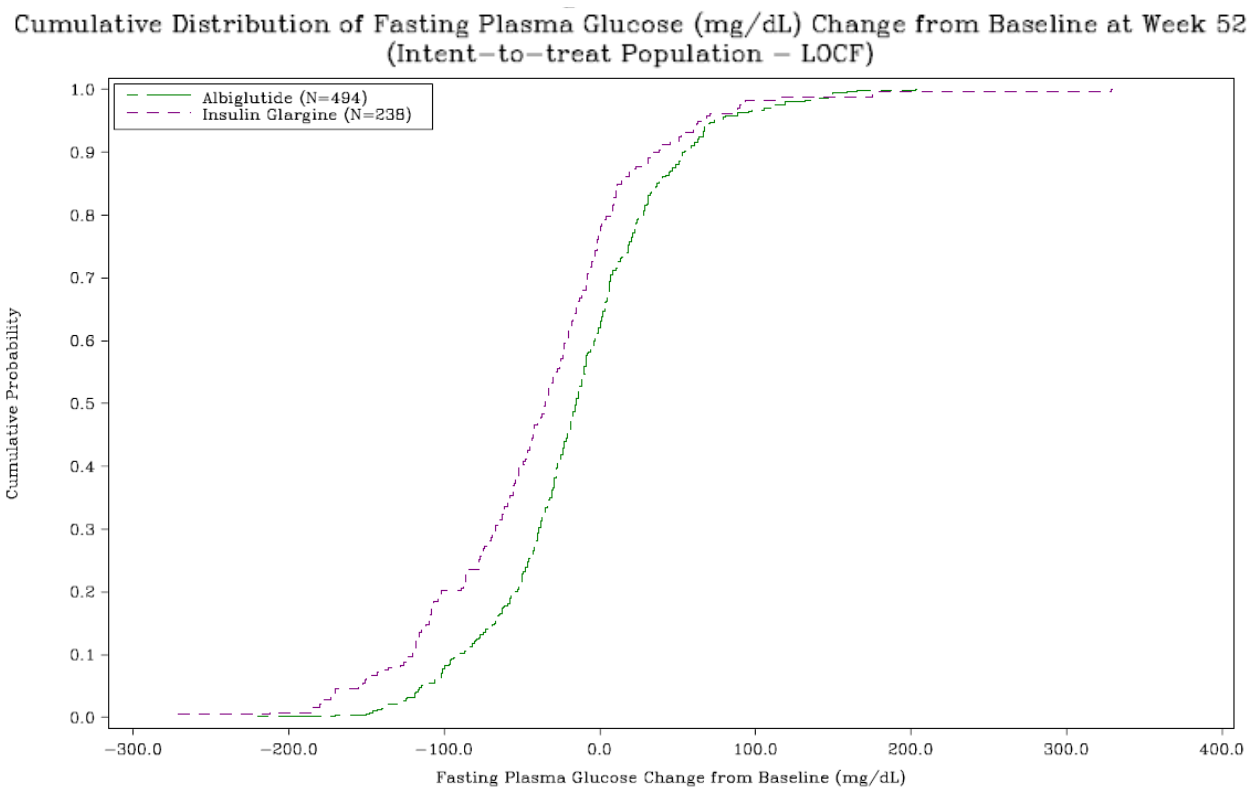

Table of Cumulative Distribution of Fasting Plasma Glucose (mg/dL) Change from Baseline at Week 52 (Intent-to-treat Population - LOCF)

Percentile	Albiglutide (N=496)	Insulin Glargine (N=239)
Number of subjects [1]	494	238
Min	-220	-271
1%	-146.0	-185.0
5%	-115.0	-155.0
10%	-90.0	-120.0
20%	-54.0	-102.0
30%	-39.0	-67.0
40%	-27.0	-51.0
50%	-15.0	-35.0
60%	-3.0	-21.0
70%	7.0	-8.0
80%	28.0	7.0
90%	53.0	38.0
95%	74.0	68.0
99%	150.0	175.0
Max	203	329

Note: This summary uses the last observation carried forward (LOCF) method for missing post-baseline fasting plasma glucose (FPG) values. FPG values obtained after hyperglycemia rescue are treated as missing and replaced with pre-rescue values.
[1] Number of subjects with a value at Week 52.

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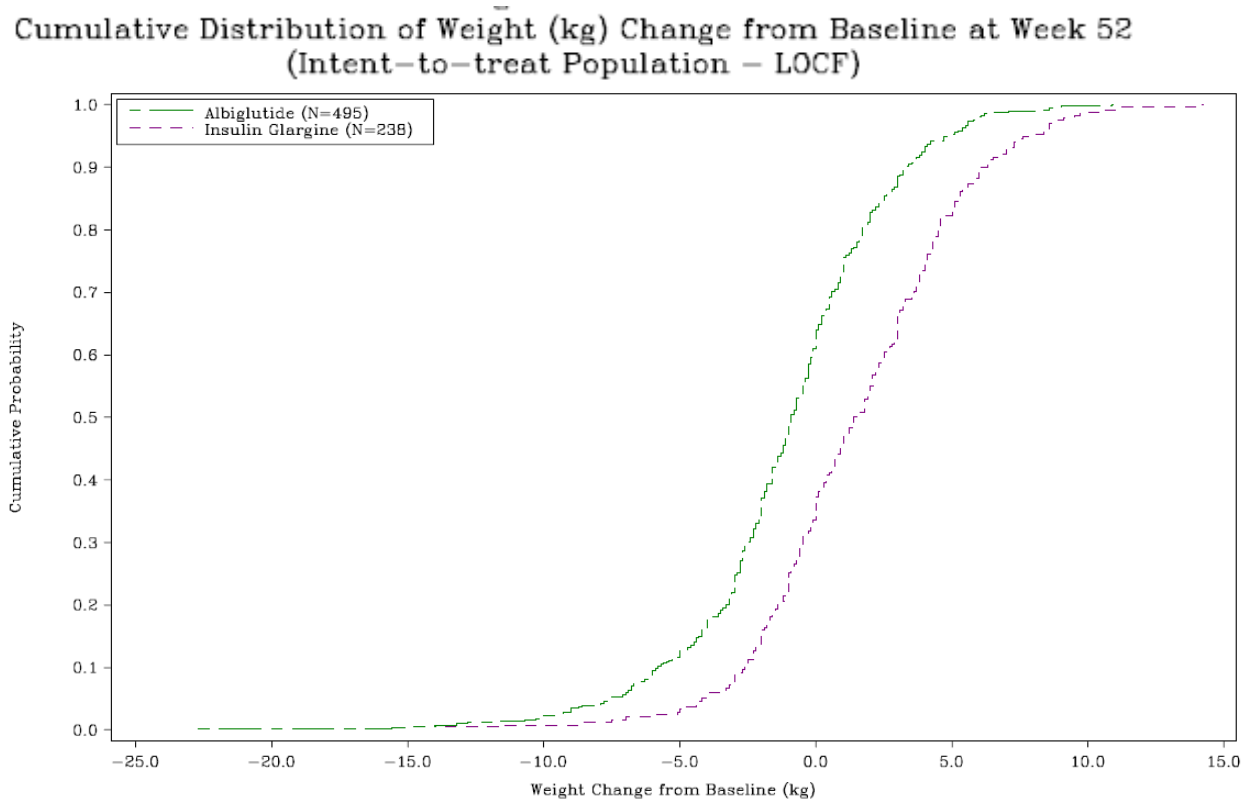

Table of Cumulative Distribution of Weight (kg) Change from Baseline at Week 52 (Intent-to-treat Population - LOCF)

Percentile	Albiglutide (N=496)	Insulin Glargine (N=239)
Number of subjects [1]	495	238
Min	-22.7	-13.6
1%	-13.20	-8.60
5%	-7.50	-4.20
10%	-5.80	-2.60
20%	-3.25	-1.40
30%	-2.50	-0.50
40%	-1.60	0.40
50%	-0.90	1.45
60%	-0.10	2.50
70%	0.60	3.60
80%	1.70	4.50
90%	3.30	6.30
95%	5.00	8.00
99%	8.30	10.40
Max	10.9	14.2

Note: This summary uses the last observation carried forward (LOCF) method for missing post-baseline weight values. Weight values obtained after hyperglycemia rescue are treated as missing and replaced with pre-rescue values.
[1] Number of subjects with a value at Week 52.

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STUDY GLP112755

Title: A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to determine the efficacy and safety of albiglutide when used in combination with pioglitazone with or without metformin in subjects with type 2 diabetes mellitus

Study centers: The study was conducted at 158 centers in 4 countries.

Study Period: 26 Jan 2009 to 30 Nov 2011

Phase of Development: III

Objectives: The primary objective of the study was to evaluate the efficacy of albiglutide administered in combination with pioglitazone (with or without metformin) as compared with pioglitazone (with or without metformin) on glycosylated hemoglobin (HbA1c) change from Baseline at Week 52.

Methodology: This randomized, double-blind, placebo-controlled, 2 parallel-group, multicenter study evaluated the efficacy and safety of a 30 mg weekly subcutaneously injected dose of albiglutide in combination with pioglitazone (with or without metformin) as compared with pioglitazone (with or without metformin) in subjects with type 2 diabetes mellitus (T2DM). Subjects with T2DM who were inadequately controlled on their current regimen of pioglitazone (with or without metformin) were recruited into the study.

The study comprised 4 study periods: Screening, Run-in/Stabilization, Treatment, and Posttreatment Follow-up. The duration of the Treatment Period for the assessment of primary efficacy and safety was 52 weeks from the time of randomization, followed by an additional 104 weeks of treatment for additional evaluation of safety and efficacy.
Subjects completed a minimum of 2 years of treatment, at which time the formal analysis for submission of regulatory marketing applications was completed. The study continued as a blinded study for up to 3 years. This Synopsis is concerned with the 2-year data.

Randomization was stratified by current antidiabetic therapy (with or without metformin), history of prior myocardial infarction (MI; yes versus no), and age <65 versus ≥65 years.

Number of subjects: 300 planned; randomized in a ratio of 1:1 to pioglitazone (with or without metformin) + albiglutide (30 mg weekly) or pioglitazone (with or without metformin) + albiglutide-matching placebo.

Diagnosis and main criteria for inclusion: Eligible subjects were men and women with a historical diagnosis of T2DM who were experiencing inadequate glycemic control on their current regimen of pioglitazone (with or without metformin).

Statistical methods: The primary endpoint of the HbA_{1c} change from Baseline at

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Week 52, was applied to the intent-to-treat (ITT) population, using an analysis of covariance (ANCOVA) model with treatment group, region, current antidiabetic therapy, history of prior MI, and age category as covariates and with baseline HbA_{1c} as a continuous covariate. The treatment effect estimate for the albiglutide group (and the associated hypothesis tests) was evaluated within this ANCOVA model as the least squares (LS) means contrast relative to the placebo group. This contrast was evaluated inferentially with a 2-sided *t* test at the 0.05 significance level.

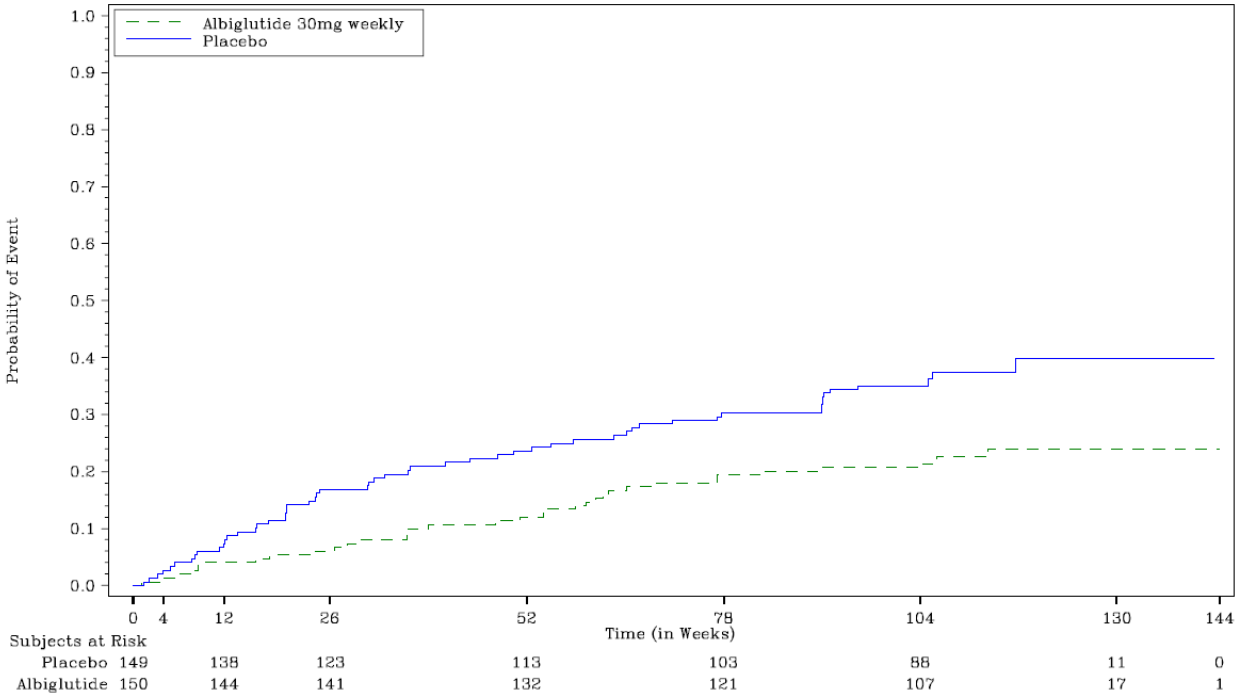
Subjects who qualified for hyperglycemia rescue had their primary endpoint value of HbA_{1c} change from Baseline recorded at the time of rescue. Follow-up assessments continued beyond rescue, and postrescue HbA_{1c} assessments were used in supportive analysis. Subjects who withdrew from the study had their last valid recorded observation (scheduled or unscheduled) carried forward to all remaining visits. Also, for subjects in the ITT analysis who had missing observations before their last observation on treatment, the closest previous nonmissing on-treatment observation was carried forward to missing visits. If a subject had missing observation(s) immediately after Baseline, the baseline observation was not carried forward and the visit(s) was left as missing. In general, the last observation carried forward (LOCF) method was used for all efficacy endpoints that were evaluated at or before Week 52. Beyond Week 52, all analyses did not impute any missing data; this nonimputation method was referred to as the observed case (OC). Further exploratory analyses included additional covariates such as baseline body mass index (BMI) and duration of diabetes.

Patient Disposition

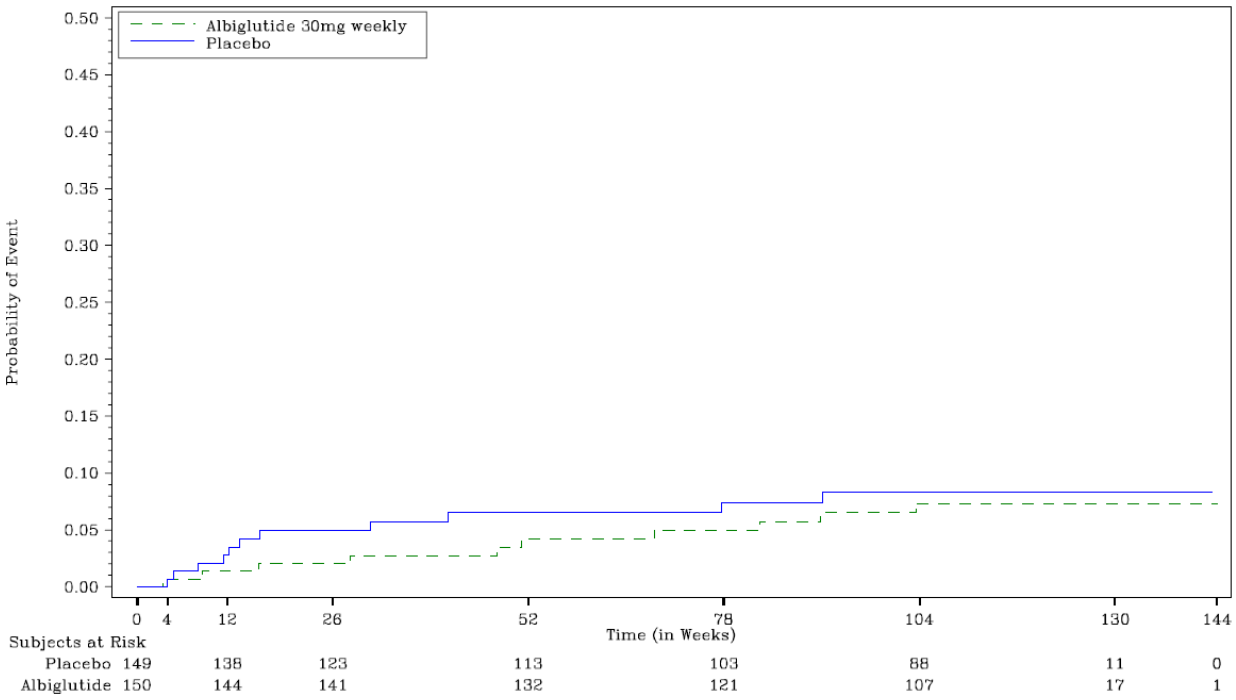
As seen from the following Kaplan-Meier plots for dropouts, the dropout rate was higher for placebo, even due to adverse events.

Reference ID: 3392698

Kaplan-Meier Plot of Time to Withdrawal from Active Treatment (Intent-to-treat Population)



Kaplan-Meier Plot of Time to Withdrawal from Active Treatment due to Adverse Event (Intent-to-treat Population)



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As seen from the following Table of demographics,
The mean age was 55.2 in the albiglutide group and was 54.9 in the placebo group.
Race was widely represented (details in the above Table), with the percentage of White 70.7 in the albiglutide group and 70.2 in the placebo group, with the percentage of African American/African heritage 12.7 in the albiglutide group and 13.2 in the placebo group.
The percentage of male was 61.3 in the albiglutide group and was 58.3 in the placebo group.
The mean weight (kg) was 97.6 in the albiglutide group and was 100.2 in the placebo group.

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Demographic Characteristics (Safety Population)

	Placebo (N=151)	Albiglutide 30 mg weekly (N=150)	Total (N=301)
Age at randomization (years)			
n	151	150	301
Mean (SD)	54.9 (9.40)	55.2 (9.98)	55.0 (9.67)
Median	55.0	56.0	56.0
Minimum, maximum	31, 80	29, 77	29, 80
Age category, n (%)			
n	151	150	301
<65 years	129 (85.4)	124 (82.7)	253 (84.1)
≥65 years	22 (14.6)	26 (17.3)	48 (15.9)
Sex, n (%)			
n	151	150	301
Female	63 (41.7)	58 (38.7)	121 (40.2)
Male	88 (58.3)	92 (61.3)	180 (59.8)
Race[2], n (%)			
n	151	150	301
African American/African heritage	20 (13.2)	19 (12.7)	39 (13.0)
American Indian or Alaskan Native	15 (9.9)	18 (12.0)	33 (11.0)
Asian - Central/South Asian heritage	1 (0.7)	2 (1.3)	3 (1.0)
Asian - East Asian heritage	2 (1.3)	3 (2.0)	5 (1.7)
Asian - Japanese heritage	1 (0.7)	1 (0.7)	2 (0.7)
Asian - South East Asian heritage	2 (1.3)	0	2 (0.7)
Native Hawaiian or Other Pacific Islander	2 (1.3)	1 (0.7)	3 (1.0)
White - Arabic/North African heritage	2 (1.3)	3 (2.0)	5 (1.7)
White - White/Caucasian/European heritage	106 (70.2)	106 (70.7)	212 (70.4)
Other	0	0	0

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Ethnicity, n (%)			
n	151	150	301
Hispanic/Latino	37 (24.5)	38 (25.3)	75 (24.9)
Not Hispanic/Latino	114 (75.5)	112 (74.7)	226 (75.1)
Weight (kg)			
n	151	150	301
Mean (SD)	100.17 (23.11)	97.62 (22.01)	98.90 (22.57)
Median	99.70	97.90	98.50
Minimum, maximum	51.0, 164.5	50.0, 157.9	50.0, 164.5
Body mass index (kg/m^2)			
n	150	150	300
Mean (SD)	34.65 (5.64)	33.56 (5.92)	34.11 (5.80)
Median	34.00	33.00	34.00
Minimum, maximum	23.0, 46.0	23.0, 46.0	23.0, 46.0
Body mass index category, n (%)			
n	150	150	300
<25 kg/m^2	3 (2.0)	8 (5.3)	11 (3.7)
≥25 to <30 kg/m^2	28 (18.7)	39 (26.0)	67 (22.3)
≥30 to <35 kg/m^2	49 (32.7)	36 (24.0)	85 (28.3)
≥35 kg/m^2	70 (46.7)	67 (44.7)	137 (45.7)

1. The p-value was for testing the null hypothesis that the population values (mean or proportion) were equal among treatment groups. All tests were 2-sided.
2. Subjects could be counted in more than 1 category.

As seen from the following Table of Baseline Characteristics,

The mean duration of diabetes in years was 8 in the albiglutide group and was 7.9 in the placebo group.

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Baseline Diabetes Characteristics (Safety Population)

	Placebo (N=151)	Albiglutide 30 mg weekly (N=150)	Total (N=301)
Diabetic condition, n (%)			
Subjects with any diabetic condition	121 (80.1)	108 (72.0)	
Dyslipidemia	108 (71.5)	100 (66.7)	
Impotence	32 (21.2)	24 (16.0)	
Peripheral neuropathy	24 (15.9)	30 (20.0)	
Diabetic retinopathy	7 (4.6)	5 (3.3)	
Proteinuria	7 (4.6)	5 (3.3)	
Microalbuminuria	6 (4.0)	4 (2.7)	
Other	6 (4.0)	1 (0.7)	
Nephropathy	1 (0.7)	5 (3.3)	
Autonomic neuropathy	3 (2.0)	1 (0.7)	
Diabetic foot ulcer	1 (0.7)	3 (2.0)	
Duration of diabetes[2] (years)			
n	151	150	301
Mean (SD)	7.88 (6.09)	8.04 (5.60)	7.96 (5.84)
Median	6.85	7.44	7.10
Minimum, maximum	0.33, 29.38	0.31, 34.52	0.31, 34.52
Duration category, n (%)			
n	151	150	301
<2.5 years	28 (18.5)	21 (14.0)	49 (16.3)
≥2.5 to ≤5 years	26 (17.2)	26 (17.3)	52 (17.3)
>5 years	97 (64.2)	103 (68.7)	200 (66.4)
Prior myocardial infarction, n (%)			
n	151	150	301
Yes	7 (4.6)	6 (4.0)	13 (4.3)
No	144 (95.4)	144 (96.0)	288 (95.7)
Current antidiabetic therapy, n (%)			
n	151	150	301
Pioglitazone + metformin	118 (78.1)	122 (81.3)	240 (79.7)
Pioglitazone	33 (21.9)	28 (18.7)	61 (20.3)
Baseline HbA_{1c} (%)			
n	151	150	301
Mean (SD)	8.13 (0.85)	8.10 (0.95)	8.11 (0.90)
Median	8.00	7.80	7.90
Minimum, maximum	6.9, 10.2	6.1, 10.8	6.1, 10.8
Baseline HbA_{1c} category, n (%)			
n	151	150	301
<8.0%	73 (48.3)	85 (56.7)	158 (52.5)
≥8.0%	78 (51.7)	65 (43.3)	143 (47.5)

HbA_{1c} = glycosylated hemoglobin; SD = standard deviation.

1. The p-value was for testing the null hypothesis that the population values (mean or proportion) were equal among treatment groups. All tests were 2-sided.
2. To calculate duration from a partial diagnosis date, a missing month was imputed as January and a missing day was imputed as the first of the month.

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Results and Conclusions

Primary Efficacy Endpoint

HbA_{1c} Change From Baseline at Week 52

A decrease in HbA_{1c} from Baseline to Week 52 was observed in the albiglutide treatment group When adjusted for region, history of prior MI, age category, current antidiabetic therapy, and baseline HbA_{1c}, the model-adjusted LS mean change in HbA_{1c} from Baseline to Week 52 was -0.81% in the albiglutide group and -0.05% in the placebo group. The treatment difference (albiglutide - placebo) of -0.75% (95% CI: -0.95 to -0.56%) was statistically significant ($p<0.0001$).

Analysis of Change From Baseline in HbA_{1c} (%) Through Week 52 (Intent-to-Treat Population – LOCF)

As seen from the following Table of results, statistical evidence for the efficacy of albiglutide 30 mg has been provided.

	Placebo (N=149)	Albiglutide 30 mg weekly (N=150)
Number of subjects[1]	149	149
Number (%) of values carried forward	87 (58.4)	48 (32.2)
Baseline mean (SD)	8.13 (0.851)	8.10 (0.955)
Week 52 mean (SD)	8.08 (0.994)	7.29 (1.085)
Model-adjusted change from Baseline[2]		
Least squares mean	-0.05	-0.81
Standard error	0.071	0.071
95% confidence interval	(-0.19, 0.08)	(-0.95, -0.67)
Difference from placebo[2]		
Difference of least squares means		-0.75
95% confidence interval		(-0.95, -0.56)
p-value[3]		<0.0001

SD = standard deviation
Note: This analysis used the last observation carried forward (LOCF) method for missing postbaseline glycosylated hemoglobin (HbA_{1c}) values. The HbA_{1c} values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values. One intent-to-treat (ITT) subject had all postbaseline HbA_{1c} measurements occur after hyperglycemic rescue. This subject was included in the header ITT population counts but did not contribute to this analysis.

1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on analysis of covariance (ANCOVA): Change = treatment + baseline HbA_{1c} + prior myocardial infarction history + age category + region + current antidiabetic therapy. The difference of least squares means (albiglutide – placebo) was from the ANCOVA model.
3. The p-value is from a 2-sided *t* test for the difference in means.

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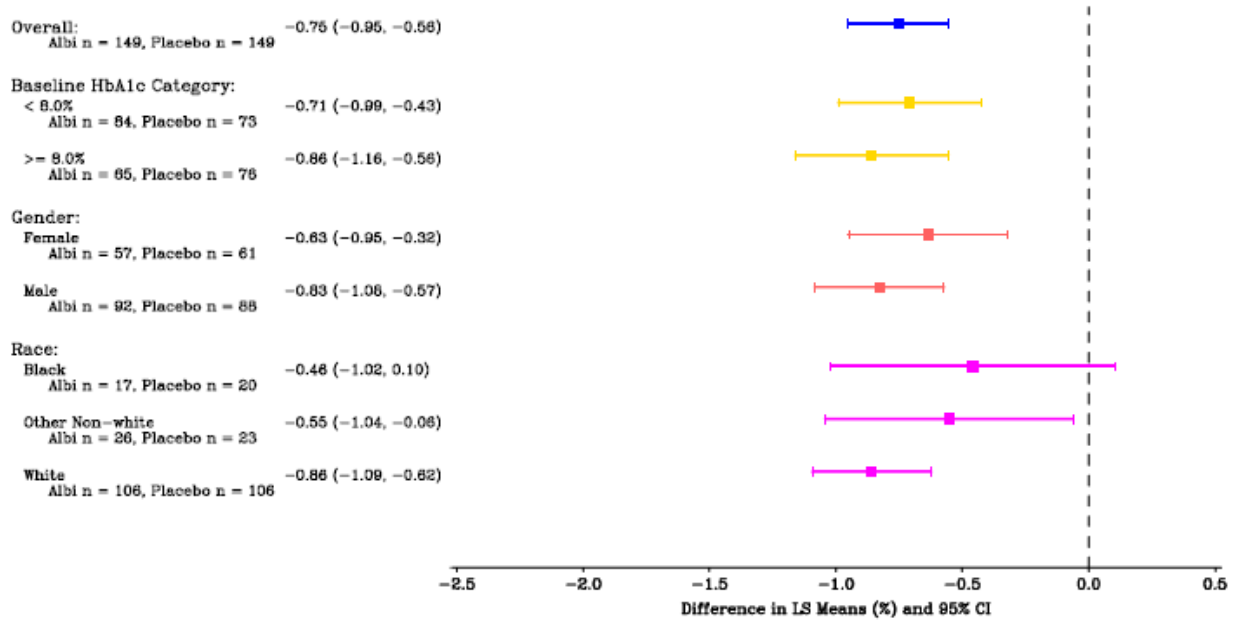
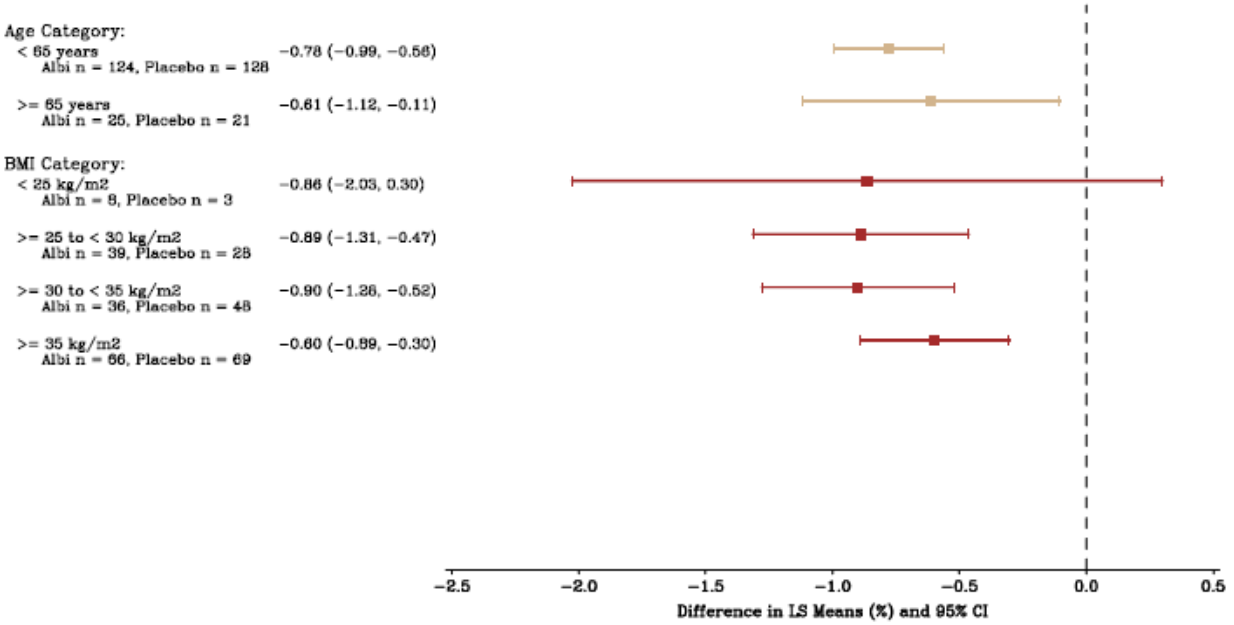
As seen from the following Forest plots, in two subgroups, the possibility of albiglutide being numerically inferior to placebo was not excluded. Obviously, these are the results of very long confidence intervals due to small sample sizes and are not dependable.

Forest Plot of Model-Adjusted Change From Baseline in HbA_{1c} (%) and 95% CI for Albiglutide Versus Placebo at Week 52 by Subgroup Category (Intent-to-Treat Population – LOCF)





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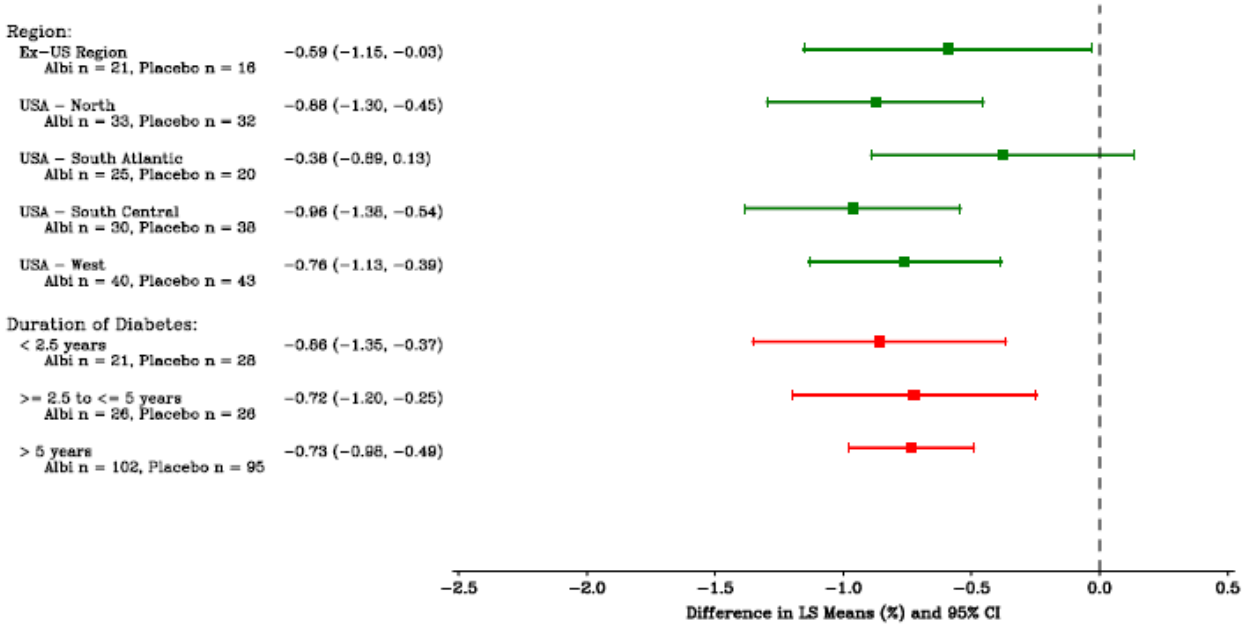

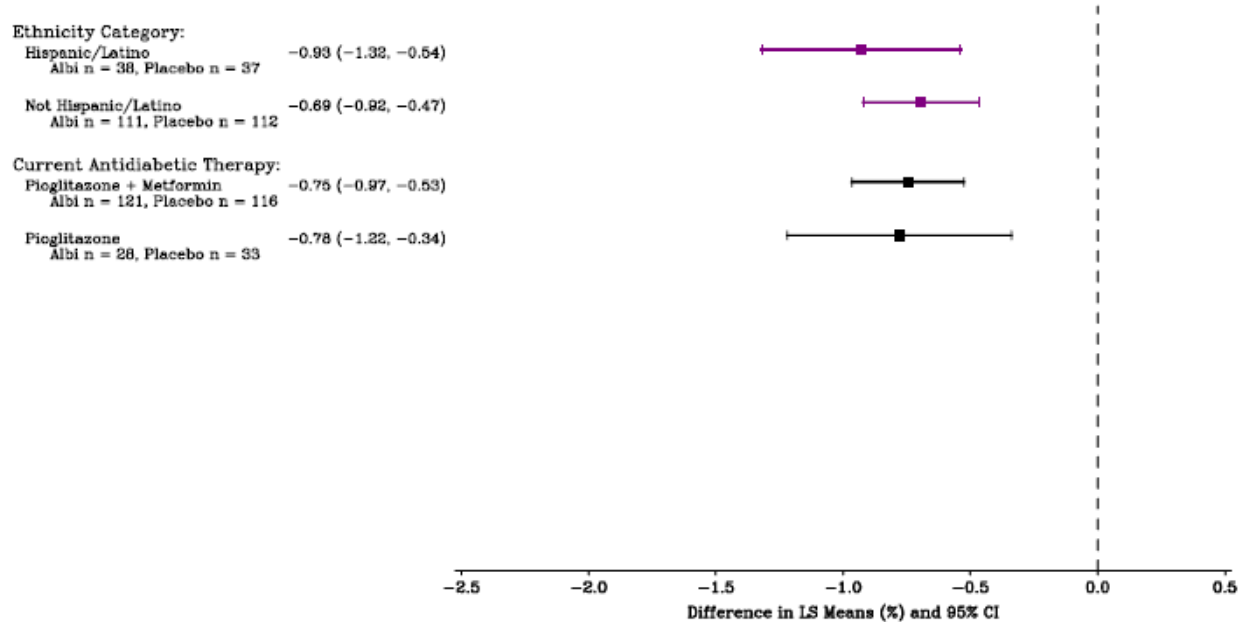

Albi = albiglutide; BMI = body mass index; CI = confidence interval; HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; LS = least squares.
Note: The difference on X-axis is the difference in the albiglutide least squares mean change from Baseline minus placebo least squares mean change from Baseline.

From the interaction p-values given by the sponsor, there were no statistically significant (<=.1) treatment by factor interaction p-values.

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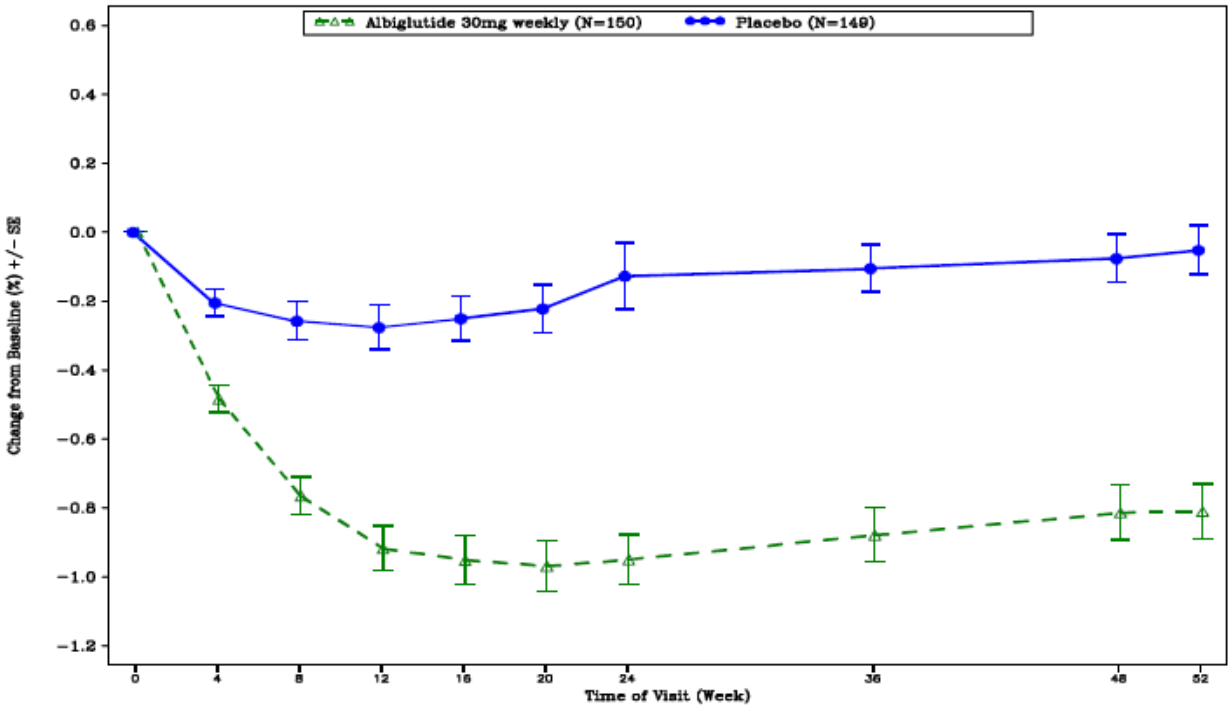
As seen from the following curves of responses, the superiority of albiglutide to placebo was shown almost immediately. However, the reduction from baseline in HBA1c for albiglutide started diminishing slightly from Week 24.

Line Graph of Mean (±SE) Change From Baseline in HbA_{1c} (%) Through Week 52 (Intent-to-Treat Population – LOCF)



HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; SE = standard error.

Mean Fasting Plasma Glucose (mmol/L) over time is provided in the following graph, while the results on change from baseline in FPG at Week 52 is given in the Table following the graph.

Line Graph of Mean (±SE) Fasting Plasma Glucose (mmol/L) Through Week 52 (Intent-to-Treat Population – LOCF)

As seen from the following graph, mean FPG started decreasing almost immediately in the albiglutide arm with almost no further decrease after Week 4. I wonder about the irregularities at Weeks 8 and 12 affecting both arms similarly (parallel), sudden increases at Week 8 in both groups and decreases at Week 12 in both groups. In the placebo arm, mean FPG started increasing slightly over time.

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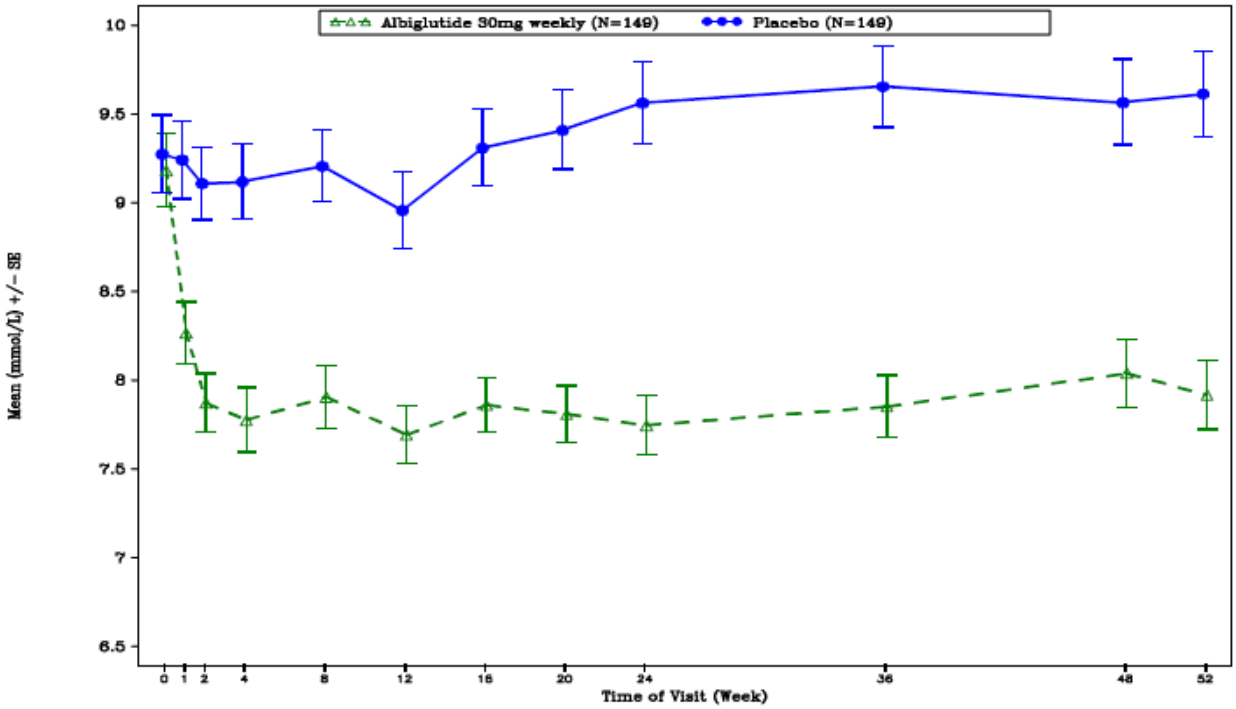
Line Graph of Mean (±SE) Fasting Plasma Glucose (mmol/L) Through Week 52 (Intent-to-Treat Population – LOCF)



LOCF = last observation carried forward; SE = standard error.

Analysis of Change From Baseline in Fasting Plasma Glucose (mmol/L) at Week 52 (Intent-to-Treat Population – LOCF)

As seen from the following Table, *statistical evidence for the efficacy of albiglutide 30 mg, with respect to FPG, has been provided.*

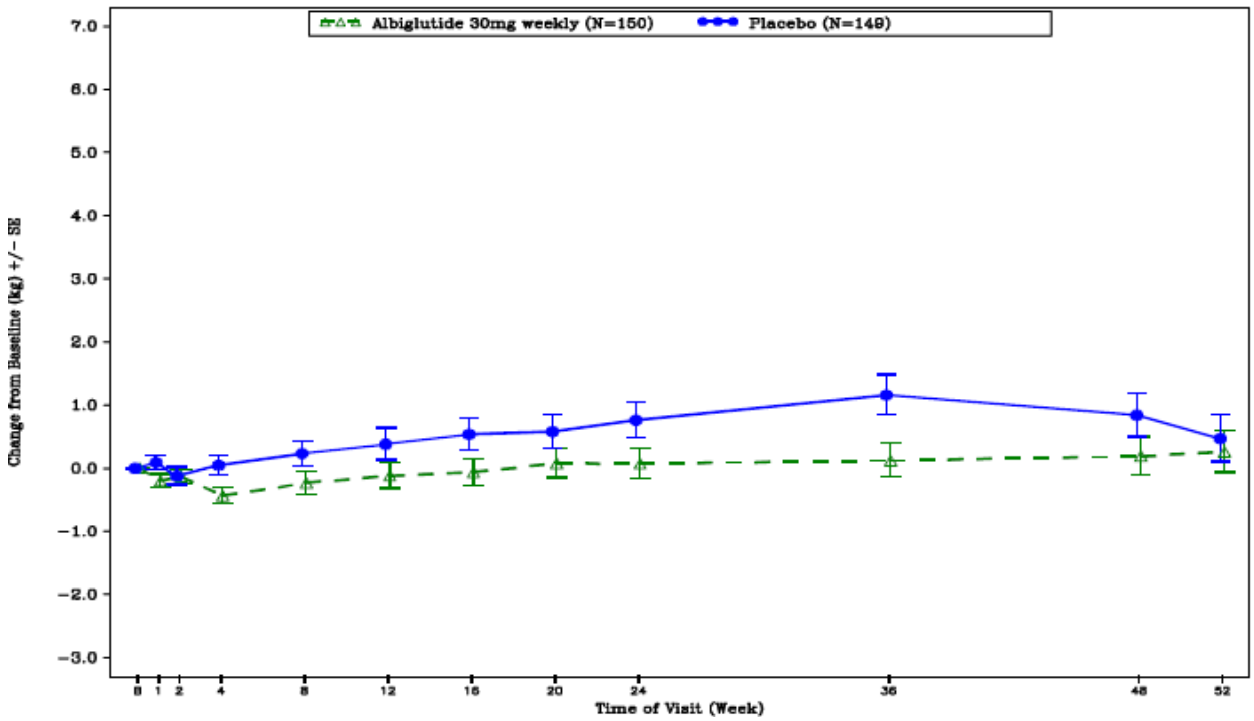
	Placebo (N=149)	Albiglutide 30 mg weekly (N=150)
Number of subjects[1]	149	149
Number (%) of values carried forward	87 (58.4)	48 (32.2)
Baseline mean (SD)	9.27 (2.65)	9.18 (2.51)
Week 52 mean (SD)	9.61 (2.96)	7.92 (2.40)
Model-adjusted change from Baseline[2]		
Least squares mean	0.35	-1.28
Standard error	0.197	0.197
95% confidence interval	(-0.03, 0.74)	(-1.67, -0.89)
Difference from placebo[2]		
Difference of least squares means		-1.64
95% confidence interval		-2.19, -1.09
p-value[3]		<0.0001

LOCF = last observation carried forward; SD = standard deviation.
Note: This analysis used the last observation carried forward (LOCF) method for missing postbaseline fasting plasma glucose (FPG) values. The FPG values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values.

1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on analysis of covariance (ANCOVA): Change = treatment + baseline FPG + prior myocardial infarction history + age category + region + current antidiabetic therapy. The difference of least squares means (albiglutide–placebo) was from the ANCOVA model.
3. The p-value is from a 2-sided *t* test for the difference in means.

Line Graph of Mean (±SE) Change From Baseline in Weight (kg) Through Week 52 (Intent-to-Treat Population – LOCF)

As seen from the following change from baseline in weight, weight remained almost unchanged at Week 52. However, before that time, weight increased slightly in the placebo group.



B = Baseline; LOCF = last observation carried forward; SE = standard error

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Analysis of Change From Baseline in Weight (kg) at Week 52 (Intent-to-Treat Population – LOCF)

As seen from the following analyses at Week 52, numerically, there was slight weight gain in both treatment arms, more in the placebo arm.

	Placebo (N=149)	Albiglutide 30 mg weekly (N=150)
Number of subjects[1]	149	149
Number (%) of values carried forward	87 (58.4)	47 (31.5)
Baseline mean (SD)	100.20 (23.253)	97.59 (22.079)
Week 52 mean (SD)	100.68 (23.814)	97.85 (21.839)
Change from Baseline - mean (SD)	0.47 (4.578)	0.26 (4.011)
Model-adjusted change from Baseline[2]		
Least squares mean	0.45	0.28
Standard error	0.348	0.348
95% confidence interval	(-0.23, 1.14)	(-0.41, 0.96)
Difference from placebo[2]		
Difference of least squares means		-0.18
95% confidence interval		(-1.15, 0.79)
p-value		0.7193

LOCF = last observation carried forward; SD = standard deviation.

Note: This analysis used the last observation carried forward (OCF) method for missing postbaseline weight values. Weight values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values.

1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on analysis of covariance (ANCOVA): Change = treatment + baseline weight + prior myocardial infarction history + age category + region + current antidiabetic therapy. The difference of least squares means (albiglutide – placebo) was from the ANCOVA model. The p-value was from a 2-sided t test for the difference in means.

§ Graphs of cumulative distribution functions by treatment groups for the primary efficacy variable (percent change from baseline in HbA1c) at the study endpoint are provided below. From these, the percent of patients (y-axis value) with a value of percent change from baseline in HbA1c at endpoint, smaller than or equal to a value on the x-axis, can be read.

Cumulative Distribution of HbA1c (%) Change from Baseline at Week 52 (Intent-to-treat Population- LOCF)

As seen from the following cumulative distributions, extreme reductions were far more in the albiglutide arm compared with placebo with respect to HBA1c but not with respect to FPG, though even with respect to FPG greater decreases were more frequent in the albiglutide arm than in the placebo arm, over the whole range of changes.

With respect to weight, there were no appreciable differences between the two treatment groups; the curves intersecting each other multiple times.

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Cumulative Distribution of HbA1c (%) Change from Baseline at Week 52 (Intent-to-treat Population- LOCF)

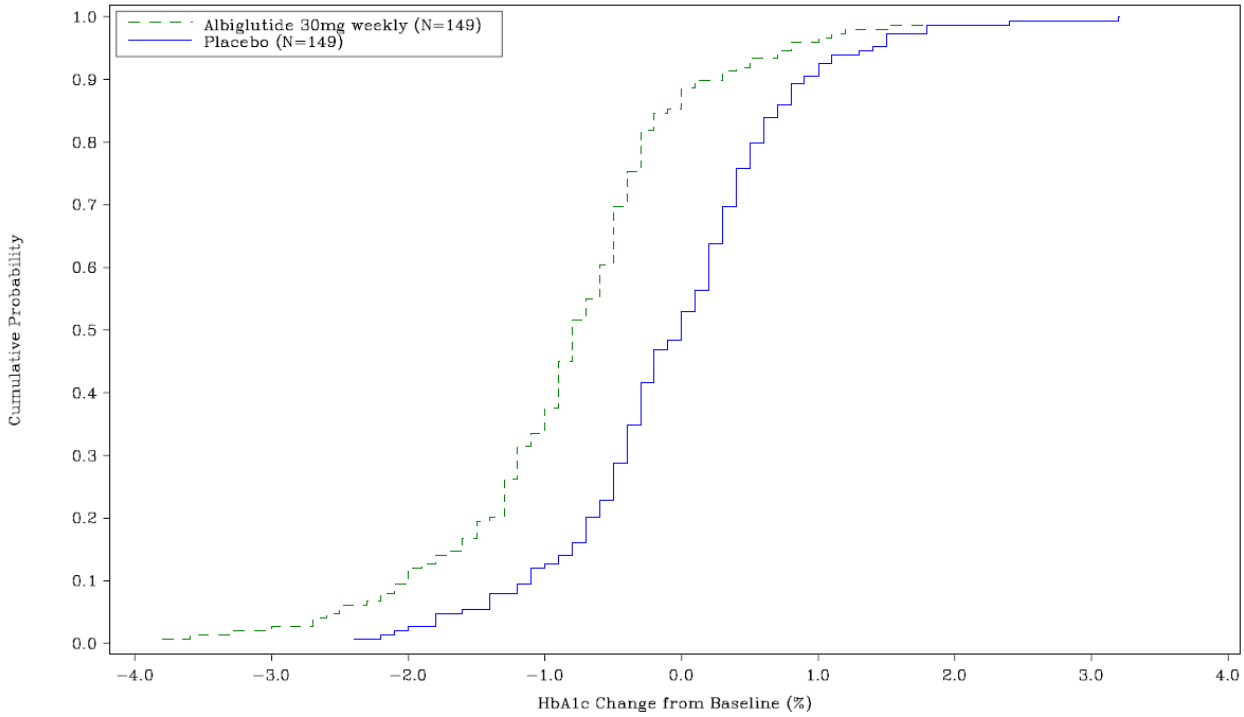

Table of Cumulative Distribution of HbA1c (%) Change from Baseline at Week 52
(Intent-to-treat Population - LOCF)

Percentile	Placebo (N=149)	Albiglutide 30mg weekly (N=150)
Number of subjects [1]	149	149
Min	-2.4	-3.8
1%	-2.20	-3.60
5%	-1.60	-2.50
10%	-1.10	-2.00
20%	-0.70	-1.40
30%	-0.40	-1.20
40%	-0.30	-0.90
50%	0.00	-0.80
60%	0.20	-0.60
70%	0.40	-0.40
80%	0.60	-0.30
90%	0.90	0.30
95%	1.40	0.80
99%	2.40	2.40
Max	3.2	2.8

Note: This summary uses the last observation carried forward (LOCF) method for missing post-baseline HbA1c values. HbA1c values obtained after hyperglycemia rescue are treated as missing and replaced with pre-rescue values. [1] Number of subjects with a value at Week 52.
[1] Number of subjects with a value at Week 52.

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Cumulative Distribution of Fasting Plasma Glucose (mg/dL) Change from Baseline at Week 52 (Intent-to-treat Population- LOCF)

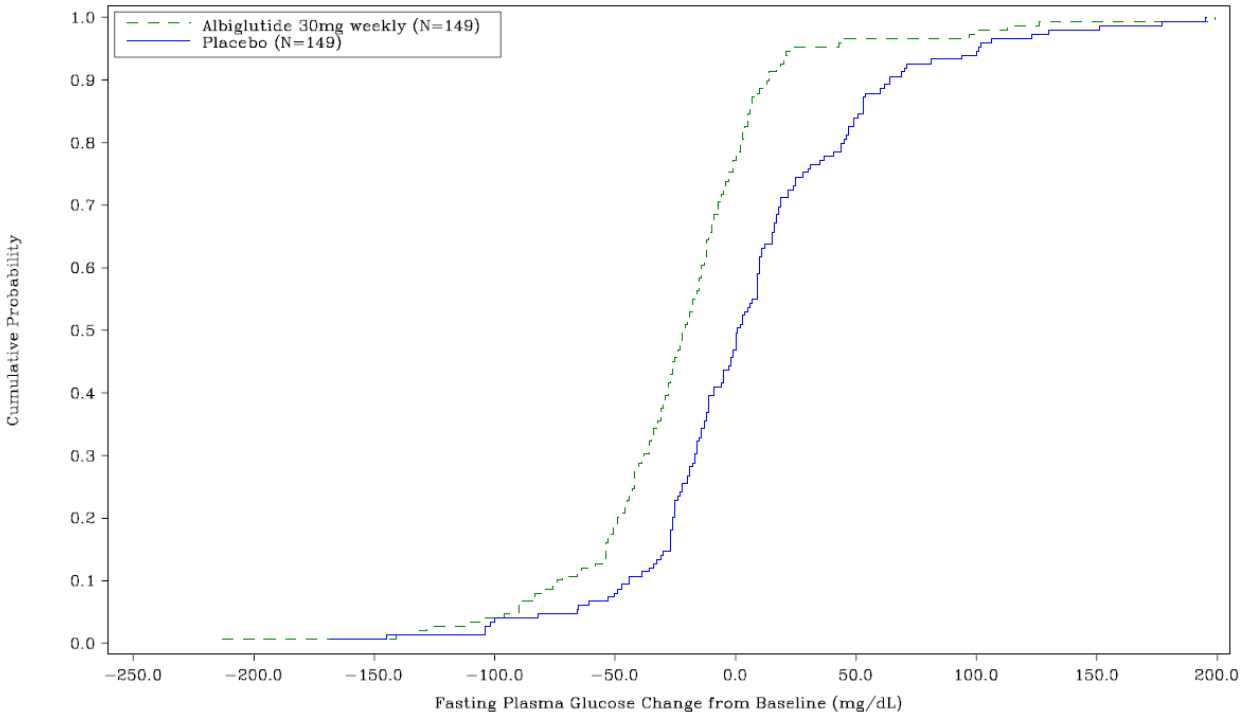

Table of Cumulative Distribution of Fasting Plasma Glucose (mg/dL) Change from Baseline at Week 52 (Intent-to-treat Population - LOCF)

Percentile	Placebo (N=149)	Albiglutide 30mg weekly (N=150)
Number of subjects [1]	149	149
Min	-168	-213
1%	-145.0	-141.0
5%	-66.0	-90.0
10%	-44.0	-74.0
20%	-26.0	-49.0
30%	-17.0	-38.0
40%	-9.0	-28.0
50%	1.0	-22.0
60%	10.0	-14.0
70%	19.0	-7.0
80%	45.0	2.0
90%	64.0	14.0
95%	101.0	23.0
99%	177.0	126.0
Max	195	199

Note: This summary uses the last observation carried forward (LOCF) method for missing post-baseline fasting plasma glucose (FPG) values. FPG values obtained after hyperglycemia rescue are treated as missing and replaced with pre-rescue values. [1] Number of subjects with a value at Week 52.

Reference ID: 3392698

Cumulative Distribution of Weight(kg) Change from Baseline at Week 52
(Intent-to-treat Population – LOCF)

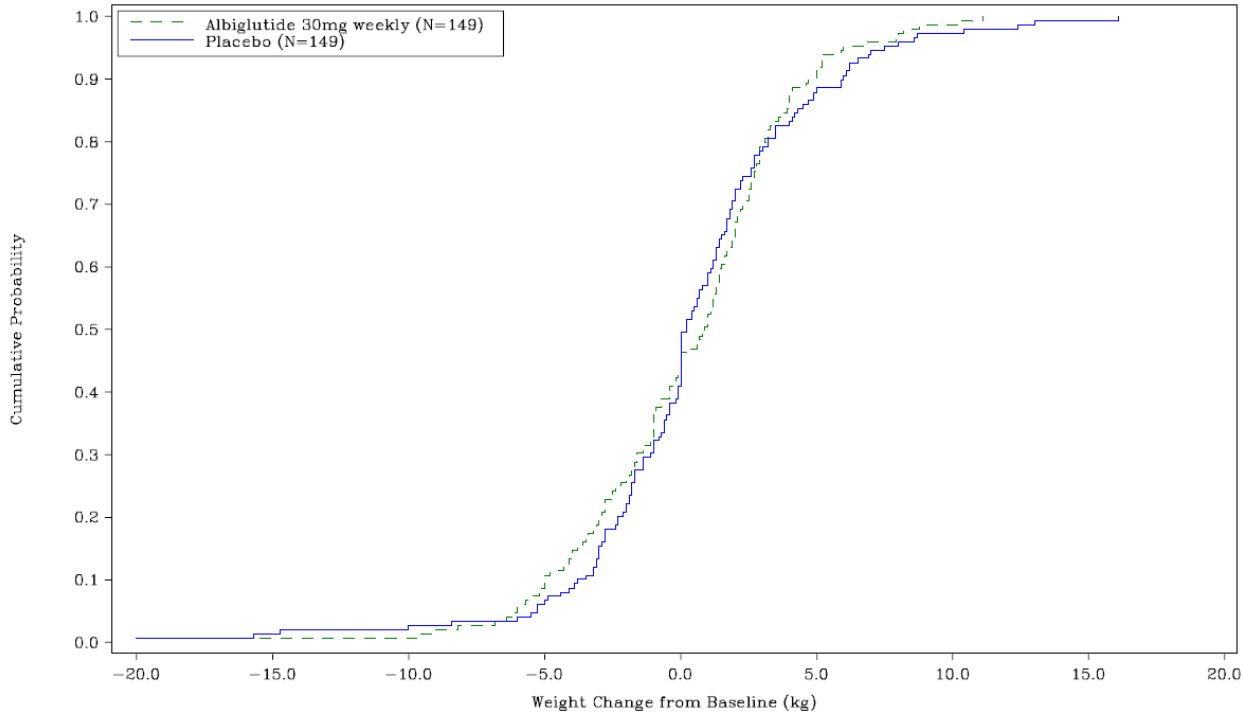

Table of Cumulative Distribution of Weight (kg) Change from Baseline at Week 52
(Intent-to-treat Population - LOCF)

Percentile	Placebo (N=149)	Albiglutide 30mg weekly (N=150)
Number of subjects [1]	149	149
Min	-20.0	-17.0
1%	-15.70	-9.70
5%	-5.30	-6.00
10%	-3.80	-5.00
20%	-2.30	-3.00
30%	-1.10	-1.60
40%	-0.10	-0.40
50%	0.20	0.90
60%	1.20	1.50
70%	1.90	2.40
80%	3.20	3.10
90%	6.00	5.00
95%	7.50	6.00
99%	13.00	10.20
Max	16.1	11.1

Note: This summary uses the last observation carried forward (LOCF) method for missing post-baseline weight values. Weight values obtained after hyperglycemia rescue are treated as missing and replaced with pre-rescue values.
[1] Number of subjects with a value at Week 52.

Reference ID: 3392698

STUDY GLP112756

Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Two Dose Levels of Albiglutide Compared With Placebo in Subjects With Type 2 Diabetes Mellitus

Study center(s): This study was conducted at 143 study centers in 2 countries.
Publication(s): None at the time of this report.

Study Period: 01-Apr-2009 – 17-Nov-2011

Phase of Development: III

Objectives: The primary objective of the study was to evaluate the efficacy of albiglutide as compared with placebo on HbA1c change from Baseline at Week 52.

Methodology: This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study of 170 weeks duration to evaluate the efficacy and safety of 2 dose levels (30 mg and 50 mg) of weekly subcutaneously injected albiglutide compared with placebo in subjects with type 2 diabetes mellitus (T2DM).

The study comprised 4 study periods: approximately 2 weeks of Prescreening and Screening; 4 weeks of Run-in/Stabilization; a 156-week Treatment Period including 52 weeks of initial treatment and evaluation for primary efficacy and safety followed by an additional 104 weeks of treatment for additional efficacy and safety; and 8 weeks of posttreatment follow-up. Subjects completed a minimum of 2 years of treatment, at which time the formal analysis for submission of regulatory marketing applications was completed. The study continued as a blinded study for up to 3 years. This Synopsis is concerned with the 2-year data.

Randomization was based on a sequestered fixed randomization schedule. Eligible subjects were stratified based on the HbA_{1c} level obtained at Visit 5 (<8.0% and ≥8.0%), history of prior myocardial infarction (MI) (yes versus no), and age (<65 years versus ≥65 years).

Number of subjects: Approximately 315 subjects were planned for randomization in a 1:1:1 ratio to 1 of 3 treatments. A total of 309 subjects were randomized: 102 in the albiglutide 30-mg group, 102 in the albiglutide 50-mg group, and 105 in the placebo group. At a subset of sites, a subgroup of approximately 55 subjects per treatment group was to undergo a mixed-meal tolerance test that was to be conducted at Baseline and Visit 19 (Week 52).

Statistical methods: The primary analysis of the HbA1c change from Baseline response at Week 26 was applied to the ITT Population using an analysis of covariance (ANCOVA) model with main effects for treatment group, region, history of prior MI, and age category as factors and with baseline HbA1c as a continuous covariate.

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To control for the potential inflation of the overall significance level due to multiple hypothesis testing, the hypotheses of treatment effects of 2 dose levels of study drug was evaluated using the order that prioritizes the comparison of high dose albiglutide versus placebo over the comparison of low dose albiglutide versus placebo.

Subjects who qualified for hyperglycemia rescue had their primary endpoint value of HbA1c change from Baseline recorded at the time of rescue. Follow up assessments continued beyond rescue, and postrescue HbA1c assessments were used in supportive efficacy analysis. Subjects who discontinued from active participation in the study (e.g., withdrew consent or were lost to glycemic follow up) had their last HbA1c observation carried forward for the primary analysis.

Using a 2-sided, 2-sample *t* test and a sequential test-wise significance level of 0.05, with 89 subjects in each albiglutide group, the albiglutide versus placebo comparison had at least a 91% power to reject the null hypothesis of no treatment benefit if the actual albiglutide treatment superiority was no smaller than 0.5% and the standard deviation for HbA_{1c} change from Baseline was no larger than 1.0%.

The other continuous secondary efficacy endpoints were analyzed analogously. The HbA1c change from Baseline at Week 52 and over time, and the FPG and body weight changes over time were each analyzed as secondary efficacy endpoints, with ANCOVA modeling analogous to the primary endpoint.

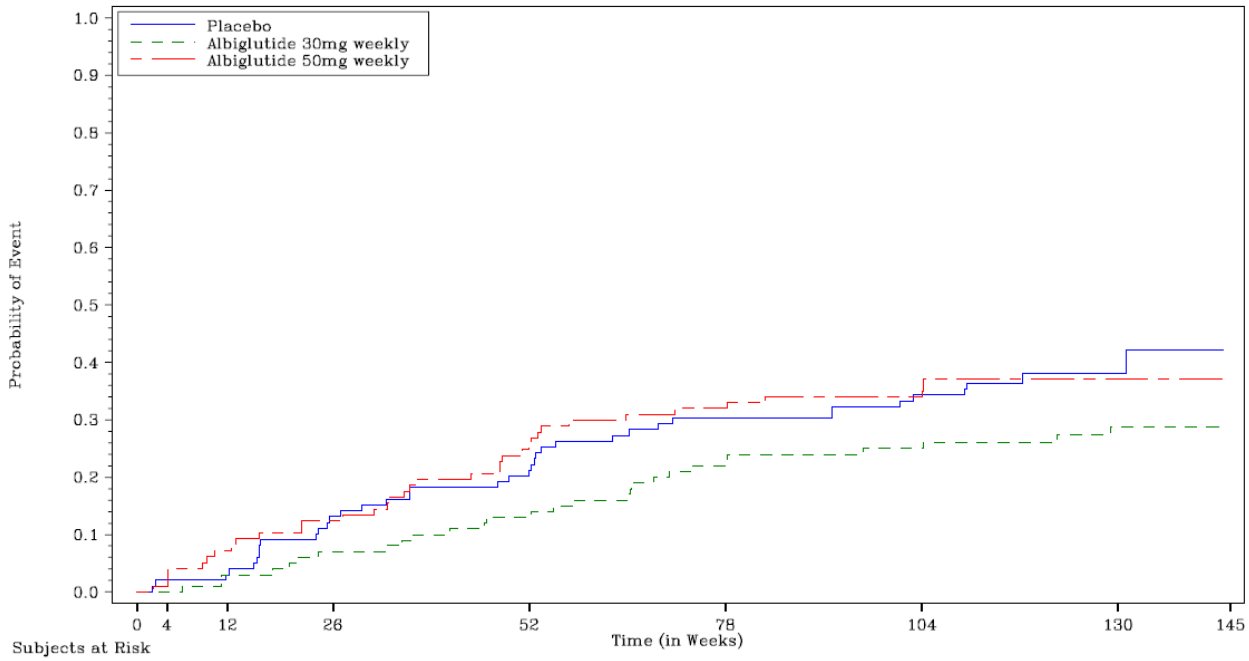
The mixed-meal tolerance test was to be evaluated by determining the change from Baseline in 2-hour postprandial glucose, 4-hour area under the curve above the baseline, maximum concentration (Cmax) of insulin, preinsulin and C-peptide. These parameters were to be analyzed using an ANCOVA model similar to that described for the primary endpoint.

Patient Disposition

As seen from the following Kaplan-Meier plots, the rate of dropout from the albiglutide 50 mg group due to adverse events was the highest. Dropout due to adverse event was only slightly higher in the 30 mg arm than the placebo arm (same after Week 112). Overall dropout rate was also the highest in the 50 mg arm but almost similar to that in the placebo arm and lowest in the 30 mg arm.

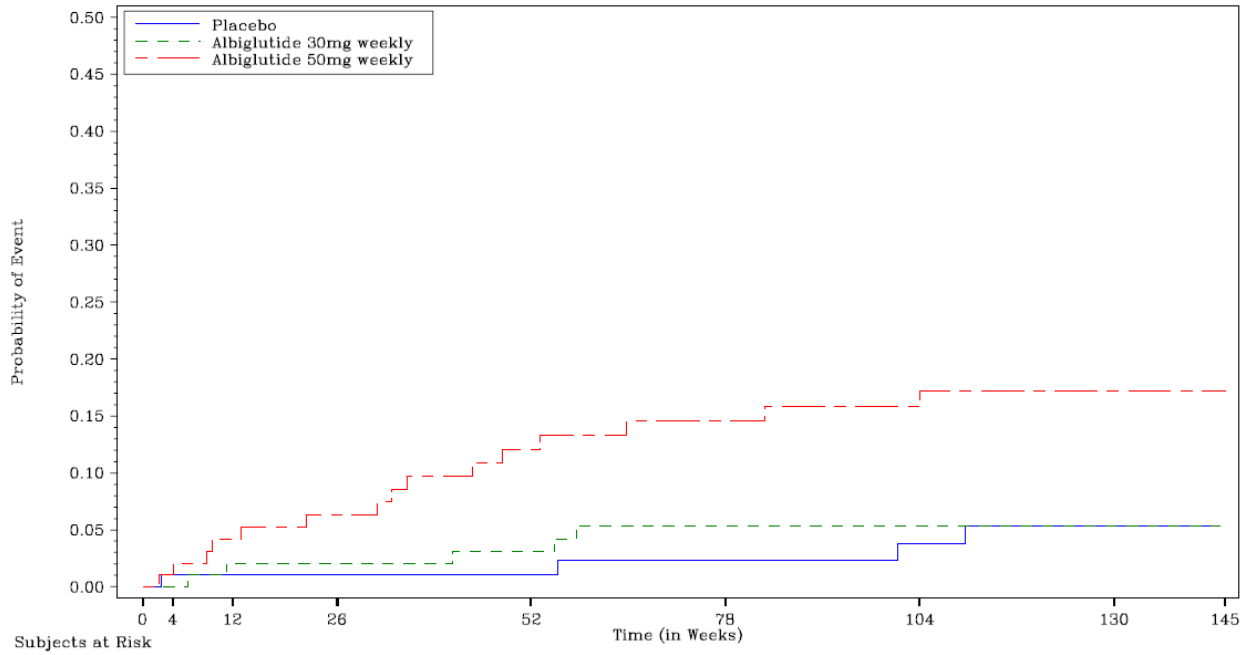
Reference ID: 3392698

Kaplan–Meier Plot of Time to Withdrawal from Active Treatment
(Intent–to–treat Population)



Subjects at Risk								
Placebo	99	96	86	79	69	65	37	0
30mg weekly	100	97	93	87	77	75	40	0
50mg weekly	97	90	85	72	66	64	31	1

Kaplan–Meier Plot of Time to Withdrawal from Active Treatment due to Adverse Event
(Intent–to–treat Population)



Subjects at Risk								
Placebo	99	96	86	79	69	65	37	0
30mg weekly	100	97	93	87	77	75	40	0
50mg weekly	97	90	85	72	66	64	31	1

Reference ID: 3392698

As seen from the following Table of demographics, in the three treatment arms Placebo, albiglutide30, and albiglutide50, respectively,

the mean age was 53.1, 53.6, and 52.0;
the percentage of male was 57. 4, 57.4, and 50.5;
the percentage of White was 78.2, 84.2, and 78.8;
the percentage of African was 13.9, 9.9, and 14.1;
the mean weight (kg) was 95.4, 95.7, and 97.1.

Demographics and Baseline Characteristics (Intent-to-treat Population)

	Placebo (N=99)	Albiglutide 30mg weekly (N=100)	Albiglutide 50mg weekly (N=97)	Total (N=296)
Age at Randomization (years)				
n	99	100	97	296
Mean	53.2	53.7	52.1	53.0
Standard Deviation	11.55	10.94	11.84	11.43
Median	53.0	54.0	53.0	53.0
Minimum	20	29	24	20
Maximum	78	79	78	79
p-value (Pairwise Comparison) [2]		0.7937	0.4960	
Age Category				
n	99	100	97	296
< 65 years	81 (81.8%)	84 (84.0%)	81 (83.5%)	246 (83.1%)
>= 65 years	18 (18.2%)	16 (16.0%)	16 (16.5%)	50 (16.9%)
p-value (Pairwise Comparison) [2]		0.6826	0.7552	
Sex				
n	99	100	97	296
Female	43 (43.4%)	43 (43.0%)	49 (50.5%)	135 (45.6%)
Male	56 (56.6%)	57 (57.0%)	48 (49.5%)	161 (54.4%)
p-value (Pairwise Comparison) [2]		0.9507	0.3206	
Ethnicity				
n	99	100	97	296
Hispanic/Latino	29 (29.3%)	30 (30.0%)	26 (26.8%)	85 (28.7%)
Not Hispanic/Latino	70 (70.7%)	70 (70.0%)	71 (73.2%)	211 (71.3%)

As seen from the following Table of baseline characteristics, the mean duration of diabetes in years was 4.3 in the placebo, 3.4 in the albiglutide30 group and was 4.2 in the albiglutide50 group.

Reference ID: 3392698

Demographics and Baseline Characteristics
(Intent-to-treat Population)

	Placebo (N=99)	Albiglutide 30mg weekly (N=100)	Albiglutide 50mg weekly (N=97)	Total (N=296)
Height (cm)				
n	99	100	97	296
Mean	169.53	168.05	169.22	168.93
Standard Deviation	10.745	10.677	11.053	10.806
Median	168.30	168.00	170.00	168.00
Minimum	144.8	143.5	146.0	143.5
Maximum	198.0	190.5	198.1	198.1
p-value (Pairwise Comparison) [2]		0.3312	0.8431	
Weight (kg)				
n	99	100	97	296
Mean	95.54	95.82	96.81	96.05
Standard Deviation	20.068	19.642	17.884	19.174
Median	94.30	93.65	95.50	94.55
Minimum	50.1	55.0	61.9	50.1
Maximum	162.0	153.8	142.2	162.0
p-value (Pairwise Comparison) [2]		0.9230	0.6416	
Body Mass Index (BMI) (kg/m2)				
n	99	100	97	296
Mean	33.07	33.75	33.80	33.54
Standard Deviation	5.397	5.108	5.582	5.356
Median	33.00	34.00	34.00	34.00
Minimum	22.0	21.0	22.0	21.0
Maximum	45.0	44.0	45.0	45.0

Demographics and Baseline Characteristics
(Intent-to-treat Population)

	Placebo (N=99)	Albiglutide 30mg weekly (N=100)	Albiglutide 50mg weekly (N=97)	Total (N=296)
Body Mass Index (BMI) Category				
n	99	100	97	296
< 25 kg/m2	3 (3.0%)	5 (5.0%)	3 (3.1%)	11 (3.7%)
>= 25 to < 30 kg/m2	26 (26.3%)	16 (16.0%)	22 (22.7%)	64 (21.6%)
>= 30 to < 35 kg/m2	33 (33.3%)	32 (32.0%)	28 (28.9%)	93 (31.4%)
>= 35 kg/m2	37 (37.4%)	47 (47.0%)	44 (45.4%)	128 (43.2%)
p-value (Pairwise Comparison) [2]		0.2558	0.7050	
Prior Myocardial Infarction (MI)				
n	99	100	97	296
Yes	4 (4.0%)	3 (3.0%)	2 (2.1%)	9 (3.0%)
No	95 (96.0%)	97 (97.0%)	95 (97.9%)	287 (97.0%)
p-value (Pairwise Comparison) [2]		0.7209	0.6827	
Baseline HbA1c (%)				
n	99	100	97	296
Mean	8.03	8.05	8.21	8.09
Standard Deviation	0.908	0.867	0.942	0.906
Median	7.80	7.80	8.10	7.90
Minimum	6.8	6.5	6.8	6.5
Maximum	10.5	10.2	10.3	10.5

Demographics and Baseline Characteristics
(Intent-to-treat Population)

	Placebo (N=99)	Albiglutide 30mg weekly (N=100)	Albiglutide 50mg weekly (N=97)	Total (N=296)
Baseline HbA1c Category				
n	99	100	97	296
< 8.0%	57 (57.6%)	55 (55.0%)	44 (45.4%)	156 (52.7%)
>= 8.0%	42 (42.4%)	45 (45.0%)	53 (54.6%)	140 (47.3%)
p-value (Pairwise Comparison) [2]		0.7142	0.0871	

Reference ID: 3392698

Duration of Diabetes Disease History
(Intent-to-treat Population)

	Placebo (N=99)	Albiglutide 30mg weekly (N=100)	Albiglutide 50mg weekly (N=97)	Total (N=296)
Duration (years) [2]				
n	99	100	97	296
Mean	4.126	3.391	4.227	3.911
Standard Deviation	3.9118	3.6721	4.5780	4.0705
Median	3.239	1.901	3.099	2.611
Minimum	0.04	0.01	0.04	0.01
Maximum	24.54	14.50	29.58	29.58
p-value (Pairwise Comparison) [3]		0.1732	0.8691	
Duration Category				
n	99	100	97	296
< 2.5 years	41 (41.4%)	59 (59.0%)	43 (44.3%)	143 (48.3%)
>= 2.5 to <= 5 years	26 (26.3%)	14 (14.0%)	22 (22.7%)	62 (20.9%)
> 5 years	32 (32.3%)	27 (27.0%)	32 (33.0%)	91 (30.7%)
p-value (Pairwise Comparison) [3]		0.0265 *	0.8350	

[1] P-value is for testing the null hypothesis that population values (means or proportions) are equal among treatment groups. All tests are two-sided. * indicates statistical significance at 0.05 level.
[2] To calculate duration from a partial diagnosis date, a missing month is imputed as January and a missing day is imputed as the first of the month.
[3] P-value from pairwise comparison is for testing the null hypothesis that population values (means or proportions) are equal between each albiglutide arm (albiglutide 30mg arm and albiglutide 50mg arm) and placebo arm. All tests are two-sided. * indicates statistical significance at 0.05 level.

Results and Conclusions

Primary Efficacy Endpoint

HbA_{1c} Change From Baseline at Week 52

Reviewer's Conclusion: Statistical evidence for the efficacy of both the doses of albiglutide has been provided.

Mean Baseline HbA_{1c} values were similar across treatment groups. A decrease in HbA_{1c} from Baseline to Week 52 was observed in both albiglutide groups while an increase was observed in the placebo group. When baseline HbA_{1c}, history of prior MI, age category, and region, the model-adjusted LS mean change in HbA_{1c} from Baseline to Week 52 was -0.70% in the albiglutide 30-mg group, -0.89% in the albiglutide 50-mg group, and 0.15% in the placebo group. The treatment differences (albiglutide minus placebo) of -0.84% (95% CI: -1.11%, -0.58%) for the albiglutide 30-mg group, and -1.04% (95% CI: -1.31, -0.77%) for the albiglutide 50-mg group were both statistically significant ($p<0.0001$), indicating superiority over placebo.

Reference ID: 3392698

HbA_{1c} Change From Baseline at Week 52

	Placebo (N=99) n (%)	Albiglutide 30 mg Weekly (N=100) n (%)	Albiglutide 50 mg Weekly (N=97) n (%)
Number of subjects[1]	98	100	97
Number (%) of values carried forward	62 (63.3)	34 (34.0)	40 (41.2)
Baseline – mean (SD)	8.02 (0.908)	8.05 (0.867)	8.21 (0.942)
Week 52 – mean (SD)	8.20 (1.458)	7.35 (1.150)	7.29 (1.104)
Change from Baseline – mean (SD)	0.18 (0.942)	-0.70 (1.009)	-0.92 (0.946)
Model-adjusted change from Baseline[2]			
LS mean (SE)	0.15 (0.097)	-0.70 (0.096)	-0.89 (0.097)
95% CI	(-0.04, 0.34)	(-0.89, -0.51)	(-1.08, -0.70)
Difference from placebo[2]			
Difference of LS means		-0.84	-1.04
95% CI		(-1.11, -0.58)	(-1.31, -0.77)
P-values for sequentially ordered hypotheses			
Superiority over placebo[3]		<0.0001	<0.0001

CI = confidence interval; HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; SE = standard error.

Note: This analysis used the LOCF method for missing postbaseline HbA_{1c} values. The glycosylated hemoglobin (HbA_{1c}) values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values. One ITT subject had all postbaseline HbA_{1c} measurements occur more after hyperglycemia rescue. This subject is included in the header ITT Population counts but does not contribute to any of the ITT efficacy summaries.

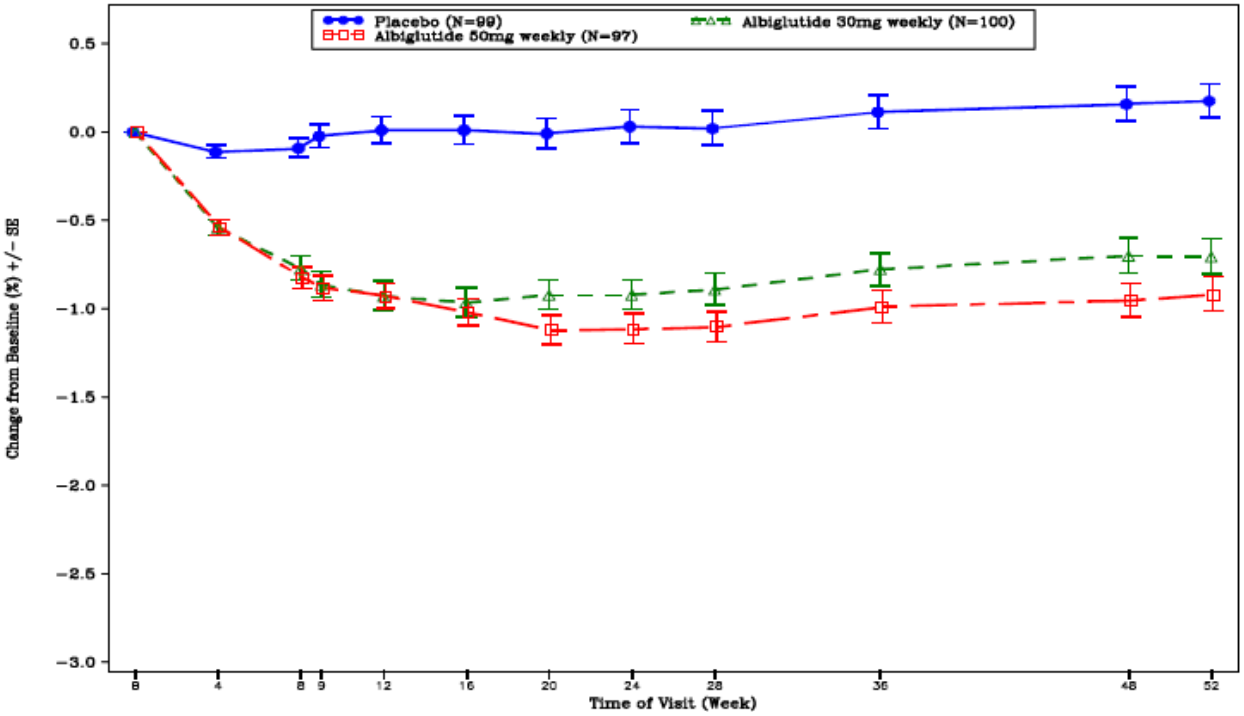
1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on analysis of covariance (ANCOVA): Change = treatment + baseline HbA_{1c} + prior myocardial infarction (MI) history + age category + region. Difference of least squares means (albiglutide – placebo) from ANCOVA model.
3. This p-value is for superiority testing of albiglutide 50 mg over placebo (or albiglutide 30 mg over placebo) at the 0.05 level. The p-value is from 2-sided *t* tests to test whether the difference of least square means (albiglutide 50 mg – placebo, albiglutide 30 mg – placebo) is equal to 0. If the superiority testing of albiglutide 50 mg over placebo was not significant, no superiority testing of albiglutide 30 mg over placebo was performed and the p-value was not applicable.

Line Graph of Mean Change From Baseline in HbA_{1c} (%) Through Week 52 (Intent-to-Treat Population - LOCF)

As seen from the following graph, HBA1c increased slightly in the placebo group and decreased a lot in the albiglutide groups, with more decrease in the 50 mg group. These decreases occurred within Week 20, with no further decrease after that.

Reference ID: 3392698

Line Graph of Mean Change From Baseline in HbA_{1c} (%) Through Week 52 (Intent-to-Treat Population - LOCF)



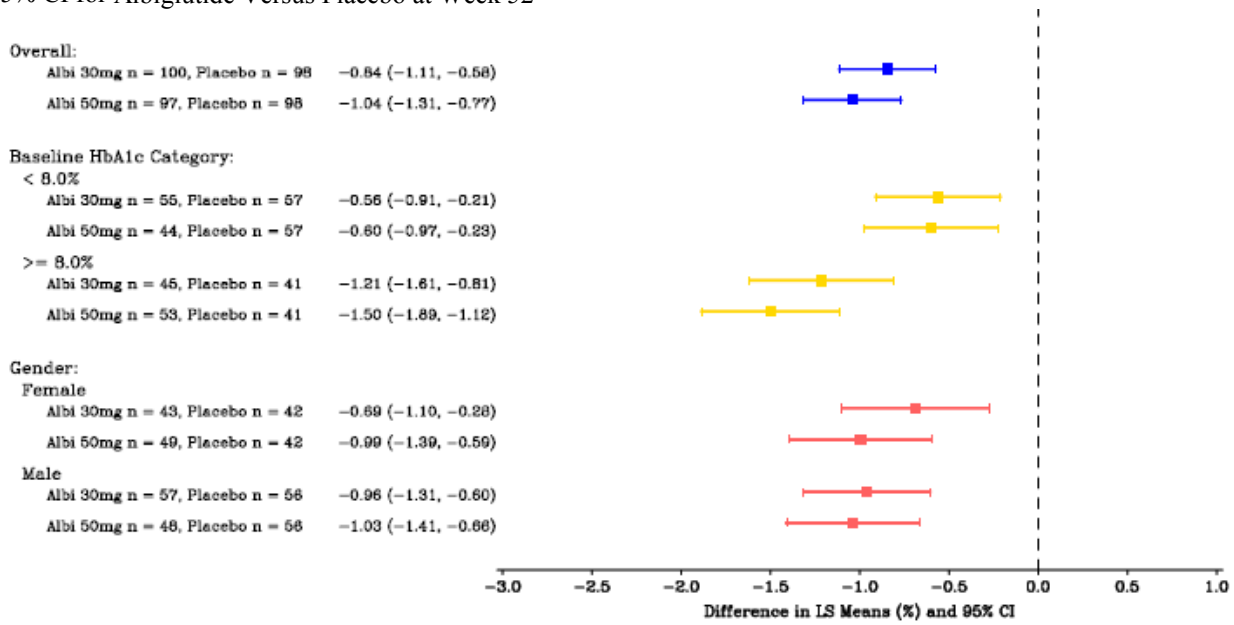
Note: Values to the left of the vertical line favor albiglutide over placebo.
B = Baseline, HbA_{1c} = glycosylated hemoglobin, ITT = intent-to-treat, LOCF =last observation carried forward.

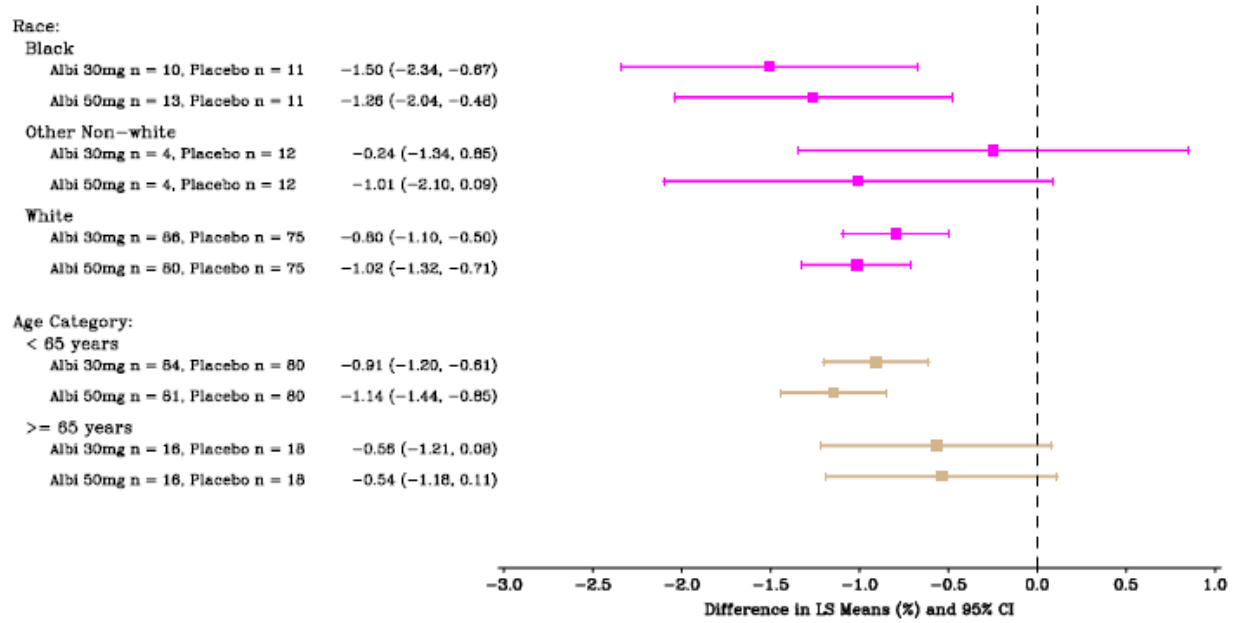
Forest Plots of the Difference of Least Squares Mean Model-Adjusted Change From Baseline in HbA_{1c} (%) and 95% CI for Albiglutide Versus Placebo at Week 52 by Subgroup Category (Intent-to-Treat Population – LOCF)

There was a statistically significant Treatment by Baseline HbA1c (<8.0, >=8.0) (p=0.0032) interaction, with smaller effects in the <8 group.

Reference ID: 3392698

Forest Plots of the Difference of Least Squares Mean Model-Adjusted Change From Baseline in HbA_{1c} (%) and 95% CI for Albiglutide Versus Placebo at Week 52





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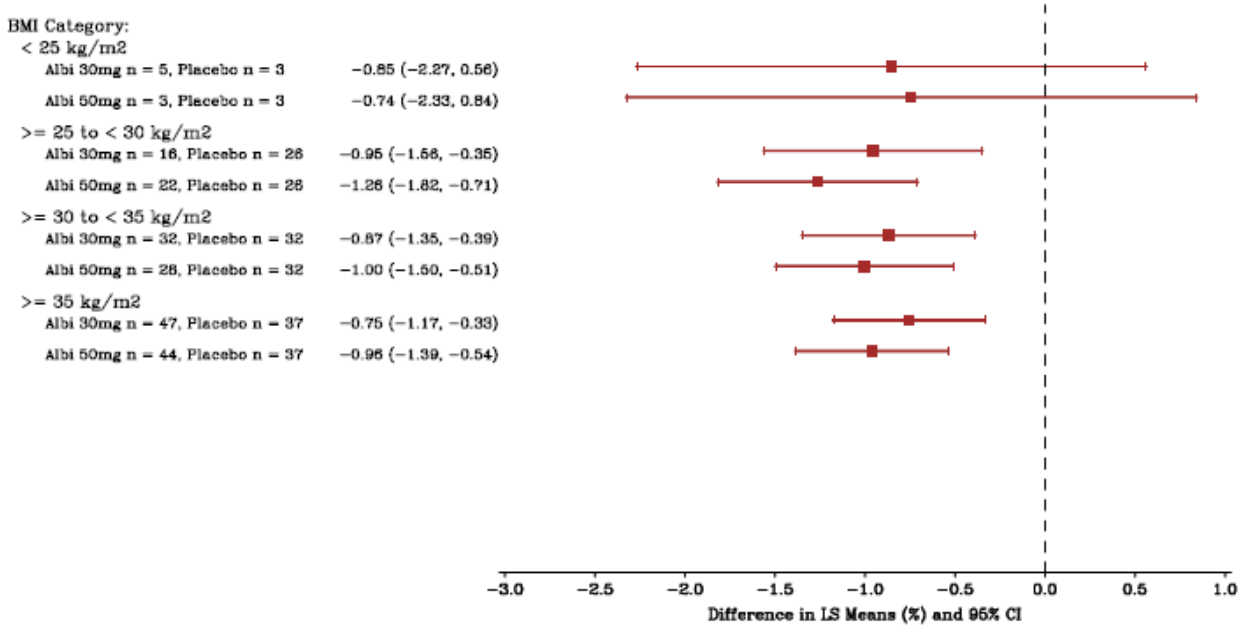
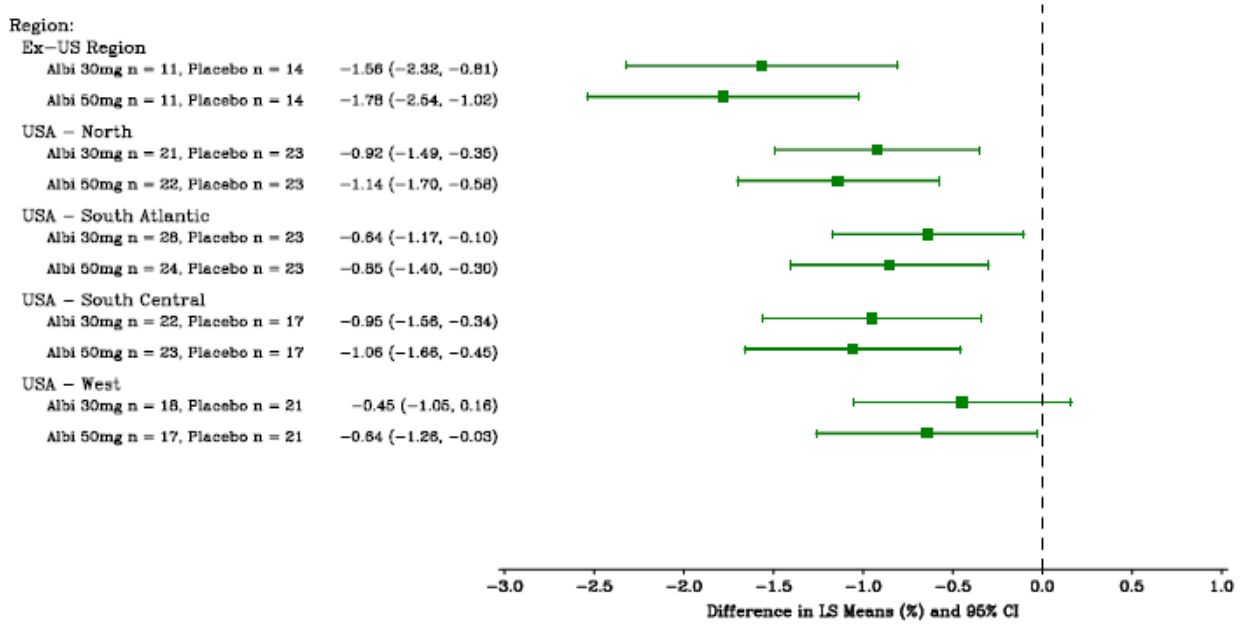
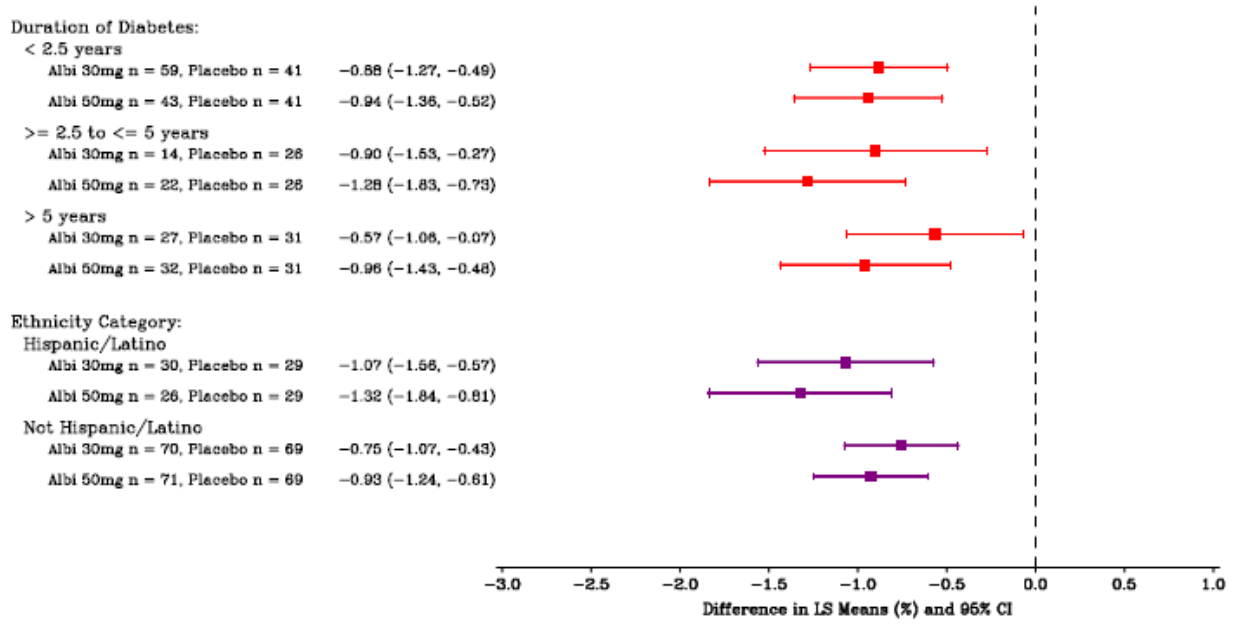




Reference ID: 3392698



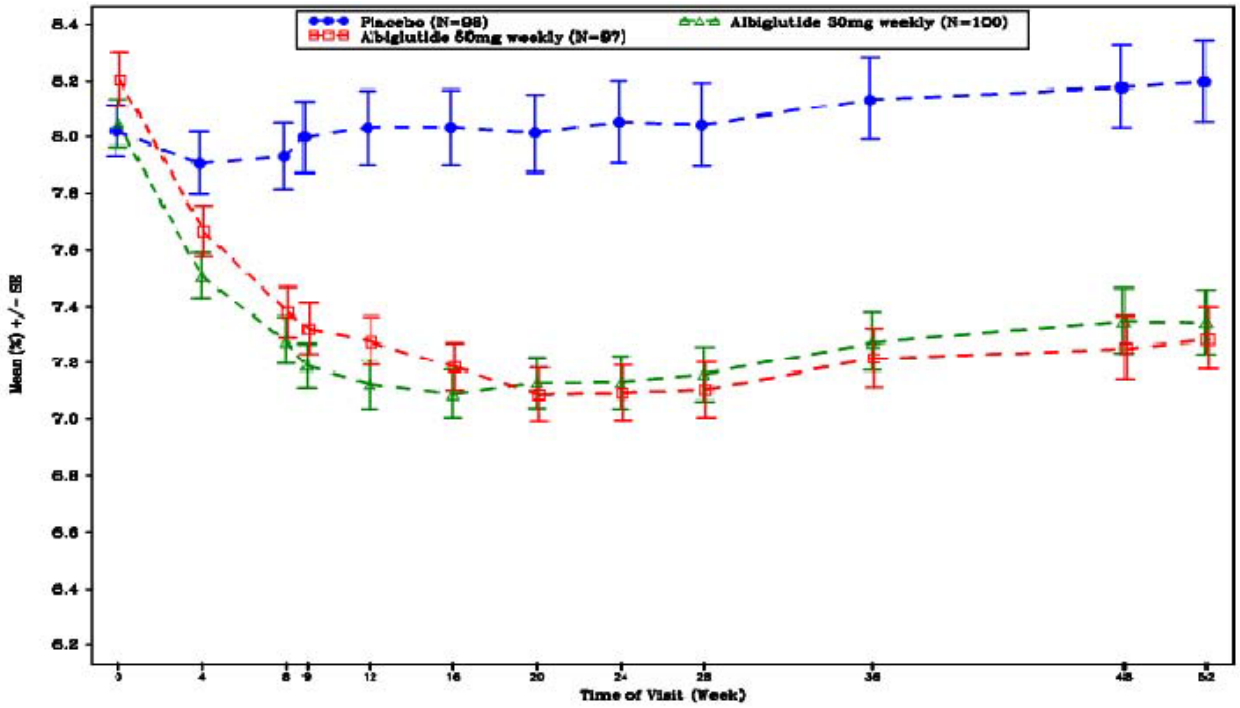
Albi = albiglutide; BMI = body mass index; CI = confidence interval; HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; LS = least squares
Note: The difference on the X-axis is the difference in the albiglutide least squares mean change from Baseline minus the placebo least squares mean change from Baseline.

Line Graph of Mean HbA_{1c} (%) Through Week 52 (Intent-to-Treat Population - LOCF)

As seen from the following graph, the two albiglutide arms were parallel (similar drops in HBA1c) up to Week 16. At Week 20, the two curves crossed and the drop in HBA1c in the 50 mg arm was larger.

Reference ID: 3392698

Line Graph of Mean HbA_{1c} (%) Through Week 52 (Intent-to-Treat Population - LOCF)



HbA_{1c} – glycosylated hemoglobin; LOCF – last observation carried forward; SE = standard error.

Reference ID: 3392698

Analysis of Change From Baseline in Fasting Plasma Glucose (mmol/L) at Week 52 (Intent-to-Treat Population – LOCF)

As seen from the following Table of results, statistical evidence for the efficacy of both the doses of albiglutide with respect to change from baseline in FPG has been provided.

	Placebo (N=99)	Albiglutide 30 mg Weekly (N=100)	Albiglutide 50 mg Weekly (N=97)
Number of subjects[1]	99	100	97
Number (%) of values carried forward	63 (63.6)	34 (34.0)	41 (42.3)
Baseline – mean (SD)	9.07 (2.372)	9.09 (2.309)	9.51 (2.400)
Week 52 – mean (SD)	10.12 (3.414)	8.21 (2.503)	8.07 (2.762)
Change from Baseline – mean (SD)	1.05 (2.399)	-0.88 (2.593)	-1.44 (2.673)
Model-adjusted change from Baseline[2]			
LS mean (SE)	1.00 (0.239)	-0.88 (0.237)	-1.38 (0.241)
95% CI	(0.53, 1.47)	(-1.35, -0.42)	(-1.85, -0.90)
Difference from placebo[2]			
Difference of LS means		-1.89	-2.38
95% CI		(-2.55, -1.22)	(-3.05, -1.71)
P-values for sequentially ordered hypotheses			
Superiority over placebo[3]		<0.0001	<0.0001

CI = confidence interval; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; SE = standard error.

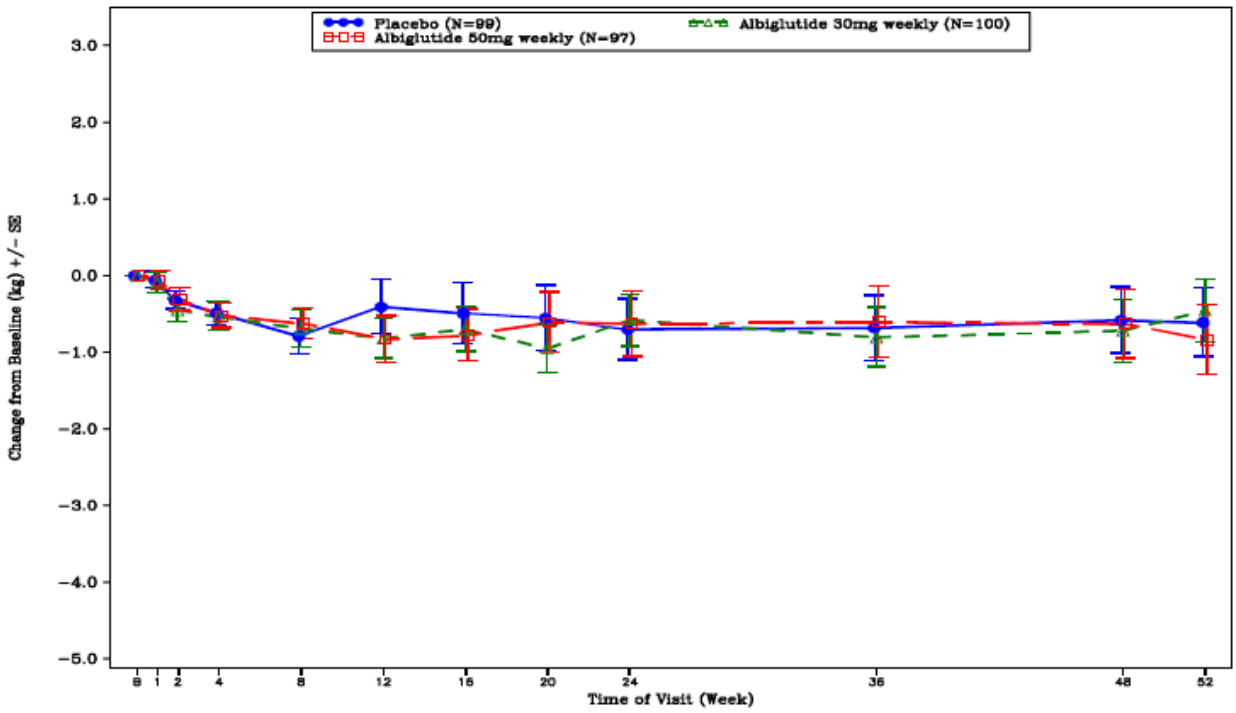
Note: This analysis used the LOCF method for missing postbaseline fasting plasma glucose (FPG) values. The FPG values obtained after hyperglycemia rescue are treated as missing and replaced with prerescue values.

1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on analysis of covariance (ANCOVA): Change = treatment + baseline FPG + baseline HbA_{1c} category + prior myocardial infarction history + age category + region. Difference of least squares means (albiglutide – placebo) from ANCOVA model.
3. This p-value is for superiority testing of albiglutide 50 mg over placebo (or albiglutide 30 mg over placebo) at 0.05 level. The p-value is from a 2-sided *t* test to test whether the difference of least square means (albiglutide 50 mg – placebo, albiglutide 30 mg – placebo) is equal to zero. If the superiority test for the HbA_{1c} treatment comparison of (albiglutide 50 mg – placebo) was not significant, then no superiority test was performed and the p-value was not applicable. If the superiority test for the HbA_{1c} treatment comparison of (albiglutide 30 mg – placebo) was not significant, then the superiority testing of (albiglutide 30 mg – placebo) for FPG was not performed and the p-value was not applicable.

Reference ID: 3392698

As seen from the following graph and Table, *there were reductions in weight in all arms; most in Albiglutide 50 mg (statistically significant reduction), then placebo, and the least in albiglutide 30 mg.*

Line Graph of Mean (+/- SE) Change From Baseline in Weight (kg) Through Week 52 (Intent-to-Treat Population – LOCF)



B = baseline; LOCF = last observation carried forward; SE = standard error.

Reference ID: 3392698

Analysis of Change From Baseline in Weight (kg) at Week 52 (Intent-to-Treat Population – LOCF)

	Placebo (N=99)	Albiglutide 30 mg Weekly (N=100)	Albiglutide 50 mg Weekly (N=97)
Number of subjects[1]	99	100	97
Number (%) of values carried forward	63 (63.6)	35 (35.0)	40 (41.2)
Baseline – mean (SD)	95.54 (20.068)	95.82 (19.642)	96.81 (17.884)
Week 52 – mean (SD)	94.93 (20.086)	95.36 (19.862)	95.97 (18.136)
Change from Baseline – mean (SD)	-0.61 (4.408)	-0.46 (4.084)	-0.84 (4.403)
Model-adjusted change from Baseline[2]			
LS mean (SE)	-0.66 (0.428)	-0.39 (0.424)	-0.86 (0.432)
95% confidence interval	(-1.50, 0.18)	(-1.22, 0.45)	(-1.71, -0.01)
Difference from placebo[2]			
Difference of LS means		0.27	-0.20
95% confidence interval		(-0.91, 1.46)	(-1.40, 1.01)
p-values		0.6526	0.7485

LOCF = last observation carried forward; LS = least squares; SD = standard deviation.

Note: This analysis used the LOCF method for missing postbaseline weight values. Weight values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values.

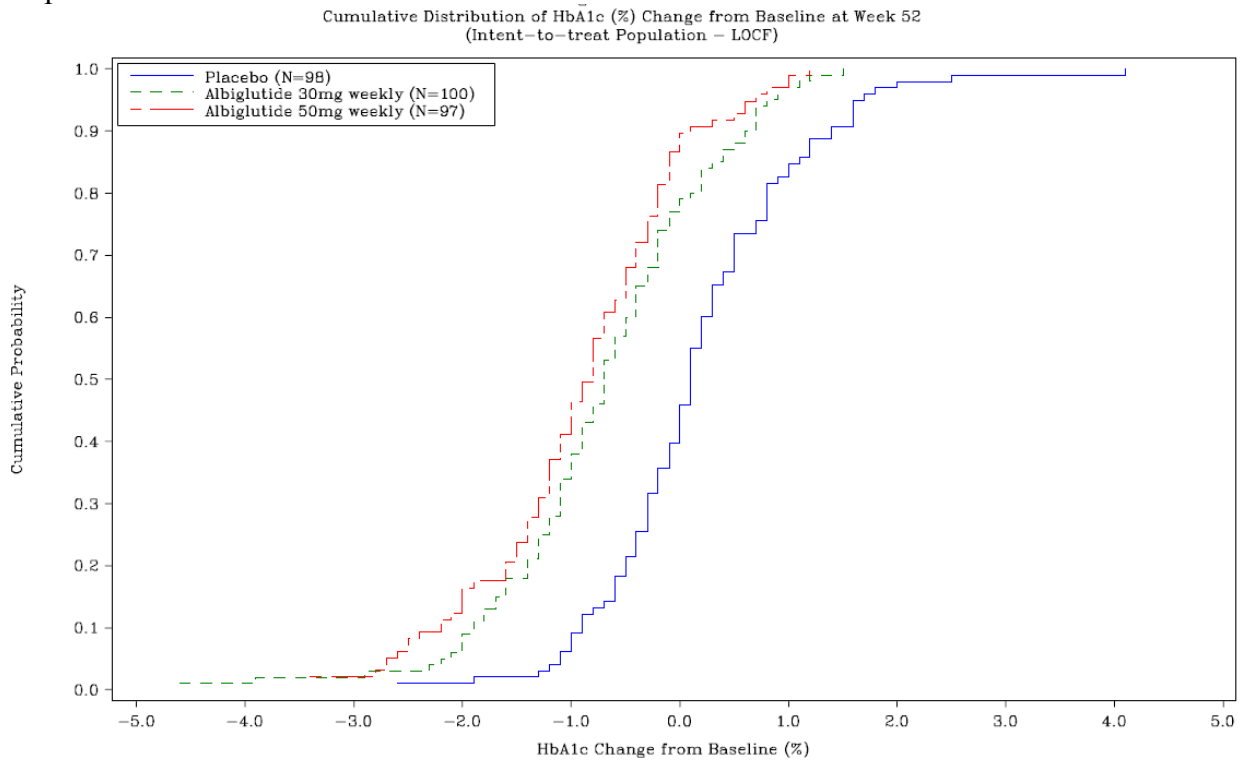
1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on analysis of covariance (ANCOVA): Change = treatment + baseline weight + baseline glycosylated hemoglobin category + prior myocardial infarction history + age category + region. Difference of least squares means (albiglutide - placebo) from ANCOVA model. The p-value was from a 2-sided *t* test for the difference in means.

§ Graphs of cumulative distribution functions by treatment groups for the primary efficacy variable (percent change from baseline in HbA1c) at the study endpoint are provided below. From these, the percent of patients (y-axis value) with a value of percent change from baseline in HbA1c at endpoint, smaller than or equal to a value on the x-axis, can be read.

As seen from the following cumulative distribution function, the percent of decreases in HBA1c was the smallest in the placebo group and the largest in the 50 mg group with that for the 30 mg group being very near to 50 mg group.

Reference ID: 3392698

Graph



Table

Cumulative Distribution of HbA1c (%) Change from Baseline at Week 52
(Intent-to-treat Population - LOCF)

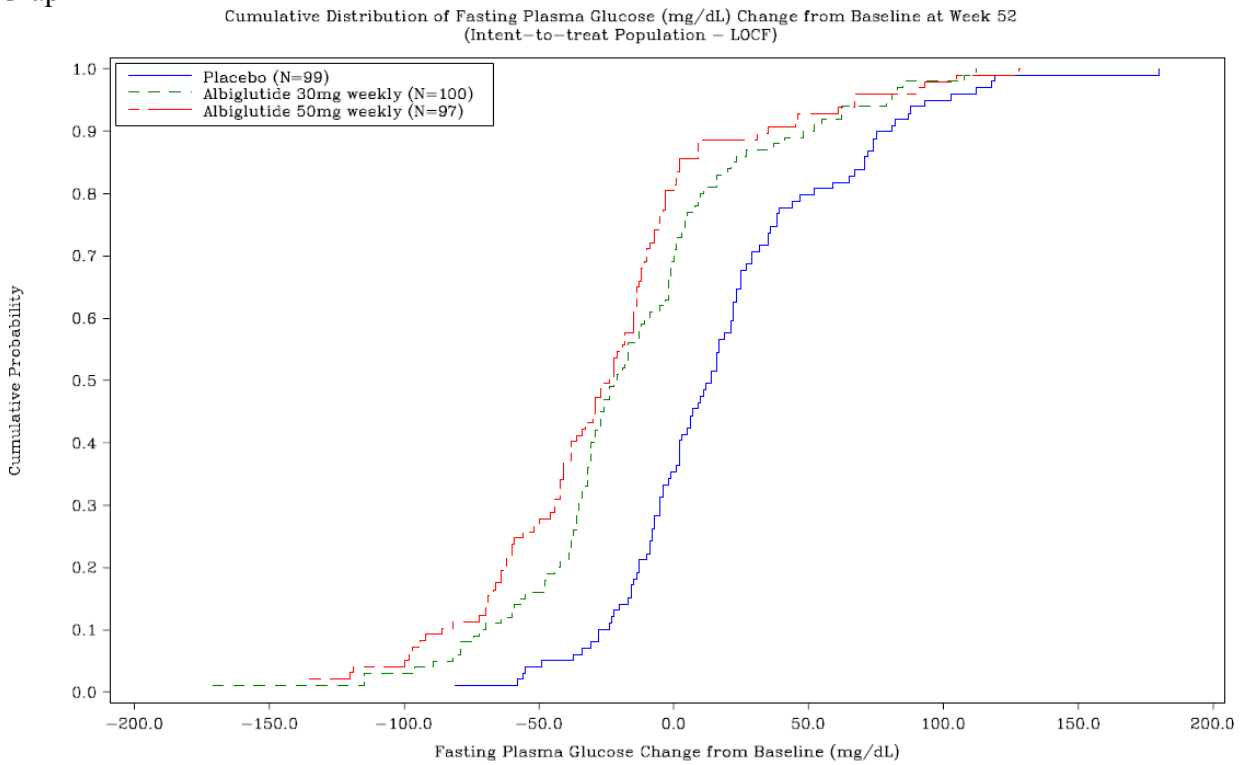
Percentile	Placebo (N=99)	Albiglutide 30mg weekly (N=100)	Albiglutide 50mg weekly (N=97)
Number of subjects [1]	98	100	97
Min	-2.6	-4.6	-3.4
1%	-2.60	-4.25	-3.40
5%	-1.10	-2.15	-2.70
10%	-0.90	-1.90	-2.20
20%	-0.50	-1.40	-1.60
30%	-0.30	-1.10	-1.30
40%	0.00	-0.90	-1.10
50%	0.10	-0.70	-0.80
60%	0.20	-0.45	-0.70
70%	0.50	-0.20	-0.40
80%	0.80	0.15	-0.20
90%	1.40	0.65	0.10
95%	1.70	0.85	0.70
99%	4.10	1.35	1.20
Max	4.1	1.5	1.2

Note: This summary uses the last observation carried forward (LOCF) method for missing post-baseline HbA1c values. HbA1c values obtained after hyperglycemia rescue are treated as missing and replaced with pre-rescue values.
[1] Number of subjects with a value at Week 52.

As seen from the following cumulative distribution function, the percent of decreases in FPG was the smallest in the placebo group and the largest in the 50 mg group with that for the 30 mg group being very near to 50 mg group.

Reference ID: 3392698

Graph



Table

Cumulative Distribution of Fasting Plasma Glucose (mg/dL) Change from Baseline at Week 52
(Intent-to-treat Population - LOCF)

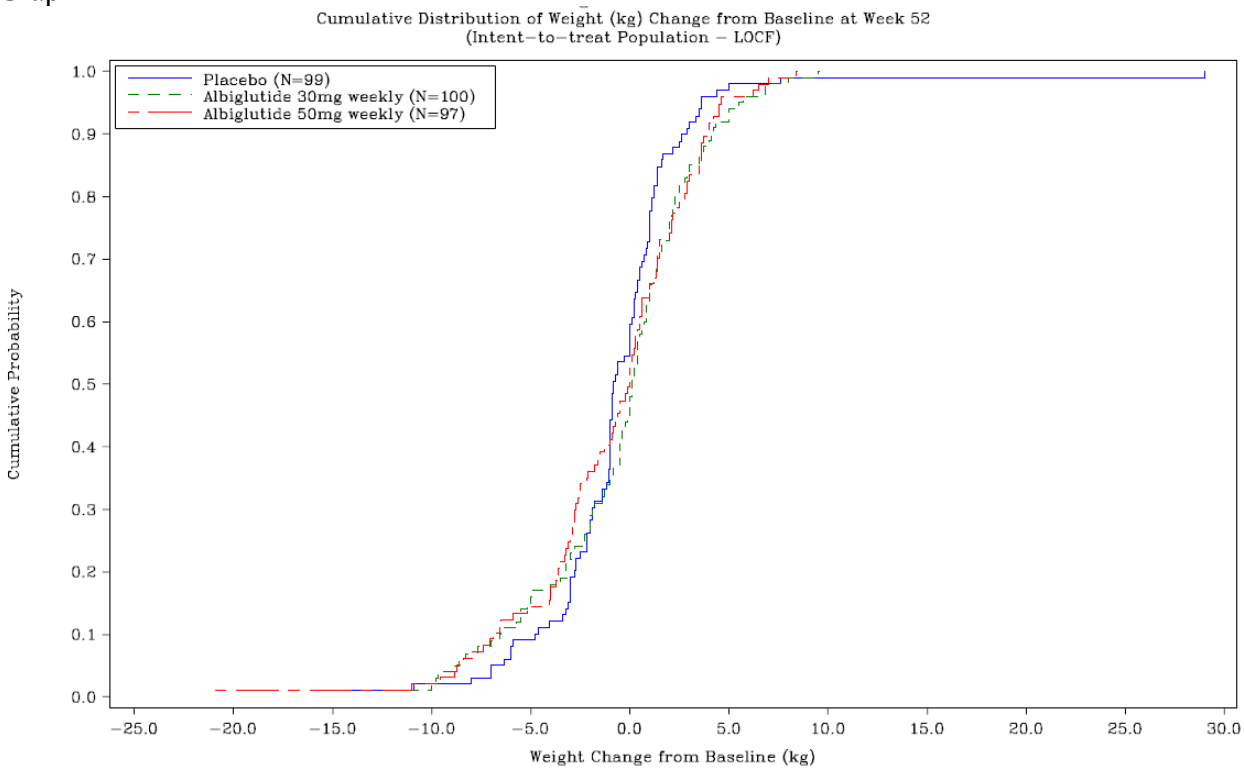
Percentile	Placebo (N=99)	Albiglutide 30mg weekly (N=100)	Albiglutide 50mg weekly (N=97)
Number of subjects [1]	99	100	97
Min	-81	-171	-135
1%	-81.0	-143.0	-135.0
5%	-49.0	-85.5	-100.0
10%	-28.0	-71.0	-86.0
20%	-13.0	-43.0	-62.0
30%	-5.0	-35.0	-44.0
40%	2.0	-30.0	-38.0
50%	14.0	-21.5	-24.0
60%	22.0	-10.0	-15.0
70%	29.0	0.0	-10.0
80%	52.0	10.5	-3.0
90%	81.0	50.0	35.0
95%	103.0	80.0	67.0
99%	180.0	110.0	128.0
Max	180	112	128

Note: This summary uses the last observation carried forward (LOCF) method for missing post-baseline fasting plasma glucose (FPG) values. FPG values obtained after hyperglycemia rescue are treated as missing and replaced with pre-rescue values.
[1] Number of subjects with a value at Week 52.

Reference ID: 3392698

As seen from the following cumulative distribution function, the percent of bigger reductions in Weight was the smallest in the placebo group and that of increases was the largest in the placebo group. However, all three arms showed almost nearby percentages.

Graph



Table

Cumulative Distribution of Weight (kg) Change from Baseline at Week 52
(Intent-to-treat Population - LOCF)

Percentile	Placebo (N=99)	Albiglutide 30mg weekly (N=100)	Albiglutide 50mg weekly (N=97)
Number of subjects [1]	99	100	97
Min	-15.8	-11.2	-20.9
1%	-15.80	-10.60	-20.90
5%	-7.00	-8.75	-8.70
10%	-4.80	-6.55	-6.90
20%	-2.80	-3.20	-3.60
30%	-1.90	-1.85	-2.70
40%	-1.00	-0.50	-1.30
50%	-0.80	0.10	0.00
60%	0.10	0.75	0.50
70%	0.70	1.40	1.40
80%	1.20	2.40	2.80
90%	2.90	4.15	4.00
95%	3.60	5.60	4.60
99%	29.00	8.75	8.40
Max	29.0	9.5	8.4

Note: This summary uses the last observation carried forward (LOCF) method for missing post-baseline weight values. Weight values obtained after hyperglycemia rescue are treated as missing and replaced with pre-rescue values.
[1] Number of subjects with a value at Week 52.

Reference ID: 3392698

STUDY GLP112757

Title: A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide Administered in Combination With Metformin and Glimepiride Compared With Metformin Plus Glimepiride and Placebo and With Metformin Plus Glimepiride and Pioglitazone in Subjects With Type 2 Diabetes Mellitus

Study centers: This study was conducted at 234 study centers.

Study Period: 13-Apr-2009 to 31-Jan-2012

Phase of Development: III

Objectives/Endpoints: The primary objective of the study was to evaluate the efficacy of albiglutide administered in combination with metformin and glimepiride compared with metformin plus glimepiride and placebo and with metformin plus glimepiride and pioglitazone on glycosylated hemoglobin (HbA_{1c}) change from Baseline at Week 52.

Methodology: This was a Phase III, randomized, double-blind, placebo- and active-controlled, 3 parallel-group, multicenter study evaluating the efficacy and safety of a weekly subcutaneously injected dose of albiglutide in combination with metformin and glimepiride compared with metformin plus glimepiride and placebo and with metformin plus glimepiride and pioglitazone in subjects with type 2 diabetes mellitus (T2DM) whose glycemia was not adequately controlled on their current regimen of metformin plus a sulfonylurea (SU). The study comprised 4 study periods: 2 weeks of Prescreening and Screening; 6 to 8 weeks of Run-in/stabilization; a 156-week Treatment Period evaluating efficacy and safety, followed by 8 weeks of Posttreatment follow-up. Subjects completed a minimum of 2 years of treatment, at which time the formal analysis for submission of regulatory marketing applications was completed. The study continued as a blinded study for up to 3 years. This Synopsis is concerned with the 2-year data.

During the 156-week Treatment Period, subjects, the investigator, or designated site staff administered study medication by subcutaneous injection at home or the study site. In addition to the randomly assigned study medication and background diabetic medications, the addition of nonrandomized diabetic rescue medications was allowed in the study if hyperglycemic rescue criteria were met. The subjects remained on randomly assigned study medication after the addition of hyperglycemic rescue medications.
Unless otherwise specified, the overall study Safety Population included all subjects both pre- and post-hyperglycemic rescue.

Randomization was stratified based on the HbA_{1c} value obtained at Visit 7 (<8.0% versus ≥8.0%), history of prior myocardial infarction (MI) (yes versus no), and age (<65 years versus ≥65 years). Adjudication and review of all major cardiovascular and pancreatitis events took place over the entire Treatment Period.

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The subject must have received at least 1500 mg metformin daily and an SU dose that was equivalent to at least 4 mg of glimepiride for at least the 3 months before Screening. Subjects who were receiving greater than 4 mg of glimepiride were to be downtitrated to 4 mg of glimepiride at Screening. After Screening, the metformin and glimepiride doses had to be stable for at least 8 weeks before randomization.

Number of subjects: Approximately 600 subjects were to be randomly assigned in a ratio of 5:5:2 albiglutide (30 mg weekly; treatment-masked uptitration if needed to 50 mg weekly) to pioglitazone (30 mg daily; with treatment-masked uptitration if needed to 45 mg daily) to placebo. A total of 685 subjects were randomized: 281 albiglutide, 288 pioglitazone, and 116 placebo.

Diagnosis and main criteria for inclusion: Eligible subjects were men and women with a historical diagnosis of T2DM who were experiencing inadequate glycemic control on their current regimen of metformin plus SU.

Statistical methods: The primary analysis of the HbA_{1c} change from Baseline response at Week 52 was applied to the intent-to-treat (ITT) Population, using an analysis of covariance (ANCOVA) model with main effects for treatment group, region, history of prior MI, and age category and with baseline HbA_{1c} as a continuous covariate. The difference in treatment effect on HbA_{1c} was evaluated as a contrast of the albiglutide add-on group versus the placebo add-on group. With significance for this contrast, the noninferiority of the albiglutide add-on group relative to the pioglitazone add-on group was evaluated inferentially with a 1-sided *t* test at the 0.025 significance level. If significant, the superiority of the albiglutide add-on group relative to the pioglitazone add-on group was to be evaluated using a 2-sided *t* test at the 0.05 significance level.

Subjects who were rescued for hyperglycemia before Week 52 had their HbA_{1c} recorded at the time of rescue and carried forward for primary analyses. Subjects who discontinued from active treatment for any reason before Week 52 also had their last post-Baseline HbA_{1c} observation carried forward for the analyses.

Sample size calculation and power analyses assumptions/considerations for this study were as follows. Using a 2-sided, 2-sample *t* test and a test-wise significance level of 0.05, with 213 subjects in the albiglutide add-on group and 85 subjects in the placebo add-on group, the albiglutide add-on versus placebo add-on comparison will have at least a 90% power to reject the null hypotheses of no treatment benefit if the actual albiglutide superiority treatment effect was no smaller than 0.5% and the standard deviation for HbA_{1c} change from Baseline was no larger than 1.2%. Using a noninferiority margin of 0.3% and a 1-sided, 2-sample *t* test and a test-wise significance level of 0.025, with 213 subjects per group, the noninferiority test (albiglutide add-on versus pioglitazone add-on) will have at least a 93% power to reject the null hypotheses of albiglutide inferiority if the actual albiglutide add-on treatment superiority was no smaller than 0.1%. With significance on noninferiority, the superiority test of albiglutide add-on versus pioglitazone add-on will have at least a 93% power to reject the null hypothesis of no treatment benefit if the actual albiglutide add-on treatment superiority was no smaller than 0.4%, using a 2-sided, 2-sample *t* test and a test-wise significance level of 0.05. If the actual albiglutide add-on superiority was as small as 0.35%, the superiority hypothesis would have at least 85% statistical power.

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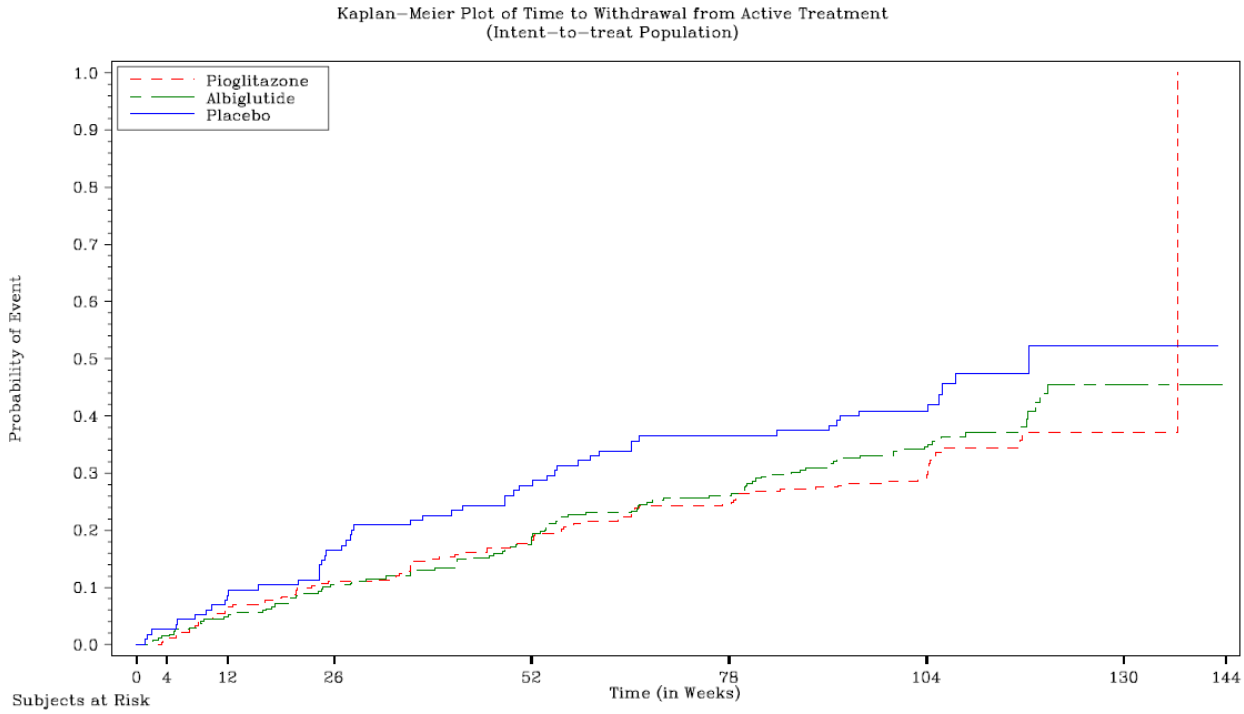
Patient Disposition

As seen from the following Kaplan-Meier Plots, the dropout rate was the highest from the placebo group. The plots for the albiglutide and pioglitazone arms were near and cross each other a few times.

The dropout due to adverse events was the lowest in the albiglutide arm and, surprisingly, highest from the placebo group after Week 104 and in between the other two arms before that.



Subjects at Risk								
Placebo	115	105	96	83	73	63	9	0
Pioglitazone	273	255	243	225	205	179	30	0
Albiglutide	269	256	241	222	199	163	31	1

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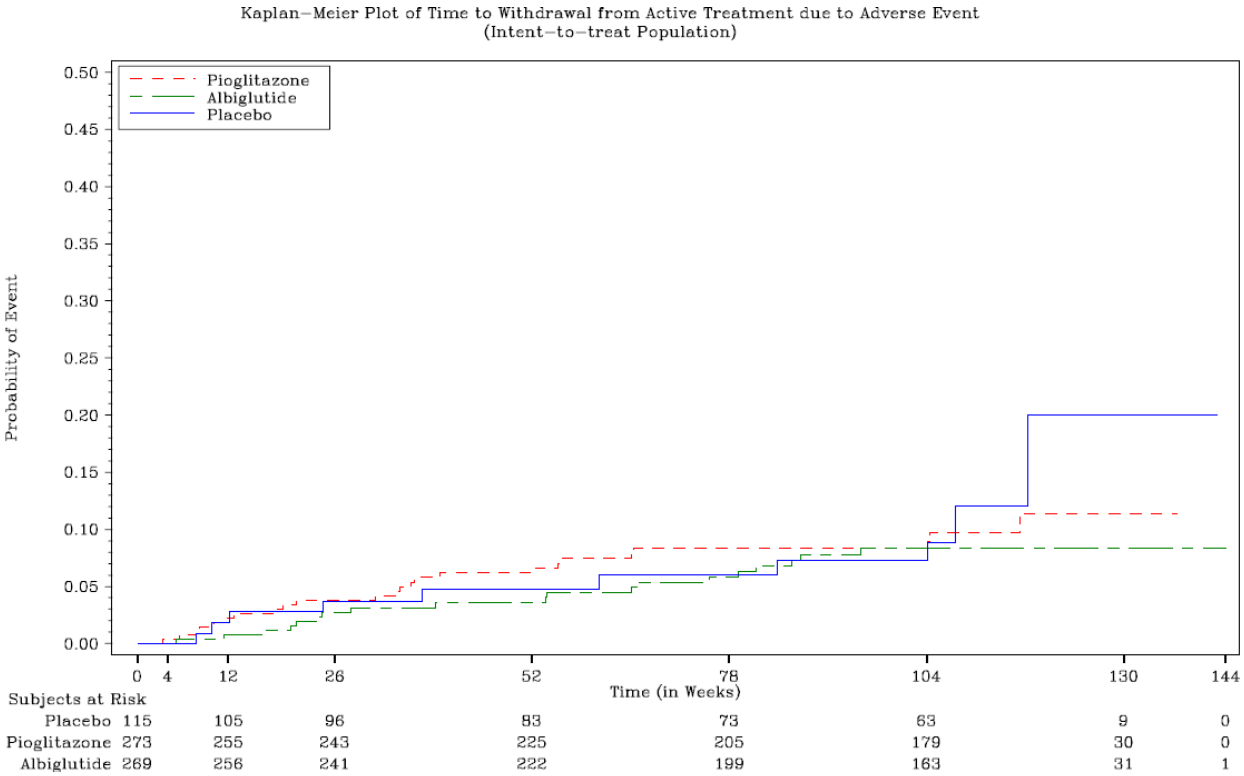

Demographics and Baseline Characteristics (Intent-to-treat Population)

As seen from the following Table of demographics,

in the three treatment arms Placebo, pioglitazone, and albiglutide, respectively,

the mean age was 55.7, 55.7, and 54.5;
the percentage of male was 60.9, 53.4, and 49.8;
the percentage of White was 68.7, 72.6, and 65.7;
the percentage of African was 8.7, 8.7, and 12.5;
the mean weight (kg) was 89.9, 91.0, and 90.9.

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Demographics and Baseline Characteristics
(Intent-to-treat Population)

	Placebo (N=115)	Pioglitazone (N=273)	Albiglutide (N=269)	Total (N=657)
Height (cm)				
n	115	273	269	657
Mean	167.87	167.73	167.23	167.55
Standard Deviation	11.354	11.500	10.682	11.132
Median	168.00	168.00	167.60	167.60
Minimum	142.6	142.0	142.6	142.0
Maximum	193.4	195.7	199.0	199.0
p-value (Pairwise Comparison) [2]	0.5994	0.6007		
Weight (kg)				
n	115	273	269	657
Mean	89.90	91.08	91.14	90.90
Standard Deviation	18.820	21.216	20.146	20.352
Median	87.00	89.60	90.50	89.60
Minimum	53.0	47.4	51.2	47.4
Maximum	150.9	172.2	143.0	172.2
p-value (Pairwise Comparison) [2]	0.5748	0.9746		
Body Mass Index (BMI) (kg/m2)				
n	115	273	269	657
Mean	31.76	32.14	32.39	32.18
Standard Deviation	4.911	5.707	5.517	5.494
Median	31.00	31.00	32.00	32.00
Minimum	23.0	20.0	20.0	20.0
Maximum	46.0	45.0	45.0	46.0

As seen from the following Table of demographics,

in the three treatment arms Placebo, pioglitazone, and albiglutide, respectively,

the mean age was 55.7, 55.7, and 54.5;
the percentage of male was 60.9, 53.4, and 49.8;
the percentage of White was 68.7, 72.6, and 65.7;
the percentage of African was 8.7, 8.7, and 12.5;
the mean weight (kg) was 89.9, 91.0, and 90.9.

Demographics and Baseline Characteristics
(Intent-to-treat Population)

	Placebo (N=115)	Pioglitazone (N=273)	Albiglutide (N=269)	Total (N=657)
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Maximum	46.0	45.0	45.0	46.0
p-value (Pairwise Comparison) [2]	0.2905	0.6135		

Reference ID: 3392698

	Placebo (N=115)	Pioglitazone (N=273)	Albiglutide (N=269)	Total (N=657)
Age at Randomization (years)				
n	115	273	269	657
Mean	55.7	55.8	54.6	55.3
Standard Deviation	9.59	9.43	9.50	9.49
Median	56.0	57.0	54.0	55.0
Minimum	29	28	25	25
Maximum	81	81	74	81
p-value (Pairwise Comparison) [2]	0.2853	0.1441		
Age Category				
n	115	273	269	657
< 65 years	94 (81.7%)	225 (82.4%)	223 (82.9%)	542 (82.5%)
>= 65 years	21 (18.3%)	48 (17.6%)	46 (17.1%)	115 (17.5%)
p-value (Pairwise Comparison) [2]	0.7837	0.8822		
Sex				
n	115	273	269	657
Female	45 (39.1%)	126 (46.2%)	134 (49.8%)	305 (46.4%)
Male	70 (60.9%)	147 (53.8%)	135 (50.2%)	352 (53.6%)
p-value (Pairwise Comparison) [2]	0.0546	0.3938		
Ethnicity				
n	115	273	269	657
Hispanic/Latino	36 (31.3%)	71 (26.0%)	80 (29.7%)	187 (28.5%)
Not Hispanic/Latino	79 (68.7%)	202 (74.0%)	189 (70.3%)	470 (71.5%)
p-value (Pairwise Comparison) [2]	0.7597	0.3325		

Demographics and Baseline Characteristics
(Intent-to-treat Population)

	Placebo (N=115)	Pioglitazone (N=273)	Albiglutide (N=269)	Total (N=657)
Height (cm)				
n	115	273	269	657
Mean	167.87	167.73	167.23	167.55
Standard Deviation	11.354	11.500	10.682	11.132
Median	168.00	168.00	167.60	167.60
Minimum	142.6	142.0	142.6	142.0
Maximum	193.4	195.7	199.0	199.0
p-value (Pairwise Comparison) [2]	0.5994	0.6007		
Weight (kg)				
n	115	273	269	657
Mean	89.90	91.08	91.14	90.90
Standard Deviation	18.820	21.216	20.146	20.352
Median	87.00	89.60	90.50	89.60
Minimum	53.0	47.4	51.2	47.4
Maximum	150.9	172.2	143.0	172.2
p-value (Pairwise Comparison) [2]	0.5748	0.9746		
Body Mass Index (BMI) (kg/m2)				
n	115	273	269	657
Mean	31.76	32.14	32.39	32.18
Standard Deviation	4.911	5.707	5.517	5.494
Median	31.00	31.00	32.00	32.00
Minimum	23.0	20.0	20.0	20.0
Maximum	46.0	45.0	45.0	46.0
p-value (Pairwise Comparison) [2]	0.2905	0.6135		

[1] P-value is for testing the null hypothesis that population values (means or proportions) are equal among treatment groups. All tests are two-sided. * indicates statistical significance at 0.05 level.

[2] P-value from pairwise comparison is for testing the null hypothesis that population values (means or proportions) are equal between albiglutide arm and each comparator arm (placebo arm and pioglitazone arm). All tests are two-sided. * indicates statistical significance at 0.05 level.

As seen from the following Table of baseline characteristics, the mean duration of diabetes in years was 8.5 in the albiglutide group, 9.2 in pioglitazone, and was 9.3 in the placebo group.

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Demographics and Baseline Characteristics
(Intent-to-treat Population)

	Placebo (N=115)	Pioglitazone (N=273)	Albiglutide (N=269)	Total (N=657)
Body Mass Index (BMI) Category				
n	115	273	269	657
< 25 kg/m2	6 (5.2%)	24 (8.8%)	21 (7.8%)	51 (7.8%)
>= 25 to < 30 kg/m2	34 (29.6%)	76 (27.8%)	64 (23.8%)	174 (26.5%)
>= 30 to < 35 kg/m2	45 (39.1%)	78 (28.6%)	96 (35.7%)	219 (33.3%)
>= 35 kg/m2	30 (26.1%)	95 (34.8%)	88 (32.7%)	213 (32.4%)
p-value (Pairwise Comparison) [2]	0.3573	0.3436		
Prior Myocardial Infarction (MI)				
n	115	273	269	657
Yes	4 (3.5%)	14 (5.1%)	10 (3.7%)	28 (4.3%)
No	111 (96.5%)	259 (94.9%)	259 (96.3%)	629 (95.7%)
p-value (Pairwise Comparison) [2]	>0.9999	0.4247		
Baseline HbA1c (%)				
n	115	273	269	657
Mean	8.26	8.29	8.18	8.24
Standard Deviation	0.978	0.889	0.906	0.912
Median	8.20	8.10	8.00	8.10
Minimum	6.7	6.5	4.9	4.9
Maximum	11.4	10.5	12.0	12.0
p-value (Pairwise Comparison) [2]	0.4805	0.1753		
Baseline HbA1c Category				
n	115	273	269	657
< 8.0%	50 (43.5%)	114 (41.8%)	129 (48.0%)	293 (44.6%)
>= 8.0%	65 (56.5%)	159 (58.2%)	140 (52.0%)	364 (55.4%)
p-value (Pairwise Comparison) [2]	0.4205	0.1469		

Duration of Diabetes Disease History
(Intent-to-treat Population)

	Placebo (N=115)	Pioglitazone (N=273)	Albiglutide (N=269)	Total (N=657)
Duration (years) [2]				
n	115	273	269	657
Mean	9.321	9.232	8.482	8.940
Standard Deviation	6.0954	6.1149	6.3325	6.2040
Median	7.792	8.036	6.869	7.639
Minimum	0.74	0.63	0.51	0.51
Maximum	30.64	39.83	41.42	41.42
p-value (Pairwise Comparison) [3]	0.2300	0.1613		
Duration Category				
n	115	273	269	657
< 5.5 years	38 (33.0%)	89 (32.6%)	96 (35.7%)	223 (33.9%)
>= 5.5 to <= 10.5 years	37 (32.2%)	91 (33.3%)	96 (35.7%)	224 (34.1%)
> 10.5 years	40 (34.8%)	93 (34.1%)	77 (28.6%)	210 (32.0%)
p-value (Pairwise Comparison) [3]	0.4840	0.3916		

[1] P-value is for testing the null hypothesis that population values (means or proportions) are equal among treatment groups. All tests are two-sided. * indicates statistical significance at 0.05 level.

[2] To calculate duration from a partial diagnosis date, a missing month is imputed as January and a missing day is imputed as the first of the month.

[3] P-value from pairwise comparison is for testing the null hypothesis that population values (means or proportions) are equal between albiglutide arm and each comparator arm (placebo arm and pioglitazone arm). All tests are two-sided. * indicates statistical significance at 0.05 level.

Reference ID: 3392698

Results and Conclusions

Primary Efficacy Endpoint HbA_{1c} Change From Baseline at Week 52

Note: Pioglitazone was statistically superior to albiglutide.

A decrease in HbA_{1c} from Baseline to Week 52 was observed in both the pioglitazone and albiglutide treatment groups . When Baseline HbA_{1c}, history of prior MI, age category, and region, the model-adjusted LS mean change in HbA_{1c} from Baseline at Week 52 was -0.55% in the albiglutide group, -0.80% in the pioglitazone group, and 0.33% in the placebo group. The treatment difference for albiglutide - placebo was -0.87% (95% CI: -1.07, -0.68) which was statistically significant (p<0.0001). The treatment difference for albiglutide - pioglitazone was 0.25% (95% CI: 0.10, 0.40). Because the upper bound of 95% CI is 0.4% which exceeds the pre-specified non-inferiority margin 0.3%, non-inferiority was not shown.

	Placebo (N=115)	Pioglitazone (N=273)	Albiglutide (N=269)
Number of subjects[1]	115	268	265
Number (%) of values carried forward	80 (69.6)	92 (34.3)	92 (34.7)
Baseline mean (SD)	8.26 (0.978)	8.28 (0.879)	8.18 (0.908)
Week 52 mean	8.57 (1.169)	7.47 (1.015)	7.66 (1.093)
Model-adjusted change from Baseline[2]			
Least squares mean	0.33	-0.80	-0.55
Standard error	0.083	0.055	0.055
95% confidence interval	(0.16, 0.49)	(-0.90, -0.69)	(-0.65, -0.44)
Difference from albiglutide[2]			
Difference of least squares means	-0.87	0.25	
95% confidence interval	(-1.07, -0.68)	(0.10, 0.40)	
p-value	<0.0001	0.0012	
Non-inferiority p-value[3]			0.2685
Superiority p-value[4]			N/A

ANCOVA = analysis of covariance, LOCF = last observation carried forward; SD = standard deviation.
Note: This analysis uses the LOCF method for missing post-Baseline HbA_{1c} values. HbA_{1c} values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values. Seven ITT subjects had all post-baseline HbA_{1c} measurements occur more than 14 days after last dose and 1 ITT subject had all post-baseline HbA_{1c} measurements occur after hyperglycemic rescue. One subject had HbA_{1c} measurements that either occurred after hyperglycemia rescue or more than 14 days after last dose. These 9 subjects are included in the header ITT population counts but do not contribute to any of the ITT efficacy analyses.

1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on ANCOVA: Change = treatment + Baseline HbA_{1c} + prior myocardial infarction history + age category + region. The difference of least squares means (albiglutide - placebo, albiglutide - pioglitazone) is from the ANCOVA model.
3. The p-value is from a 1-sided t-test testing at the 0.025 level of significance whether or not the difference of least squares means (albiglutide - pioglitazone) is less than or equal to the pre-specified non-inferiority margin of 0.3%.
4. Albiglutide non-inferiority to pioglitazone is not established, therefore, superiority testing of albiglutide versus pioglitazone was not performed.

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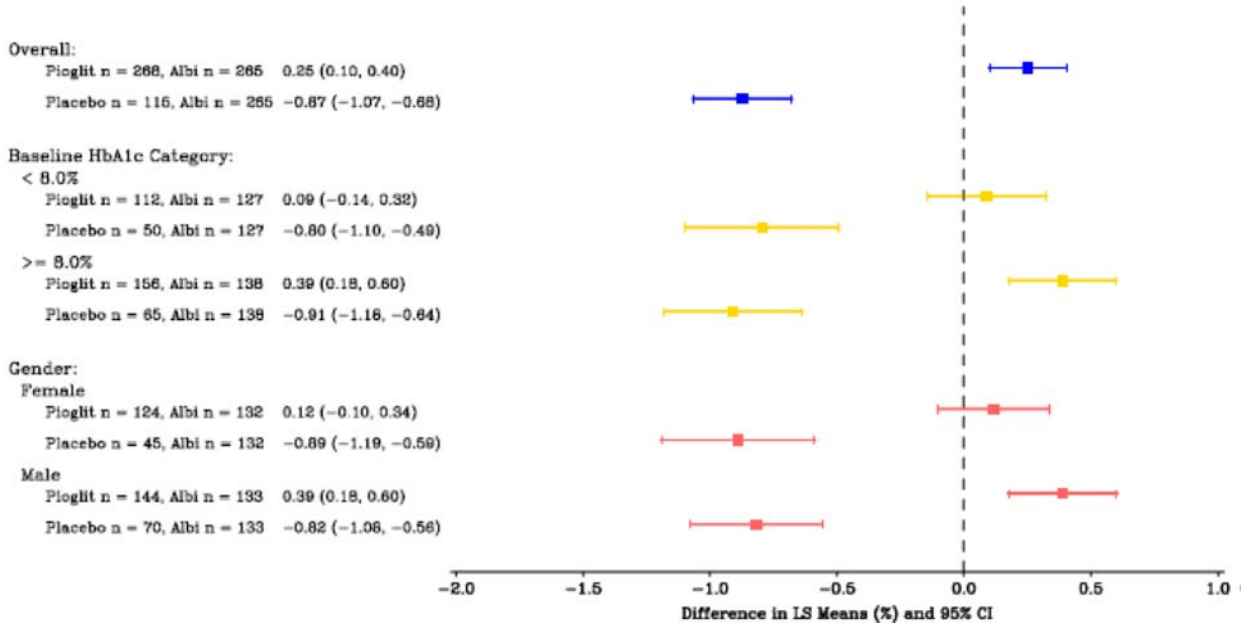
In the following forest plots, the left side indicates the superiority of albiglutide. There were statistically significant Treatment by Baseline HBA1C Category (<8, >= 8) (p= .072) and by Baseline BMI category (<25 kg/m2, ≥25 to <30 kg/m2, ≥30 to <35 kg/m2, ≥35 kg/m2) (p= 0.093) interactions.

Note: In all subgroups, albiglutide was superior to placebo and pioglitazone at least numerically superior to albiglutide, except among black and BMI category <25kg/m^2.



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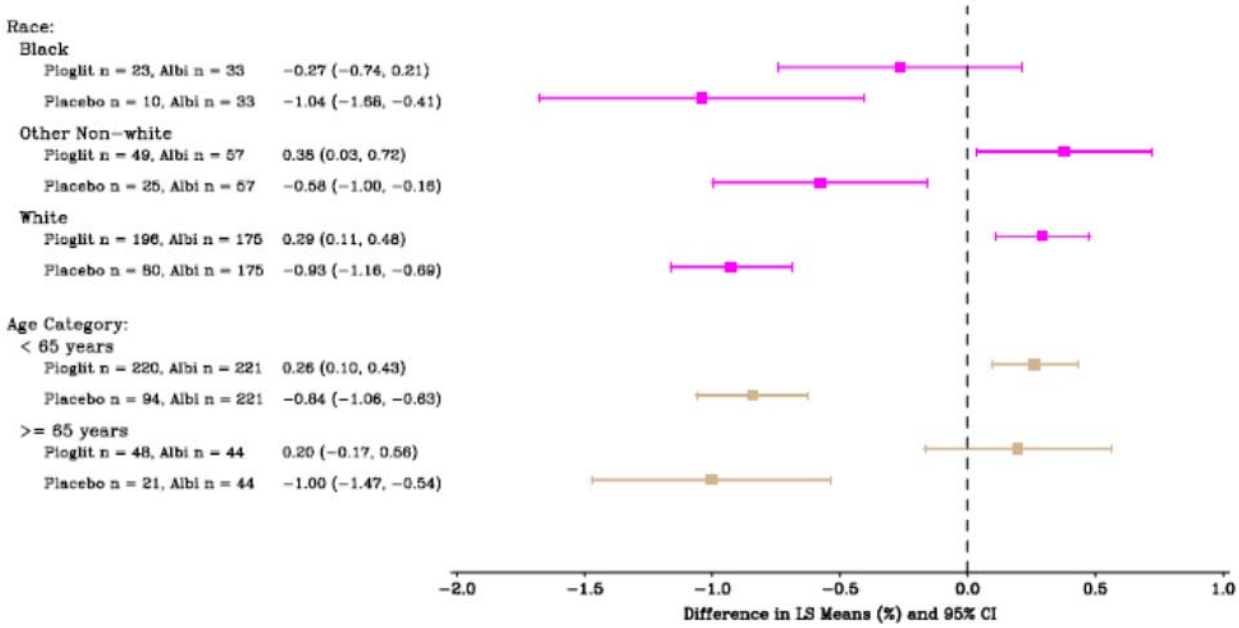

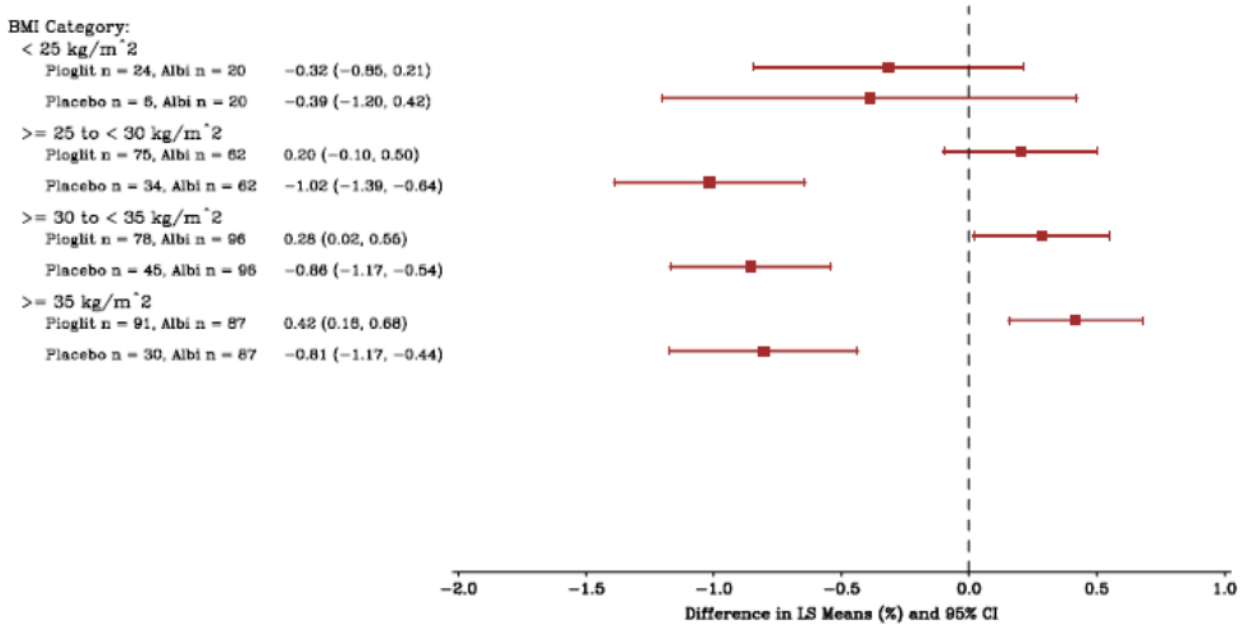

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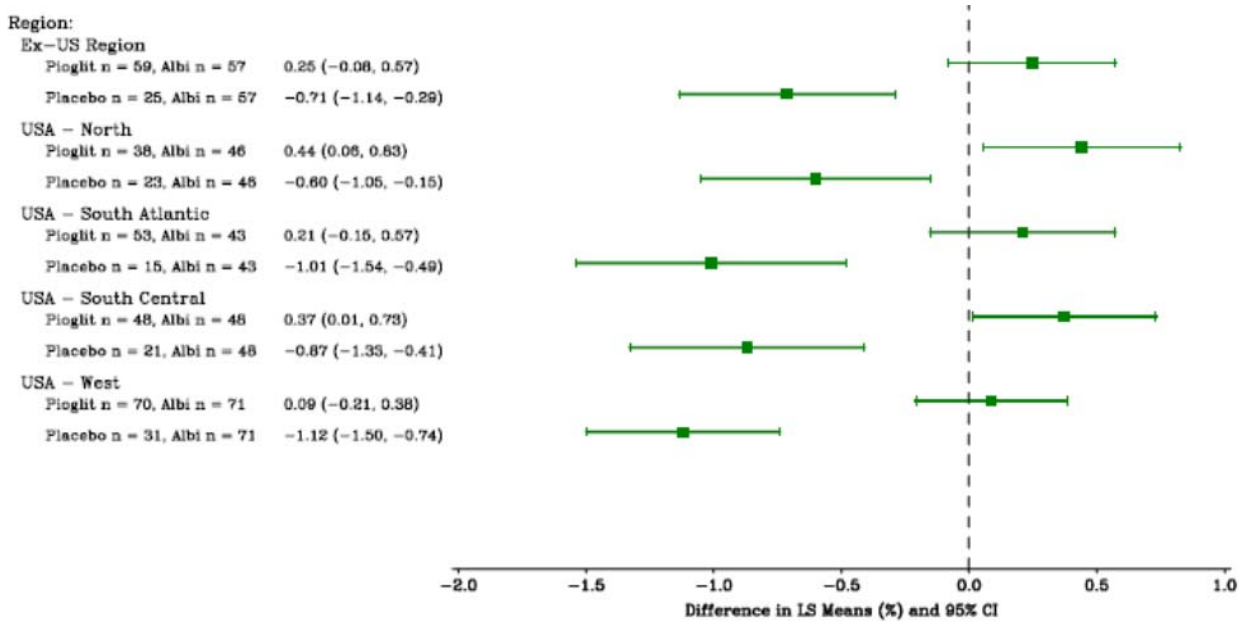

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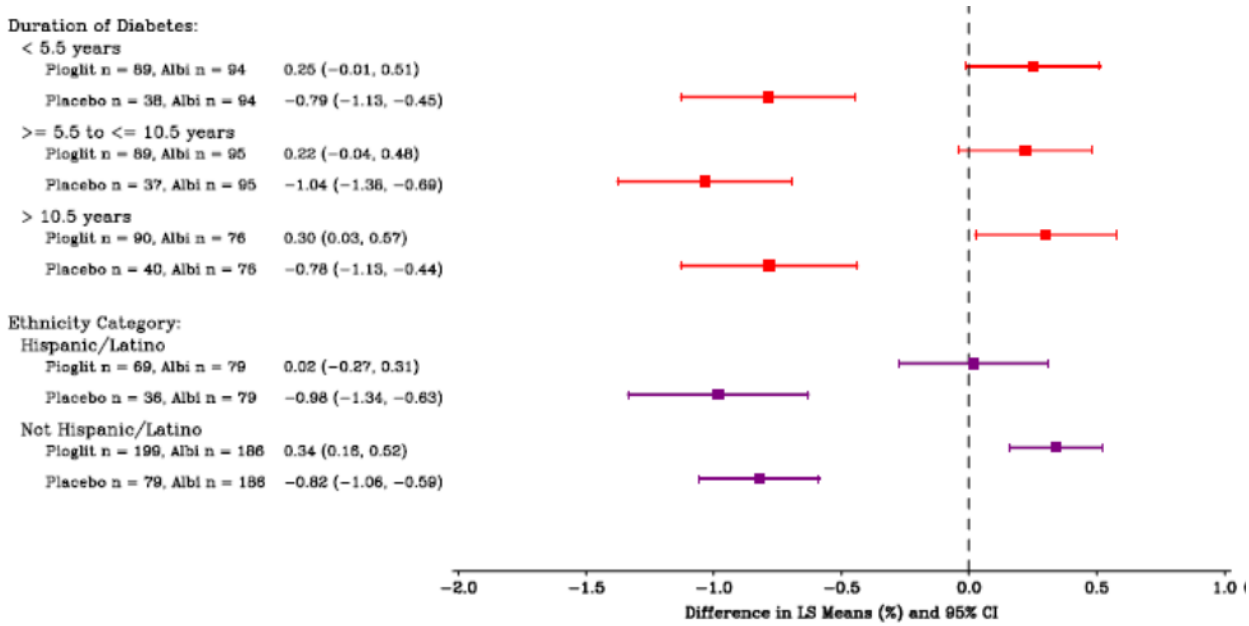

Albi = albiglutide; CI = confidence interval; LOCF = last observation carried forward; LS = least squares; Pioglit = pioglitazone.
Note: The difference on X-axis is the difference in the albiglutide least squares mean change from Baseline minus either the pioglitazone or the placebo least squares mean change from Baseline.

Analysis of Change From Baseline in Fasting Plasma Glucose (mmol/L) at Week 52 (Intent-to-Treat Population - LOCF)

Note: Albiglutide was statistically superior to placebo and statistically inferior to pioglitazone with respect to FPG.

	Placebo (N=115)	Pioglitazone (N=273)	Albiglutide (N=269)
Number of subjects[1]	115	272	268
Number (%) of values carried forward	81 (70.4)	96 (35.3)	95 (35.4)
Baseline mean (SD)	9.65 (2.731)	9.84 (3.114)	9.48 (2.896)
Week 52 mean (SD)	10.29 (3.123)	8.02 (2.666)	8.87 (3.124)
Model-adjusted change from Baseline[2]			
Least squares mean	0.64	-1.74	-0.69
Standard error	0.243	0.158	0.159
95% confidence interval	(0.16, 1.11)	(-2.05, -1.43)	(-1.00, -0.38)
Difference from comparator[2]			
Difference of least squares means	-1.33	1.05	
95% confidence interval	(-1.89, -0.76)	(0.61, 1.49)	
p-value[3]	<0.0001	<0.0001	

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ANCOVA = analysis of covariance, LOCF = last observation carried forward; SD = standard deviation.
Note: This analysis used the last observation carried forward (LOCF) method for missing post-Baseline FPG values. The FPG values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values.

1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on ANCOVA: Change = treatment + Baseline FPG + Baseline HbA_{1c} category + prior myocardial infarction history + age category + region. The difference of least squares means (albiglutide - placebo, albiglutide - pioglitazone) is from the ANCOVA model.
3. The p-value is from a 2-sided *t* test for the difference in means.

Analysis of Change From Baseline in Weight (kg) at Week 52 (Intent-to-Treat Population - LOCF)

Note: Pioglitazone increased weight statistically significantly more compared with other arms, which lowered weight at least numerically.

	Placebo (N=115)	Pioglitazone (N=273)	Albiglutide (N=269)
Number of subjects[1]	115	272	268
Number (%) of values carried forward	80 (69.6%)	96 (35.3%)	94 (35.1%)
Baseline mean (SD)	89.90 (18.820)	91.03 (21.238)	91.10 (20.174)
Week 52 mean (SD)	89.48 (18.542)	95.48 (22.505)	90.67 (20.139)
Change from Baseline - mean (SD)	-0.42 (2.550)	4.45 (4.809)	-0.43 (3.284)
Model-adjusted change from Baseline[2]			
Least squares mean	-0.40	4.43	-0.42
Standard error	0.362	0.235	0.237
95% confidence interval	(-1.11, 0.31)	(3.97, 4.89)	(-0.89, 0.04)
Difference from comparator[2]			
Difference of least squares means	-0.03	-4.85	
95% confidence interval	(-0.88, 0.82)	(-5.51, -4.20)	
p-value[3]	0.9499	<0.0001	

ANCOVA = analysis of covariance, LOCF = last observation carried forward, SD = standard deviation.

1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on ANCOVA: Change = treatment + Baseline weight + Baseline HbA_{1c} category + prior myocardial infarction history +age category + region. The difference of least squares means (albiglutide - placebo, albiglutide - pioglitazone) is from the ANCOVA model.
3. The p-value is from a 2-sided *t* test for the difference in means.

§ Graphs of cumulative distribution functions by treatment groups for the primary efficacy variable (percent change from baseline in HbA1c) at the study endpoint are provided below. From these, the percent of patients (y-axis value) with a value of percent change from baseline in HbA1c at endpoint, smaller than or equal to a value on the x-axis, can be read.

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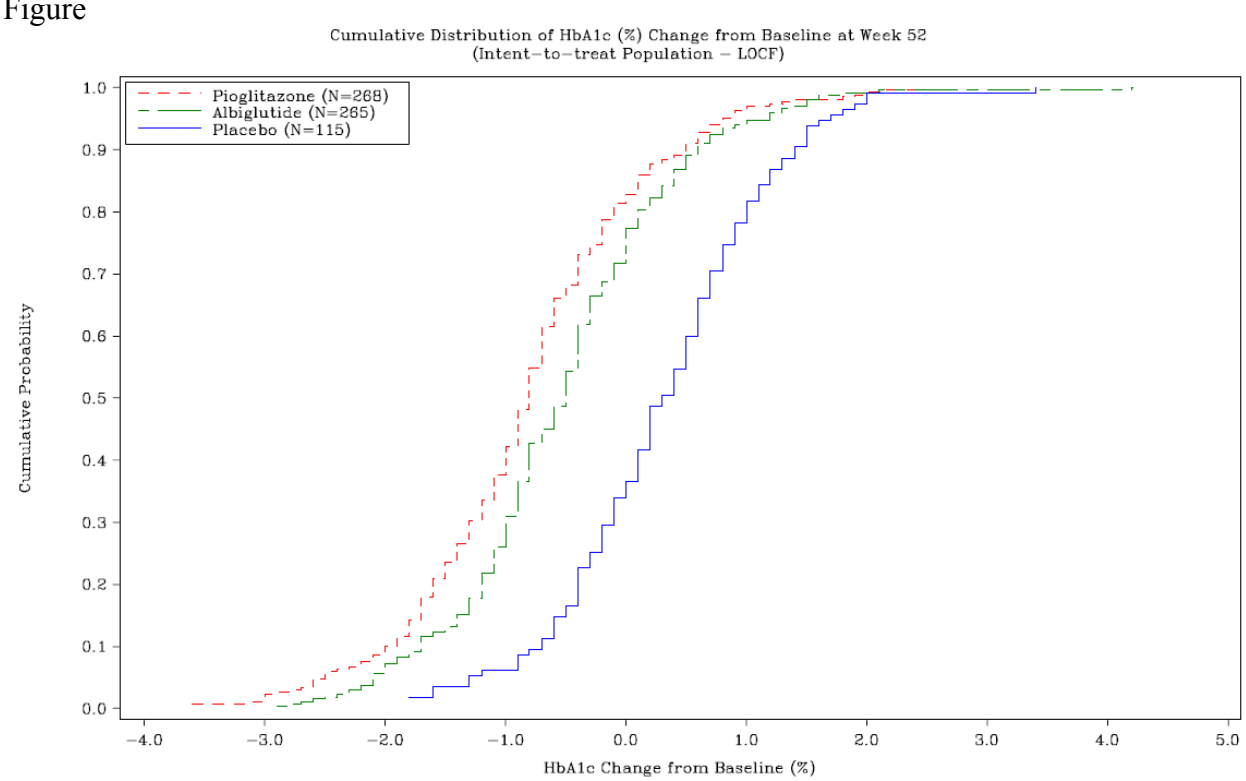
Note: All the percentiles were the largest for the placebo group and the smallest (mostly) for the pioglitazone group.

Figure



Table

Cumulative Distribution of HbA1c (%) Change from Baseline at Week 52
(Intent-to-treat Population - LOCF)

Percentile	Placebo (N=115)	Pioglitazone (N=273)	Albiglutide (N=269)
Number of subjects [1]	115	268	265
Min	-1.8	-3.6	-2.9
1%	-1.80	-3.10	-2.70
5%	-1.30	-2.50	-2.10
10%	-0.70	-2.00	-1.70
20%	-0.40	-1.60	-1.20
30%	-0.10	-1.30	-1.00
40%	0.10	-1.00	-0.80
50%	0.30	-0.80	-0.50
60%	0.55	-0.70	-0.40
70%	0.70	-0.40	-0.10
80%	1.00	-0.10	0.10
90%	1.40	0.50	0.60
95%	1.70	0.80	1.20
99%	2.00	2.00	1.80
Max	3.4	2.6	4.2

Note: This summary uses the last observation carried forward (LOCF) method for missing post-baseline HbA1c values. HbA1c values obtained after hyperglycemia rescue are treated as missing and replaced with pre-rescue values.
[1] Number of subjects with a value at Week 52.

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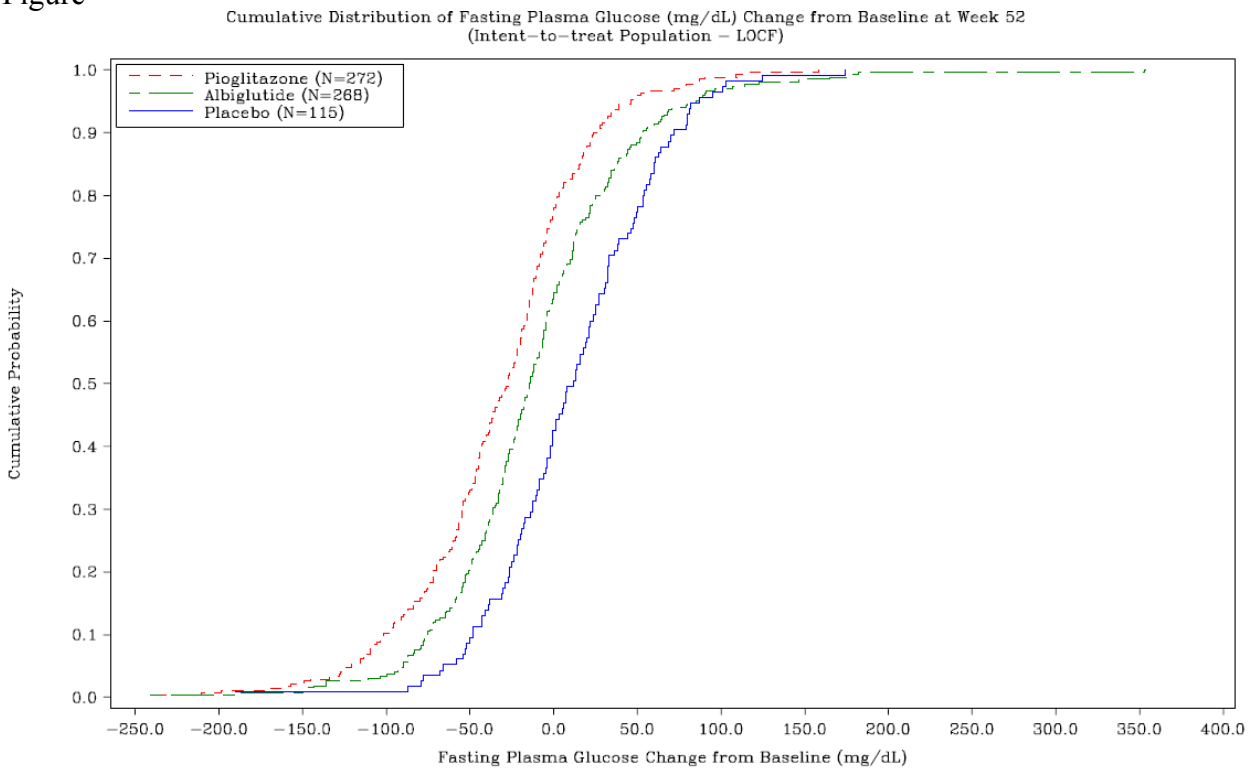
For change from baseline in FPG at Week 52, almost all the percentiles were the largest for the placebo group and the smallest for the pioglitazone group. However, the differences of placebo from other groups are not as pronounced as in the case of HBA1c.

Figure



Reference ID: 3392698

Table

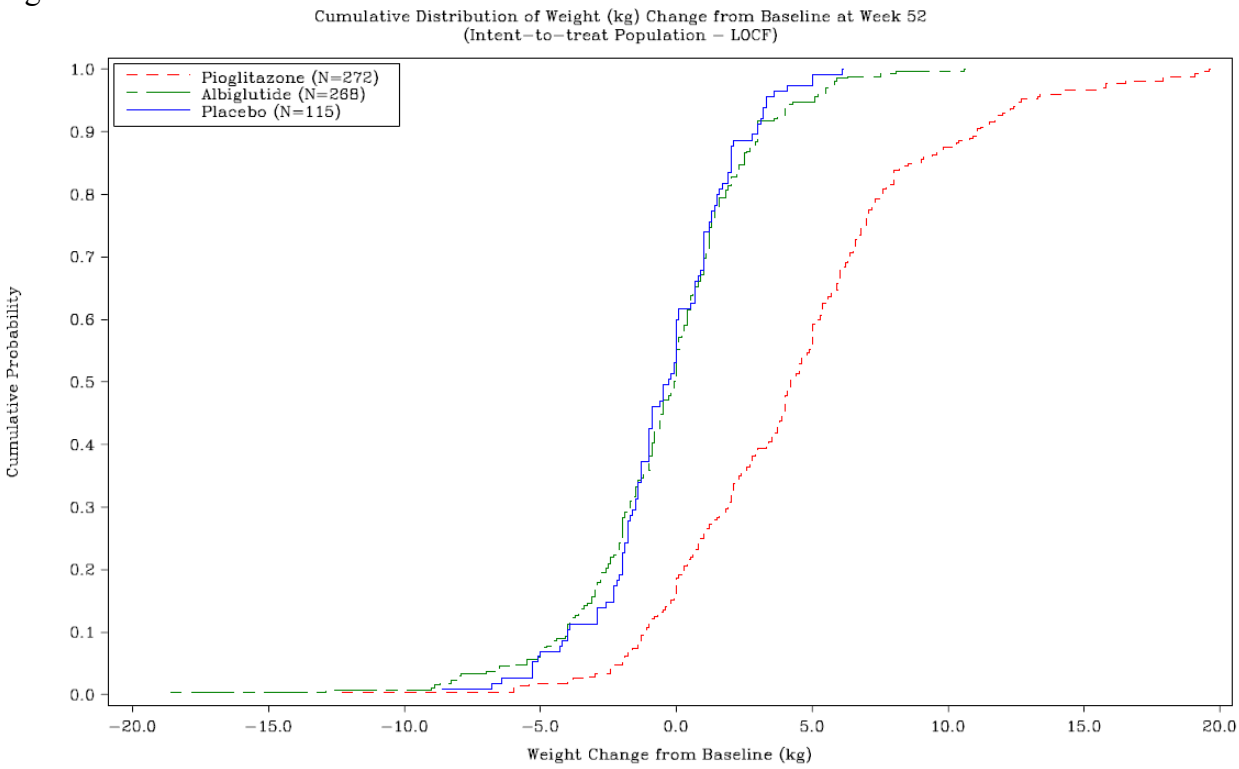
Cumulative Distribution of Fasting Plasma Glucose (mg/dL) Change from Baseline at Week 52
(Intent-to-treat Population - LOCF)

Percentile	Placebo (N=115)	Pioglitazone (N=273)	Albiglutide (N=269)
Number of subjects [1]	115	272	268
Min	-190	-238	-241
1%	-87.0	-199.0	-150.0
5%	-66.0	-121.0	-90.0
10%	-48.0	-102.0	-75.0
20%	-26.0	-72.0	-51.0
30%	-13.0	-54.0	-36.0
40%	-1.5	-43.0	-25.0
50%	12.0	-27.0	-14.5
60%	23.0	-16.0	-5.0
70%	33.0	-8.0	11.0
80%	53.5	3.0	28.0
90%	72.0	24.0	53.0
95%	87.0	46.0	85.0
99%	125.0	109.0	177.0
Max	174	158	353

Note: This summary uses the last observation carried forward (LOCF) method for missing post-baseline fasting plasma glucose (FPG) values. FPG values obtained after hyperglycemia rescue are treated as missing and replaced with pre-rescue values.
[1] Number of subjects with a value at Week 52.

For change from baseline in Weight at Week 52, almost all the percentiles were the largest for the pioglitazone group. Albiglutide and placebo curves crossed each other multiple times and the percentiles for both arms were nearby.

Figure



Reference ID: 3392698

Table

Cumulative Distribution of Weight (kg) Change from Baseline at Week 52
(Intent-to-treat Population - LOCF)

Percentile	Placebo (N=115)	Pioglitazone (N=273)	Albiglutide (N=269)
Number of subjects [1]	115	272	268
Min	-8.6	-12.3	-18.6
1%	-6.80	-6.00	-9.00
5%	-5.30	-2.00	-5.50
10%	-4.00	-1.10	-4.00
20%	-2.00	0.30	-2.60
30%	-1.50	1.90	-1.70
40%	-1.00	3.40	-0.90
50%	-0.30	4.20	-0.05
60%	0.05	5.30	0.40
70%	1.00	6.40	1.10
80%	1.55	7.60	1.80
90%	3.00	11.00	3.00
95%	3.30	12.70	5.10
99%	5.00	19.10	7.50
Max	6.1	19.6	10.6

Note: This summary uses the last observation carried forward (LOCF) method for missing post-baseline weight values. Weight values obtained after hyperglycemia rescue are treated as missing and replaced with pre-rescue values.
[1] Number of subjects with a value at Week 52.

STUDY GLP114179

Title: A Randomized, Open-Label, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide as Compared With Liraglutide in Subjects With Type 2 Diabetes Mellitus

Study center(s): This study was conducted at 162 study centers.

Study Period: 05 May 2010 to 09 Sep 2011

Phase of Development: III

Objectives/Endpoints: The primary objective of the study was to evaluate the efficacy of albiglutide as compared with liraglutide on glycosylated hemoglobin (HbA_{1c}) change from Baseline at Week 32.

Methodology: This was a randomized, open-label, 2-parallel group, multicenter study of 46 weeks duration evaluating the efficacy and safety of albiglutide as compared with liraglutide administered subcutaneously for subjects with type 2 diabetes mellitus (T2DM). The study comprised 4 study periods: 2 weeks of Prescreening and Screening; 4 weeks of Run-in/stabilization; a 32-week Treatment Period evaluating efficacy and safety, followed by 8 weeks of Posttreatment Follow-Up. During the 32-week Treatment Period, subjects, the investigator, or

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designated site staff administered study medication by subcutaneous injection at home or the site.

Randomization was stratified by HbA_{1c} (<8.0% or ≥8.0%), prior history of myocardial infarction (MI) (yes versus no), and age (<65 or ≥65 years of age). Adjudication and review of all major cardiovascular and pancreatitis events took place over the entire Treatment Period.

Subjects continued on their current regimen of oral antidiabetic medication for the duration of their participation in the study, with the exception that use of sulfonylurea (SU) may have been modified.

Number of subjects: Approximately 800 subjects were planned for randomization in a ratio of 1:1 albiglutide to liraglutide. A total of 841 subjects were randomly assigned: 422 albiglutide, 419 liraglutide.

Diagnosis and main criteria for inclusion: Eligible subjects were men and women with a historical diagnosis of T2DM who were experiencing inadequate glycemic control on their current regimen of metformin, SU, thiazolidinedione, or any combination of these oral antidiabetic medications.

Statistical methods: The primary analysis of the HbA_{1c} change from Baseline response at Week 32 was applied to the ITT population, using an analysis of covariance (ANCOVA) model with main effects for treatment group, region, history of prior MI, and age category and with baseline HbA_{1c} as a continuous covariate. The difference in treatment-effect between the albiglutide group and the liraglutide group was evaluated within this ANCOVA model as least squares means contrast. The contrast was evaluated with a 1-sided *t* test at the 0.025 significance level with a noninferiority margin of 0.3% on the change of HbA_{1c}. With significance on the noninferiority hypothesis, the superiority hypothesis has at least 88% power to reject the null hypothesis if the actual albiglutide superiority was as small as 0.275% using a 2-sided, 2-sample *t* test and test-wise significance level of 0.05.

Subjects who qualified for hyperglycemia rescue had their primary endpoint value of HbA_{1c} change from Baseline recorded at the time of rescue. Follow-up assessments continued beyond rescue, and postrescue HbA_{1c} assessments were used in supportive analyses. Subjects who discontinued from active participation in the study (e.g., withdrew consent or were lost to glycemic follow-up) had their last HbA_{1c} observation that was taken within 14 days of the last dose and prior to hyperglycemia rescue carried forward for the primary analysis.

Assuming an expected treatment effect of 0% and a standard deviation of 1.1%, the test of albiglutide versus liraglutide has at least 93% power using a 1-sided, 2-sample *t* test and a test-wise significance level of 0.025 with 320 completed subjects per treatment group for a noninferiority margin of 0.3%. Loss to follow-up was expected to be very low, since all subjects were to be followed until active study completion. The planned sample size of 400 per group allowed for as great as 20% early withdrawal or loss to glycemic follow-up and rescue.

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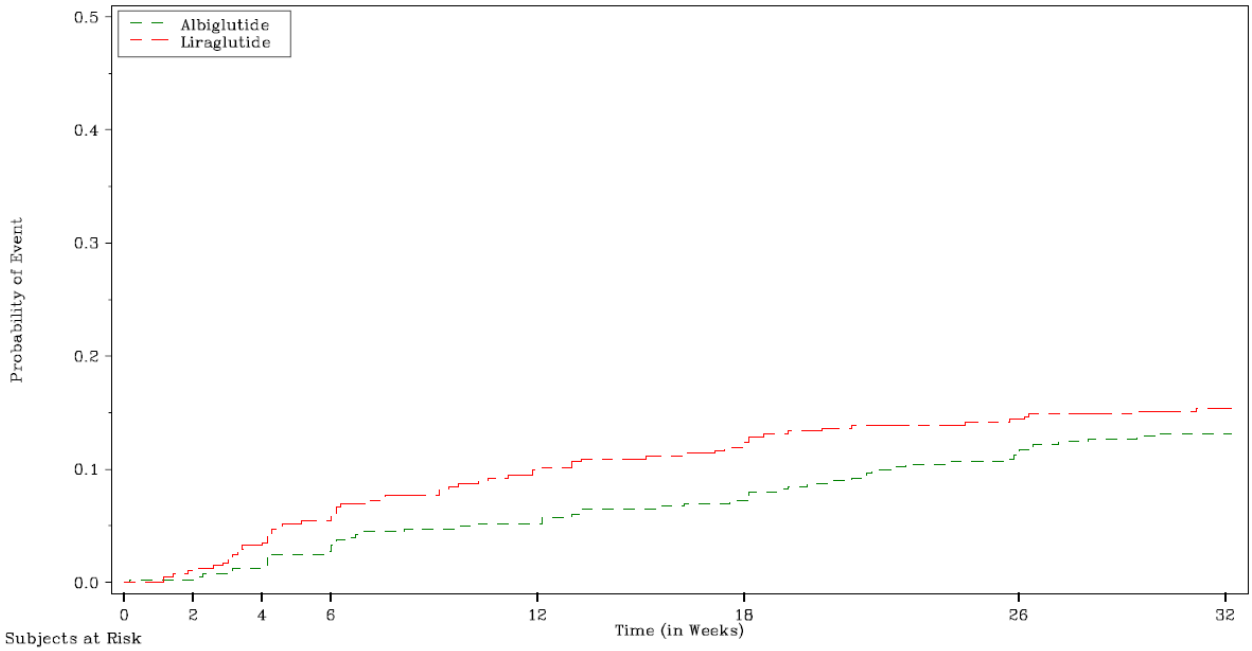
Patient Disposition

As seen from the following Kaplan-Meier Plots of Time to Withdrawal from Treatment, time to withdrawal was smaller (smaller rate of withdrawal) for the albiglutide group. Withdrawal due to adverse effects was also smaller (smaller rate of withdrawal) for the albiglutide group.

Kaplan-Meier Plot of Time to Withdrawal from Treatment (Intent-to-treat Population)



Subjects at Risk								
Albiglutide	402	401	397	391	381	373	357	295
Liraglutide	403	399	390	381	363	355	345	297

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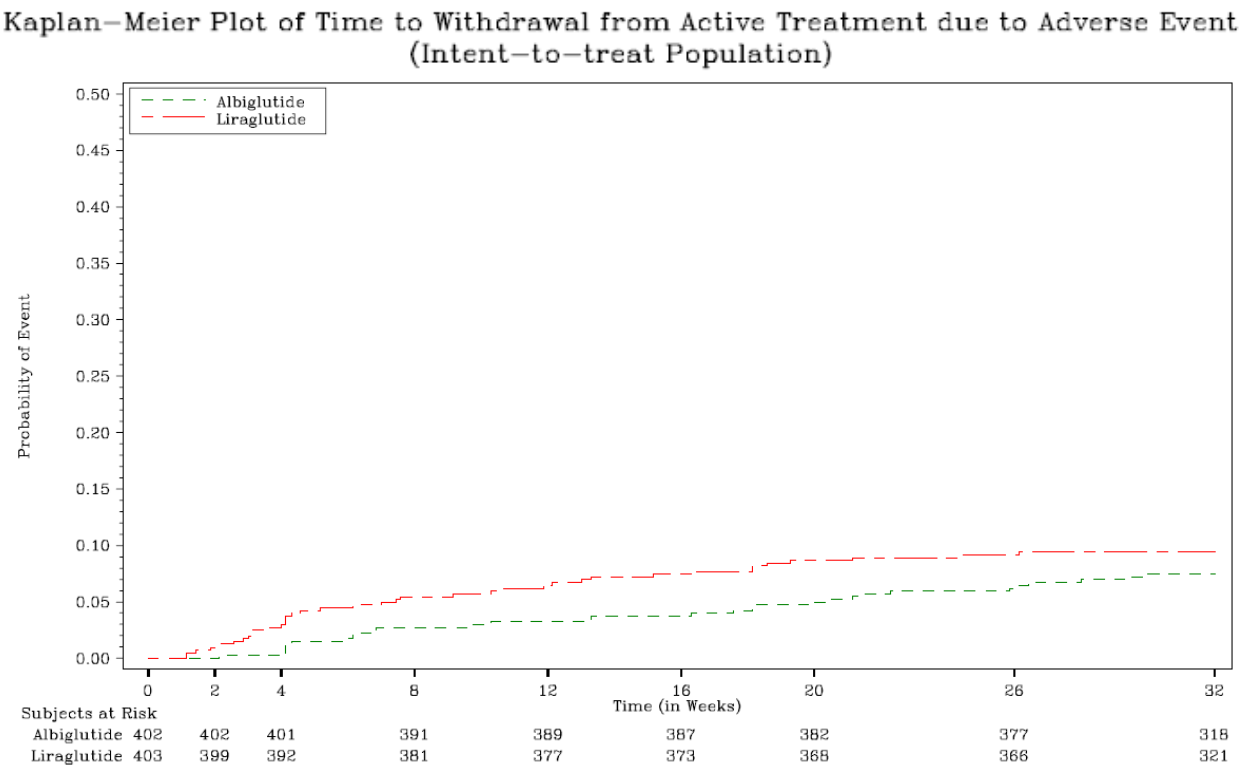

Demographic Characteristics (Safety Population)

As seen from the following Table of demographics,

The mean age was 55.4 in the albiglutide group and was 55.8 in the liraglutide group.

Race was widely represented (details in the above Table), except for Asian - Japanese heritage - 0 in albiglutide 3 (0.7%) in liraglutide and
for Native Hawaiian or other Pacific Islander 0 for albiglutide and 2 (0.5%) for liraglutide.

The percentage of male was 47.3 in the albiglutide group and was 53.4 in the liraglutide group.
The mean weight (kg) was 91.7 in the albiglutide group and was 92.8 in the liraglutide group.

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Demographic Characteristics (Safety Population)

	Albiglutide (N=404)	Liraglutide (N=408)	Total (N=812)
Age at randomization (years)			
Mean (SD)	55.4 (10.11)	55.8 (9.95)	55.6 (10.03)
Median	55.5	56.0	56.0
Min, max	25, 77	21, 82	21, 82
Age category, n (%)			
<65 years	331 (81.9)	336 (82.4)	667 (82.1)
≥65 years	73 (18.1)	72 (17.6)	145 (17.9)
Sex, n (%)			
Female	213 (52.7)	190 (46.6)	403 (49.6)
Male	191 (47.3)	218 (53.4)	409 (50.4)
Race,[2] n (%)			
African American/African heritage	47 (11.6)	29 (7.1)	76 (9.4)
American Indian or Alaskan Native	31 (7.7)	37 (9.1)	68 (8.4)
Asian - Central/South Asian heritage	3 (0.7)	9 (2.2)	12 (1.5)
Asian - East Asian heritage	26 (6.4)	18 (4.4)	44 (5.4)
Asian - Japanese heritage	0	3 (0.7)	3 (0.4)
Asian - South East Asian heritage	17 (4.2)	19 (4.7)	36 (4.4)
Native Hawaiian or other Pacific Islander	0	2 (0.5)	2 (0.2)
White - Arabic/North African heritage	5 (1.2)	6 (1.5)	11 (1.4)
White - White/Caucasian/European heritage	277 (68.6)	285 (69.9)	562 (69.2)
Ethnicity, n (%)			
Hispanic/Latino	113 (28.0)	128 (31.4)	241 (29.7)
Not Hispanic/Latino	291 (72.0)	280 (68.6)	571 (70.3)
Weight (kg)			
Mean (SD)	91.67 (21.215)	92.83 (22.144)	92.25 (21.681)
Median	90.00	90.35	90.00
Minimum, maximum	47.8, 155.4	48.6, 154.0	47.8, 155.4
	Albiglutide (N=404)	**Liraglutide (N=408)**	**Total (N=812)**
Body mass index (kg/m^2)			
Mean (SD)	32.83 (5.960)	32.76 (5.850)	32.79 (5.902)
Median	33.00	32.00	32.00
Minimum, maximum	20.0, 48.0	21.0, 46.0	20.0, 48.0
Body mass index category, n (%)			
<25 kg/m^2	30 (7.4)	26 (6.4)	56 (6.9)
≥25 to <30 kg/m^2	99 (24.5)	108 (26.5)	207 (25.5)
≥30 to <35 kg/m^2	123 (30.4)	122 (29.9)	245 (30.2)
≥35 kg/m^2	152 (37.6)	152 (37.3)	304 (37.4)

1. The p-value was for testing the null hypothesis that the summary statistics (mean or proportion) were equal among treatment groups. All tests were 2-sided.
2. Two subjects in the albiglutide group were counted in more than 1 category of race.

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Baseline Diabetes Characteristics (Safety Population)

As seen from the following Table of baseline characteristics, the mean duration of diabetes in years was 8.4 in the albiglutide group and was 8.3 in the lispro group.

	Albiglutide (N=404)	Liraglutide (N=408)	Total (N=812)
Subjects with any conditions, n (%)	323 (80.0)	342 (83.8)	
Dyslipidaemia	290 (71.8)	300 (73.5)	
Peripheral neuropathy	94 (23.3)	107 (26.2)	
Impotence	48 (11.9)	38 (9.3)	
Diabetic retinopathy	31 (7.7)	25 (6.1)	
Proteinuria	16 (4.0)	25 (6.1)	
Nephropathy	10 (2.5)	11 (2.7)	
Microalbuminuria	7 (1.7)	15 (3.7)	
Autonomic neuropathy	5 (1.2)	1 (0.2)	
Diabetic foot ulcer	4 (1.0)	2 (0.5)	
Chronic renal insufficiency	3 (0.7)	4 (1.0)	
Other	9 (2.2)	10 (2.5)	
Duration (years)[2]			
Mean (SD)	8.43 (6.076)	8.30 (5.561)	8.37 (5.820)
Median	7.39	7.62	7.53
Min, max	0.1, 35.6	0.2, 36.7	0.1, 36.7
Duration Category, n (%)			
<5 years	146 (36.1)	123 (30.1)	269 (33.1)
≥5 to <10 years	114 (28.2)	154 (37.7)	268 (33.0)
≥10 years	144 (35.6)	131 (32.1)	275 (33.9)
Baseline HbA_{1c} (%)			
Mean (SD)	8.19 (0.903)	8.15 (0.840)	8.17 (0.872)
Median	8.10	8.10	8.10
Min, max	6.6, 11.3	6.5,10.5	6.5,11.3
Baseline HbA_{1c} category, n (%)			
<8.0%	177 (43.8)	179 (43.9)	356 (43.8)
≥8.0%	227 (56.2)	229 (56.1)	456 (56.2)
Current antihyperglycemia oral therapy, n (%)			
No current antihyperglycemia oral therapy	0	1 (0.2)	1 (0.1)
Metformin and SU	180 (44.6)	185 (45.3)	365 (45.0)
Metformin only	141 (34.9)	149 (36.5)	290 (35.7)
Metformin, SU and TZD	35 (8.7)	26 (6.4)	61 (7.5)
Metformin and TZD	18 (4.5)	23 (5.6)	41 (5.0)
SU only	21 (5.2)	15 (3.7)	36 (4.4)
SU and TZD	4 (1.0)	6 (1.5)	10 (1.2)
TZD only	5 (1.2)	3 (0.7)	8 (1.0)
Prior myocardial infarction, n (%)			
Yes	20 (5.0)	12 (2.9)	32 (3.9)
No	384 (95.0)	396 (97.1)	780 (96.1)

1. The p-value was for testing the null hypothesis that the summary statistics (mean or proportion) were equal among treatment groups. All tests were 2-sided.

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2. To calculate duration from a partial diagnosis date, a missing month was imputed as January and a missing day was imputed as the first of the month.
3. Statistically significant at the 0.05 level.

Results and Conclusions

Primary Efficacy Endpoint

Change From Baseline in HbA_{1c} at Week 32

Baseline HbA_{1c} values were comparable between the albiglutide group (8.18%) and the liraglutide group (8.15%). Both treatment groups had significant decreases in HbA_{1c}, -0.78% with 95% CI of (–0.87, –0.69) and –0.99% with 95% CI of (–1.08, –0.90) for the albiglutide group and the liraglutide group, respectively. The treatment difference for albiglutide minus liraglutide was 0.21% with a 95% CI of (0.08, 0.34). Since the upper bound of the 95% CI was 0.34%, which exceeded the prespecified noninferiority margin of 0.3%, noninferiority was not established (p=0.0846).

Analysis of Change From Baseline in HbA_{1c} (%) at Week 32 (Intent- to-Treat Population – LOCF)

	Albiglutide (N=402)	Liraglutide (N=403)
Number of subjects[1]	398	402
Number (%) of values carried forward	122 (30.7)	98 (24.4)
Baseline mean (SD)	8.18 (0.892)	8.15 (0.841)
Week 32 mean (SD)	7.39 (1.114)	7.18 (1.079)
Model-adjusted change from Baseline[2]		
Least squares mean	–0.78	–0.99
Standard error	0.047	0.046
95% confidence interval	(–0.87, –0.69)	(–1.08, –0.90)
Difference from liraglutide[2]		
Difference of least squares means	0.21	
95% confidence interval	(0.08, 0.34)	
Noninferiority p-value[3]	0.0846	

Note: This analysis used the LOCF method for missing postbaseline HbA_{1c} values. The HbA_{1c} values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values. Four subjects in the intent-to-treat (ITT) population had all postbaseline HbA_{1c} measurements occur more than 14 days after the last dose, and 1 ITT subject had all postbaseline HbA_{1c} measurements occur after hyperglycemic rescue. These 5 subjects are included in the ITT population counts but do not contribute to any of the ITT efficacy analyses for HbA_{1c}.

1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on ANCOVA: Change = treatment + baseline HbA_{1c} + prior myocardial infarction history + age category + region. The difference of least squares means (albiglutide – liraglutide) was from the ANCOVA model.
3. The p-value was from a 1-sided *t* test testing whether or not the difference of least square means (albiglutide – liraglutide) was less than or equal to the prespecified noninferiority margin of 0.3%.

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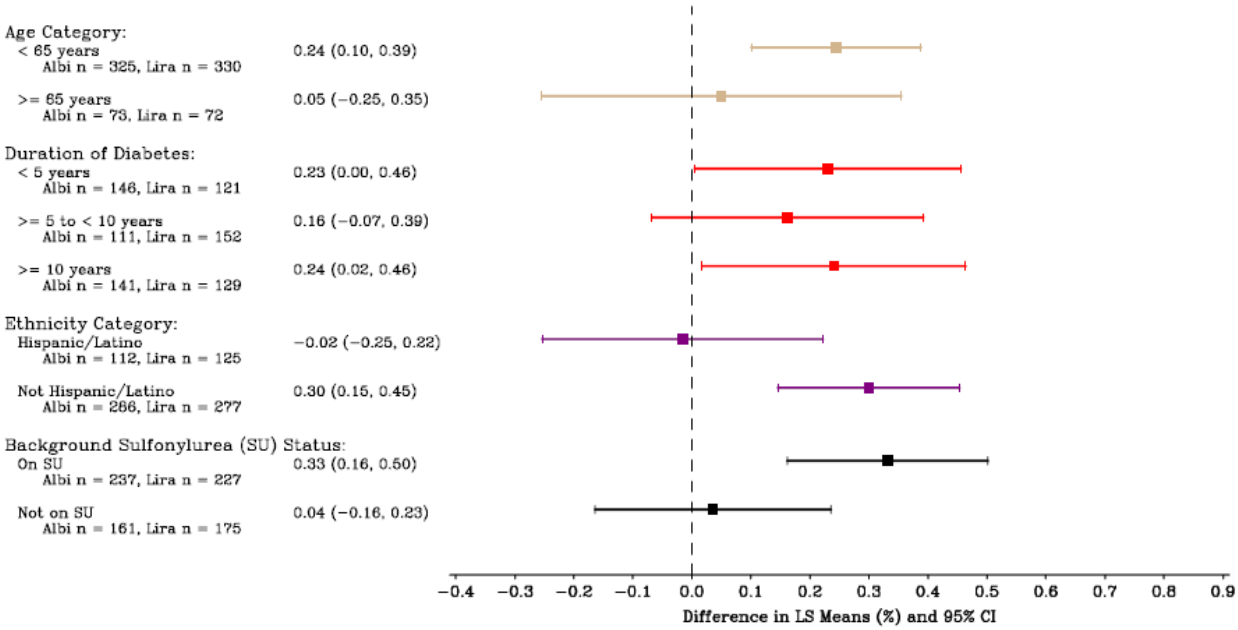
Reviewer's Conclusion: Non-inferiority of albiglutide to liraglutide was not shown. By my analyses, liraglutide was statistically superior to albiglutide.

Forest Plot of the Difference of Least Squares Mean Model-Adjusted Change From Baseline in HbA_{1c} (%) and 95% CI for Albiglutide Versus Liraglutide at Week 32 by Subgroup Category (Intent-to-Treat Population – LOCF)

The left side of the of the perpendicular line at zero represents the at least the numerical superiority of albiglutide.

There were statistically significant Treatment by Gender (male, female) (p=0.0079), by Ethnicity group (Hispanic/Latino, not Hispanic/Latino) (p=0.0288), and by Background therapy (With SU, Without SU) (p=0.0265) interactions.

The superiority of the liraglutide treatment was less pronounced in the male group. In the Hispanic/Latino group, albiglutide was marginally numerically superior to liraglutide. The superiority of the liraglutide treatment was less pronounced in the 'Not on SU' group.



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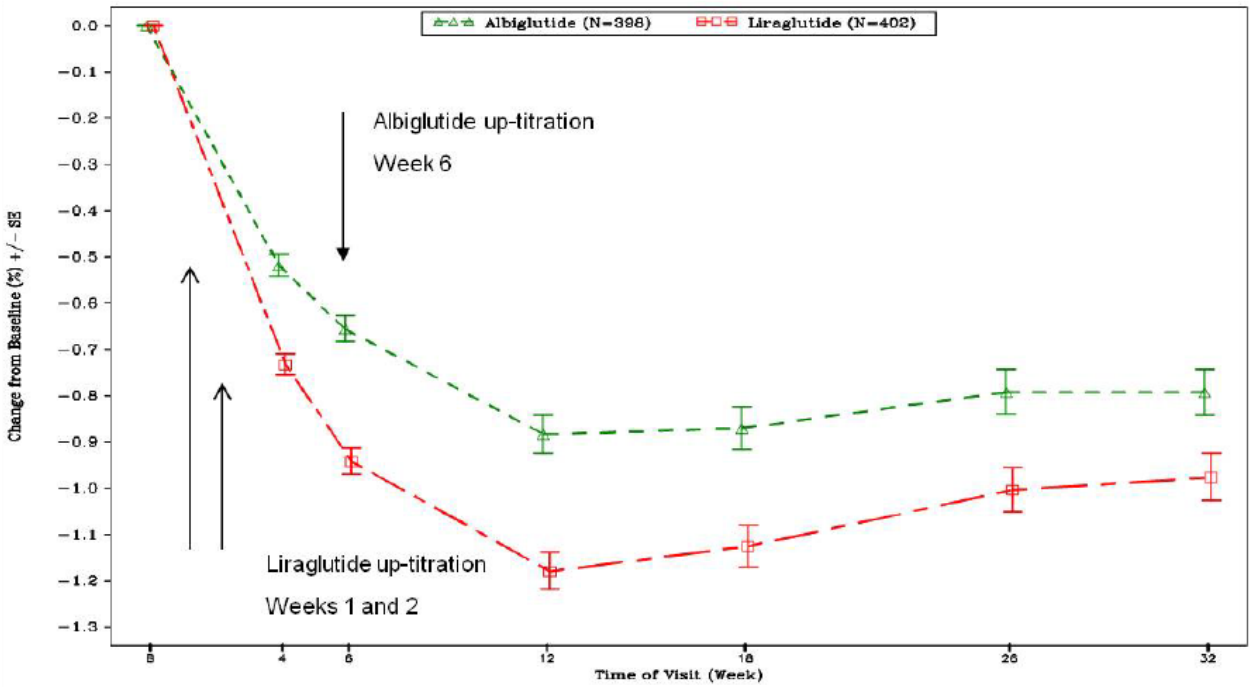
Line Graph of Mean (±SE) Change From Baseline in HbA_{1c} (%) Through Week 32 (Intent-to-Treat Population – LOCF)

Following line graphs show the superiority of liraglutide to albiglutide at all visits, at least numerically, with respect to HBA1c and FPG



Analysis of Change From Baseline in Fasting Plasma Glucose (mmol/L) at Week 32 (Intent-to-Treat Population – LOCF)

	Albiglutide (N=402)	Liraglutide (N=403)
Number of subjects[1]	400	402
Number (%) of values carried forward	123 (30.8)	98 (24.4)
Baseline mean (SD)	9.39 (2.912)	9.27 (2.697)
Week 32 mean (SD)	8.12 (2.722)	7.63 (2.580)
Model-adjusted change from Baseline[2]		
Least squares mean	−1.22	−1.68
Standard error	0.115	0.115
95% confidence interval	(−1.45, −1.00)	(−1.91, −1.46)
Difference from liraglutide[2]		
Difference of least squares means	0.46	
95% confidence interval	(0.14, 0.78)	
p-value	0.0048	

Note: This analysis used the LOCF method for missing postbaseline fasting plasma glucose (FPG) values. The FPG values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values.

1. Number of subjects with a value at Baseline and at the specified visit.

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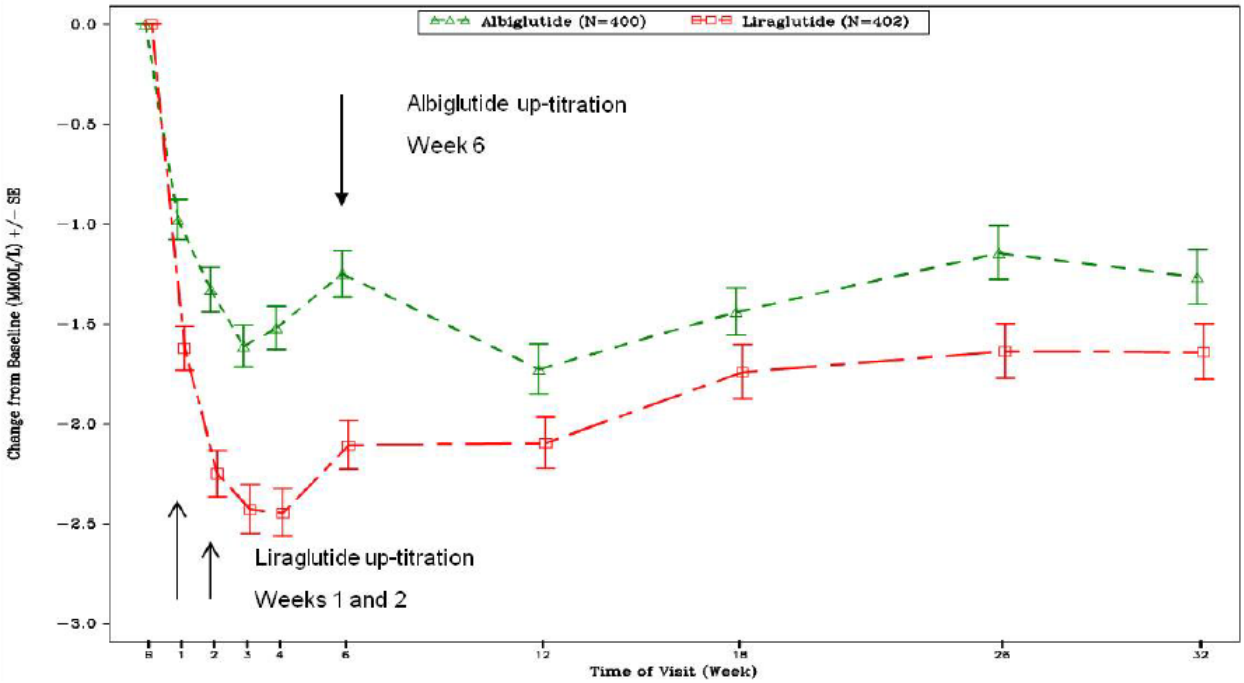
2. Based on ANCOVA: Change = treatment + baseline FPG + baseline HbA_{1c} category + prior myocardial infarction history + age category + region. The difference of least squares means (albiglutide – liraglutide) was from the ANCOVA model. The p-value was from a 2-sided *t* test for the difference in means.

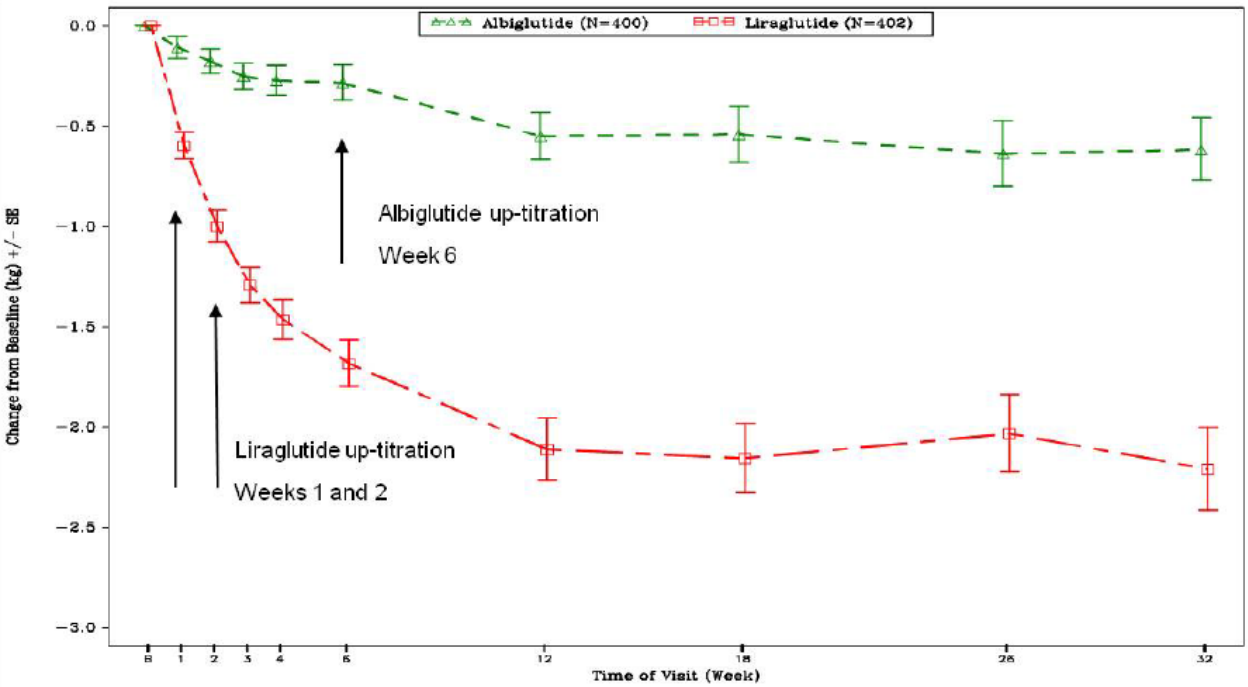
Note: Liraglutide was statistically superior to albiglutide.

Line Graph of Mean (±SE) Change From Baseline Fasting Plasma Glucose (mmol/L) Through Week 32 (Intent-to-Treat Population – LOCF)



Reference ID: 3392698

Line Graph of Mean (±SE) Change From Baseline in Weight (kg) Through Week 32 (Intent-to-Treat Population –LOCF)



Note: Liraglutide reduced weight statistically significantly more than albiglutide.

Analysis of Change From Baseline in Weight (kg) at Week 32 (Intent-to-Treat Population – LOCF)

	Albiglutide (N=402)	Liraglutide (N=403)
Number of subjects[1]	400	402
Number (%) of values carried forward	122 (30.5)	96 (23.9)
Baseline mean (SD)	91.54 (21.274)	92.94 (22.202)
Week 32 mean (SD)	90.92 (21.254)	90.73 (22.086)
Change from Baseline mean (SD)	−0.62 (3.118)	−2.21 (4.147)
Model-adjusted change from Baseline[2]		
Least squares mean	−0.64	−2.19
Standard error	0.182	0.182
95% confidence interval	(−1.00, −0.28)	(−2.55, −1.83)
Difference from liraglutide[2]		
Difference of least squares means	1.55	
95% confidence interval	(1.05, 2.06)	
p-value	<0.0001	

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Note: This analysis used the LOCF method for missing postbaseline weight values. Weight values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values.

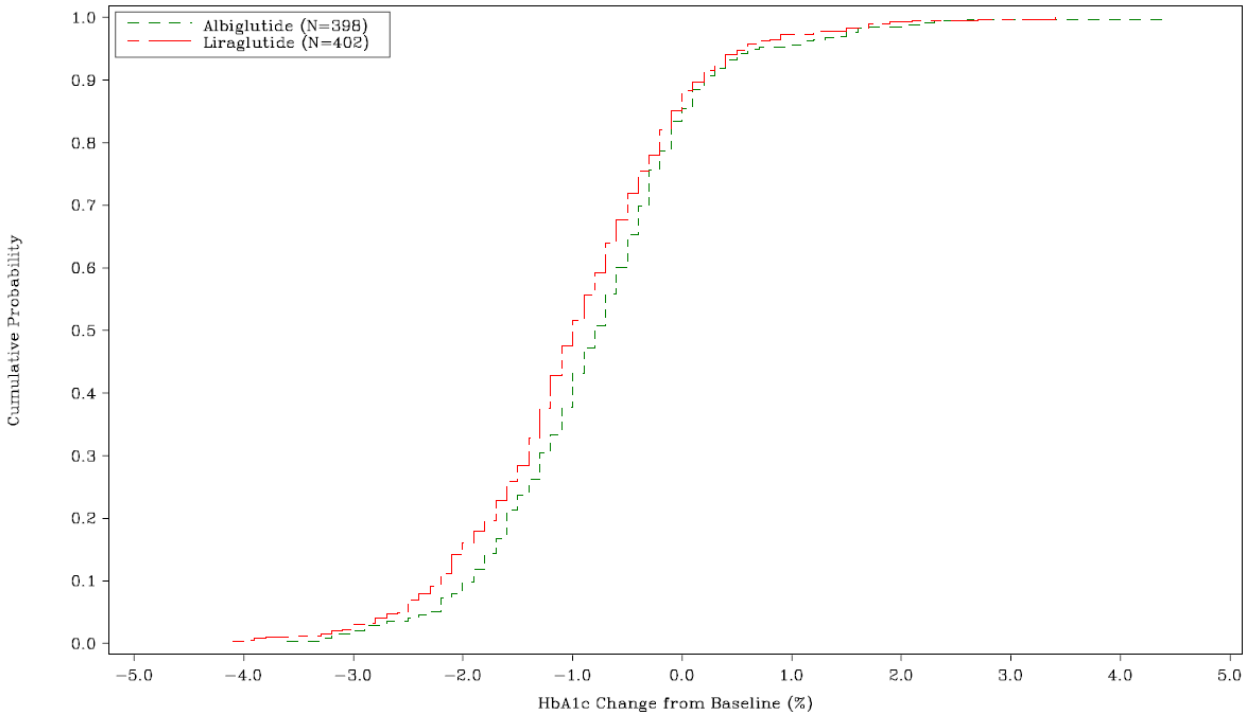
1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on ANCOVA: Change = treatment + baseline weight + baseline HbA_{1c} category + prior myocardial infarction history +

age category + region. The difference of least squares means (albiglutide – liraglutide) was from the ANCOVA model. The p-value was from a 2-sided *t* test for the difference in means.

§ Graphs of cumulative distribution functions by treatment groups for the primary efficacy variable (percent change from baseline in HbA1c) at the study endpoint are provided below. From these, the percent of patients (y-axis value) with a value of percent change from baseline in HbA1c at endpoint, smaller than or equal to a value on the x-axis, can be read.

Figure for Cumulative Distribution of HbA1c (%) Change From Baseline at Week 32 (Intent-to-treat Population-LOCF)

All percentiles of liraglutide were smaller than those for albiglutide.



Reference ID: 3392698

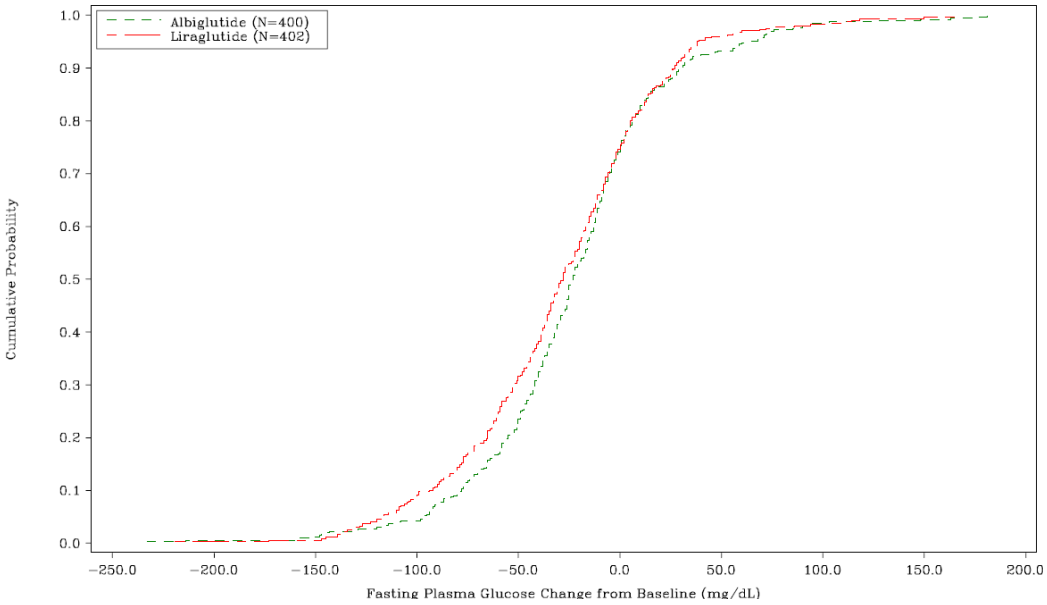
Cumulative Distribution of HbA1c (%) Change from Baseline at Week 32
(Intent-to-treat Population - LOCF)

Percentile	Albiglutide (N=402)	Liraglutide (N=403)
Number of subjects [1]	398	402
Min	-3.6	-4.1
1%	-3.20	-3.50
5%	-2.30	-2.50
10%	-1.90	-2.20
20%	-1.60	-1.70
30%	-1.30	-1.40
40%	-1.00	-1.20
50%	-0.80	-1.00
60%	-0.60	-0.70
70%	-0.30	-0.50
80%	-0.10	-0.20
90%	0.20	0.20
95%	0.70	0.60
99%	2.20	1.70
Max	4.4	3.4

Note: This summary uses the last observation carried forward (LOCF) method for missing post-baseline HbA1c values. HbA1c values obtained after hyperglycemia rescue are treated as missing and replaced with pre-rescue values.
[1] Number of subjects with a value at Week 32.

Cumulative Distribution of Fasting Plasma Glucose (mg/dL) Change from Baseline at Week 32 (Intent-to-treat Population-LOCF)

Except the first percentile, all other percentiles of liraglutide were smaller than those for albiglutide.



Reference ID: 3392698

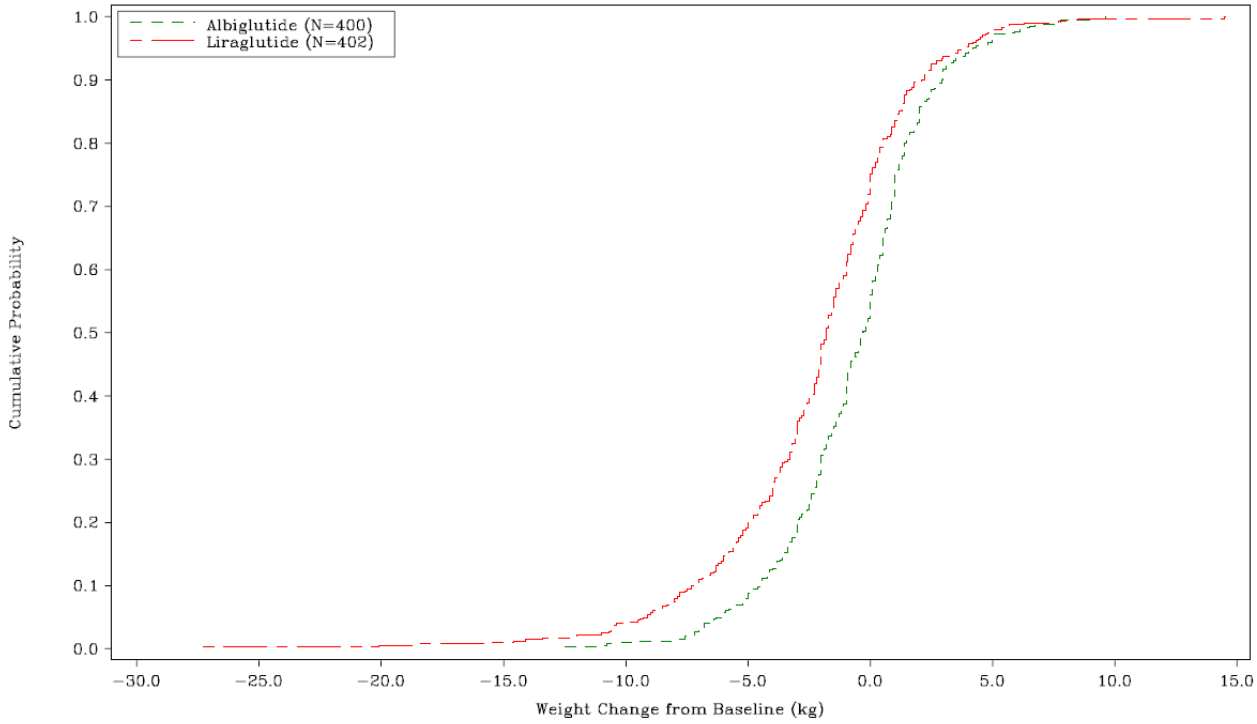
Cumulative Distribution of Fasting Plasma Glucose (mg/dL) Change from Baseline at Week 32 (Intent-to-treat Population - LOCF)

Percentile	Albiglutide (N=402)	Liraglutide (N=403)
Number of subjects [1]	400	402
Min	-233	-219
1%	-155.5	-145.0
5%	-97.0	-117.0
10%	-78.0	-92.0
20%	-55.0	-65.0
30%	-42.0	-52.0
40%	-32.0	-38.0
50%	-23.0	-28.0
60%	-13.0	-16.0
70%	-5.0	-6.0
80%	6.5	5.0
90%	30.0	27.0
95%	64.5	38.0
99%	136.0	114.0
Max	181	166

Note: This summary uses the last observation carried forward (LOCF) method for missing post-baseline fasting plasma glucose (FPG)values. FPG values obtained after hyperglycemia rescue are treated as missing and replaced with pre-rescue values.
[1] Number of subjects with a value at Week 32.

Cumulative Distribution of Weight (kg) Change from Baseline at Week 32 (Intent-to-treat Population- LOCF)

All percentiles of liraglutide were smaller than those for albiglutide.



Reference ID: 3392698

Cumulative Distribution of Weight (kg) Change from Baseline at Week 32
(Intent-to-treat Population - LOCF)

Percentile	Albiglutide (N=402)	Liraglutide (N=403)
Number of subjects [1]	400	402
Min	-12.5	-27.3
1%	-10.05	-14.60
5%	-6.15	-9.10
10%	-4.50	-7.20
20%	-3.00	-5.00
30%	-2.00	-3.30
40%	-1.00	-2.40
50%	-0.35	-1.80
60%	0.30	-1.00
70%	0.90	-0.20
80%	1.45	0.50
90%	2.95	2.10
95%	4.25	3.70
99%	7.60	6.30
Max	9.6	14.5

STUDY GLP114130

Title: A Randomized, Double-Blind, Active-Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide as Compared With Sitagliptin in Subjects With Type 2 Diabetes Mellitus With Renal Impairment

Study centers: This study was conducted at 134 study centers in 15 countries.

Study Period: 07-May-2010 through 30-May-2012

Phase of Development: III

Objectives: The primary objective of the study was to evaluate the efficacy of albiglutide as compared with sitagliptin on the glycosylated hemoglobin (HbA_{1c}) change from Baseline at Week 26.

Secondary efficacy objectives at the time points specified in the reporting and analysis plan (RAP) included the following evaluations of treatment with albiglutide compared with sitagliptin:

- HbA_{1c} change from Baseline over time
- Fasting plasma glucose (FPG) change from Baseline over time

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- Proportion of subjects at a HbA_{1c} treatment goal of less than 7.0%
- Proportion of subjects at a HbA_{1c} treatment goal of less than 6.5%
- Time to hyperglycemia rescue
- Change from Baseline in body weight
- Population pharmacokinetics of albiglutide and the effect of plasma concentrations of albiglutide on glycemic control (population pharmacokinetics/pharmacodynamics).

Methodology: This Phase III, randomized, double-blind, active-controlled, 2 parallel-group, multicenter, 52-week study evaluated the efficacy and safety of a weekly subcutaneously injected dose of albiglutide as compared with sitagliptin in renally impaired subjects with type 2 diabetes mellitus (T2DM). Renally impaired subjects with T2DM whose glycemia was inadequately controlled on their current regimen of diet and exercise or their antidiabetic therapy regimen of metformin, thiazolidinedione (TZD), sulfonylurea (SU), or any combination of these oral antidiabetic (OAD) medications were recruited into the study. Investigators must have adhered to the local labeling of the respective country (e.g., the summary of product characteristics in relevant European countries or the US Food and Drug Administration-approved prescribing information) when including subjects on a current regimen of metformin (protocol standardized on an eGFR of <60 mL/min/1.73 m^2), SU, or TZD. Subjects continued on their current regimen of OAD medication for the duration of the study, with the exception of those subjects who were on a regimen of metformin and/or an SU.

The study comprised 4 study periods: approximately 2 weeks of Prescreening and Screening, 4 weeks of Run-in, 52-week Treatment Period, including 26 weeks of initial treatment and evaluation for primary efficacy and safety followed by an additional 26 weeks of treatment for additional efficacy and safety, and 8 weeks of Posttreatment Follow-up.

Eligible subjects were stratified by severity of renal impairment (mild, moderate, and severe), prior history of myocardial infarction (MI) (yes and no), and age (<65 and ≥65 years of age). Adjudication and review of all major cardiovascular and pancreatitis events took place over the entire Treatment Period.

Number of subjects: Approximately 500 subjects were planned to be randomly assigned in a 1:1 ratio with albiglutide or sitagliptin. It was generally expected that not more than 50% of the subjects enrolled in the study would have mild renal impairment, with an original goal of enrolling 40% of the subjects with mild renal impairment and 60% of the subjects with moderate to severe renal impairment.

Diagnosis and main criteria for inclusion: Male and nonpregnant, nonlactating female subjects at least 18 years of age, with a historical diagnosis of T2DM who were experiencing inadequate glycemic control on their current regimen of diet and exercise or their antidiabetic therapy of metformin, TZD, SU, or any combination of these OAD medications. The subject's renal function was determined using the modification of diet in renal disease formula. The subject's eGFR was ≥15 and <90 mL/min/1.73 m^2 to be eligible for entry into the study. Mild

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renal impairment was defined as an eGFR of ≥60 and ≤89 mL/min/1.73 m^2, moderate renal impairment was defined as an eGFR of ≥30 and ≤59 mL/min/1.73 m^2, and severe renal impairment defined as an eGFR of ≥15 and ≤29 mL/min/1.73 m^2.

Treatment administration: The dosage and administration for each treatment groups was as follows:

- Albiglutide (30 mg weekly with treatment-masked uptitration, if needed, to 50 mg weekly) + sitagliptin matching placebo
- Albiglutide matching placebo + sitagliptin

The dose of sitagliptin was based on the subject's severity of renal impairment using the modification of diet and renal disease formula.

Albiglutide/matching placebo was supplied by GlaxoSmithKline (GSK) as a fixed-dose, fully disposable pen injector system for delivery of the investigational product from a prefilled, dual chamber glass cartridge that was an integral part of the pen. Each pen was intended for a single use by the subject and was designed for manual reconstitution of the dose, priming and insertion of the pen needle, and manual injection by the subject. Albiglutide was injected subcutaneously into the abdomen, alternating between left and right sides of the body. The pen was designed to work with standard pen needles. When the injector pen product was reconstituted by the subject (via rotation of the pen housing parts), a neutral, isotonic solution was produced. The pen delivered 30 or 50 mg of investigational product in a 0.5-mL injection volume.

Commercially available sitagliptin 25-, 50-, and 100-mg tablets that were either overencapsulated or overcoated were used. The placebo to match the sitagliptin was supplied as either an overencapsulated or overcoated tablet identical in appearance and packaging to sitagliptin.

Statistical methods (More details are in Appendix III)**:** The primary analysis of the HbA_{1c} change from Baseline response at Week 26 was applied to the intent-to-treat Population, using an analysis of covariance (ANCOVA) model with main effects for treatment group, region, renal impairment (mild, moderate, and severe) history of prior MI (yes and no), and age category (<65 years and >65 years) and with baseline HbA_{1c} as a continuous covariate. Treatment-effects estimates (and associated hypothesis tests) of albiglutide were evaluated within this ANCOVA model as least squares (LS) means contrasts relative to sitagliptin. The treatment effect was evaluated as a contrast of albiglutide versus sitagliptin. The albiglutide versus sitagliptin contrast was evaluated inferentially with a 1-sided *t* test at the 0.025 significance level. With significance for the noninferiority test, the superiority test was evaluated.

Subjects who were rescued for hyperglycemia before Week 26 had their last prerescue HbA_{1c} recorded and carried forward for primary analyses. Subjects who discontinued from active treatment for any reason before Week 26 had their last postbaseline HbA_{1c} observation (that was 14 days after last dose) carried forward for the analyses.

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The study randomly assigned approximately 250 subjects to each of the 2 treatment groups in a 1:1 ratio, for a total of 500 subjects. Eligible subjects were stratified by severity of renal impairment (mild, moderate, and severe), prior history of MI (yes and no), and age (<65 and ≥65 years of age).

Assuming an expected treatment effect of 0% and a standard deviation of 1.2%, the test of albiglutide versus sitagliptin had at least 91% power using a 1 sided, 2 sample *t* test and a test wise significance level of 0.025, with 200 completed subjects per treatment group for a noninferiority margin of 0.4. With the significance on the noninferiority hypothesis, the superiority hypothesis had at least 90% power to reject the null hypothesis if the actual albiglutide superiority was as small as 0.35% using a 2 sided, 2 sample *t* test and a test wise significance level of 0.05. Allowing for as great as 20% early withdrawal, loss to glycemic follow-up and rescue, the study randomly assigned 250 subjects to each of the 2 treatment groups.

Approximately 57% of albiglutide subjects had their doses uptitrated. The mean albiglutide dose at Week 26 was 40.2 mg, and the mean albiglutide dose at Week 52 was 42.4 mg.

More details on Study Design and Endpoints are in Appendix II.

Patient Disposition

This study was conducted at 134centers in 15 countries: United States of America (USA) (73 sites), South Africa (11 sites), India (10 sites), Peru (7 sites), Philippines (5 sites), Republic of Korea (5 sites), Australia (4 sites), Brazil (4 sites), Colombia (3 sites), Spain (3 sites), Israel (2 sites), Taiwan (2 sites), United Kingdom (2 sites), Germany (1 site), and Russia (1 site).

A total of 771 subjects were assessed for eligibility, and 507 subjects were randomly assigned to 1 of the 2 treatment groups. At least 97% of subjects in each of the treatment group received at least 1 dose of study medication.

The percentage of subjects completing active treatment through Week 26 was 86.6% in the albiglutide group compared with 81.4% in the sitagliptin group. The 2 most common reasons for discontinuing active treatment before Week 26 in both groups were AEs (5.1% of albiglutide subjects and 4.3% of sitagliptin subjects) and subject withdrew consent (2.4% of albiglutide subjects and 6.7% of sitagliptin subjects). Two subjects overall (1 subject in each treatment group) discontinued due to protocol violations.

The most common reasons for discontinuing active treatment before Week 60 in both groups were AEs and subject withdrawal of consent. Five subjects overall (1 subject in the albiglutide treatment group and 4 subjects in the sitagliptin treatment group) discontinued active treatment due to protocol violations.

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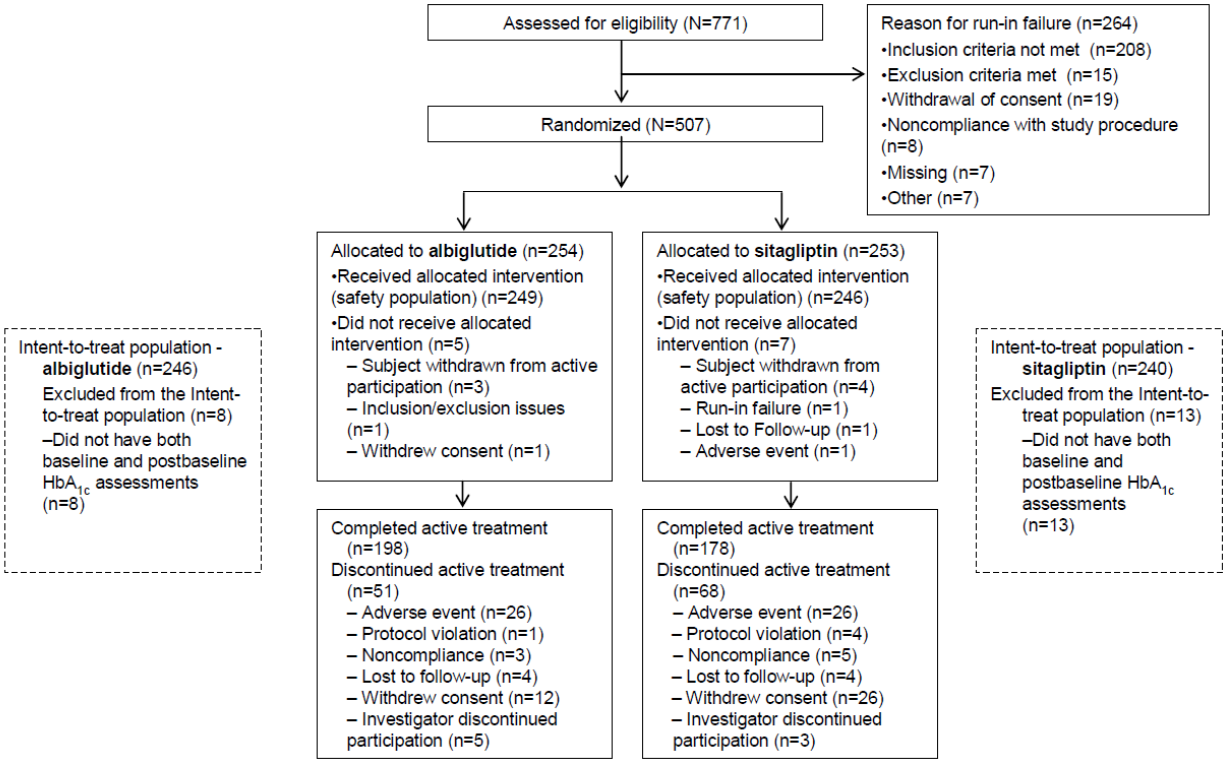
The number of subjects with mild, moderate, or severe renal impairment was similar between the treatment groups, but there were few subjects with severe renal impairment in both treatment groups. Therefore, results for subjects with severe renal impairment should be reviewed with caution.

Flow Diagram of Subject Disposition: Overall Data



Reference ID: 3392698

Subject Disposition: Overall Data Presented by Treatment Group and Renal Impairment Severity (Randomized Population)

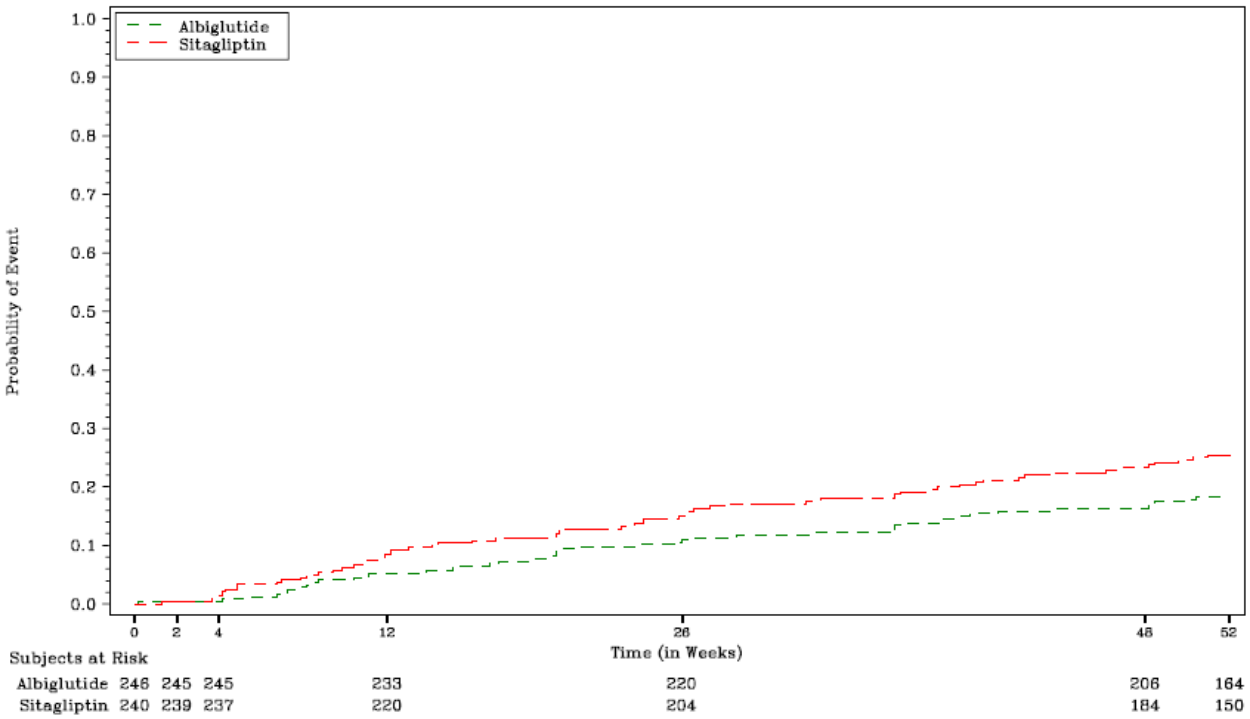
	Albiglutide (N=254) n (%)				Sitagliptin (N=253) n (%)				Overall Total (N=507) n (%)
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total	
Randomized Population	130 (100)	105 (100)	19 (100)	**254 (100.0)**	130 (100)	105 (100)	18 (100)	**253 (100.0)**	507 (100.0)
Intent-to-treat Population	126 (96.9)	101 (96.2)	19 (100)	**246 (96.9)**	124 (95.4)	99 (94.3)	17 (94.4)	**240 (94.9)**	486 (95.9)
Received at least 1 treatment dose (Safety Population)	128 (98.5)	102 (97.1)	19 (100)	**249 (98.0)**	128 (98.5)	101 (96.2)	17 (94.4)	**246 (97.2)**	495 (97.6)
Completed active treatment	107 (82.3)	76 (72.4)	15 (78.9)	**198 (78.0)**	107 (82.3)	61 (58.1)	10 (55.6)	**178 (70.4)**	376 (74.2)
Discontinued active treatment	21 (16.2)	26 (24.8)	4 (21.1)	**51 (20.1)**	21 (16.2)	40 (38.1)	7 (38.9)	**68 (26.9)**	119 (23.5)
Reason for discontinuing active treatment									
Adverse event	6 (4.6)	17 (16.2)	3 (15.8)	**26 (10.2)**	4 (3.1)	15 (14.3)	7 (38.9)	**26 (10.3)**	52 (10.3)
Protocol violation	0	1 (1.0)	0	**1 (0.4)**	0	4 (3.8)	0	**4 (1.6)**	5 (1.0)
Noncompliance	3 (2.3)	0	0	**3 (1.2)**	3 (2.3)	2 (1.9)	0	**5 (2.0)**	8 (1.6)
Severe or repeated occurrences of hypoglycaemia				**0**				**0**	0
Lost to follow-up	2 (1.5)	1 (1.0)	1 (5.3)	**4 (1.6)**	3 (2.3)	1 (1.0)	0	**4 (1.6)**	8 (1.6)
Subject withdrew consent from active participation	8 (6.2)	4 (3.8)	0	**12 (4.7)**	11 (8.5)	15 (14.3)	0	**26 (10.3)**	38 (7.5)
Investigator decided to discontinue participation	2 (1.5)	3 (2.9)	0	**5 (2.0)**	0	3 (2.9)	0	**3 (1.2)**	8 (1.6)

More than 94% of randomized subjects in each treatment group were included in the Safety and ITT Populations.

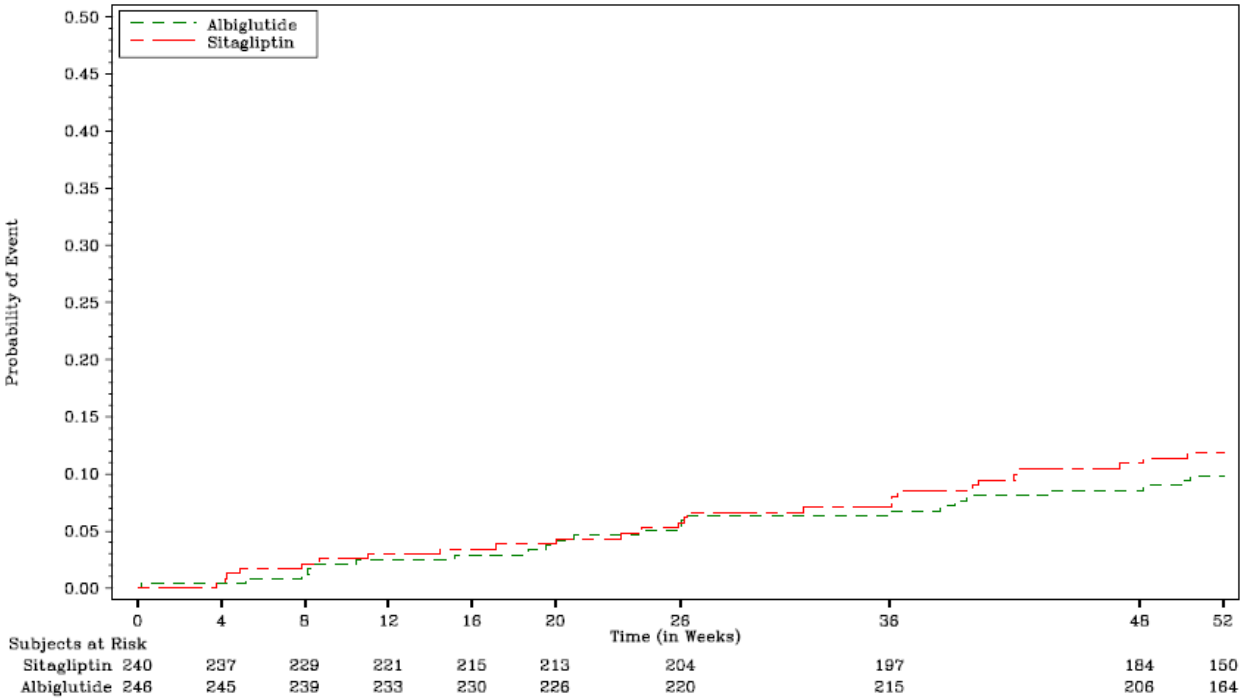
As seen from the following Kaplan-Meier plots, there were consistently more dropouts from the sitagliptin group. The dropouts due to adverse events were similar in the two treatment arms except after Week 32, when the sitagliptin arm had slightly more dropouts.

Reference ID: 3392698

Kaplan–Meier Plot of Time to Withdrawal from Treatment
(Intent–to–treat Population)



Kaplan–Meier Plot of Time to Withdrawal from Active Treatment due to Adverse Event
(Intent–to–treat Population)



Reference ID: 3392698

As seen from the following Table of demographics, the mean age was 63.2 in the albiglutide group and was 63.5 in the sitagliptin group.

Race was widely represented (details in the above Table), except almost none for two races - Native Hawaiian or other Pacific Islander and White - Arabic/North African heritage.

The percentage of male was 54.6 in the albiglutide group and was 52.8 in the sitagliptin group.

The mean weight was 83.3 in the albiglutide group and was 82.8 in the sitagliptin group.

Reference ID: 3392698

Demographic Characteristics: Overall Data Presented by Treatment Group and Renal Impairment Severity (Safety Population)

	Albiglutide				Sitagliptin				Overall
	Mild (N=128)	Moderate (N=102)	Severe (N=19)	Total (N=249)	Mild (N=128)	Moderate (N=101)	Severe (N=17)	Total (N=246)	Total (N=495)
Age at randomization (years)									
Mean (SD)	61.9 (7.82)	65.3 (8.67)	60.4 (8.21)	63.2 (8.37)	61.8 (8.83)	65.2 (9.02)	65.5 (8.63)	63.5 (9.02)	63.3 (8.69)
Median	61.0	65.5	62.0	63.0	62.0	65.0	64.0	64.0	63.0
Minimum, maximum	41, 80	43, 83	47, 74	41, 83	23, 80	33, 81	46, 82	23, 82	23, 83
Age category, n (%)									
<65 years	79 (61.7)	49 (48.0)	13 (68.4)	141 (56.6)	79 (61.7)	49 (48.5)	10 (58.8)	138 (56.1)	279 (56.4)
≥65 years	49 (38.3)	53 (52.0)	6 (31.6)	108 (43.4)	49 (38.3)	52 (51.5)	7 (41.2)	108 (43.9)	216 (43.6)
Sex, n (%)									
Female	61 (47.7)	42 (41.2)	10 (52.6)	113 (45.4)	55 (43.0)	48 (47.5)	13 (76.5)	116 (47.2)	229 (46.3)
Male	67 (52.3)	60 (58.8)	9 (47.4)	136 (54.6)	73 (57.0)	53 (52.5)	4 (23.5)	130 (52.8)	266 (53.7)
Race[2] n (%)				249				246	495
African American/African heritage				36 (14.5)				42 (17.1)	78 (15.8)
American Indian or Alaskan Native				16 (6.4)				16 (6.5)	32 (6.5)
Asian - Central/South Asian heritage				45 (18.1)				33 (13.4)	78 (15.8)
Asian - East Asian heritage				26 (10.4)				29 (11.8)	55 (11.1)
Asian - South East Asian heritage				13 (5.2)				14 (5.7)	27 (5.5)
Native Hawaiian or other Pacific Islander				1 (0.4)				0	1 (0.2)
White - Arabic/North African heritage				0				1 (0.4)	1 (0.2)
White - White/Caucasian/European heritage				113 (45.4)				113 (45.9)	226 (45.7)
Ethnicity, n (%)									
Hispanic/Latino	20 (15.6)	15 (14.7)	5 (26.3)	40 (16.1)	10 (7.8)	18 (17.8)	3 (17.6)	31 (12.6)	71 (14.3)

Reference ID: 3392698

	Albiglutide				Sitagliptin				Overall
	Mild (N=128)	Moderate (N=102)	Severe (N=19)	Total (N=249)	Mild (N=128)	Moderate (N=101)	Severe (N=17)	Total (N=246)	Total (N=495)
Not Hispanic/Latino	108 (84.4)	87 (85.3)	14 (73.7)	**209 (83.9)**	118 (92.2)	83 (82.2)	14 (82.4)	**215 (87.4)**	424 (85.7)
Weight (kg)									
Mean (SD)	84.74 (19.510)	81.71 (19.959)	81.46 (22.435)	**83.25 (19.902)**	86.17 (22.503)	78.25 (17.588)	84.95 (18.701)	**82.84 (20.649)**	83.04 (20.257)
Median	84.05	80.00	79.40	**81.60**	84.05	76.00	83.90	**79.60**	80.90
Minimum, maximum	45.9, 141.0	48.0, 135.4	49.3, 129.0	**45.9, 141.0**	49.0, 157.5	48.9, 130.1	49.0, 111.9	**48.9, 157.5**	45.9, 157.5
Body mass index (kg/m^2)									
Mean (SD)	30.34 (5.147)	30.19 (5.729)	31.26 (6.288)	**30.35 (5.466)**	31.06 (6.142)	29.34 (5.286)	32.18 (5.659)	**30.43 (5.828)**	30.39 (5.644)
Median	30.00	29.50	31.00	**30.00**	30.00	28.00	32.00	**30.00**	30.00
Minimum, maximum	21.0, 43.0	20.0, 46.0	21.0, 43.0	**20.0, 46.0**	21.0, 46.0	21.0, 45.0	23.0, 42.0	**21.0, 46.0**	20.0, 46.0
Body mass index category									
<25 kg/m^2	13 (10.2)	16 (15.7)	4 (21.1)	**33 (13.3)**	20 (15.6)	16 (15.8)	2 (11.8)	**38 (15.4)**	71 (14.3)
≥25 to <30 kg/m^2	50 (39.1)	35 (34.3)	4 (21.1)	**89 (35.7)**	37 (28.9)	42 (41.6)	3 (17.6)	**82 (33.3)**	171 (34.5)
≥30 to <35 kg/m^2	39 (30.5)	30 (29.4)	4 (21.1)	**73 (29.3)**	34 (26.6)	27 (26.7)	7 (41.2)	**68 (27.6)**	141 (28.5)
≥35 kg/m^2	26 (20.3)	21 (20.6)	7 (36.8)	**54 (21.7)**	37 (28.9)	16 (15.8)	5 (29.4)	**58 (23.6)**	112 (22.6)

1. The p-value was for testing the null hypothesis that the population values (mean or proportion) were equal among the 2 treatment groups (albiglutide and sitagliptin). All tests were 2-sided.
2. Subjects could be counted in more than 1 race category.

Most subjects (approximately 50% in each treatment group) had mild renal impairment at Baseline. A greater proportion of subjects in the albiglutide group had a baseline HbA_{1c} value of less than 8.0% compared with subjects in the sitagliptin group. No other statistically significant differences were observed for any other baseline diabetes characteristic.

The frequency of diabetic conditions, duration of diabetes, and percentage of subjects with previous MIs was higher for subjects with moderate or severe renal impairment than for subjects with mild renal impairment in both treatment groups. For subjects with mild renal impairment, there were statistically more subjects in the albiglutide group with a baseline HbA_{1c} value less than 8%; no other statistically significant difference between treatment groups by renal impairment was observed for any baseline diabetes characteristic.

Reference ID: 3392698

Baseline Diabetes Characteristics: Overall Data Presented by Treatment Group and Renal Impairment Severity (Safety Population)

	Albiglutide				Sitagliptin				Overall
	Mild (N=128)	Moderate (N=102)	Severe (N=19)	Total (N=249)	Mild (N=128)	Moderate (N=101)	Severe (N=17)	Total (N=246)	Total (N=495)
Subjects with any diabetic condition, n (%)	107 (83.6)	98 (96.1)	19 (100)	**224 (90.0)**	117 (91.4)	98 (97.0)	17 (100)	**232 (94.3)**	
Dyslipidaemia	88 (68.8)	79 (77.5)	10 (52.6)	**177 (71.1)**	89 (69.5)	70 (69.3)	13 (76.5)	**172 (69.9)**	
Chronic renal insufficiency	41 (32.0)	62 (60.8)	16 (84.2)	**119 (47.8)**	36 (28.1)	63 (62.4)	14 (82.4)	**113 (45.9)**	
Nephropathy	16 (12.5)	37 (36.3)	13 (68.4)	**66 (26.5)**	18 (14.1)	35 (34.7)	8 (47.1)	**61 (24.8)**	
Peripheral neuropathy	27 (21.1)	27 (26.5)	8 (42.1)	**62 (24.9)**	33 (25.8)	22 (21.8)	3 (17.6)	**58 (23.6)**	
Diabetic retinopathy	14 (10.9)	20 (19.6)	6 (31.6)	**40 (16.1)**	16 (12.5)	27 (26.7)	6 (35.3)	**49 (19.9)**	
Proteinuria	8 (6.3)	23 (22.5)	12 (63.2)	**43 (17.3)**	14 (10.9)	19 (18.8)	7 (41.2)	**40 (16.3)**	
Microalbuminuria	13 (10.2)	20 (19.6)	3 (15.8)	**36 (14.5)**	11 (8.6)	17 (16.8)	5 (29.4)	**33 (13.4)**	
Impotence	13 (10.2)	11 (10.8)	4 (21.1)	**28 (11.2)**	11 (8.6)	10 (9.9)	0	**21 (8.5)**	
Diabetic foot ulcer	1 (0.8)	2 (2.0)	4 (21.1)	**7 (2.8)**	1 (0.8)	2 (2.0)	1 (5.9)	**4 (1.6)**	
Autonomic neuropathy	3 (2.3)	0	2 (10.5)	**5 (2.0)**	1 (0.8)	0	0	**1 (0.4)**	
Other: renal arthro dystrophy	0	1 (1.0)	0	**1 (0.4)**	0	0	0	**0**	
Duration of diabetes (years)[2]									
Mean (SD)	9.41 (6.834)	11.70 (7.502)	15.77 (8.074)	**10.83 (7.403)**	10.01 (7.141)	13.53 (9.076)	12.49 (11.660)	**11.62 (8.476)**	11.23 (7.956)
Median	7.91	10.88	16.12	**9.47**	8.76	11.62	10.92	**10.62**	9.84
Minimum, Maximum	0.3, 35.8	0.3, 32.7	5.0, 29.9	**0.3, 35.8**	0.4, 32.7	0.7, 43.9	1.8, 51.0	**0.4, 51.0**	0.3, 51.0
Duration Category, n (%)									
<7 years	57 (44.5)	36 (35.3)	6 (31.6)	**99 (39.8)**	56 (43.8)	25 (24.8)	7 (41.2)	**88 (35.8)**	187 (37.8)
≥7 to ≤13 years	45 (35.2)	29 (28.4)	1 (5.3)	**75 (30.1)**	35 (27.3)	34 (33.7)	4 (23.5)	**73 (29.7)**	148 (29.9)
>13 years	26 (20.3)	37 (36.3)	12 (63.2)	**75 (30.1)**	27 (28.9)	42 (41.6)	6 (35.3)	**85 (34.6)**	160 (32.3)
Baseline HbA_{1c} (%)									
Mean (SD)	8.03 (1.147)	8.26 (0.924)	8.05 (0.746)	**8.13 (1.036)**	8.16 (0.896)	8.26 (0.945)	8.60 (1.196)	**8.23 (0.942)**	8.18 (0.991)
Median	7.80	8.00	8.00	**7.90**	8.00	8.20	8.40	**8.10**	8.00
Minimum, Maximum	6.9, 17.3	6.9, 10.9	7.0, 9.7	**6.9, 17.3**	6.6, 10.4	6.0, 11.0	7.2, 11.4	**6.0, 11.4**	6.0, 17.3
Baseline HbA_{1c} category, n (%)									
<8.0%	77 (60.2)	45 (44.1)	9 (47.4)	**131 (52.6)**	57 (44.5)	44 (43.6)	6 (35.3)	**107 (43.5)**	238 (48.1)
	Albiglutide				Sitagliptin				Overall
	Mild (N=128)	Moderate (N=102)	Severe (N=19)	Total (N=249)	Mild (N=128)	Moderate (N=101)	Severe (N=17)	Total (N=246)	Total (N=495)
≥8.0%	51 (39.8)	57 (55.9)	10 (52.6)	**118 (47.4)**	71 (55.5)	57 (56.4)	11 (64.7)	**139 (56.5)**	257 (51.9)
Severity of renal impairment, n (%)									
Mild				**128 (51.4)**				**128 (52.0)**	256 (51.7)
Moderate				**102 (41.0)**				**101 (41.1)**	203 (41.0)
Severe				**19 (7.6)**				**17 (6.9)**	36 (7.3)
Prior myocardial infarction, n (%)									
Yes	9 (7.0)	10 (9.8)	2 (10.5)	**21 (8.4)**	9 (7.0)	10 (9.9)	3 (17.6)	**22 (8.9)**	43 (8.7)
No	119 (93.0)	92 (90.2)	17 (89.5)	**228 (91.6)**	119 (93.0)	91 (90.1)	14 (82.4)	**224 (91.1)**	452 (91.3)

HbA1c = glycosylated hemoglobin; SD = standard deviation.

1. The p-value was for testing the null hypothesis that the summary statistics (mean or proportion) were equal among 2 treatment groups (albiglutide and sitagliptin). All tests were 2-sided.
2. To calculate duration from a partial diagnosis date, a missing month was imputed as January and a missing day was imputed as the first of the month.

Results and Conclusions

The primary efficacy objective was to evaluate the efficacy of albiglutide administered as 30 mg (optionally uptitrated to 50 mg, if required) once per week compared with sitagliptin. The dose of albiglutide was the same in all subjects regardless of renal impairment severity (mild, moderate, or severe), while the dose of sitagliptin varied by degree of renal impairment severity consistent with the sitagliptin prescribing information (25 mg, 50 mg, or 100 mg). The primary efficacy endpoint was the change in HbA_{1c} from Baseline to Week 26 and is a combination of 30-mg and 50-mg albiglutide.

Results from the primary efficacy endpoint analysis are presented first in this section followed by supporting and sensitivity analyses on this endpoint. Additionally, subgroup analyses were

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conducted for the primary efficacy endpoint based on Baseline and demographic characteristics, GI AE (nausea/vomiting/diarrhea and nausea/vomiting) experience, and timing of hyperglycemia rescue. Subgroup analysis results are presented following the supporting and sensitivity analyses on the primary endpoint. In addition, analyses for the primary efficacy endpoint based on renal impairment severity and GI AE experience based on renal impairment severity are also presented.

After primary efficacy and associated results, results for key secondary efficacy variables are presented, including change from Baseline in HbA_{1c} and FPG over time, time to hyperglycemia rescue, proportions of subjects meeting prespecified HbA_{1c} treatment goals, and changes in body weight over time. Subgroup analyses were also conducted for the key secondary endpoint of change from Baseline in FPG through Week 26, as well as change from Baseline in FPG by renal impairment severity. Analyses on proportion of subjects meeting prespecified HbA_{1c} treatment goals and change from Baseline in weight are also presented. These results are briefly summarized following results for FPG in the overall ITT Population.

Exploratory analyses are presented including fasting insulin change from Baseline over time, the proportion of subjects with hyperglycemia rescue, time to withdrawal from randomly assigned treatment, the EQ-5D questionnaires, and the eGFR change from Baseline over time. Finally, results for change from Baseline through Week 52 for the above endpoints are then presented. Albumin/creatinine ratio results are presented with the safety analyses in Section 7.3.2.4.

For each of the primary, secondary, and exploratory endpoints, results are presented with emphasis on Week 26 results and using the LOCF algorithm unless otherwise specified. Results are presented using the traditional LOCF algorithm with missing data imputation and, in addition, results are presented using OC (Observed Cases) results excluding data points obtained after hyperglycemic rescue (OC algorithm excluding postrescue values). The OC (Observed Cases) algorithm excluding postrescue value may be considered a best case scenario. Finally, results were also analyzed using a second OC (Observed Cases) algorithm method, in which the postrescue values were included in the analyses and no missing data imputation was performed. The OC (Observed Cases) algorithm including postrescue values may be considered the “real world” situation, as diabetic patients are not typically removed from treatment because they require additional glucose-lowering rescue medications. This allows the reader to examine the data after the addition of nonrandomized rescue medications given to subjects in this study which has the potential to impact the underlying treatment effect.

Where data were summarized using both International System of Units (SI) and conventional units, SI units are presented and summarized in the text. Posttext tables presenting data using the OC (Observed Cases) algorithm (where not presented in text), with and without postrescue values, and using conventional units are referenced throughout the text.

Primary Efficacy Endpoint

Reviewer’s Conclusion: Albiglutide was statistically superior to sitagliptin.

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HbA_{1c} Change From Baseline at Week 26

A decrease in mean HbA_{1c} from Baseline to Week 26 was observed in both the albiglutide and sitagliptin treatment groups. The HbA_{1c} values for subjects in the albiglutide group were lower than for subjects in the sitagliptin group at each time point through Week 26. When adjusted for renal impairment, region, history of prior MI, age category, and baseline HbA_{1c}, the model-adjusted LS mean change in HbA_{1c} from Baseline to Week 26 was –0.83% in the albiglutide group and –0.52% in the sitagliptin group. The treatment difference (albiglutide - sitagliptin) was –0.32% (95% CI: –0.49%, –0.15%). The upper bound of the CI was below the prespecified noninferiority margin of 0.4%, indicating noninferiority of albiglutide to sitagliptin. In accordance with a prespecified, step-wise procedure, a superiority test of the albiglutide group versus the sitagliptin group at Week 26 was performed and the result showed that albiglutide was statistically superior to sitagliptin (p=0.0003).

Analysis of Change From Baseline in HbA_{1c} (%) at Week 26: Overall Data (ITT Population – LOCF)

	Albiglutide (N=246)	Sitagliptin (N=240)
Number of subjects[1]	242	236
Number (%) of values carried forward	40 (16.5)	58 (24.6)
Baseline – mean (SD)	8.08 (0.858)	8.22 (0.908)
Week 26 – mean (SD)	7.27 (1.017)	7.68 (1.246)
Change from Baseline – mean (SD)	-0.82 (0.900)	-0.54 (1.115)
Model-adjusted change from Baseline[2]		
LS mean (SE)	-0.83 (0.062)	-0.52 (0.063)
95% CI	(-0.96, -0.71)	(-0.64, -0.39)
Difference from sitagliptin[2]		
Difference of LS means	-0.32	
95% CI	(-0.49, -0.15)	
Noninferiority p-value[3]	<0.0001	
Superiority p-value[4]	0.0003	

ANCOVA = analysis of covariance; CI = confidence interval; HbA1c = glycosylated hemoglobin; ITT = intent to treat; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; SE = standard error.

Note: This analysis used the LOCF method for missing postbaseline HbA1c values. The HbA1c values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values. Five ITT subjects had all post-baseline HbA1c measurements occur more than 14 days after last dose and three ITT subjects had all post-baseline HbA1c measurements occur after hyperglycemic rescue. These eight subjects are included in the header ITT population counts but did not contribute to any of the ITT efficacy analyses.

1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on ANCOVA: Change = treatment + baseline HbA1c + renal impairment + prior myocardial infarction history + age category + region. The difference of LS means (albiglutide – sitagliptin) is from the ANCOVA model. The p-value is from a 2-sided *t* test for the difference in means.
3. This p-value was from a 1-sided *t* test to test whether the difference of LS means (albiglutide – sitagliptin) was less than or equal to the prespecified noninferiority margin of 0.4%.
4. This p-value was from a 2-sided *t* test to test whether the difference in the LS means (albiglutide – sitagliptin) was equal to zero. If the noninferiority test was not significant then no superiority testing was performed and p-value was not applicable.

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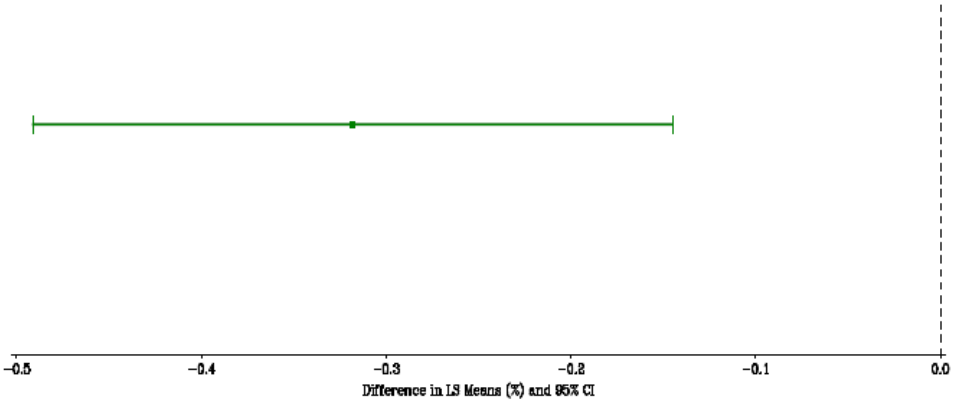
Model-Adjusted Change From Baseline in HbA_{1c} (%) for Albiglutide Versus Sitagliptin and 95% CI at Week 26: Overall Data (ITT Population – LOCF)



CI = confidence interval; HbA_{1c} = glycosylated hemoglobin; ITT = intent to treat; LS = least squares; LOCF = last observation carried forward.

Supporting Analyses on Primary Efficacy Endpoint

Supportive analyses on the primary efficacy endpoint did not show any treatment by variable interactions of concern for region, age category, history of prior MI, renal impairment severity, or baseline HbA_{1c} and were supportive of the use of the main effects model to evaluate the primary efficacy hypothesis. All the secondary analyses were consistent with the primary analysis.

Sensitivity Analyses on Primary Efficacy Endpoint

Two sensitivity analyses on the primary endpoint were performed.

A sensitivity analysis was performed to evaluate the LOCF algorithm in the presence of rescue medication. This analysis was an OC (Observed Cases) analysis that used observed HbA_{1c} values with no missing data imputation. It was conducted to include results with the presence of rescue medication and adjust for the rescue medication effect. The results of this analysis are consistent with the model using the LOCF algorithm in that the LS mean decrease from Baseline in HbA_{1c} was larger in the albiglutide arm. The analysis produced a smaller treatment difference of –0.27% (95% CI: –0.42%, –0.12%), which was statistically significant (p=0.0004). The results also indicated that the rescue status had a significant effect on HbA_{1c} change from Baseline (p=0.001). Subjects who required rescue medication had less HbA_{1c}

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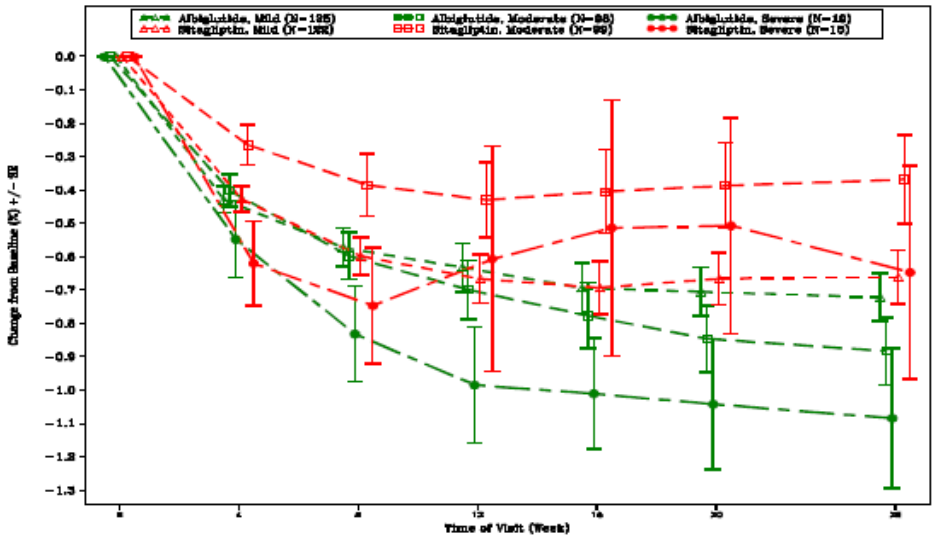
reduction than those who did not require rescue medication, and there was a treatment-by-rescue interaction (p=0.0005).

Another sensitivity analysis was performed to evaluate the primary endpoint in the ITT Population using the LOCF algorithm after excluding major protocol violations identified before database freeze. The results of this sensitivity analysis were similar to those for the primary analysis, indicating that the exclusion of data obtained from subjects with a major protocol violation did not bias the results for the primary efficacy endpoint.

HbA_{1c} Change From Baseline at Week 26 by Renal Impairment Severity

The mean change from Baseline HbA_{1c} value was consistently greater in the albiglutide group than in the sitagliptin group at Week 26 for subjects with baseline renal impairment severity mild, moderate or severe. The treatment difference at Week 26 (albiglutide - sitagliptin) was –0.13 (95% CI: –0.37, 0.11), –0.53 (95% CI: (–0.80, –0.26), and –0.47 (95% CI: –1.12, 0.18) for subjects with mild, moderate or severe renal impairment, respectively.

Line Graph of Mean Change from Baseline in HbA_{1c} (%) Through Week 26 by Renal Impairment Severity (ITT Population – LOCF)



B = Baseline; ITT = intent to treat; LOCF = last observation carried forward; SE = standard error.

To evaluate consistency of efficacy among subjects with different baseline renal impairment severity, the change from Baseline of HbA_{1c} at Week 26 was plotted against baseline eGFR. Baseline eGFR did not appear to have an effect on HbA_{1c} change from Baseline at Week 26.

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Table for Analysis of Change From Baseline in HbA_{1c} (%) at Week 26 by Renal Impairment Severity (ITT Population – LOCF)

	Albiglutide (N=246)			Sitagliptin (N=240)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Number of subjects[1]	125	98	19	122	99	15
Number (%) of values carried forward	17 (13.6)	21 (21.4)	2 (10.5)	15 (12.3)	37 (37.4)	6 (40.0)
Baseline – mean (SD)	7.96 (0.804)	8.26 (0.922)	8.05 (0.746)	8.16 (0.894)	8.28 (0.927)	8.32 (0.922)
Week 26 – mean (SD)	7.23 (0.887)	7.37 (1.144)	6.97 (1.103)	7.50 (1.066)	7.91 (1.413)	7.67 (1.261)
Change from Baseline – mean (SD)	-0.72 (0.807)	-0.88 (0.998)	-1.08 (0.914)	-0.66 (0.879)	-0.37 (1.325)	-0.65 (1.239)
Model-adjusted change from Baseline[2]						
LS mean (SE)	-0.80 (0.087)	-0.83 (0.097)	-1.08 (0.221)	-0.67 (0.087)	-0.31 (0.097)	-0.61 (0.249)
95% CI	(-0.97, -0.63)	(-1.03, -0.64)	(-1.52, -0.65)	(-0.84, -0.50)	(-0.50, -0.12)	(-1.10, -0.12)
Difference from sitagliptin[2]						
Difference of LS means	-0.13	-0.53	-0.47			
95% CI	(-0.37, 0.11)	(-0.80, -0.26)	(-1.12, 0.18)			

CI = confidence interval; HbA_{1c} = glycosylated hemoglobin; ITT = intent to treat; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; SE = standard error.

Note: This analysis used the LOCF method for missing postbaseline HbA_{1c} values. The HbA_{1c} values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values.

1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on analysis of covariance (ANCOVA): Change = treatment + baseline HbA_{1c} + renal impairment + prior myocardial infarction history + age category + region + treatment*renal impairment. The difference of least squares means (albiglutide - sitagliptin) is from ANCOVA model. The p-value for the interaction term = 0.0855.

The HbA_{1c} values for subjects in the albiglutide group were generally lower than for subjects in the sitagliptin group at each time point through Week 26 and irrespective of baseline renal impairment status.

§ Graphs of cumulative distribution functions by treatment groups for the primary efficacy variable (percent change from baseline in HbA1c) at the study endpoint are provided below. From these, the percent of patients (y-axis value) with a value of percent change from baseline in HbA1c at endpoint, smaller than or equal to a value on the x-axis, can be read.

As seen from the cumulative distribution curve below, all the percentiles of albiglutide were smaller than those of sitagliptin.

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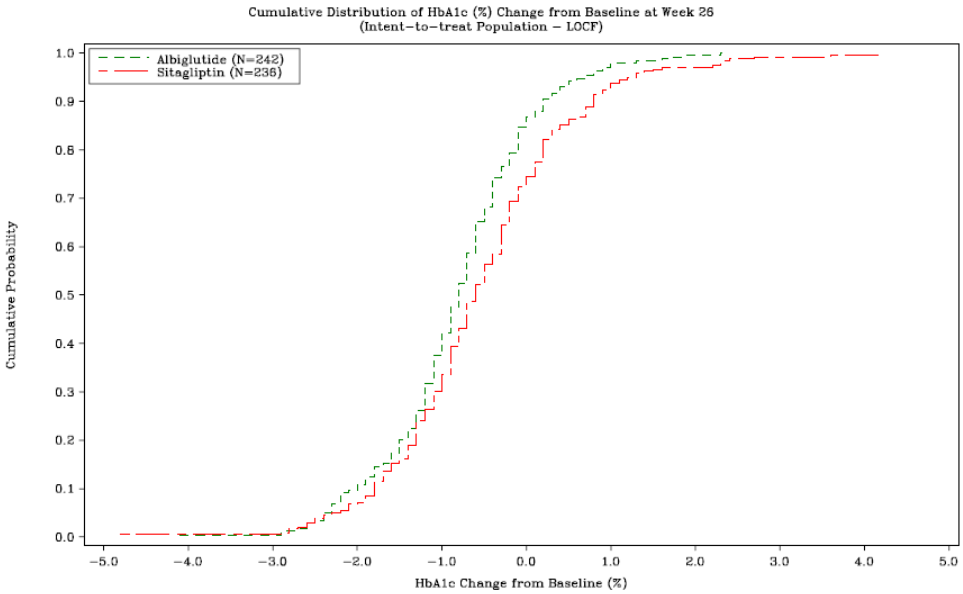

Secondary Endpoints

HbA_{1c} Change From Baseline Over Time Through Week 26

Decreases in HbA_{1c} from Baseline to Week 26 were observed in both the albiglutide and sitagliptin treatment groups, with an initial steep decline from Baseline through Week 12. After Week 12, the HbA_{1c} change from Baseline continued to decrease in the albiglutide group while it appeared to reach a plateau in the sitagliptin group. At each visit, the magnitude of change from Baseline was greater for the albiglutide group.

As seen from the following line graph, albiglutide was at least numerically superior to sitagliptin at all visits.

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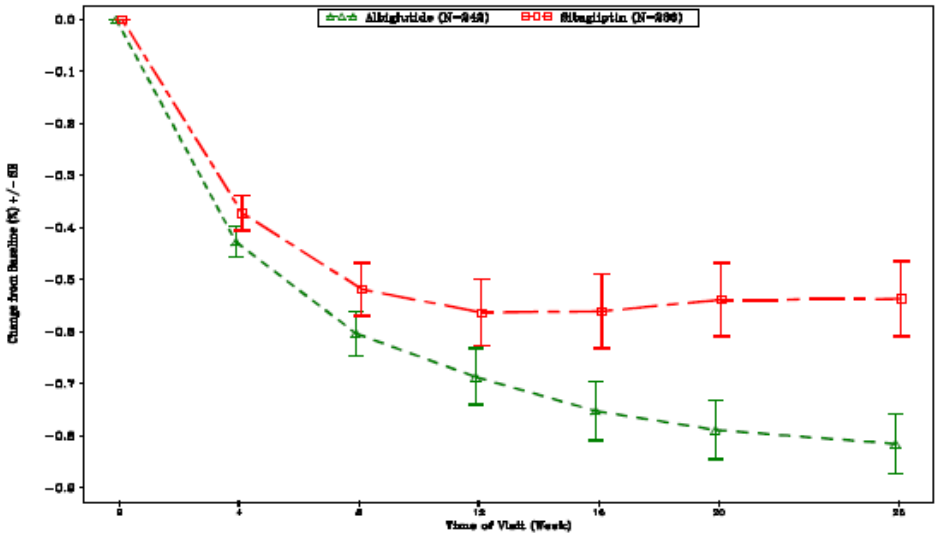
Line Graph of Mean Change From Baseline in HbA_{1c} (%) Through Week 26 (ITT Population – LOCF)



B = Baseline; HbA_{1c} = glycosylated hemoglobin; ITT = intent to treat; LOCF = last observation carried forward; SE = standard error.

Summary Statistics for Change From Baseline in HbA_{1c} (%) Through Week 26 (ITT Population – LOCF)

	Albiglutide (N=246)	Sitagliptin (N=240)
Week 4 change from Baseline – number of subjects[1]	237	234
Mean (SD)	-0.43 (0.460)	-0.37 (0.512)
Median	-0.40	-0.40
Minimum, maximum	-2.3, 0.6	-2.8, 1.3
Week 8 change from Baseline – number of subjects[1]	242	236
Mean (SD)	-0.60 (0.663)	-0.52 (0.785)
Median	-0.60	-0.60
Minimum, maximum	-3.2, 1.3	-4.0, 3.6
Week 12 change from Baseline – number of subjects[1]	242	236
Mean (SD)	-0.69 (0.840)	-0.56 (0.989)
Median	-0.70	-0.60
Minimum, maximum	-3.8, 2.1	-4.5, 3.6
Week 16 change from Baseline – number of subjects[1]	242	236
Mean (SD)	-0.75 (0.886)	-0.56 (1.103)
Median	-0.80	-0.60
Minimum, maximum	-4.1, 2.0	-4.8, 4.2
Week 20 change from Baseline – number of subjects[1]	242	236
Mean (SD)	-0.79 (0.890)	-0.54 (1.083)
Median	-0.80	-0.60
Minimum, maximum	-4.0, 2.3	-4.8, 4.2
Week 26 change from Baseline – number of subjects[1]	242	236
Mean (SD)	-0.82 (0.900)	-0.54 (1.115)
Median	-0.80	-0.60
Minimum, maximum	-4.1, 2.3	-4.8, 4.2

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HbA_{1c} = glycosylated hemoglobin; ITT = intent to treat; LOCF = last observation carried forward; SD = standard deviation.

Note: This summary used the last observation carried forward (LOCF) method for missing postbaseline HbA_{1c} values. The HbA_{1c} values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values. Baseline was defined as the last available assessment on or prior to the first dose of study medication.

1. Number of subjects with a value at Baseline and at the specified visit is displayed.

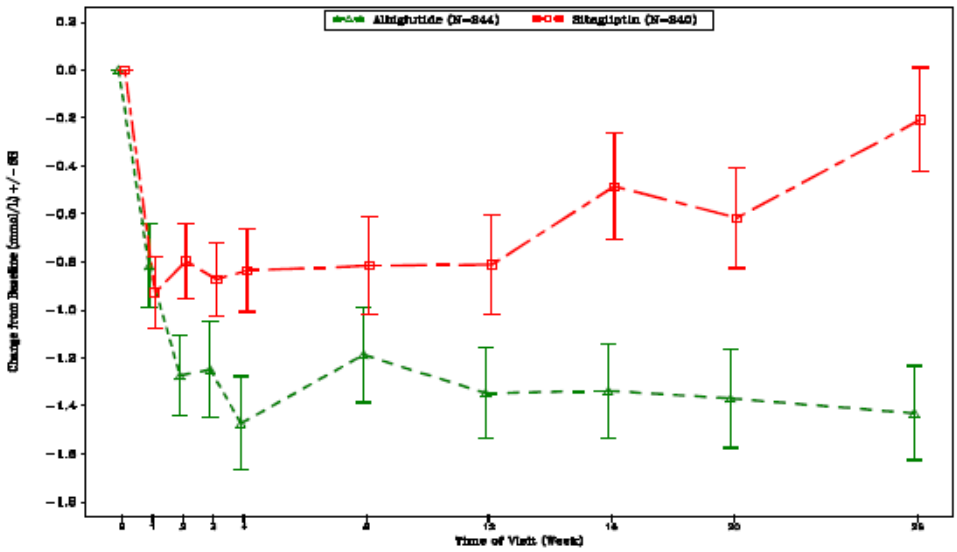
Fasting Plasma Glucose Change From Baseline Over Time Through Week 26

For the albiglutide group, changes in FPG over time were consistent with results for changes in HbA_{1c} from Baseline over time with an initial steep decline from Baseline through Week 4 which was maintained through Week 26. For the sitagliptin group, the changes were also consistent with results for changes in HbA_{1c} from Baseline. Importantly, from Week 12 through Week 26, the results in the albiglutide group were durable whereas the mean FPG in the sitagliptin group increased. The change from Baseline at each visit was less in the sitagliptin treatment group than for the albiglutide treatment group.

At Week 26, significant differences were observed in favor of albiglutide ($p<0.0001$).

As seen from the following line graph, albiglutide was at least numerically superior to sitagliptin at all visits, with respect to FPG.

Line Graph of Mean Change From Baseline in FPG (mmol/L) Through Week 26 (ITT Population – LOCF)



B = baseline; FPG = fasting plasma glucose; ITT = intent to treat; LOCF = last observation carried forward; SE = standard error.

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Analysis of Change From Baseline in FPG (mmol/L) at Week 26:
Overall Data (ITT Population – LOCF)

Note: Albiglutide was statistically superior to sitagliptin with respect to FPG.

	Albiglutide (N=246)	Sitagliptin (N=240)
Number of subjects[1]	244	240
Number (%) of values carried forward	44 (18.0)	63 (26.3)
Baseline – mean (SD)	9.18 (3.231)	9.16 (2.873)
Week 26 – mean (SD)	7.75 (3.104)	8.95 (3.456)
Change from Baseline – mean (SD)	-1.43 (3.085)	-0.21 (3.351)
Model-adjusted change from Baseline[2]		
LS mean (SE)	-1.42 (0.183)	-0.22 (0.184)
95% CI	(-1.78, -1.06)	(-0.58, 0.14)
Difference from sitagliptin[2]		
Difference of LS means	-1.20	
95% CI	(-1.71, -0.69)	
p-value	<0.0001	

CI = confidence interval; FPG = fasting plasma glucose; ITT = intent to treat; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; SE = standard error.
Note: This analysis used the LOCF method for missing postbaseline fasting plasma glucose (FPG) values. The FPG values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values.
1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on analysis of covariance (ANCOVA): Change = treatment + baseline FPG + renal impairment + prior myocardial infarction history + age category + region. The difference of least squares means (albiglutide – sitagliptin) is from the ANCOVA model. The p-value is from a 2-sided *t* test for the difference in means.

§ Graphs of cumulative distribution functions by treatment groups for the primary efficacy variable (percent change from baseline in HbA1c) at the study endpoint are provided below. From these, the percent of patients (y-axis value) with a value of percent change from baseline in HbA1c at endpoint, smaller than or equal to a value on the x-axis, can be read.

Note: All the percentiles were smaller for the albiglutide group.

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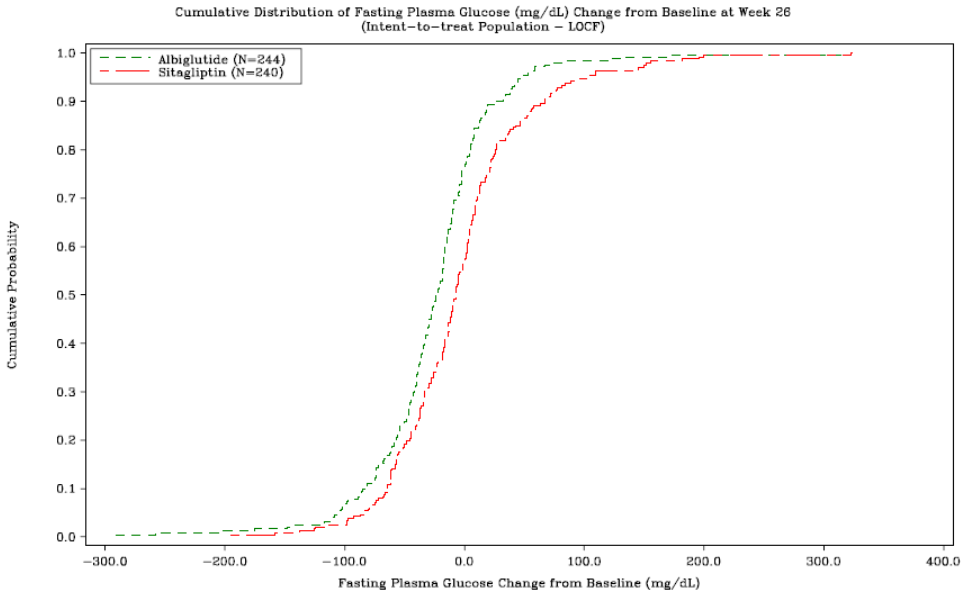

Fasting Plasma Glucose Change From Baseline by Renal Impairment Severity Through Week 26

As seen from the following line graph and Table of results,

due to large variability in FPG at all time-points through Week 26, although generally supportive, the data do not demonstrate a strong pattern of effect.

For subjects with baseline renal impairment severity of mild, moderate, or severe, the magnitude of change from Baseline at each visit was generally less in the sitagliptin treatment group than for the albiglutide treatment group.

At Week 26, the difference of LS means (albiglutide – sitagliptin) was –0.83 mmol/L, –1.60 mmol/L and –1.56 mmol/L for subjects with baseline renal impairment severity of mild, moderate or severe, respectively.

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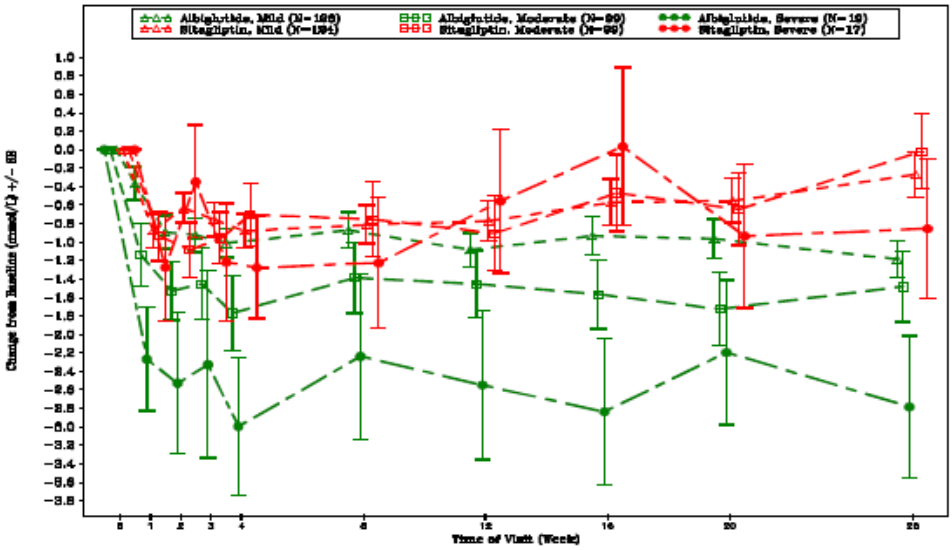
Line Graph of Mean Change From Baseline in Fasting Plasma Glucose (mmol/L) Through Week 26 by Renal Impairment Severity (ITT Population – LOCF)



B = baseline; ITT = intent to treat; LOCF = last observation carried forward; SE = standard error.
Note: For conversion, 1 mmol/L = 18 mg/dL, or 1 mg/dL = 0.05550 mmol/L.

Analysis of Change From Baseline in Fasting Plasma Glucose (mmol/L) at Week 26 by Renal Impairment Severity (ITT Population – LOCF)

	Albiglutide (N=246)			Sitagliptin (N=240)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Number of subjects[1]	126	99	19	124	99	17
Number (%) of values carried forward	18 (14.3)	24 (24.2)	2 (10.5)	17 (13.7)	37 (37.4)	9 (52.9)
Baseline – mean (SD)	8.78 (2.380)	9.58 (3.967)	9.82 (3.668)	8.59 (2.246)	9.85 (3.335)	9.24 (3.305)
Week 26 – mean (SD)	7.59 (2.205)	8.10 (4.045)	7.04 (2.421)	8.32 (2.843)	9.83 (3.930)	8.39 (3.668)
Change from Baseline – mean (SD)	-1.19 (2.239)	-1.48 (3.834)	-2.78 (3.349)	-0.27 (2.746)	-0.02 (4.031)	-0.85 (3.101)
Model-adjusted change from Baseline[2]						
LS mean (SE)	-1.41 (0.257)	-1.24 (0.289)	-2.45 (0.659)	-0.58 (0.260)	0.36 (0.291)	-0.89 (0.696)
95% CI	(-1.92, -0.91)	(-1.81, -0.67)	(-3.74, -1.15)	(-1.09, -0.07)	(-0.21, 0.93)	(-2.25, 0.48)
Difference from sitagliptin[2]						
Difference of LS means	-0.83	-1.60	-1.56			
95% CI	(-1.54, -0.12)	(-2.40, -0.81)	(-3.44, 0.31)			

CI = confidence interval; ITT = intent to treat; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; SE = standard error.

Note: This analysis used the LOCF method for missing postbaseline fasting plasma glucose (FPG) values. FPG values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values.

1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on analysis of covariance (ANCOVA): Change = treatment + baseline FPG + renal impairment + prior myocardial infarction history + age category + region + treatment*renal impairment. The difference of least squares means (albiglutide – sitagliptin) is from ANCOVA model. The p-value for the interaction term = 0.3366.

Proportion of Subjects Who Achieved Clinically Meaningful HbA_{1c} Response Levels Through Week 26

As seen from the following Table of results. a higher percentage of subjects in the albiglutide treatment group achieved the treatment goal of HbA_{1c} less than 6.5% and less than 7.0% at Week 26 (albiglutide: 15.3% and 42.6%, respectively compared with sitagliptin: 12.3% and 30.5%, respectively). The treatment difference between albiglutide and sitagliptin was statistically significant for the treatment goal of HbA_{1c} less than 7.0% at Week 26. Through Week 26, in the mild, moderate, and severe renal impairment subgroups, of those receiving albiglutide 42.4%, 41.8%, and 47.4% respectively compared to 31.1%, 28.3%, and 40.0% respectively in the sitagliptin group, achieved a treatment goal of HbA_{1c} <7.0%.

Analysis of Proportion of Subjects Achieving Clinically Meaningful HbA_{1c} Response Levels (<6.5%, and <7.0%) at Week 26: Overall Data (ITT Population – LOCF)

	Albiglutide (N=246)	Sitagliptin (N=240)
HbA_{1c} Level: <6.5%		
Number of subjects[1] at Week 26	242	236
Number (%) of values carried forward	40 (16.5)	58 (24.6)
Number (%) of subjects achieving HbA_{1c} response	37 (15.3)	29 (12.3)
Difference from sitagliptin[2]		
Odds Ratio	1.292	
(95% confidence interval)	(0.741, 2.250)	
p-value	0.3658	
Difference from sitagliptin[3]		
Odds Ratio	1.265	
(95% confidence interval)	(0.744, 2.149)	
p-value	0.3850	
HbA_{1c} Level: <7.0%		
Number of subjects[1] at Week 26	242	236
Number (%) of values carried forward	40 (16.5)	58 (24.6)
Number (%) of subjects achieving HbA_{1c} response	103 (42.6)	72 (30.5)
Difference from sitagliptin[2]		
Odds Ratio	1.597	
(95% confidence interval)	(1.076, 2.372)	
p-value	0.0077	
Difference from sitagliptin[3]		
Odds Ratio	1.704	
(95% confidence interval)	(1.162, 2.499)	
p-value	0.0064	

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HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward.

Note: This analysis used the LOCF method for missing postbaseline HbA_{1c} values. The HbA_{1c} values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values.

1. Number of subjects with a value at the specified visit.
2. The p-value was based on nonparametric Cochran Mantel-Haenszel (CMH) test after adjusting for renal impairment, prior myocardial infarction history, age category, and region. The odds ratio and confidence intervals are Mantel-Haenszel (MH) estimates; (for HbA_{1c} level: <6.5%: the CMH and MH estimates were not reported in the case of sparse data).
3. Based on logistic regression: Logit(proportion of response) = treatment + renal impairment + prior myocardial infarction history + age category + region. Logistic regression estimates were not reported in the case of sparse data.

As seen from the following Table of results, the proportion of subjects reaching the treatment goal at Week 26 of improvement in HbA_{1c} by at least 1.0%, 1.5% or 2.0% was higher in the albiglutide group than in the sitagliptin group.

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Analysis of Proportion of Subjects Achieving Clinically Meaningful Improvement in HbA_{1c} Response Levels (at least 1.0%, at least 1.5%, at least 2.0%) at Week 26: Overall Data (ITT Population – LOCF)

	Albiglutide (N=246)	Sitagliptin (N=240)
HbA_{1c} Improvement: ≥1.0%		
Number of subjects[1] at Week 26	242	236
Number (%) of values carried forward	40 (16.5)	58 (24.6)
Number (%) of subjects achieving HbA_{1c} response	102 (42.1)	77 (32.6)
Difference from sitagliptin[2]		
Odds Ratio	1.545	
(95% confidence interval)	(1.044, 2.288)	
p-value	0.0202	
Difference from sitagliptin[3]		
Odds Ratio	1.524	
(95% confidence interval)	(1.045, 2.222)	
p-value	0.0287	
HbA_{1c} Improvement: ≥1.5%		
Number of subjects[1] at Week 26	242	236
Number (%) of values carried forward	40 (16.5)	58 (24.6)
Number (%) of subjects achieving HbA_{1c} response	49 (20.2)	38 (16.1)
Difference from sitagliptin[2]		
Odds Ratio	1.268	
(95% confidence interval)	(0.780, 2.062)	
p-value	0.2514	
Difference from sitagliptin[3]		
Odds Ratio	1.312	
(95% confidence interval)	(0.820, 2.100)	
p-value	0.2575	
HbA_{1c} Improvement: ≥2.0%		
Number of subjects[1] at Week 26	242	236
Number (%) of values carried forward	40 (16.5)	58 (24.6)
Number (%) of subjects achieving HbA_{1c} response	26 (10.7)	17 (7.2)
Difference from sitagliptin[2]		
Odds Ratio	1.356	
(95% confidence interval)	(0.702, 2.619)	
p-value	0.2463	
Difference from sitagliptin[3]		
Odds Ratio	1.561	
(95% confidence interval)	(0.817, 2.982)	
p-value	0.1777	

HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward;

Note: This analysis used the LOCF method for missing postbaseline HbA_{1c} values. HbA_{1c} values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values. Improvement was assessed for postbaseline visits by comparing to baseline values. Baseline was defined as the last available assessment on or prior to the first dose of study medication

1. Number of subjects with a value at Baseline and at the specified visit.
2. The p-value was based on nonparametric Cochran Mantel-Haenszel (CMH) test after adjusting for renal impairment, prior myocardial infarction history, age category, and region. The odds ratio and confidence intervals are Mantel-Haenszel (MH) estimates. The CMH and MH estimates were not reported in the case of sparse data.
3. Based on logistic regression: Logit(proportion of response) = treatment + renal impairment + prior myocardial infarction history + age category + region. Logistic regression estimates were not reported in the case of sparse data.

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As seen from the following Tables of results by renal impairment severity, through Week 26, there were no significant differences between the albiglutide and sitagliptin groups at treatment goal of HbA_{1c} less than 7.0%. However, there were small numbers of subjects in each group.

Analysis of Proportion of Subjects Achieving HbA1c < 7.0% Response Through Week 26 by Renal Impairment Severity (Intent-to-treat Population - LOCF)

Renal Impairment Severity: Mild- Week 26

	Albiglutide (N=246)	Sitagliptin (N=240)
Number of Subjects [1]	125	122
Number (%) of Values Carried Forward	17 (13.6%)	15 (12.3%)
Subjects Achieving HbAlc Response	53 (42.4%)	38 (31.1%)
Difference from Sitagliptin [2]		
Odds Ratio	1.557	
95% Confidence Interval	(0.905, 2.677)	
p-value	0.0786	
Difference from Sitagliptin [3]		
Odds Ratio	1.627	
95% Confidence Interval	(0.959, 2.759)	
p-value	0.0712	

Renal Impairment Severity: Moderate- Week 26

	Albiglutide (N=246)	Sitagliptin (N=240)
Number of Subjects [1]	98	99
Number (%) of Values Carried Forward	21 (21.4%)	37 (37.4%)
Subjects Achieving HbAlc Response	41 (41.8%)	28 (28.3%)
Difference from Sitagliptin [2]		
Odds Ratio	1.781	
95% Confidence Interval	(0.955, 3.321)	
p-value	0.0619	
Difference from Sitagliptin [3]		
Odds Ratio	1.885	
95% Confidence Interval	(1.025, 3.469)	
p-value	0.0416	

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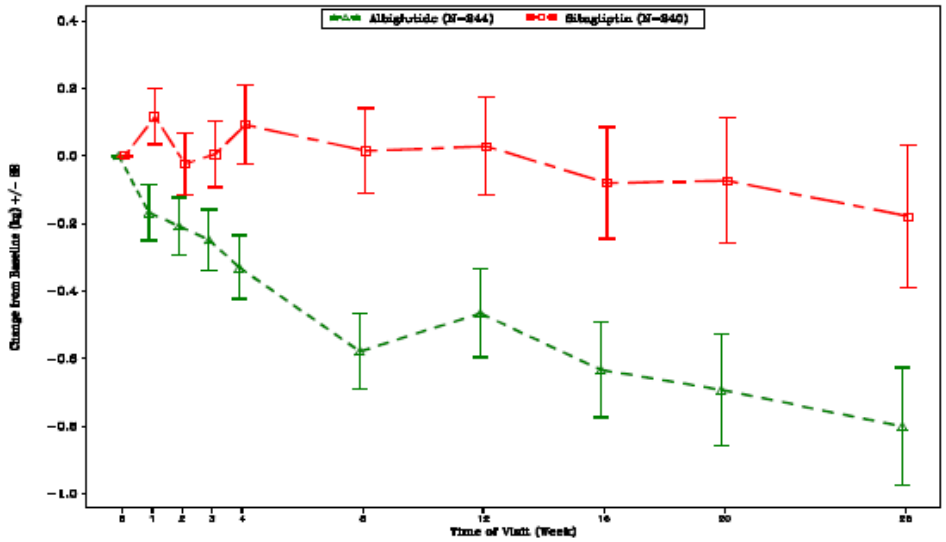
Renal Impairment Severity: Severe- Week 26

	Albiglutide (N=246)	Sitagliptin (N=240)
Number of Subjects [1]	19	15
Number (%) of Values Carried Forward	2 (10.5%)	6 (40.0%)
Subjects Achieving HbA1c Response	9 (47.4%)	6 (40.0%)
Difference from Sitagliptin [2]		
Odds Ratio	1.014	
95% Confidence Interval	(0.218, 4.717)	
p-value	0.4124	
Difference from Sitagliptin [3]		
Odds Ratio	1.144	
95% Confidence Interval	(0.262, 5.002)	
p-value	0.8582	

Change From Baseline in Body Weight Through Week 26

As seen from the following line-graph and Table of results, in both treatment groups, there was continual body weight loss through Week 26. The magnitude of change from baseline was larger for albiglutide subjects. At Week 26, the model-adjusted LS mean weight change from Baseline was –0.79 kg for albiglutide subjects and –0.19 kg for sitagliptin subjects. The difference in weight change from Baseline to Week 26 was statistically significant (p=0.0281). The percent change from Baseline in body weight was –0.95% in the albiglutide group and –0.16% in the sitagliptin group at Week 26.

Line Graph of Mean Change From Baseline in Weight (kg) Through Week 26: Overall Data (ITT Population – LOCF)



B = baseline; ITT = intent to treat; LOCF = last observation carried forward; SE = standard error.

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Analysis of Change From Baseline in Weight (kg) at Week 26: Overall Data (ITT Population – LOCF) Overall Data (ITT Population – LOCF)

	Albiglutide (N=246)	Sitagliptin (N=240)
Number of Subjects[1]	244	240
Number (%) of Values Carried Forward	42 (17.2)	62 (25.8)
Baseline mean (SD)	83.69 (19.846)	82.73 (20.633)
Week 26 mean (SD)	82.88 (19.753)	82.55 (20.695)
Change from Baseline - mean (SD)	-0.80 (2.724)	-0.18 (3.281)
Model-adjusted change from Baseline[2]		
LS mean	-0.79	-0.19
Standard error	0.192	0.194
95% confidence interval	(-1.17, -0.41)	(-0.57, 0.19)
Difference from sitagliptin[2]		
Difference of LS means	-0.60	
95% confidence interval	(-1.14, -0.06)	
p-value	0.0281	

ITT = intent to treat; LOCF = last observation carried forward; LS = least squares; SD = standard deviation.
Note: This analysis used the last observation carried forward (LOCF) method for missing postbaseline weight values. Weight values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values.

1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on ANCOVA: Change = treatment + baseline weight + renal impairment + prior myocardial infarction history + age category + region. The difference of least squares means (albiglutide – sitagliptin) was from the ANCOVA model. The p-value was from a 2-sided *t* test for the difference in means.

§ Graphs of cumulative distribution functions by treatment groups for the primary efficacy variable (percent change from baseline in HbA1c) at the study endpoint are provided below. From these, the percent of patients (y-axis value) with a value of percent change from baseline in HbA1c at endpoint, smaller than or equal to a value on the x-axis, can be read.

Note: Almost all the percentiles of the change from baseline in weight were larger for the sitagliptin group and smaller for the albiglutide group.

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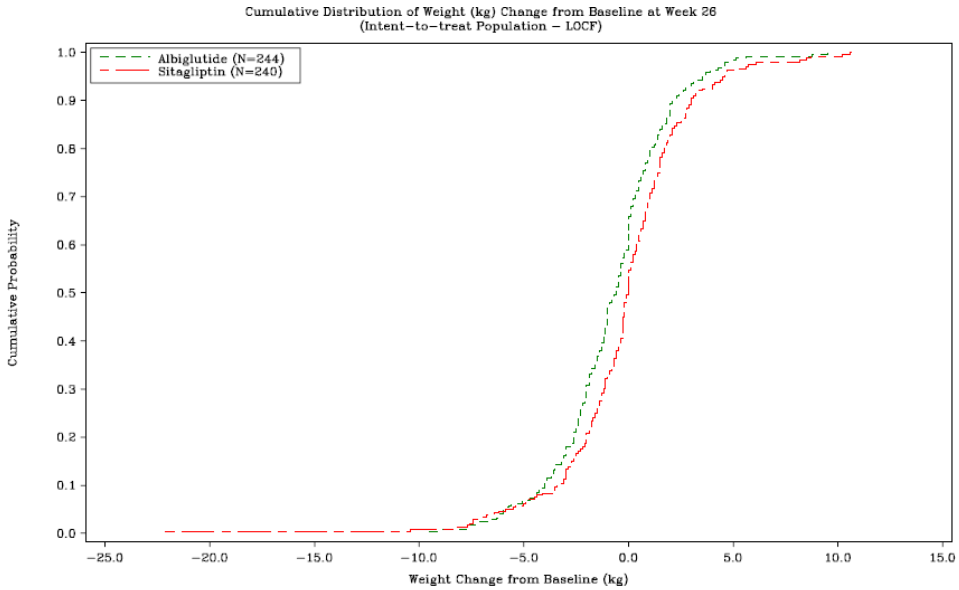

Change From Baseline in Body Weight by Renal Impairment Severity Through Week 26

As seen from the following line-graph and Table of results, in the albiglutide group, there was a loss of body weight through Week 26 for subjects with mild, moderate, or severe renal impairment. The mean weight loss values for subjects in the albiglutide group were generally of greater magnitude than for subjects in the sitagliptin group at each time point through Week 26, and with a baseline renal impairment severity mild, moderate, or severe. The treatment difference at Week 26 (albiglutide - sitagliptin) was –0.31 (95% CI: –1.06, 0.44), –0.94 (95% CI: –1.79, –0.10), and –0.74 (95% CI: –2.72, 1.23) for subjects with mild, moderate, or severe renal impairment, respectively. The analysis results should be interpreted with caution due to the small number of subjects in each renal impairment subgroup.

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Analysis of Change From Baseline in Weight (kg) at Week 26 by Renal Impairment Severity (ITT Population – LOCF)

	Albiglutide (N=246)			Sitagliptin (N=240)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Number of subjects[1]	126	99	19	124	99	17
Number (%) of values carried forward	18 (14.3)	22 (22.2)	2 (10.5)	17 (13.7)	37 (37.4)	8 (47.1)
Baseline – mean (SD)	85.12 (19.425)	82.29 (19.933)	81.46 (22.435)	85.90 (22.520)	78.38 (17.661)	84.95 (18.701)
Week 26 – mean (SD)	84.28 (19.030)	81.68 (20.360)	79.91 (21.561)	85.37 (22.442)	78.76 (18.253)	84.06 (18.225)
Change from Baseline – mean (SD)	-0.84 (2.795)	-0.60 (2.650)	-1.56 (2.623)	-0.53 (3.566)	0.38 (2.920)	-0.88 (2.722)
Model-adjusted change from Baseline[2]						
LS mean (SE)	-0.83 (0.270)	-0.59 (0.303)	-1.62 (0.694)	-0.52 (0.272)	0.36 (0.306)	-0.88 (0.733)
95% CI	(-1.36, -0.30)	(-1.18, 0.01)	(-2.98, -0.26)	(-1.06, 0.01)	(-0.24, 0.96)	(-2.32, 0.56)
Difference from sitagliptin[2]						
Difference of LS means	-0.31	-0.94	-0.74			
95% CI	(-1.06, 0.44)	(-1.79, -0.10)	(-2.72, 1.23)			

CI = confidence interval; ITT = intent to treat; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; SE = standard error.

Note: This analysis used the LOCF method for missing postbaseline weight values. Weight values obtained after hyperglycemia rescue were treated as missing and replaced with prerescue values.

1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on analysis of covariance (ANCOVA): Change = treatment + baseline weight + renal impairment + prior myocardial infarction history + age category + region + treatment*renal impairment. The difference of least squares means (albiglutide - sitagliptin) is from ANCOVA model. The p-value for the interaction term = 0.5363.

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STUDY GLP114856 (Phase 2 Bioequivalent study)

Title - A Multidose Study in Subjects With Type 2 Diabetes Mellitus to Assess the Pharmacokinetics and Pharmacodynamics of Albiglutide: Single- and Multiple-Dose Phase CSR

Phase: I/IIa

Effective Date: 04-DEC-2012

Initiation Date: 26-Jul-2011
Completion Date: 30-Oct-2012 (Single- and Multiple-Dose Phase CSR)

Earlier CSRs: 07-Aug-2012 (Bioequivalence Phase CSR)

Reference ID: 3392698

Study Design and Endpoints

Study GLP114856 is an ongoing, randomized, double-blind, multicenter, 2 parallel-group study in subjects with T2DM to show the clinical comparability of Process 2 and Process 3 albiglutide. This study has a completed 28-day single-dose phase (BE phase) that was used for the comparative PK assessment of Process 2 versus Process 3 albiglutide; data from this phase are summarized in this clinical study report. Subsequently, subjects continue in the ongoing, repeat-dose phase that will evaluate Process 2 and Process 3 with regard to glycemic effect (e.g., HbA_{1c}, FPG), immunogenicity, and safety; data from the repeat-dose phase will be summarized in a separate clinical study report.

The BE phase evaluated the PK BE of 1 dose of 30 mg of albiglutide from Process 2 compared with albiglutide from Process 3 from Baseline (Visit 6) through the Week 5 (Visit 15) predose sample. Subjects subsequently entered the 12-week repeat-dose phase of the study, Week 5 (Visit 15) through Week 17 (Visit 27), where they received weekly subcutaneous injections of 30 mg of albiglutide from Process 2 or Process 3 to evaluate additional PK parameters, pharmacodynamic parameters, immunogenicity, effects on HbA_{1c} and FPG, and the safety and tolerability of albiglutide. Subjects with T2DM whose glycemia was inadequately controlled on their current regimen of diet and exercise or stable dose of metformin maintained for approximately 8 weeks prior to Screening were recruited into the study. Subjects continued on their current regimen of diet and exercise or stable dose of metformin for the duration of their participation in the study.

Eligible subjects were stratified by age (<65 or ≥65 years of age), weight (<90 kg or ≥90 kg), and background antidiabetic therapy (diet and exercise or stable dose of metformin). Approximately 240 subjects were to be randomly assigned in a 1:1 ratio to either 30 mg of albiglutide from Process 2 or 30 mg of albiglutide from Process 3.

The overall study comprised 4 study periods: Screening, Run-in/Stabilization, Treatment, and Posttreatment Follow-up. The Treatment Period had a single-dose phase (BE phase) and a 12-week repeat-dose phase. The total duration of a subject's participation in the overall study was approximately 32 weeks. Following approximately 6 weeks of Screening and Run-in/Stabilization, the BE phase was 28 days in duration.

This report describes the results from the BE phase of the study only; results from the repeat-dose phase and posttreatment follow-up will be provided in a separate report at the conclusion of the study.

EFFICACY RESULTS

The main efficacy objectives were to evaluate the efficacy of 30 mg of albiglutide (from Process 2 relative to Process 3) drug product administered weekly on HbA1c change from

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Baseline at Week 17 and on FPG change from Baseline at Week 17.

Exploratory analyses examined proportions of subjects meeting prespecified HbA1c treatment goals, and changes in body weight over time (Process 2 relative to Process 3) and results are presented after HbA1c and FPG.

For each of the efficacy endpoints, results are presented using the LOCF algorithm unless otherwise specified. Additionally, where data were summarized using both SI and conventional units, SI units are presented and summarized in the text. Tables presenting data using the OC (Observed Cases) algorithm or LOCF algorithm (where not presented in text) and using conventional units are referenced throughout the text.

Efficacy Endpoints

HbA1c Change From Baseline at Week 17

Note: Both processes statistically significantly reduced HBA1C by Week 17. However, the 95% confidence interval (-.31, .15) is slightly out of the non-inferiority margin (-.3, .3). Therefore, the equivalence of the two processes has not been statistically confirmed. Process 3 is marginally numerically superior to Process 2.

As seen from the following Table of results and graphs, a decrease in HbA1c from Baseline to Week 17 was observed in both treatment groups When adjusted for baseline HbA1c, age category, weight category and background antidiabetic therapy category, the model adjusted LS mean change in HbA1c from Baseline at Week 17 was -0.75% in the Process 2 treatment group, and -0.84% in the Process 3 treatment group. The treatment difference for Process 3 - Process 2 was -0.08% (95% CI: -0.31, 0.15), which was not statistically significant (p=0.4874).

Analysis of Change From Baseline in HbA1c (%) Through Week 17: Overall (Efficacy Population – LOCF)

	Albiglutide Process 2 (N=141)	Albiglutide Process 3 (N=141)
Number of subjects[1]	135	135
Number (%) of values carried forward	18 (13.3)	16 (11.9)
Baseline mean (SD)	8.17 (0.991)	8.14 (0.955)
Week 17 mean (SD)	7.41 (1.299)	7.31 (1.010)
Model-adjusted change from Baseline[2]		
Least squares mean	-0.75	-0.84
Standard error	0.082	0.082
95% confidence interval	(-0.92, -0.59)	(-1.00, -0.67)
Difference from Process 2[2]		
Difference of least squares means		-0.08
95% confidence interval		(-0.31, 0.15)
p-value		0.4874

HbA_{1c} = glycosylated hemoglobin; LOCF = last observation carried forward; SD = standard deviation. Note: Overall results include data from both the single- and multiple-dose phases.

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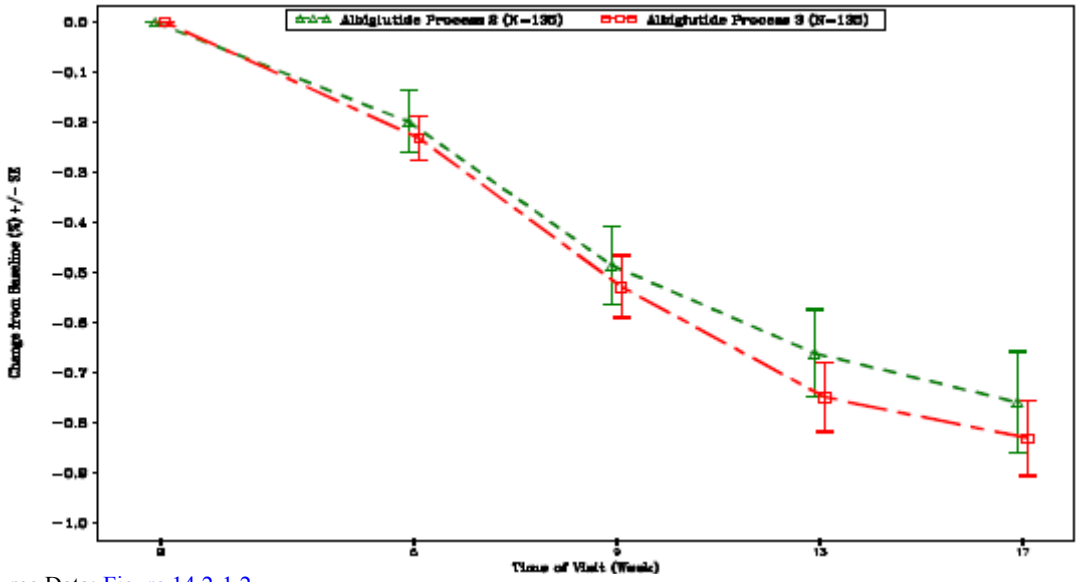
Note: This analysis used the LOCF method for missing post-baseline HbA_{1c} values. HbA_{1c} values obtained after hyperglycemic rescue were treated as missing and replaced with pre-rescue values. Four Efficacy Population subjects had all post-baseline HbA_{1c} measurements occur more than 14 days after the last dose, six had all measurements occur after hyperglycemic rescue, one had all measurements occur more than 14 days after the last dose and after hyperglycemic rescue, and one Efficacy Population subject did not have any post-baseline HbA_{1c} measurements. These twelve subjects are included in the header Efficacy Population counts but do not contribute to any of the Efficacy Population HbA_{1c} analyses.

1. Number of subjects with a value at Baseline and at the specified visit.
2. Based on ANCOVA: Change = treatment + baseline HbA_{1c} + age category + weight category + background antidiabetic therapy category. The difference of least squares means (Process 3 - Process 2) is from the ANCOVA model. The p-value is from a two sided t-test for the difference in means.

Line Graph of Mean (±SE) Change From Baseline in HbA_{1c} (%) Over Time (Efficacy Population – LOCF)



Source Data: Figure 14.2-1.2.
B = Baseline; HbA1c = glycosylated hemoglobin; LOCF = last observation carried forward; SE = standard error. Note: Overall results include data from both the single- and multiple-dose phases.
Note: This figure used the LOCF method for missing post-baseline HBA1c values. HBA1c values obtained after hyperglycemic rescue were treated as missing and replaced with pre-rescue values.

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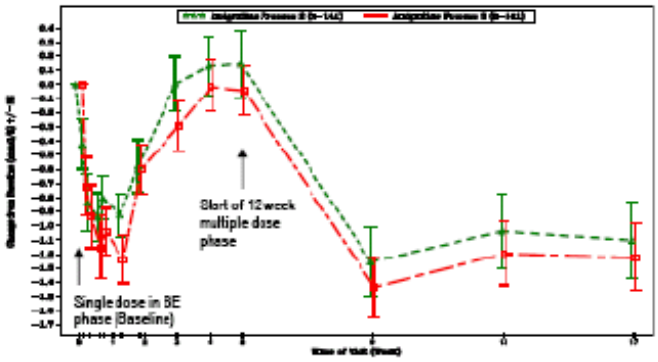
Line Graph of Mean (±SE) Change from Baseline in Fasting Plasma Glucose (mmol/L) Through Week 17 (Efficacy Population – LOCF)



B = Baseline; LOCF = last observation carried forward; SE = standard error.
This figure used the LOCF method for missing post-baseline FPG values. FPG values obtained after hyperglycemic rescue are treated as missing and replaced with pre-rescue values.
Note: The arrows denote when the single-dose was administered (Week 0) and the start of the multiple-dose phase of the study (Week 5).

Exploratory Efficacy Endpoints

Proportion of Subjects who Achieved HbA1c Less Than 7% by Visit

As seen from the following Table, the proportion of subjects who achieved HbA1c <7% by visit up to end of the study was similar for the Process 2 and the Process 3 treatment groups. Overall, 41.5% of subjects in the Process 2 treatment group and 42.2% of subjects in the Process 3 treatment groups achieved the treatment goal of HbA1c <7.0% at Week 17.

Note: The Process 3 had numerical superiority after Week 5.

Summary Statistics for the Proportion of Subjects Achieving HbA1c Less Than 7% Responses by Visit Overall (Efficacy Population – LOCF)

	Albiglutide Process 2 (N=141) n/n (%)	**Albiglutide Process 3 (N=141) n/n (%)**
Week 5	23/131 (17.6)	18/129 (14.0)
Week 9	34/135 (25.2)	40/134 (29.9)
Week 13,	50/135 (37.0)	51/135 (37.8)
Week 17 (End of Treatment)	56/135 (41.5)	57/135 (42.2)

LOCF = last observation carried forward.
Note: This summary used the last observation carried forward (LOCF) method for missing post-baseline HbA1c values. HbA1c values obtained after hyperglycemic rescue were treated as missing and replaced with pre-rescue values.

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Summary Statistics for Weight (kg) Through Week 17: Overall (Efficacy Population – LOCF)

Note: Weight decreased under both processes; however, more under Process 3.

	Albiglutide Process 2 (N=141)	Albiglutide Process 3 (N=141)
Week 1, Day 1 – number of subjects[1]	86	81
Mean (SD)	93.28 (23.300)	93.30 (18.748)
Median	90.10	92.20
Minimum, maximum	51.7, 153.9	55.1, 144.2
Week 5 change from Baseline – number of subjects[1]	141	141
Mean (SD)	-0.15 (1.520)	-0.24 (1.793)
Median	0.00	-0.30
Minimum, maximum	-3.9, 3.9	-6.9, 5.2
Week 9 change from Baseline – number of subjects[1]	141	141
Mean (SD)	-0.45 (2.141)	-0.82 (2.234)
Median	-0.50	-0.80
Minimum, maximum	-7.3, 6.7	-9.6, 5.2
Week 13 change from Baseline – number of subjects[1]	141	141
Mean (SD)	-0.71 (2.588)	-0.92 (2.715)
Median	-0.50	-0.90
Minimum, maximum	-8.5, 5.2	-11.0, 7.3
Week 17 change from Baseline – number of subjects[1]	141	141
Mean (SD)	-0.97 (2.974)	-1.17 (2.906)
Median	-0.90	-1.00
Minimum, maximum	-11.2, 5.2	-10.9, 9.2

LOCF = last observation carried forward, SD = standard deviation.
Note: Overall results include data from both the single- and multiple-dose phases.
Note: This summary used the LOCF method for missing post-baseline weight values. Weight values obtained after hyperglycemia rescue were treated as missing and replaced with pre-rescue values. Baseline was defined as the last available assessment on or prior to the first dose of study drug.
1. Number of subjects with a value at Baseline and at the specified visit.

3.3 Evaluation of Safety

I have not performed any safety assessment.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Note: Adjustments for multiplicity in so many subgroups cannot be properly done on a post hoc basis, when an adjustment method is not mentioned prospectively.

Statistically significant interactions are difficult to detect because of lack of power. On the other hand, how much multiple comparison adjustment is needed in this situation is unknown.

Reference ID: 3392698

I have pointed out inconsistencies in some subgroup results based on confidence intervals (not that convincing because of smaller sample sizes in subgroups of smaller individual studies, but more convincing when the sample sizes are big) and some based on statistically significant interaction p-values, without multiple comparison adjustments. Subgroup results, when not planned to be confirmatory, are not confirmatory. Further evidences are needed to reach the level of confirmation.

When there are more than two subgroups for a factor, a statistically significant result for this interaction test leads to a general conclusion that the treatment difference/effect is not the same across the subgroups. However, the test does not lead to any specific conclusion on how the treatment difference/effect compares across any two subgroups of that factor.

4.1 Gender, Race, Age, and Geographic Region

Change From Baseline in HbA_{1c} by Baseline and Demographic Characteristics –

Grouping by Drug Comparator

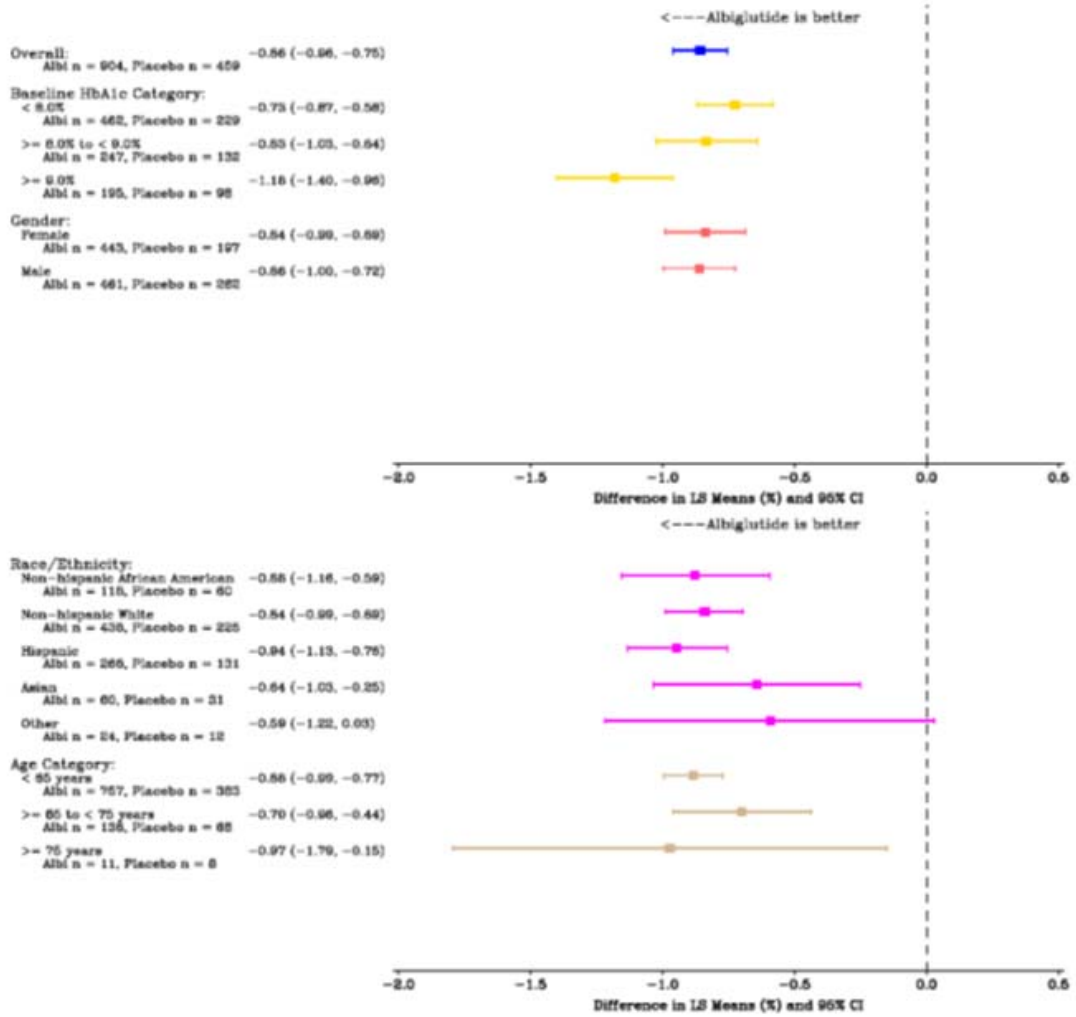
Note: The left sides of the Forest Plots indicate the numerical superiority of albiglutide. If a confidence interval crosses the vertical line at zero to the right, the possibility of albiglutide being inferior to the comparator has not been ruled out with 95% confidence.

Study Group A (Placebo Comparator Studies, GLP112753, GLP112755, GLP112756, and GLP112757**), Intent-to-Treat Population**

Forest plots of the model-adjusted mean difference in change from Baseline in HbA_{1c} by subgroup category at the primary endpoint show that the treatment differences for albiglutide - placebo ranged from -0.59% to -1.18% across all of the Baseline and demographic subgroup categories indicating a consistent treatment benefit in favor of albiglutide over placebo regardless of subgroup. Importantly, the positive treatment difference for albiglutide - placebo was consistently seen across all race/ethnic groups including African-Americans, Hispanics, and Asians, and also in both older age subgroups (≥65 to <75 years and ≥75 years).

Reference ID: 3392698

Forest Plot of Model-Adjusted Mean Difference in Change From Baseline in HbA1c (%) and 95% CI Between Albiglutide and Placebo at Primary Endpoint by Subgroup Category (Intent-to-Treat Population, Study Group A [Placebo Comparator Studies] - LOCF)



Best Available Copy

Albi = albiglutide; CI = confidence interval; HbA_{1c} = glycosylated hemoglobin; ITT = intent-to-treat; LOCF = last observation carried forward; LS = least squares; USA = United States of America.

Note: Week 52 data are presented as the primary endpoint for all studies in Group A.

1. Normal is defined as eGFR ≥90 mL/min/1.73 m^2; renally impaired is defined as <90 mL/min/1.73 m^2 (MDRD Study Group formulae). Subjects were excluded from studies if creatinine clearance was <60 mL/min using the Cockcroft-Gault method of determining creatinine clearance.

Reference ID: 3392698

Subjects were excluded from studies if creatinine clearance was <60mL/min using the Cockcroft-Gault method of determining creatinine clearance. Because the Cockcroft-Gault equation is known to overestimate renal function in obese individuals analysis of the change from Baseline in HbA_{1c} by renal status was evaluated using estimates of creatinine clearance as calculated using the Cockcroft-Gault method and the MDRD Study Group formula. Both analyses demonstrate that regardless of renal status, improvements in HbA_{1c} occur with albiglutide compared to placebo.

Study Group B (OAD Comparator Studies), Intent-to-Treat Population

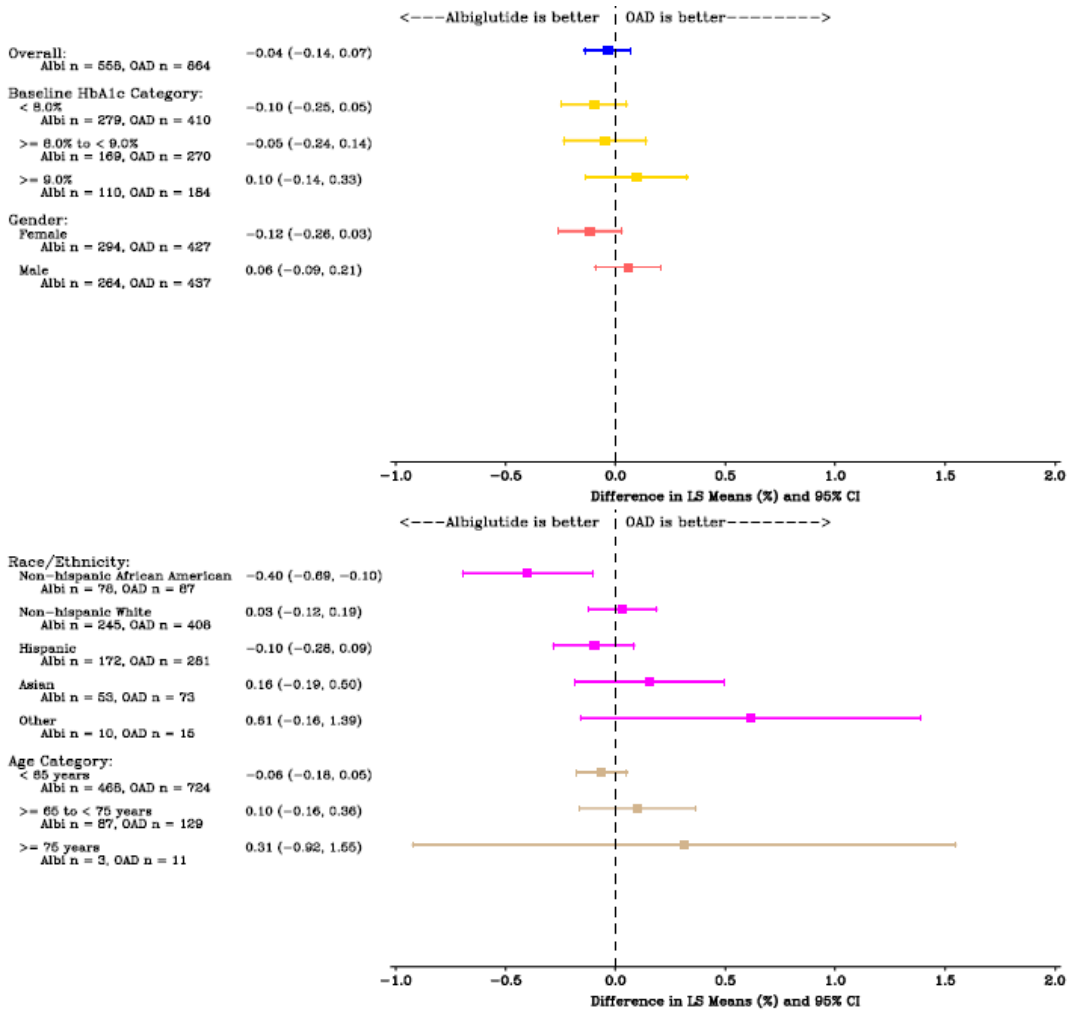
Note: These OAD's include sitagliptin and glimepiride which are inferior to albiglutide and pioglitazone which is superior to albiglutide. Therefore, pooling all these OAD's for comparing with albiglutide is inappropriate.

Forest plots of the model-adjusted mean difference in change from Baseline in HbA_{1c} by subgroup category at the primary endpoint overall shows no treatment difference for albiglutide - comparator OAD. There were generally no treatment differences across subgroups; however, a small treatment difference in favor of albiglutide was identified in the African American, ROW, and short diabetes duration (<5 years) subgroups.

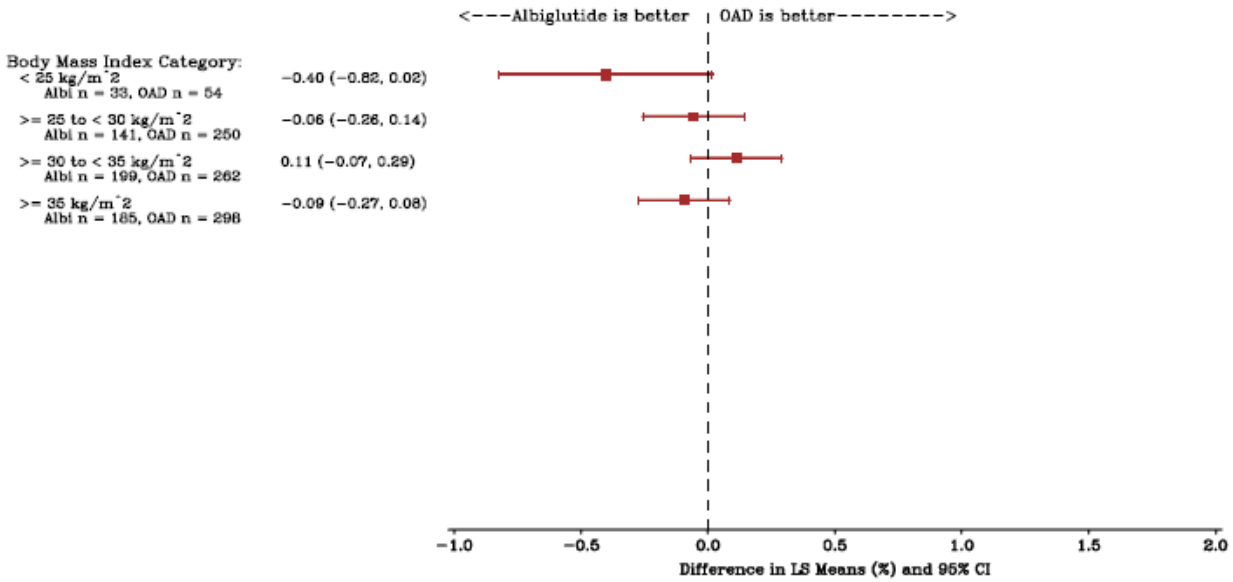
Forest plots of the model-adjusted mean difference in change from Baseline in HbA_{1c} by subgroup category 6 months after initiation of treatment show results similar to those at the primary endpoint.

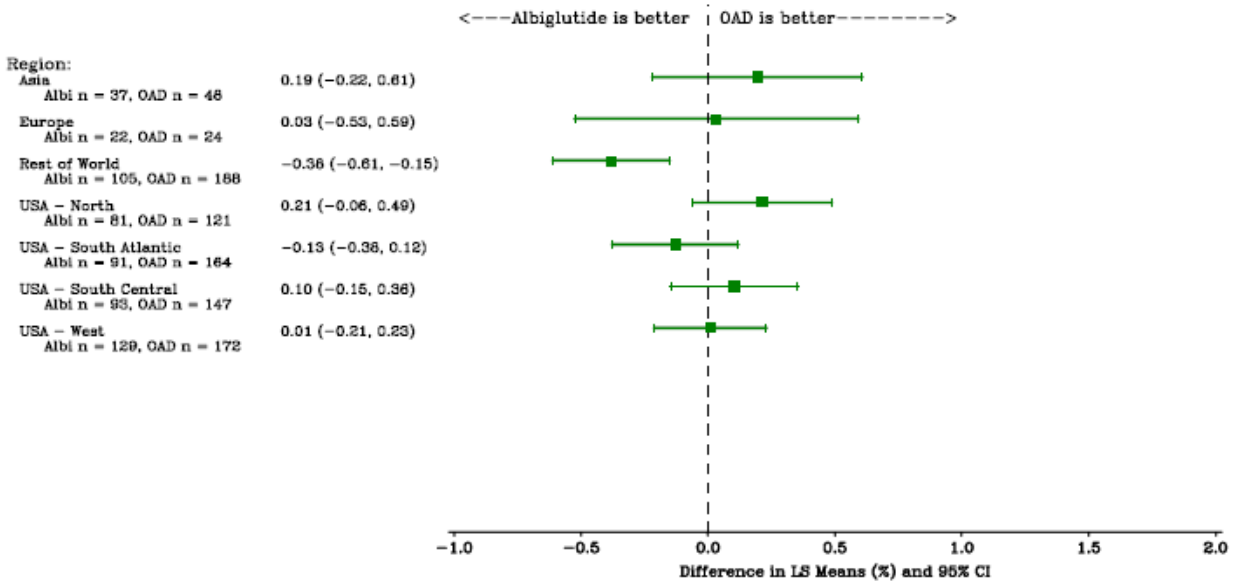
Reference ID: 3392698

Forest Plot of Model-Adjusted Mean Difference in Change From Baseline in HbA1c (%) and 95% CI Between Albiglutide and OAD at Primary Endpoint by Subgroup Category (Intent-to-Treat Population, Study Group B [OAD Comparator Studies] - LOCF)

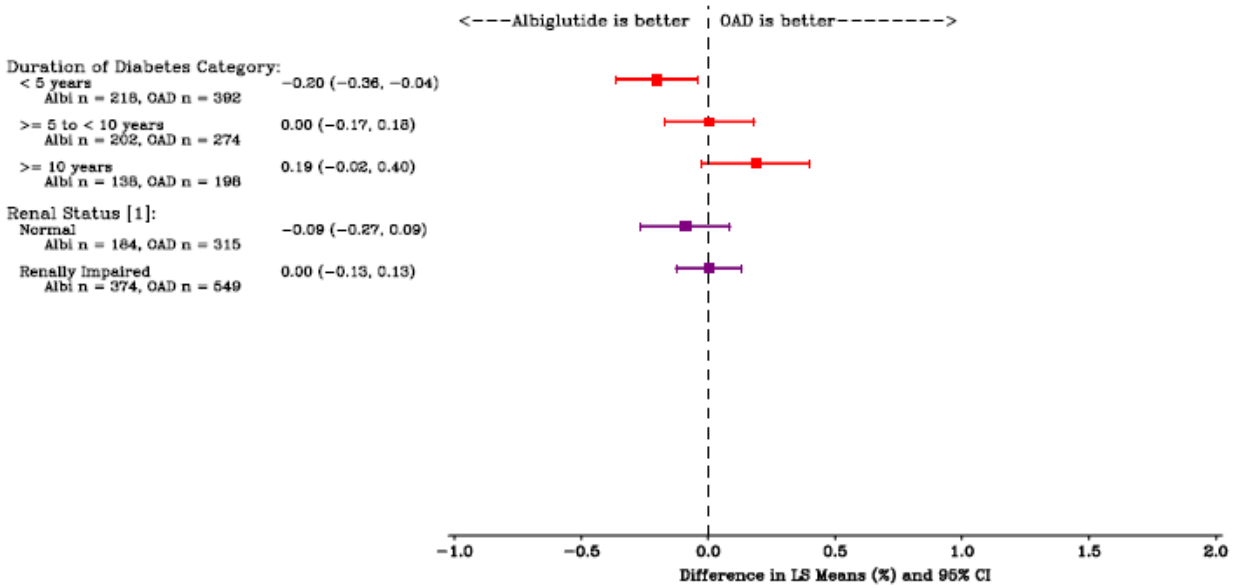


Reference ID: 3392698





Reference ID: 3392698



Albi = albiglutide; CI = confidence interval; HbA_{1c} = glycosylated hemoglobin; ITT = intent-to-treat; LOCF = last observation carried forward; LS = least squares; OAD = oral antidiabetic drug; USA = United States of America.
Note: Week 52 data are presented as the primary endpoint for all studies in Group B.

1. Normal is defined as eGFR ≥90 mL/min/1.73 m^2; renally impaired is defined as <90 mL/min/1.73 m^2 (MDRD Study Group formulae). Subjects were excluded from studies if creatinine clearance was <60 mL/min using the Cockcroft-Gault method of determining creatinine clearance.

Analysis of the change from Baseline in HbA_{1c} by renal status was also determined using the Cockcroft-Gault method to compare with the renal status analysis which uses the MDRD Study Group formula to categorize renal status. There was a similar treatment response with albiglutide or OAD irrespective of the method used to evaluate renal function at Baseline.

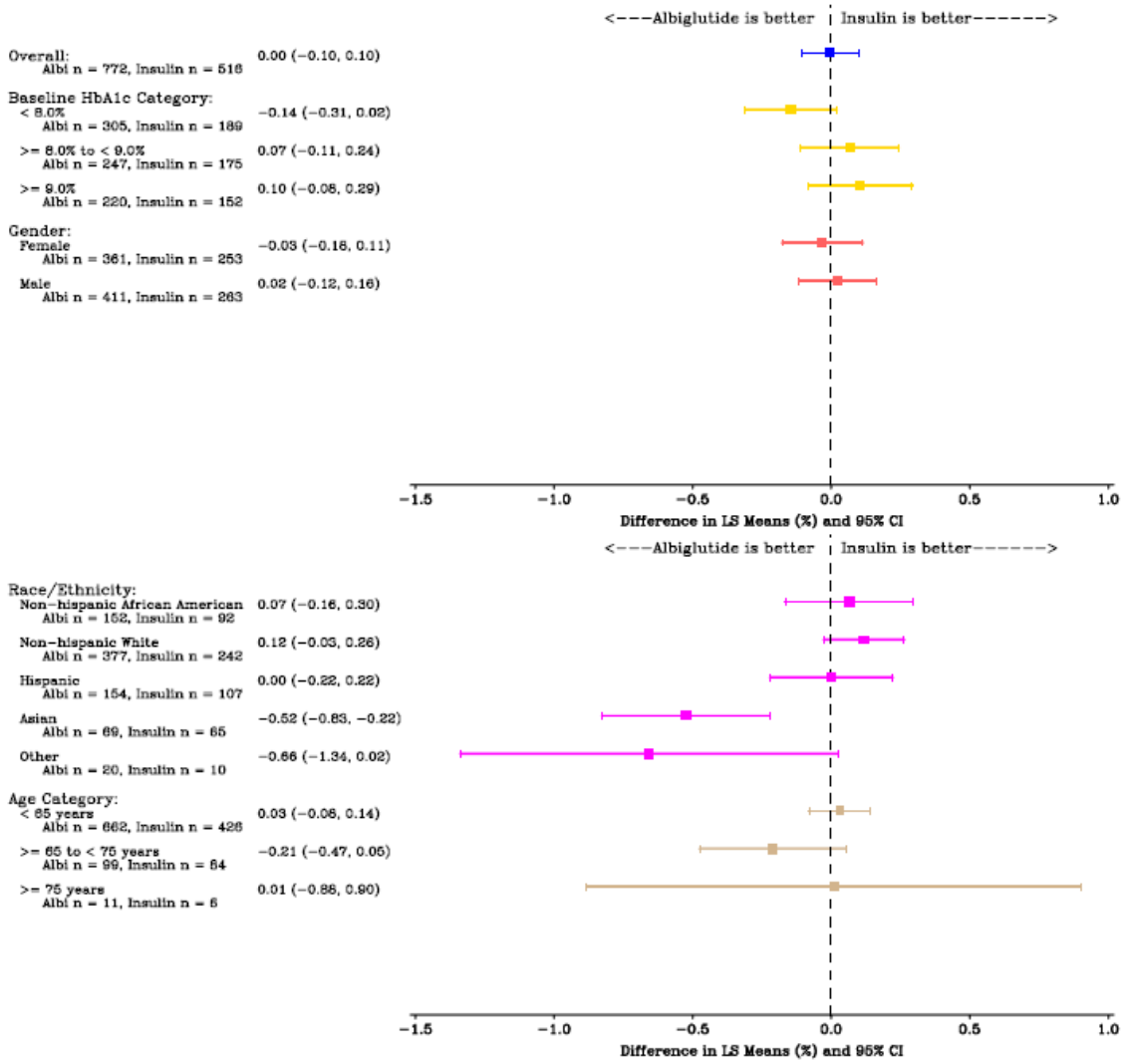
Study Group C (Insulin Comparator Studies), Intent-to-Treat Population

Note: Group C also is not based on pooling of drugs of similar effects. Though albiglutide was noninferior to both, one insulin was numerically superior and another numerically inferior.

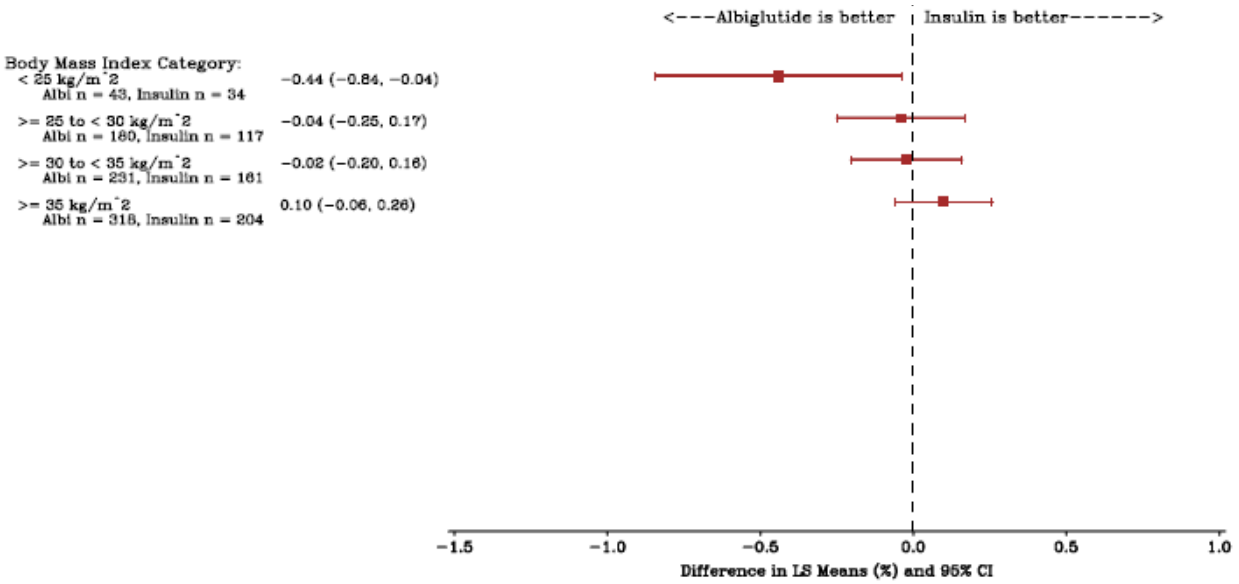
Forest plots of the model-adjusted mean difference in change from Baseline in HbA_{1c} by subgroup category at 6 months show, in general, no treatment difference for albiglutide - insulin. There were generally no treatment differences across subgroups; however, a small treatment difference in favor of albiglutide was identified in the Asian race, Asia region, and normal BMI (<25 kg/m^2) subgroups.

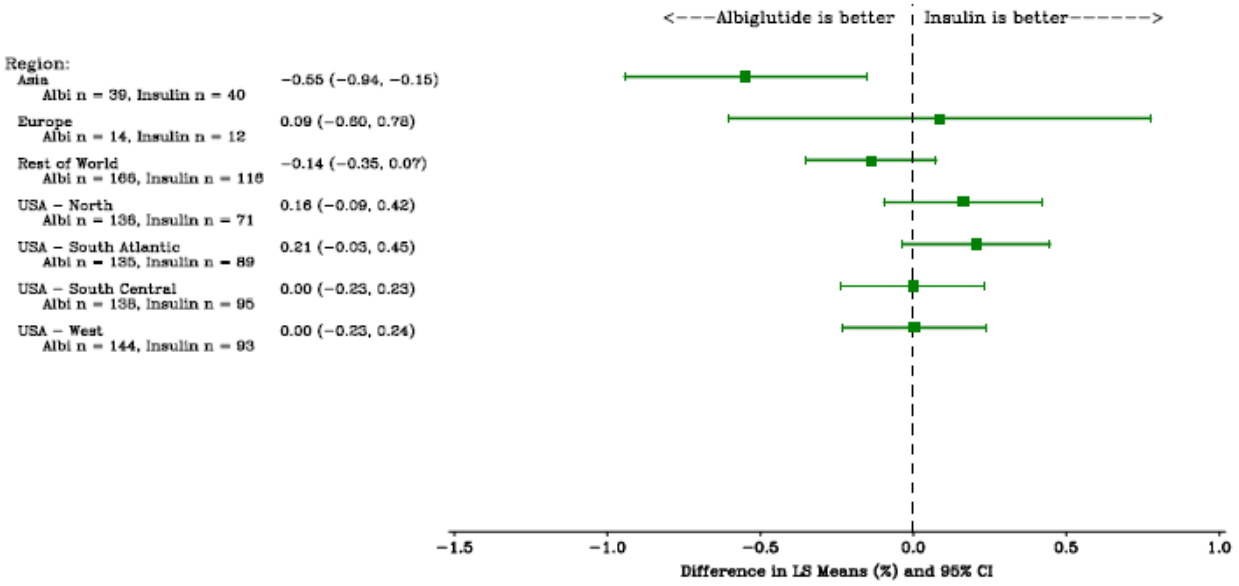
Reference ID: 3392698

Forest Plot of Model-Adjusted Mean Difference in Change From Baseline in HbA_{1c} (%) and 95% CI Between Albiglutide and Insulin at 6 Months by Subgroup Category (Intent-to-Treat Population, Study Group C [Insulin Comparator Studies] - LOCF)

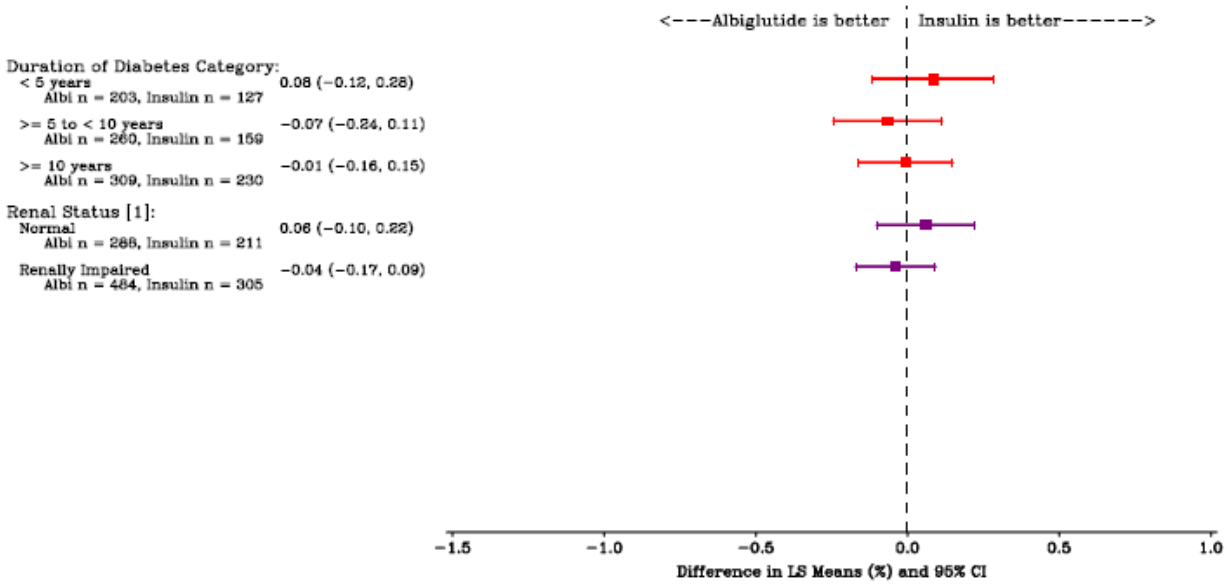


Reference ID: 3392698





Reference ID: 3392698



Albi = albiglutide; CI = confidence interval; HbA_{1c} = glycosylated hemoglobin; ITT = intent-to-treat; LOCF = last observation carried forward; LS = least squares; USA = United States of America.

1. Normal is defined as eGFR ≥90 mL/min/1.73 m^2; renally impaired is defined as <90 mL/min/1.73 m^2 (MDRD Study Group formulae). Subjects were excluded from studies if creatinine clearance was <60 mL/min using the Cockcroft-Gault method of determining creatinine clearance.

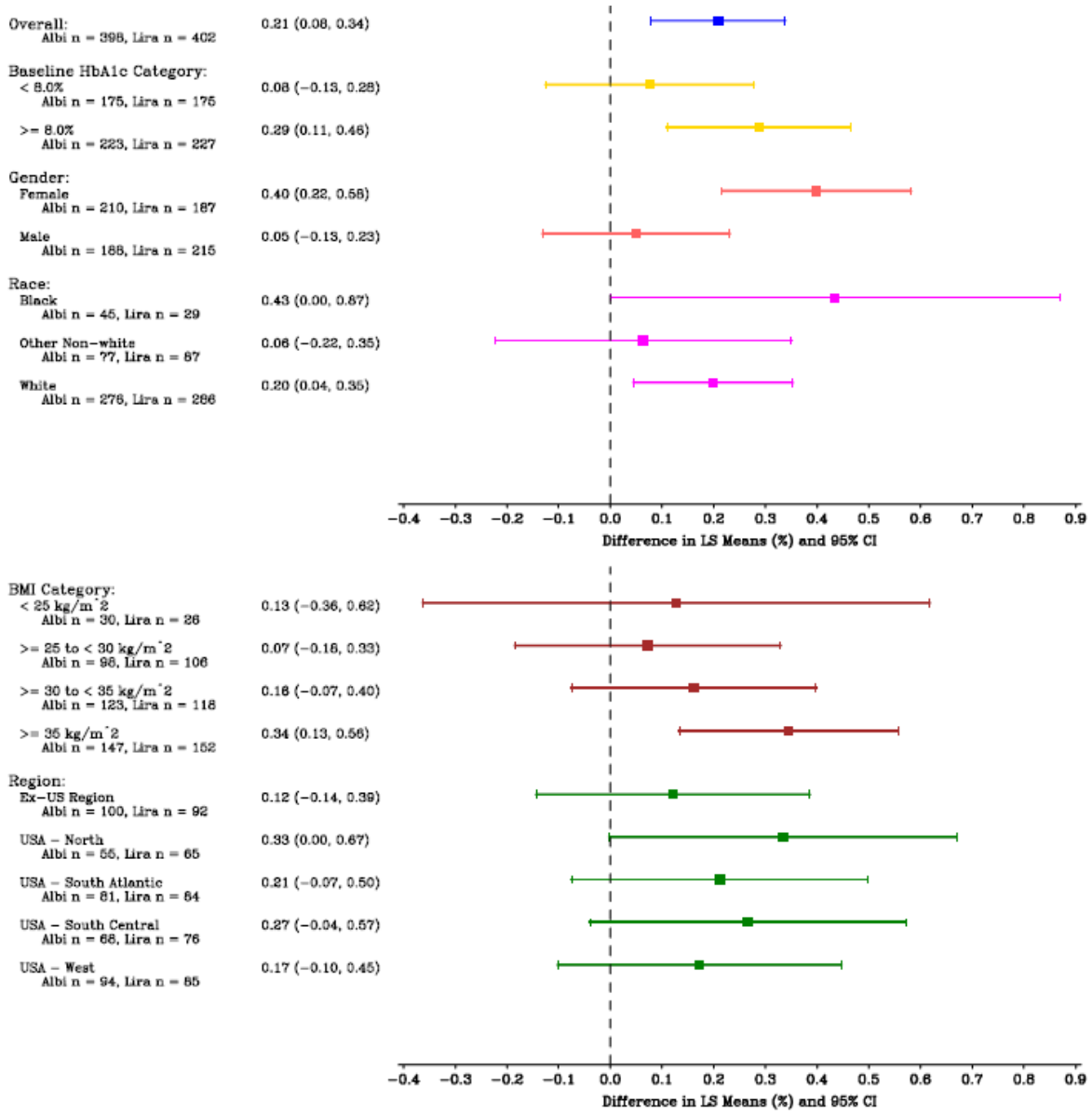
Analysis of the change from Baseline in HbA_{1c} by renal status was also determined using the Cockcroft-Gault method to compare with the renal status analysis presented in which uses the MDRD Study Group formula to categorize renal status. Although no difference in treatment response to albiglutide or OAD was evident in the MDRD defined renal impaired subgroup, using the Cockcroft-Gault equation, there was a small treatment difference in LS means of 0.26% in favor of albiglutide in the renal impaired group.

Study Group D (Liraglutide Comparator Study), Intent-to-Treat Population

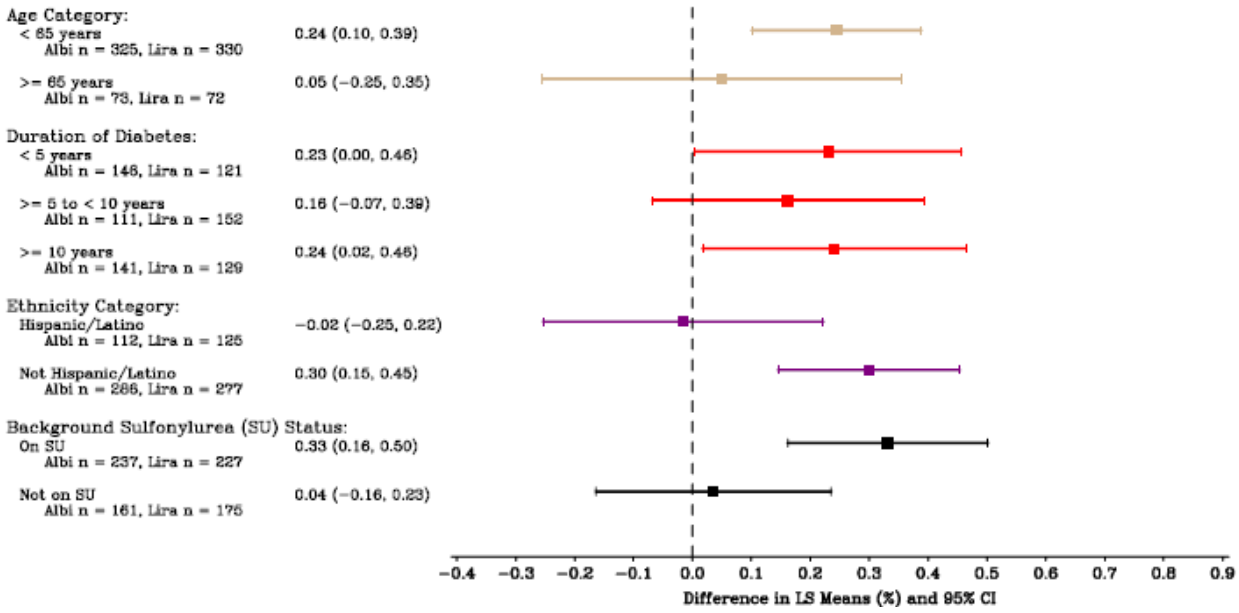
Forest plots of the model-adjusted mean difference in change from Baseline in HbA_{1c} by subgroup category at the primary endpoint overall shows a small treatment difference for albiglutide - liraglutide (0.21%) in favor of liraglutide. The treatment difference in favor of liraglutide was generally consistent across most subgroups evaluated.

Reference ID: 3392698

Forest Plot of Model-Adjusted Change From Baseline in HbA_{1c} (%) and 95% CI Between Albiglutide and Liraglutide at Week 32 by Subgroup Category (Intent-to-Treat Population, Study Group D [Liraglutide Comparator Study] - LOCF) [Liraglutide Comparator Study] - LOCF)



Reference ID: 3392698



Change From Baseline in HbA_{1c} in Specific Demographic Subgroups:

Gender

In the **Study Group B** (OAD arm studies GLP112753 and GLP112757), the p-value for the treatment by Gender interaction term = 0.0389, which is statistically significant, assessed at 0.10 level. Albiglutide worked better for female and OAD worked very slightly better for male. The subgroup results follow:

Reference ID: 3392698

Analysis of Change from Baseline in HbA1c (%) at Primary Endpoint and 6 Months by Gender
(Intent-to-treat Population, Study Group B - LOCF)

Gender: Female - 6 Months

	OAD (N=875)	Albiglutide (N=566)
Number of Subjects [1]	427	294
Number (%) of Values Carried Forward	49 (11.5%)	38 (12.9%)
Baseline		
Mean	8.19	8.20
Standard Deviation	0.839	0.881
6 Months		
Mean	7.43	7.37
Standard Deviation	0.981	0.986
Change from Baseline		
Mean	-0.76	-0.83
Standard Deviation	0.929	0.805
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.74	-0.80
Standard Error	0.040	0.048
95% Confidence Interval	(-0.82, -0.66)	(-0.90, -0.71)
Difference from OAD [2]		
Difference of LS Means		-0.06
95% Confidence Interval		(-0.18, 0.06)

Gender: Male - 6 Months

	OAD (N=875)	Albiglutide (N=566)
Number of Subjects [1]	437	264
Number (%) of Values Carried Forward	59 (13.5%)	35 (13.3%)
Baseline		
Mean	8.11	8.06
Standard Deviation	0.846	0.821
6 Months		
Mean	7.34	7.43
Standard Deviation	1.059	0.915
Change from Baseline		
Mean	-0.77	-0.63
Standard Deviation	0.937	0.746
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.78	-0.66
Standard Error	0.040	0.051
95% Confidence Interval	(-0.86, -0.71)	(-0.76, -0.56)
Difference from OAD [2]		
Difference of LS Means		0.12
95% Confidence Interval		(0.00, 0.25)

Race/Ethnicity

In the **Study Group B** (OAD arm studies GLP112753 and GLP112757), the p-value for the treatment by Race/Ethnicity interaction term = 0.0269, which is statistically significant, assessed at 0.10 level. Albiglutide worked the best in the non-Hispanic African American and worst in "Asian". OAD worked best in the "Other" group and worst in non-Hispanic African American. The subgroup results follow:

Reference ID: 3392698

Analysis of Change from Baseline in HbA1c (%) at Primary Endpoint and 6 Months by Race/Ethnicity
(Intent-to-treat Population, Study Group B - LOCF)

Race/Ethnicity: Non-hispanic African American - Primary Endpoint

	OAD (N=875)	Albiglutide (N=566)
Number of Subjects [1]	87	78
Number (%) of Values Carried Forward	38 (43.7%)	23 (29.5%)
Baseline		
Mean	8.05	8.19
Standard Deviation	0.822	0.918
Primary Endpoint		
Mean	7.75	7.45
Standard Deviation	1.452	1.028
Change from Baseline		
Mean	-0.30	-0.74
Standard Deviation	1.383	1.049
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.36	-0.76
Standard Error	0.105	0.110
95% Confidence Interval	(-0.57, -0.16)	(-0.98, -0.55)
Difference from OAD [2]		
Difference of LS Means		-0.40
95% Confidence Interval		(-0.69, -0.10)

Race/Ethnicity: Non-hispanic White - Primary Endpoint

	OAD (N=875)	Albiglutide (N=566)
Number of Subjects [1]	408	245
Number (%) of Values Carried Forward	125 (30.6%)	76 (31.0%)
Baseline		
Mean	8.10	8.08
Standard Deviation	0.811	0.804
Primary Endpoint		
Mean	7.43	7.44
Standard Deviation	1.073	0.962
Change from Baseline		
Mean	-0.67	-0.64
Standard Deviation	0.974	0.821
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.69	-0.65
Standard Error	0.050	0.063
95% Confidence Interval	(-0.78, -0.59)	(-0.78, -0.53)
Difference from OAD [2]		
Difference of LS Means		0.03
95% Confidence Interval		(-0.12, 0.19)

Reference ID: 3392698

Race/Ethnicity: Hispanic - Primary Endpoint

	OAD (N=875)	Albiglutide (N=566)
Number of Subjects [1]	281	172
Number (%) of Values Carried Forward	101 (35.9%)	62 (36.0%)
Baseline		
Mean	8.26	8.21
Standard Deviation	0.875	0.901
Primary Endpoint		
Mean	7.69	7.55
Standard Deviation	1.108	1.148
Change from Baseline		
Mean	-0.57	-0.66
Standard Deviation	1.100	0.945
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.53	-0.63
Standard Error	0.059	0.074
95% Confidence Interval	(-0.64, -0.41)	(-0.77, -0.48)
Difference from OAD [2]		
Difference of LS Means		-0.10
95% Confidence Interval		(-0.28, 0.09)

Race/Ethnicity: Asian - Primary Endpoint

	OAD (N=875)	Albiglutide (N=566)
Number of Subjects [1]	73	53
Number (%) of Values Carried Forward	19 (26.0%)	12 (22.6%)
Baseline		
Mean	8.12	8.00
Standard Deviation	0.926	0.869
Primary Endpoint		
Mean	7.53	7.60
Standard Deviation	1.183	1.152
Change from Baseline		
Mean	-0.58	-0.40
Standard Deviation	1.077	1.158
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.58	-0.43
Standard Error	0.117	0.137
95% Confidence Interval	(-0.81, -0.35)	(-0.69, -0.16)
Difference from OAD [2]		
Difference of LS Means		0.16
95% Confidence Interval		(-0.19, 0.50)

Reference ID: 3392698

Race/Ethnicity: Other - Primary Endpoint

	OAD (N=875)	Albiglutide (N=566)
Number of Subjects [1]	15	10
Number (%) of Values Carried Forward	2 (13.3%)	5 (50.0%)
Baseline		
Mean	8.23	8.41
Standard Deviation	0.678	0.561
Primary Endpoint		
Mean	7.14	7.83
Standard Deviation	0.674	0.881
Change from Baseline		
Mean	-1.09	-0.58
Standard Deviation	0.720	0.715
Model-Adjusted Change from Baseline [2]		
LS Mean	-1.07	-0.45
Standard Error	0.249	0.304
95% Confidence Interval	(-1.56, -0.58)	(-1.05, 0.14)
Difference from OAD [2]		
Difference of LS Means		0.61
95% Confidence Interval		(-0.16, 1.39)

Age Category

In the **Study Group A** (Placebo arm studies GLP112753, GLP112755, GLP112756 and GLP112757), the p-value for the treatment by Age category interaction term = 0.0232, which is statistically significant. The subgroup results follow:

Analysis of Change from Baseline in HbA1c (%) at Primary Endpoint and 6 Months by Age Category
(Intent-to-treat Population, Study Group A - LOCF)

Age Category: < 65 years - 6 Months

	Placebo (N=463)	Albiglutide (N=913)
Number of Subjects [1]	383	757
Number (%) of Values Carried Forward	135 (35.2%)	104 (13.7%)
Baseline		
Mean	8.18	8.16
Standard Deviation	0.918	0.893
6 Months		
Mean	8.17	7.31
Standard Deviation	1.292	0.986
Change from Baseline		
Mean	-0.01	-0.85
Standard Deviation	1.035	0.848
Model-Adjusted Change from Baseline [2]		
LS Mean	0.03	-0.85
Standard Error	0.043	0.031
95% Confidence Interval	(-0.06, 0.11)	(-0.91, -0.79)
Difference from Placebo [2]		
Difference of LS Means		-0.87
95% Confidence Interval		(-0.98, -0.77)

Reference ID: 3392698

Age Category: >= 65 to < 75 years - 6 Months

	Placebo (N=463)	Albiglutide (N=913)
Number of Subjects [1]	68	136
Number (%) of Values Carried Forward	13 (19.1%)	20 (14.7%)
Baseline		
Mean	7.90	7.94
Standard Deviation	0.781	0.787
6 Months		
Mean	7.69	7.22
Standard Deviation	1.065	0.810
Change from Baseline		
Mean	-0.21	-0.72
Standard Deviation	0.785	0.678
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.29	-0.79
Standard Error	0.102	0.072
95% Confidence Interval	(-0.49, -0.09)	(-0.94, -0.65)
Difference from Placebo [2]		
Difference of LS Means		-0.50
95% Confidence Interval		(-0.75, -0.26)

Age Category: >= 75 years - 6 Months

	Placebo (N=463)	Albiglutide (N=913)
Number of Subjects [1]	8	11
Number (%) of Values Carried Forward	3 (37.5%)	2 (18.2%)
Baseline		
Mean	8.08	7.97
Standard Deviation	1.031	1.010
6 Months		
Mean	8.14	7.04
Standard Deviation	1.355	0.679
Change from Baseline		
Mean	0.06	-0.94
Standard Deviation	0.441	0.676
Model-Adjusted Change from Baseline [2]		
LS Mean	0.05	-0.92
Standard Error	0.298	0.254
95% Confidence Interval	(-0.54, 0.63)	(-1.42, -0.42)
Difference from Placebo [2]		
Difference of LS Means		-0.97
95% Confidence Interval		(-1.73, -0.20)

Reference ID: 3392698

4.2 Other Special/Subgroup Populations

Baseline HBA1C Category

In the **Study Group A** (Placebo arm studies GLP112753, GLP112755, GLP112756 and GLP112757), the p-value for the treatment by baseline HBA1C category interaction term = 0.0030, which is statistically significant. The subgroup results follow:

Analysis of Change from Baseline in HbA1c (%) at Primary Endpoint and 6 Months by Baseline HbA1c Category
(Intent-to-treat Population, Study Group A - LOCF)

Baseline HbA1c Category: < 8.0% - Primary Endpoint

	Placebo (N=463)	Albiglutide (N=913)
Number of Subjects [1]	229	462
Number (%) of Values Carried Forward	91 (39.7%)	98 (21.2%)
Baseline		
Mean	7.38	7.42
Standard Deviation	0.308	0.337
Primary Endpoint		
Mean	7.58	6.92
Standard Deviation	0.928	0.725
Change from Baseline		
Mean	0.20	-0.50
Standard Deviation	0.867	0.743
Model-Adjusted Change from Baseline [2]		
LS Mean	0.23	-0.50
Standard Error	0.060	0.042
95% Confidence Interval	(0.11, 0.35)	(-0.58, -0.41)
Difference from Placebo [2]		
Difference of LS Means		-0.73
95% Confidence Interval		(-0.87, -0.58)

Baseline HbA1c Category: >= 8.0% to < 9.0% - Primary Endpoint

	Placebo (N=463)	Albiglutide (N=913)
Number of Subjects [1]	132	247
Number (%) of Values Carried Forward	100 (75.8%)	92 (37.2%)
Baseline		
Mean	8.42	8.39
Standard Deviation	0.291	0.277
Primary Endpoint		
Mean	8.51	7.68
Standard Deviation	0.877	0.993
Change from Baseline		
Mean	0.09	-0.71
Standard Deviation	0.878	0.978
Model-Adjusted Change from Baseline [2]		
LS Mean	0.10	-0.74
Standard Error	0.079	0.058
95% Confidence Interval	(-0.06, 0.25)	(-0.85, -0.62)
Difference from Placebo [2]		
Difference of LS Means		-0.83
95% Confidence Interval		(-1.03, -0.64)

Reference ID: 3392698

Baseline HbA1c Category: >= 9.0% - Primary Endpoint

	Placebo (N=463)	Albiglutide (N=913)
Number of Subjects [1]	98	195
Number (%) of Values Carried Forward	88 (89.8%)	110 (56.4%)
Baseline		
Mean	9.51	9.47
Standard Deviation	0.416	0.412
Primary Endpoint		
Mean	9.49	8.29
Standard Deviation	1.051	1.199
Change from Baseline		
Mean	-0.01	-1.18
Standard Deviation	0.995	1.163
Model-Adjusted Change from Baseline [2]		
LS Mean	0.00	-1.18
Standard Error	0.092	0.065
95% Confidence Interval	(-0.18, 0.18)	(-1.31, -1.06)
Difference from Placebo [2]		
Difference of LS Means		-1.18
95% Confidence Interval		(-1.40, -0.96)

In the **Study Group C** (Insulin arm studies GLP108486 and GLP112754), the p-value for the treatment by baseline HBA1C category interaction term = 0.0927, which is statistically significant, assessed at 0.10 level. The subgroup results follow:

Analysis of Change from Baseline in HbA1c (%) at 6 Months by Baseline HbA1c Category
(Intent-to-treat Population, Study Group C - LOCF)

Baseline HbA1c Category: < 8.0% - 6 Months

	Insulin (N=520)	Albiglutide (N=778)
Number of Subjects [1]	189	305
Number (%) of Values Carried Forward	31 (16.4%)	48 (15.7%)
Baseline		
Mean	7.45	7.44
Standard Deviation	0.308	0.313
6 Months		
Mean	7.19	7.02
Standard Deviation	0.793	0.728
Change from Baseline		
Mean	-0.26	-0.42
Standard Deviation	0.807	0.715
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.27	-0.41
Standard Error	0.066	0.052
95% Confidence Interval	(-0.40, -0.14)	(-0.51, -0.31)
Difference from Insulin [2]		
Difference of LS Means		-0.14
95% Confidence Interval		(-0.31, 0.02)

Reference ID: 3392698

Baseline HbA1c Category: >= 8.0% to < 9.0% - 6 Months

	Insulin (N=520)	Albiglutide (N=778)
Number of Subjects [1]	175	247
Number (%) of Values Carried Forward	38 (21.7%)	35 (14.2%)
Baseline		
Mean	8.44	8.43
Standard Deviation	0.291	0.284
6 Months		
Mean	7.61	7.64
Standard Deviation	0.929	0.851
Change from Baseline		
Mean	-0.84	-0.79
Standard Deviation	0.873	0.833
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.85	-0.78
Standard Error	0.069	0.058
95% Confidence Interval	(-0.98, -0.71)	(-0.89, -0.67)
Difference from Insulin [2]		
Difference of LS Means		0.07
95% Confidence Interval		(-0.11, 0.24)

Baseline HbA1c Category: >= 9.0% - 6 Months

	Insulin (N=520)	Albiglutide (N=778)
Number of Subjects [1]	152	220
Number (%) of Values Carried Forward	48 (31.6%)	66 (30.0%)
Baseline		
Mean	9.53	9.52
Standard Deviation	0.391	0.406
6 Months		
Mean	8.26	8.34
Standard Deviation	1.130	1.133
Change from Baseline		
Mean	-1.27	-1.18
Standard Deviation	1.102	1.126
Model-Adjusted Change from Baseline [2]		
LS Mean	-1.29	-1.18
Standard Error	0.074	0.061
95% Confidence Interval	(-1.43, -1.14)	(-1.30, -1.06)
Difference from Insulin [2]		
Difference of LS Means		0.10
95% Confidence Interval		(-0.08, 0.29)

Baseline Body Mass Index

In the **Study Group C** (Insulin arm studies GLP108486 and GLP112754), the p-value for the treatment by baseline Body Mass Index interaction term = 0.0963, which is statistically significant, assessed at 0.10 level. The subgroup results follow:

Reference ID: 3392698

Analysis of Change from Baseline in HbA1c (%) at 6 Months by Baseline Body Mass Index Category
(Intent-to-treat Population, Study Group C - LOCF)

Body Mass Index Category: < 25 kg/m^2 - 6 Months

	Insulin (N=520)	Albiglutide (N=778)
Number of Subjects [1]	34	43
Number (%) of Values Carried Forward	14 (41.2%)	6 (14.0%)
Baseline		
Mean	8.51	8.43
Standard Deviation	0.974	0.956
6 Months		
Mean	8.19	7.67
Standard Deviation	1.308	1.061
Change from Baseline		
Mean	-0.32	-0.77
Standard Deviation	1.163	0.974
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.28	-0.72
Standard Error	0.154	0.137
95% Confidence Interval	(-0.58, 0.02)	(-0.99, -0.45)
Difference from Insulin [2]		
Difference of LS Means		-0.44
95% Confidence Interval		(-0.84, -0.04)

Body Mass Index Category: >= 25 to < 30 kg/m^2 - 6 Months

	Insulin (N=520)	Albiglutide (N=778)
Number of Subjects [1]	117	180
Number (%) of Values Carried Forward	19 (16.2%)	37 (20.6%)
Baseline		
Mean	8.35	8.35
Standard Deviation	0.904	0.900
6 Months		
Mean	7.50	7.46
Standard Deviation	0.977	0.978
Change from Baseline		
Mean	-0.84	-0.89
Standard Deviation	1.044	0.846
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.85	-0.89
Standard Error	0.083	0.067
95% Confidence Interval	(-1.01, -0.68)	(-1.02, -0.76)
Difference from Insulin [2]		
Difference of LS Means		-0.04
95% Confidence Interval		(-0.25, 0.17)

Reference ID: 3392698

Body Mass Index Category: >= 30 to < 35 kg/m^2 - 6 Months

	Insulin (N=520)	Albiglutide (N=778)
Number of Subjects [1]	161	231
Number (%) of Values Carried Forward	40 (24.8%)	43 (18.6%)
Baseline		
Mean	8.41	8.28
Standard Deviation	0.883	0.915
6 Months		
Mean	7.64	7.53
Standard Deviation	1.055	1.034
Change from Baseline		
Mean	-0.77	-0.76
Standard Deviation	1.025	1.006
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.76	-0.79
Standard Error	0.070	0.059
95% Confidence Interval	(-0.90, -0.63)	(-0.90, -0.67)
Difference from Insulin [2]		
Difference of LS Means		-0.02
95% Confidence Interval		(-0.20, 0.16)

Body Mass Index Category: >= 35 kg/m^2 - 6 Months

	Insulin (N=520)	Albiglutide (N=778)
Number of Subjects [1]	204	318
Number (%) of Values Carried Forward	44 (21.6%)	63 (19.8%)
Baseline		
Mean	8.40	8.38
Standard Deviation	0.912	0.915
6 Months		
Mean	7.64	7.71
Standard Deviation	0.993	1.081
Change from Baseline		
Mean	-0.76	-0.67
Standard Deviation	0.940	0.927
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.77	-0.67
Standard Error	0.063	0.051
95% Confidence Interval	(-0.89, -0.64)	(-0.77, -0.57)
Difference from Insulin [2]		
Difference of LS Means		0.10
95% Confidence Interval		(-0.06, 0.26)

Region

In the **Study Group B** (OAD arm studies GLP112753 and GLP112757), the p-value for the treatment by Region interaction term = 0.0196, which is statistically significant, assessed at 0.10 level. The subgroup results follow:

Reference ID: 3392698

Analysis of Change from Baseline in HbA1c (%) at Primary Endpoint and 6 Months by Region
(Intent-to-treat Population, Study Group B - LOCF)

Region: Asia - Primary Endpoint

	OAD (N=875)	Albiglutide (N=566)
Number of Subjects [1]	48	37
Number (%) of Values Carried Forward	11 (22.9%)	8 (21.6%)
Baseline		
Mean	8.18	7.99
Standard Deviation	0.953	0.921
Primary Endpoint		
Mean	7.45	7.52
Standard Deviation	1.065	1.221
Change from Baseline		
Mean	-0.72	-0.47
Standard Deviation	0.849	1.197
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.74	-0.55
Standard Error	0.140	0.159
95% Confidence Interval	(-1.02, -0.47)	(-0.86, -0.23)
Difference from OAD [2]		
Difference of LS Means		0.19
95% Confidence Interval		(-0.22, 0.61)

Region: Europe - Primary Endpoint

	OAD (N=875)	Albiglutide (N=566)
Number of Subjects [1]	24	22
Number (%) of Values Carried Forward	7 (29.2%)	6 (27.3%)
Baseline		
Mean	8.02	8.15
Standard Deviation	0.644	0.886
Primary Endpoint		
Mean	7.52	7.58
Standard Deviation	1.288	0.769
Change from Baseline		
Mean	-0.50	-0.57
Standard Deviation	1.330	0.598
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.50	-0.47
Standard Error	0.197	0.207
95% Confidence Interval	(-0.88, -0.11)	(-0.87, -0.06)
Difference from OAD [2]		
Difference of LS Means		0.03
95% Confidence Interval		(-0.53, 0.59)

Reference ID: 3392698

Region: Rest of World - Primary Endpoint

	OAD (N=875)	Albiglutide (N=566)
Number of Subjects [1]	188	105
Number (%) of Values Carried Forward	53 (28.2%)	23 (21.9%)
Baseline		
Mean	8.18	8.23
Standard Deviation	0.865	0.940
Primary Endpoint		
Mean	7.65	7.31
Standard Deviation	1.241	1.259
Change from Baseline		
Mean	-0.53	-0.92
Standard Deviation	1.212	1.078
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.52	-0.90
Standard Error	0.072	0.094
95% Confidence Interval	(-0.66, -0.38)	(-1.09, -0.72)
Difference from OAD [2]		
Difference of LS Means		-0.38
95% Confidence Interval		(-0.61, -0.15)

Region: USA - North - Primary Endpoint

	OAD (N=875)	Albiglutide (N=566)
Number of Subjects [1]	121	81
Number (%) of Values Carried Forward	32 (26.4%)	33 (40.7%)
Baseline		
Mean	8.13	8.12
Standard Deviation	0.820	0.802
Primary Endpoint		
Mean	7.38	7.57
Standard Deviation	1.085	1.023
Change from Baseline		
Mean	-0.75	-0.55
Standard Deviation	0.991	0.983
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.76	-0.54
Standard Error	0.088	0.108
95% Confidence Interval	(-0.93, -0.58)	(-0.75, -0.33)
Difference from OAD [2]		
Difference of LS Means		0.21
95% Confidence Interval		(-0.06, 0.49)

Reference ID: 3392698

Region: USA - South Atlantic - Primary Endpoint

	OAD (N=875)	Albiglutide (N=566)
Number of Subjects [1]	164	91
Number (%) of Values Carried Forward	74 (45.1%)	31 (34.1%)
Baseline		
Mean	8.03	8.04
Standard Deviation	0.762	0.845
Primary Endpoint		
Mean	7.59	7.48
Standard Deviation	1.132	0.921
Change from Baseline		
Mean	-0.44	-0.56
Standard Deviation	1.065	0.807
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.47	-0.60
Standard Error	0.075	0.101
95% Confidence Interval	(-0.62, -0.33)	(-0.80, -0.40)
Difference from OAD [2]		
Difference of LS Means		-0.13
95% Confidence Interval		(-0.38, 0.12)

Region: USA - South Central - Primary Endpoint

	OAD (N=875)	Albiglutide (N=566)
Number of Subjects [1]	147	93
Number (%) of Values Carried Forward	44 (29.9%)	29 (31.2%)
Baseline		
Mean	8.19	8.28
Standard Deviation	0.884	0.807
Primary Endpoint		
Mean	7.52	7.67
Standard Deviation	1.072	1.012
Change from Baseline		
Mean	-0.67	-0.61
Standard Deviation	1.000	0.866
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.65	-0.55
Standard Error	0.080	0.100
95% Confidence Interval	(-0.81, -0.49)	(-0.74, -0.35)
Difference from OAD [2]		
Difference of LS Means		0.10
95% Confidence Interval		(-0.15, 0.36)

Reference ID: 3392698

Region: USA - West - Primary Endpoint

	OAD (N=875)	Albiglutide (N=566)
Number of Subjects [1]	172	129
Number (%) of Values Carried Forward	64 (37.2%)	48 (37.2%)
Baseline		
Mean	8.21	8.07
Standard Deviation	0.865	0.828
Primary Endpoint		
Mean	7.57	7.48
Standard Deviation	1.119	0.967
Change from Baseline		
Mean	-0.65	-0.59
Standard Deviation	1.042	0.813
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.63	-0.62
Standard Error	0.073	0.085
95% Confidence Interval	(-0.77, -0.48)	(-0.79, -0.45)
Difference from OAD [2]		
Difference of LS Means		0.01
95% Confidence Interval		(-0.21, 0.23)

In the **Study Group C** (Insulin arm studies GLP108486 and GLP112754), the p-value for the treatment by Region interaction term = 0.0354, which is statistically significant, assessed at 0.10 level. The subgroup results follow:

Analysis of Change from Baseline in HbA1c (%) at 6 Months by Region
(Intent-to-treat Population, Study Group C - LOCF)

Region: Asia - 6 Months

	Insulin (N=520)	Albiglutide (N=778)
Number of Subjects [1]	40	39
Number (%) of Values Carried Forward	18 (45.0%)	12 (30.8%)
Baseline		
Mean	8.61	8.43
Standard Deviation	0.867	0.856
6 Months		
Mean	8.16	7.51
Standard Deviation	1.278	1.169
Change from Baseline		
Mean	-0.45	-0.93
Standard Deviation	1.245	1.022
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.39	-0.94
Standard Error	0.144	0.146
95% Confidence Interval	(-0.68, -0.11)	(-1.23, -0.65)
Difference from Insulin [2]		
Difference of LS Means		-0.55
95% Confidence Interval		(-0.94, -0.15)

Reference ID: 3392698

Analysis of Change from Baseline in HbA1c (%) at 6 Months by Region
(Intent-to-treat Population, Study Group C - LOCF)

Region: Europe - 6 Months

	Insulin (N=520)	Albiglutide (N=778)
Number of Subjects [1]	12	14
Number (%) of Values Carried Forward	3 (25.0%)	2 (14.3%)
Baseline		
Mean	7.83	8.04
Standard Deviation	0.547	0.655
6 Months		
Mean	7.39	7.62
Standard Deviation	0.822	1.003
Change from Baseline		
Mean	-0.44	-0.41
Standard Deviation	0.854	0.897
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.70	-0.61
Standard Error	0.260	0.241
95% Confidence Interval	(-1.21, -0.19)	(-1.08, -0.14)
Difference from Insulin [2]		
Difference of LS Means		0.09
95% Confidence Interval		(-0.60, 0.78)

Region: Rest of World - 6 Months

	Insulin (N=520)	Albiglutide (N=778)
Number of Subjects [1]	116	166
Number (%) of Values Carried Forward	26 (22.4%)	32 (19.3%)
Baseline		
Mean	8.36	8.45
Standard Deviation	0.912	0.883
6 Months		
Mean	7.59	7.49
Standard Deviation	1.015	0.991
Change from Baseline		
Mean	-0.77	-0.96
Standard Deviation	1.015	0.896
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.78	-0.92
Standard Error	0.083	0.069
95% Confidence Interval	(-0.94, -0.62)	(-1.05, -0.78)
Difference from Insulin [2]		
Difference of LS Means		-0.14
95% Confidence Interval		(-0.35, 0.07)

Reference ID: 3392698

Region: USA - North - 6 Months

	Insulin (N=520)	Albiglutide (N=778)
Number of Subjects [1]	71	136
Number (%) of Values Carried Forward	8 (11.3%)	22 (16.2%)
Baseline		
Mean	8.26	8.17
Standard Deviation	0.828	0.834
6 Months		
Mean	7.43	7.51
Standard Deviation	0.878	0.985
Change from Baseline		
Mean	-0.83	-0.66
Standard Deviation	0.914	0.846
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.89	-0.73
Standard Error	0.106	0.077
95% Confidence Interval	(-1.10, -0.68)	(-0.88, -0.58)
Difference from Insulin [2]		
Difference of LS Means		0.16
95% Confidence Interval		(-0.09, 0.42)

Region: USA - South Atlantic - 6 Months

	Insulin (N=520)	Albiglutide (N=778)
Number of Subjects [1]	89	135
Number (%) of Values Carried Forward	17 (19.1%)	26 (19.3%)
Baseline		
Mean	8.41	8.19
Standard Deviation	0.959	0.950
6 Months		
Mean	7.57	7.64
Standard Deviation	0.919	1.154
Change from Baseline		
Mean	-0.84	-0.55
Standard Deviation	0.967	0.911
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.82	-0.61
Standard Error	0.095	0.078
95% Confidence Interval	(-1.00, -0.63)	(-0.76, -0.46)
Difference from Insulin [2]		
Difference of LS Means		0.21
95% Confidence Interval		(-0.03, 0.45)

Reference ID: 3392698

Region: USA - South Central - 6 Months

	Insulin (N=520)	Albiglutide (N=778)
Number of Subjects [1]	95	138
Number (%) of Values Carried Forward	22 (23.2%)	30 (21.7%)
Baseline		
Mean	8.45	8.42
Standard Deviation	0.912	0.957
6 Months		
Mean	7.69	7.66
Standard Deviation	1.026	1.052
Change from Baseline		
Mean	-0.76	-0.76
Standard Deviation	1.004	1.011
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.73	-0.73
Standard Error	0.092	0.076
95% Confidence Interval	(-0.91, -0.55)	(-0.88, -0.58)
Difference from Insulin [2]		
Difference of LS Means		0.00
95% Confidence Interval		(-0.23, 0.23)

Region: USA - West - 6 Months

	Insulin (N=520)	Albiglutide (N=778)
Number of Subjects [1]	93	144
Number (%) of Values Carried Forward	23 (24.7%)	25 (17.4%)
Baseline		
Mean	8.47	8.48
Standard Deviation	0.916	0.940
6 Months		
Mean	7.70	7.69
Standard Deviation	1.165	1.026
Change from Baseline		
Mean	-0.77	-0.79
Standard Deviation	1.028	0.959
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.73	-0.72
Standard Error	0.093	0.075
95% Confidence Interval	(-0.91, -0.55)	(-0.87, -0.58)
Difference from Insulin [2]		
Difference of LS Means		0.00
95% Confidence Interval		(-0.23, 0.24)

Duration of Diabetes

In the **Study Group B** (OAD arm studies GLP112753 and GLP112757), the p-value for the treatment by Duration of Diabetes interaction term = 0.0129, which is statistically significant, assessed at 0.10 level. The subgroup results follow:

Reference ID: 3392698

Analysis of Change from Baseline in HbA1c (%) at Primary Endpoint and 6 Months by Duration of Diabetes Category
(Intent-to-treat Population, Study Group B - LOCF)

Duration of Diabetes Category: < 5 years - Primary Endpoint

	OAD (N=875)	Albiglutide (N=566)
Number of Subjects [1]	392	218
Number (%) of Values Carried Forward	124 (31.6%)	63 (28.9%)
Baseline		
Mean	8.04	8.06
Standard Deviation	0.798	0.853
Primary Endpoint		
Mean	7.54	7.34
Standard Deviation	1.185	1.080
Change from Baseline		
Mean	-0.49	-0.71
Standard Deviation	1.124	0.907
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.55	-0.75
Standard Error	0.050	0.065
95% Confidence Interval	(-0.65, -0.45)	(-0.88, -0.62)
Difference from OAD [2]		
Difference of LS Means		-0.20
95% Confidence Interval		(-0.36, -0.04)

Duration of Diabetes Category: >= 5 to < 10 years - Primary Endpoint

	OAD (N=875)	Albiglutide (N=566)
Number of Subjects [1]	274	202
Number (%) of Values Carried Forward	96 (35.0%)	69 (34.2%)
Baseline		
Mean	8.18	8.21
Standard Deviation	0.868	0.901
Primary Endpoint		
Mean	7.58	7.60
Standard Deviation	1.142	0.988
Change from Baseline		
Mean	-0.60	-0.61
Standard Deviation	1.014	0.997
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.58	-0.58
Standard Error	0.058	0.068
95% Confidence Interval	(-0.70, -0.47)	(-0.71, -0.45)
Difference from OAD [2]		
Difference of LS Means		0.00
95% Confidence Interval		(-0.17, 0.18)

Reference ID: 3392698

Duration of Diabetes Category: >= 10 years - Primary Endpoint

	OAD (N=875)	Albiglutide (N=566)
Number of Subjects [1]	198	138
Number (%) of Values Carried Forward	65 (32.8%)	46 (33.3%)
Baseline		
Mean	8.33	8.14
Standard Deviation	0.864	0.783
Primary Endpoint		
Mean	7.52	7.59
Standard Deviation	1.038	1.060
Change from Baseline		
Mean	-0.81	-0.55
Standard Deviation	1.022	0.852
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.72	-0.53
Standard Error	0.069	0.083
95% Confidence Interval	(-0.86, -0.58)	(-0.70, -0.37)
Difference from OAD [2]		
Difference of LS Means		0.19
95% Confidence Interval		(-0.02, 0.40)

Renal Status

In the **Study Group A** (Placebo arm studies GLP112753, GLP112755, GLP112756 and GLP112757), the p-value for the treatment by baseline renal status interaction term = 0.0255, which is statistically significant. Effect of albiglutide is comparatively better in normal patients. The subgroup results follow:

Analysis of Change from Baseline in HbA1c (%) at Primary Endpoint and 6 Months by Renal Status
(Intent-to-treat Population, Study Group A - LOCF)

Renal Status: Normal (eGFR >= 90 mL/min/1.73 m^2) - 6 Months

	Placebo (N=463)	Albiglutide (N=913)
Number of Subjects [1]	147	290
Number (%) of Values Carried Forward	57 (38.8%)	42 (14.5%)
Baseline		
Mean	8.20	8.27
Standard Deviation	0.915	0.924
6 Months		
Mean	8.31	7.41
Standard Deviation	1.202	1.092
Change from Baseline		
Mean	0.11	-0.86
Standard Deviation	0.922	0.932
Model-Adjusted Change from Baseline [2]		
LS Mean	0.17	-0.81
Standard Error	0.070	0.050
95% Confidence Interval	(0.03, 0.31)	(-0.91, -0.71)
Difference from Placebo [2]		
Difference of LS Means		-0.98
95% Confidence Interval		(-1.14, -0.81)

Reference ID: 3392698

Renal Status: Renally Impaired (eGFR < 90 mL/min/1.73 m^2) - 6 Months

	Placebo (N=463)	Albiglutide (N=913)
Number of Subjects [1]	312	614
Number (%) of Values Carried Forward	94 (30.1%)	84 (13.7%)
Baseline		
Mean	8.11	8.06
Standard Deviation	0.899	0.854
6 Months		
Mean	8.00	7.24
Standard Deviation	1.293	0.884
Change from Baseline		
Mean	-0.10	-0.82
Standard Deviation	1.023	0.768
Model-Adjusted Change from Baseline [2]		
LS Mean	-0.11	-0.85
Standard Error	0.048	0.034
95% Confidence Interval	(-0.20, -0.01)	(-0.92, -0.79)
Difference from Placebo [2]		
Difference of LS Means		-0.75
95% Confidence Interval		(-0.86, -0.63)

Analysis of Change from Baseline in HbA1c (%) at Primary Endpoint and 6 Months by Renal Status
(Intent-to-treat Population, Study Group A - LOCF)

Renal Status: Normal (eGFR >= 90 mL/min/1.73 m^2) - Primary Endpoint

	Placebo (N=463)	Albiglutide (N=913)
Number of Subjects [1]	147	290
Number (%) of Values Carried Forward	100 (68.0%)	111 (38.3%)
Baseline		
Mean	8.20	8.27
Standard Deviation	0.915	0.924
Primary Endpoint		
Mean	8.52	7.61
Standard Deviation	1.235	1.184
Change from Baseline		
Mean	0.33	-0.66
Standard Deviation	0.941	1.022
Model-Adjusted Change from Baseline [2]		
LS Mean	0.37	-0.62
Standard Error	0.075	0.053
95% Confidence Interval	(0.23, 0.52)	(-0.73, -0.52)
Difference from Placebo [2]		
Difference of LS Means		-1.00
95% Confidence Interval		(-1.17, -0.82)

Reference ID: 3392698

Analysis of Change from Baseline in HbA1c (%) at Primary Endpoint and 6 Months by Renal Status
(Intent-to-treat Population, Study Group A - LOCF)

Renal Status: Renally Impaired (eGFR < 90 mL/min/1.73 m^2) - Primary Endpoint

	Placebo (N=463)	Albiglutide (N=913)
Number of Subjects [1]	312	614
Number (%) of Values Carried Forward	179 (57.4%)	189 (30.8%)
Baseline		
Mean	8.11	8.06
Standard Deviation	0.899	0.854
Primary Endpoint		
Mean	8.13	7.34
Standard Deviation	1.173	1.007
Change from Baseline		
Mean	0.03	-0.72
Standard Deviation	0.867	0.915
Model-Adjusted Change from Baseline [2]		
LS Mean	0.04	-0.75
Standard Error	0.051	0.036
95% Confidence Interval	(-0.06, 0.14)	(-0.83, -0.68)
Difference from Placebo [2]		
Difference of LS Means		-0.79
95% Confidence Interval		(-0.91, -0.67)

In Study Groups A, B, and C, subjects were excluded from the individual studies if their creatinine clearance at Screening was <60 mL/min using the Cockcroft-Gault method of determining creatinine clearance. For purposes of analyzing the renal status data in these study groups, normal renal function was defined as eGFR ≥90 mL/min/1.73 m^2 and renal impairment was defined as <90 mL/min/1.73 m^2 using the MDRD Study Group formula.

The positive HbA_{1c} treatment effect for albiglutide versus placebo was seen in subjects with normal renal function and those with renal impairment; the magnitude of the HbA_{1c} reduction for albiglutide versus placebo was also consistent within each category.

Compared to OADs or insulin, albiglutide achieved a similar treatment effect in subjects with normal renal function and those with renal impairment.

§ Supportive data demonstrating the additional benefit of uptitrating to albiglutide 50 mg once weekly comes from the integrated analysis of the 4 Phase III studies that had optional uptitration (GLP112753, GLP112754, GLP112757, and GLP108486). A total of 937 subjects across these studies uptitrated to albiglutide 50 mg once weekly at some point during the study up to the data cut-off (after at least 2 years treatment) for this regulatory submission.

The Albiglutide-Uptitrated Population is a nonrandomized subgroup and is expected to include bias as they are likely to be less responsive to albiglutide compared to subjects who did not uptitrate or generally more difficult to treat subjects due to underlying disease progression. In addition, the timing of uptitration was not standardized, but rather occurred at different time points throughout the study. This was done to reflect a “real world”

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use of albiglutide. Many subjects were titrated in the early part of the studies, and as such, have greater exposure to the 50-mg dose relative to the 30-mg dose. As expected, relative to the Albiglutide-Treated Population, the Albiglutide-Uptitrated Population had subjects with a higher baseline HbA_{1c}, more subjects in a higher baseline HbA_{1c} category and more subjects with a longer duration of diabetes. Analysis of the HbA_{1c} and FPG data by uptitration status for the Albiglutide-Uptitration Population shows further improvement in (particularly if there is early uptitration) and maintenance of glycemic control (in those who uptitrate later than Week 24) after uptitration to 50 mg.

Further, a higher percentage of uptitrated subjects completed active treatment through the primary endpoint (94% vs 87% of subjects in the Albiglutide-Uptitrated Population and Albiglutide-treated Population, respectively), suggesting an added benefit of increasing to 50 mg if glycemia is not adequately controlled at 30 mg albiglutide.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Overall Conclusion on the Eight Phase 3 Studies (see table below)**:**

Albiglutide was statistically superior to each of placebo (both 30 mg and 50 mg), sitagliptin, and glimepiride. Based on the datasets provided by the sponsor, this reviewer concludes that albiglutide has shown efficacy.

The claim of non-inferiority of albiglutide to each of preprandial insulin lispro and insulin glargine is acceptable. However, these results are from open-label studies.

Each of liraglutide and pioglitazone were statistically significantly superior to albiglutide.

Conclusion on STUDY GLP114856 (Phase 2 Bioequivalence Study)

Both processes statistically significantly reduced mean HBA1C by Week 17, from baseline, by amount 0.75% for Process 2 and by 0.84% for process 3. Process 3 is non-inferior to Process 2, based on Change from Baseline in HBA1c at Week 17 and a non-inferiority margin of .3 (the 95% confidence interval (-.31, .15)).

Note: The sponsor pre-specified a non-inferiority margin of .3% for the primary efficacy variable, HBA1C, for most studies and .4% for some. Non-inferiority margins were not pre-specified for other efficacy variables.

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I reviewed studies GLP112753 and GLP114130 in a little more details and analyzed the data for the following nine studies over all time points, by Proc Wilcoxon, Proc TTEST, and Proc Mixed. The sponsor provided many supportive and sensitivity analyses. Slight inconsistency in one or two cases does not nullify the huge amount of other results.

STUDY GLP108486, STUDY GLP112753, STUDY GLP112754, STUDY GLP112755, STUDY GLP112756, STUDY GLP112757, STUDY GLP114179, STUDY GLP114130, and the Phase 2 bioequivalent STUDY GLP114856 (HBA1C only for the last)

Note: Negative sign indicates that albiglutide lowered the measure more than the comparator.

Main Results (Primary efficacy at primary time point):

Study	Treatment	n	Vs albiglutide CI (-ve sign indicates albiglutide better)	Vs albiglutide p-value Non-inferiority	Superiority
GLP108486 Week 26	Insulin Glargine in combination with Insulin lispro Albiglutide	278 279	-.32, 00	<.0001	.0533
GLP112753 Week 104	Placebo Sitagliptin Glimepiride Albiglutide	97 297 299 293	-1.16, -.65 -.53, -.17 -.45, -.09	<.0001 <.0001	<.0001 .0001 .0033
GLP112754 Week 52	Insulin Glargine Albiglutide	238 493	-.04, .27	.0086	.1463
GLP112755 Week 52	Placebo Albiglutide 30mg/W	149 149	-.95, -.56		<.0001
GLP112756 Week 52	Placebo Albiglutide 30mg/W Albiglutide 50mg/W	98 100 97	Vs. Placebo -1.11, -.58 -1.31, -.77	<.0001 <.0001	
GLP112757 Week 52	Placebo Pioglitazone (super) Albiglutide	115 268 265	-1.07, -.68 .1,.4	.2685	<.0001 .0012 (Pio sup)
GLP114179 Week 32	Liraglutide (superio) Albiglutide	402 398	.08, .34	.0846	.0016 (Liraglutid Super., my computation)
GLP114130 Week 26	Sitagliptin Albiglutide	236 242	-.49, -.15	<.0001	.0003
GLP114856 Week 17	Process 2 Process 3	135 141	-.31, .15		.4874

FPG Results (at primary time point):

Study	Treatment	n	Vs albiglutide CI (-ve sign indicates albiglutide better)	Vs albiglutide p-value
GLP108486 Week 26	Insulin Glargine in combination with Insulin lispro Albiglutide	279 282	-.73, .18	.2366

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GLP112753 Week 104	Placebo Sitagliptin Glimepiride Albiglutide	100 299 302 296	-2.16, -.90 -1.30, -.41 -1.01, -0.12	<.0001 .0002 .0133
GLP112754 Week 52	Insulin Glargine Albiglutide	238 494	.75, 1.63	<.0001 (Glargine sup)
GLP112755 Week 52	Placebo Albiglutide 30mg/W	149 149	-2.19, -1.09	<.0001
GLP112756 Week 52	Placebo Albiglutide 30mg/W Albiglutide 50mg/W	99 100 97	Vs. Placebo -2.55, -1.22 -3.05, -1.71	 <.0001 <.0001
GLP112757 Week 52	Placebo Pioglitazone (super) Albiglutide	115 272 268	-1.89, -.76 .61,1.49	<.0001 <.0001 (Pio sup)
GLP114179 Week 32	Liraglutide (superio) Albiglutide	402 400	.14, .78	.0048 (Liraglutid Super.)
GLP114130 Week 26	Sitagliptin Albiglutide	240 244	-1.71, -.69	<.0001

Insulin Glargine, pioglitazone, and liraglutide were superior to albiglutide with respect to FPG.

Weight Change Results (at primary time point):

Study	Treatment	n	Vs albiglutide CI (-ve sign indicates albiglutide better)	Vs albiglutide p-value
GLP108486 Week 26	Insulin Glargine in combination with Insulin lispro Albiglutide	 281 282	 -2.09, -1.00	 <.0001
GLP112753 Week 104	Placebo Sitagliptin Glimepiride Albiglutide	100 300 302 296	-1.14, .73 -1.01, .31 -3.03, -1.71	.6677 .2991 <.0001
GLP112754 Week 52	Insulin Glargine Albiglutide	238 495	-3.20, -2.02	<.0001
GLP112755 Week 52	Placebo Albiglutide 30mg/W	149 149	-1.15, .79	.7193
GLP112756 Week 52	Placebo Albiglutide 30mg/W Albiglutide 50mg/W	99 100 97	Vs. Placebo -.91, 1.46 -1.40, 1.01	 .6526 .7485
GLP112757 Week 52	Placebo Pioglitazone (super) Albiglutide	115 272 268	-.88, .82 -5.51,-4.20	9499 <.0001 (Pio increased wt. more)
GLP114179 Week 32	Liraglutide (superio) Albiglutide	402 400	1.05, 2.06	<.0001 (Liraglutid reduced more)
GLP114130 Week 26	Sitagliptin Albiglutide	240 244	-1.14, -.06	.0281

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Pioglitazone increased a large amount of weight. Liraglutide reduced weight statistically significantly more than albiglutide. Albiglutide reduced weight statistically significantly more than sitagliptin, glimepiride, insulin glargine (by a good margin), and insulin lispro (insulin glargine in both arms).

When dropout rates are high, the evidence is compromised. There is no method to rescue such a study, other than doing sensitivity analyses with different methods of handling dropouts. The sponsor provided such sensitivity analyses which were consistent with the primary analyses. One consolation may be that clinical trial patients do not form a random sample from the possible patient population, anyway. Dropout rates were high in the following studies: 753 (30%), 754 (30%), 755 (Placebo exceeded 35%), 756 (>35%), 757 (40%), 179 (>20%), and moderate (around 15%) in 130. However, because of LOCF method, most of the patients were included in the analyses.

Interactions/Inconsistencies:

Statistically significant interactions are difficult to detect because of lack of power. On the other hand, how much multiple comparison adjustment is needed in this situation is unknown.

I have pointed out inconsistencies in some subgroup results based on confidence intervals (not that convincing because of smaller sample sizes in subgroups of smaller individual studies, but more convincing when the sample sizes are big) and some based on statistically significant interaction p-values, without multiple comparison adjustments. Subgroup results, when not planned to be confirmatory, are not confirmatory. Further evidences are needed to reach the level of confirmation.

When there are more than two subgroups for a factor, a statistically significant result for this interaction test leads to a general conclusion that the treatment difference/effect is not the same across the subgroups. However, the test does not lead to any specific conclusion on how the treatment difference/effect compares across any two subgroups of that factor.

1. <u>In the Integrated Summary of Efficacy</u> (Details are in Section 4)

In addition to the limitations on conclusions on subgroup results mentioned before, there are some limitations to these pooled analyses because of different primary time points, different background therapies, and differences in titration in different studies. In study groups B and C, drugs of dissimilar effects were pooled together.

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There were statistically significant treatment by factor interactions for the following factors:

Gender

In the **Study Group B** (OAD arm studies GLP112753 and GLP112757), the p-value for the treatment by Gender interaction term = 0.0389, which is statistically significant, assessed at 0.10 level.

Race/Ethnicity

In the **Study Group B** (OAD arm studies GLP112753 and GLP112757), the p-value for the treatment by Race/Ethnicity interaction term = 0.0269, which is statistically significant, assessed at 0.10 level.

Age Category

In the **Study Group A** (Placebo arm studies GLP112753, GLP112755, GLP112756 and GLP112757), the p-value for the treatment by Age category interaction term = 0.0232, which is statistically significant.

Baseline HBA1C Category

In the **Study Group A** (Placebo arm studies GLP112753, GLP112755, GLP112756 and GLP112757), the p-value for the treatment by baseline HBA1C category interaction term = 0.0030, which is statistically significant.

In the **Study Group C** (Insulin arm studies GLP108486 and GLP112754), the p-value for the treatment by baseline HBA1C category interaction term = 0.0927, which is statistically significant, assessed at 0.10 level.

Baseline Body Mass Index

In the **Study Group C** (Insulin arm studies GLP108486 and GLP112754), the p-value for the treatment by baseline Body Mass Index interaction term = 0.0963, which is statistically significant, assessed at 0.10 level.

Region

In the **Study Group B** (OAD arm studies GLP112753 and GLP112757), the p-value for the treatment by Region interaction term = 0.0196, which is statistically significant, assessed at 0.10 level.

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In the **Study Group C** (Insulin arm studies GLP108486 and GLP112754), the p-value for the treatment by Region interaction term = 0.0354, which is statistically significant, assessed at 0.10 level.

Duration of Diabetes

In the **Study Group B** (OAD arm studies GLP112753 and GLP112757), the p-value for the treatment by Duration of Diabetes interaction term = 0.0129, which is statistically significant, assessed at 0.10 level.

Renal Status

In the **Study Group A** (Placebo arm studies GLP112753, GLP112755, GLP112756 and GLP112757), the p-value for the treatment by baseline renal status interaction term = 0.0255, which is statistically significant. Effect of albiglutide is comparatively better in normal patients.

2. **Treatment by factor interactions in individual studies**

In Study 486

There was a statistically significant Treatment by Race (Black, white, other non-white) (p= 0.0023) interaction:

In the black group, the upper boundary of the confidence interval (-.42,.53) is out of the non-inferiority margin .3; so, does not exclude the possibility of the albiglutide group being inferior to lispro insulin.

There was a statistically significant current antidiabetic therapy by treatment interaction p-value of .0913. *The preprandial insulin lispro was numerically superior to albiglutide in the 'Both TZD and Metformin' subgroup.*

In Study 753

There was a statistically significant Treatment by Region (Ex-US, USA – North, USA – South Atlantic, USA – South Central, USA – West) (p= 0.0671) interaction, with better Ex-USA and USA-South Atlantic regions favoring albiglutide much more.

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In Study 754

There were statistically significant Treatment by Baseline HbA1c (<8.0, >=8.0) (p= 0.0328) and by Age at randomization category (<65, >=65) (p=0.0503) interactions, albiglutide being numerically superior in the <8 HBA1c category and in the >=65 age category.

In Study 756

There was a statistically significant quantitative Treatment by Baseline HbA1c (<8.0, >=8.0) (p=0.0032) interaction, with smaller effects in the <8 group.

In Study 179

There were statistically significant Treatment by Gender (male, female) (p=0.0079), by Ethnicity group (Hispanic/Latino, not Hispanic/Latino) (p=0.0288), and by Background therapy (With SU, Without SU) (p=0.0265) interactions.

The superiority of the liraglutide treatment was less pronounced in the male group. In the Hispanic/Latino group, albiglutide was marginally numerically superior to liraglutide. The superiority of the liraglutide treatment was less pronounced in the 'Not on SU' group.

5.2 Conclusions and Recommendations

Albiglutide was statistically superior to each of placebo (both 30 mg and 50 mg), sitagliptin, and glimepiride. Based on the datasets provided by the sponsor, this reviewer concludes that albiglutide has shown efficacy.

The claim of non-inferiority of albiglutide to each of preprandial insulin lispro and insulin glargine is acceptable. However, these results are from open-label studies.

Each of liraglutide and pioglitazone were statistically significantly superior to albiglutide.

Details are in the previous Section 5.1.

Conclusion on STUDY GLP114856 (Phase 2 Bioequivalence Study)

Both processes statistically significantly reduced mean HBA1C by Week 17, from baseline, by amount 0.75% for Process 2 and by 0.84% for process 3. Process 3 is non-inferior to Process 2,

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based on Change from Baseline in HBA1c at Week 17 and a non-inferiority margin of .3 (the 95% confidence interval (-.31, .15)).

Labeling

The non-inferiority p-values from the Tables should be removed. Instead the conclusions on non-inferiority should be put as footnotes. When information from outside the study is brought in to make an inference, a p-value should not be reported. In this case, the non-inferiority margin was based on the results from previous placebo controlled studies. Here, comparing the confidence interval with the margin is the test procedure.

Modified ITT-set patient-numbers should be written in the Tables.

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APPENDICES

Appendix I

Study Design and Endpoints for Study 753

This was a Phase III, randomized, double-blind, placebo- and active-controlled, parallel-group, multicenter study to evaluate the efficacy and safety of a weekly subcutaneously injected dose of albiglutide in combination with metformin as compared with metformin plus sitagliptin, metformin plus glimepiride and metformin plus placebo in subjects with T2DM whose glycemia was not adequately controlled on their current regimen of metformin.

The study comprised 4 study periods: approximately 2 weeks of Screening; 4 weeks of Run-in/Stabilization; a 156-week Treatment Period, including 104 weeks of treatment for evaluation of primary efficacy and safety followed by an additional 52 weeks of treatment for additional efficacy and safety; and 8 weeks of Posttherapy Follow-up. From Screening through Posttherapy Follow-up (Week 164), subjects had 26 study center visits (Screening, weekly through Run-in/Stabilization and the first 2 weeks of treatment, followed by visits at Weeks 4, 8, 12, 16, 20, 24, 36, 48, 52, 65, 78, 91, 104, 116, 130, 143, and 156 [End of Treatment], and Week 164 [Follow-up]); there was also a telephone call at Week 155. The total duration of a subject's participation was approximately 170 weeks.

Subjects completed a minimum of 2 years of treatment, at which time the formal analysis for submission of regulatory marketing applications was completed. The study continued as a blinded study for up to 3 years.

Eligible subjects were stratified based on the HbA1c value obtained at Visit 5 (<8.0% versus ≥8.0%), history of prior myocardial infarction (MI) (yes versus no), and age (<65 years versus ≥65 years). Approximately 1000 subjects were to be randomly assigned to 1 of 4 treatment groups in a 3:3:3:1 ratio, as specified in Section 4.5.2. 24-hour ambulatory blood pressure monitoring was performed at Week 0 (Baseline), Week 12, Week 24, Week 52, and Week 104 in a subset of approximately 80 subjects per treatment group at a subset of sites. Additionally, at a subset of sites, subjects had a blood sample taken at Baseline, Week 12, Week 24, Week 52, Week 104, Week 143 and End of Treatment for Biomarker (CRP, adiponectin and leptin) and detailed lipid profile.

This clinical study report (CSR) reflects data taken after all subjects had completed a minimum of 2 years of treatment (except those who withdrew before this time point). However, the study is continuing as a blinded study for up to 3 years and cardiovascular and pancreatitis events will continue to be monitored and adjudicated.

Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline in HbA_{1c} at Week 104.

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Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following:

- Change from baseline in HbA_{1c} over time
- Change from baseline in FPG at Week 104
- Change from baseline in FPG over time
- Proportion of subjects who achieve an HbA_{1c} treatment goal of <6.5%, <7.0%, or <7.5%
- Time to hyperglycemia rescue
- Change from baseline in body weight over time

Appendix II

Study Design and Endpoints for Study 130

This Phase III, randomized, double-blind, active-controlled, 2 parallel-group, multicenter, 52-week study evaluated the efficacy and safety of a weekly subcutaneously injected dose of albiglutide as compared with sitagliptin in renally impaired subjects with T2DM. Renally impaired subjects with T2DM whose glycemia was inadequately controlled on their current regimen of diet and exercise or their antidiabetic therapy regimen of metformin, TZD, SU, or any combination of these OAD medications were recruited into the study. Investigators must have adhered to the local labeling of the respective country (e.g., the summary of product characteristics in relevant European countries or the US Food and Drug Administration-approved prescribing information) when including subjects on a current regimen of metformin (protocol standardized on an eGFR of <60 mL/min/1.73 m^2), SU, or TZD. Subjects continued on their current regimen of OAD medication for the duration of the study, with the exception of those subjects who were on a regimen of metformin and/or an SU. The study comprised 4 study periods: approximately 2 weeks of Prescreening and Screening, 4 weeks of Run-in, 52-week Treatment Period, including 26 weeks of initial treatment and evaluation for primary efficacy and safety followed by an additional 26 weeks of treatment for additional efficacy and safety, and 8 weeks of Posttreatment Follow-up.

Eligible subjects were stratified by severity of renal impairment (mild, moderate, and severe), prior history of myocardial infarction (MI) (yes and no), and age (<65 and ≥65 years of age). Approximately 500 subjects were planned to be randomly assigned to one of the following 2 treatment groups in a 1:1 ratio such that

- Approximately 250 subjects were assigned to albiglutide (30 mg weekly with uptitration, if needed, to 50 mg weekly) + sitagliptin matching placebo

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- Approximately 250 subjects were assigned to albiglutide matching placebo + sitagliptin

The dose of sitagliptin was based on the subject's severity of renal impairment using the modification of diet and renal disease (MDRD) formula (see Section 4.5.2). It was generally expected that not more than 50% of the subjects enrolled in the study would have mild renal impairment, with an original goal of enrolling 40% of the subjects with mild renal impairment and 60% of the subjects with moderate to severe renal impairment.

Glycosylated hemoglobin change from Baseline at Week 26 was analyzed using an ANCOVA model with treatment group, region, renal impairment (mild, moderate, and severe), history of prior MI (yes and no), and age category (<65 years and >=65 years) as factors and baseline HbA_{1c} as a continuous covariate (Model 1).

To control for the potential inflation of the overall significance level due to multiple hypothesis testing, the hypotheses of treatment effects of noninferiority and superiority of study medication were evaluated using the order that prioritized the noninferiority claim over the superiority claim.

The primary analyses were performed on the ITT Population using LOCF algorithm. Subjects who were rescued for hyperglycemia before Week 26 had their last prerescue HbA_{1c} recorded and carried forward for primary analyses. Subjects who discontinued from active treatment for any reason before Week 26 had their last postbaseline HbA_{1c} observation (that was <=14 days after last dose) carried forward for the analyses.

SIGNATURES/DISTRIBUTION LIST (Optional)

Primary Statistical Reviewer: Japobrata Choudhury, Ph.D.
Date: 10-18-2013

Concurring Reviewer(s):

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Reference ID: 3392698

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/s/

JAPOBRATA CHOUDHURY
10/18/2013

THOMAS J PERMUTT
10/25/2013
See Dr. Rothmann's secondary review, with which I concur. I do not concur with Dr. Choudhury's review. I do not have specific points of disagreement with Dr. Choudhury, but I find that his review leaves important questions unanswered which are addressed by Dr. Rothmann.

MARK D ROTHMANN
10/18/2013
See my review

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 #:	BLA 125-431
Drug Name:	albiglutide for injection
Indication(s):	Treatment of type 2 diabetes mellitus (T2DM) in adults as an adjunct to diet and exercise to improve glycemic control
Applicant:	GlaxoSmithKline
Date(s):	Submitted: January 14, 2013
	Major Amendment: July 12, 2013
	Goal Date: April 15, 2014
Review Priority:	Standard
Biometrics Division:	Division of Biometrics VII
Statistical Reviewer:	Bo Li, Ph.D.
Concurring Reviewers:	Mat Soukup, Ph.D.
	Aloka Chakravarty, Ph.D.
Medical Division:	Division of Metabolism and Endocrinology Products (DMEP)
Clinical Team:	Medical Officer: Kaveeta Vasisht, M.D.
	Medical Team Leader: Jean-Marc Guettier, M.D.
Project Manager:	Raymond Chiang, M.S. (DMEP)

Keywords: clinical studies, meta-analysis, Type 2 diabetes mellitus, cardiovascular safety, major adverse cardiovascular event (MACE), hazard ratio margin

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1 EXECUTIVE SUMMARY

The proposed indication for albiglutide is the treatment of type 2 diabetes mellitus (T2DM) in adults as an adjunct to diet and exercise to improve glycemic control. The albiglutide Biologic License Application (BLA) was submitted to the FDA on January 14, 2013, including the report and data of a cardiovascular (CV) meta-analysis. Per the request of the Division of Metabolism and Endocrinology Products, this statistical review focuses on the pre-marketing evaluation of CV related safety in the randomized phase 2b/3 clinical development program of albiglutide.

The applicant conducted a meta-analysis of the cardiovascular events that occurred in 9 Phase 2b/3 trials in albiglutide clinical program (Studies GLP112753, GLP112754, GLP112755, GLP112756, GLP112757, GLP108486, GLP114130, GLP114179 and GLP110932; refer to Section 2 for a description of the 9 trials). This meta-analysis was the first of a two-part group sequential testing strategy that was pre-specified to control the Type I error rate with the objective of ruling out a risk margin of 1.8 of albiglutide compared with other comparators. Using this strategy, if the first formal meta-analysis of the primary composite endpoint was found to have an upper-bound less than 1.8 at a one-sided alpha-level of 0.01225 (corresponding to a 97.55% CI), the product would meet the CV guidelines outlined in the FDA "Guidance for industry: Diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes" (December 2008).

The agreed upon primary endpoint is major adverse cardiovascular event (defined here as MACE+), a composite endpoint consisting of the following adjudicated events: cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina. All CV events were adjudicated by an independent, blinded clinical endpoint committee (CEC), according to a pre-specified adjudication plan. The comparator group was comprised of subjects taking either a placebo or an active control (sitagliptin, glimepiride, pioglitazone, liraglutide and insulin). The pre-specified primary analysis is a time-to-event analysis based on a Cox proportional hazards model stratified by trial that included all primary events observed during the studies.

Among the 5,107 subjects in the CV safety analysis population, 44 of 2,524 albiglutide subjects had an event that was adjudicated as the primary composite endpoint, while 47 of 2,583 comparator subjects experienced the primary endpoint events. Based on the primary analysis model, the hazard ratio estimate of albiglutide versus comparator is 0.93 with corresponding 97.55% CI (0.55, 1.58). The primary analysis result was supported by various sensitivity analyses which were consistent with the primary analysis (see Section 3.3.4).

Based upon the 1.8 risk margin set forth in the FDA 2008 Diabetes Guidance, the upper bound of the multiplicity-adjusted 97.55% confidence interval of the hazard ratio is less than 1.8. Thus the meta-analysis of albiglutide rules out an 80% relative increase in CV risk.

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2 INTRODUCTION

2.1 Overview

Albiglutide is a novel analogue of human glucagon-like peptide-1 (GLP-1) designed to retain the therapeutic actions of GLP-1 while having an extended duration of action to treat type 2 diabetes mellitus (T2DM). The proposed indication of albiglutide is the treatment of T2DM in adults as an adjunct to diet and exercise to improve glycemic control.

Starting in 2009, several randomized, controlled, parallel-group, multi-center studies were initiated to evaluate the efficacy and safety of a weekly subcutaneous (SC) injection of albiglutide alone or in combination with approved anti-diabetic therapy. In the pivotal efficacy trials of albiglutide, cardiovascular (CV) events were prospectively defined, collected and adjudicated in a consistent manner. The applicant conducted a meta-analysis of the CV events that occurred in 9 Phase 2b/3 trials using albiglutide. These include 1 Phase 2b trial (Study GLP110932) and 8 Phase 3 trials (Studies GLP112753, GLP112754, GLP112755, GLP112756, GLP112757, GLP108486, GLP114130, and GLP114179). The summary of design characteristics of these 9 trials is presented in Table 1. The meta-analysis was planned to address the December 2008 FDA Diabetes Guidance which states that "sponsors should compare the incidence of important cardiovascular events occurring with the investigational agent to [that of] the control group to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8."

The pre-specified primary CV safety endpoint is adjudicated major adverse cardiovascular event (defined here as MACE+), a composite endpoint consisting of acute myocardial Infarction (MI), stroke, CV death and hospitalization for unstable angina. The primary objective of the CV meta-analysis was to evaluate whether albiglutide alters the risk of CV events in subjects with T2DM relative to all comparators (placebo and active) that comprise the standard of care in the albiglutide Phase 3 program.

The electronic documents and data of CV meta-analysis were submitted by the applicant on January 14, 2013, as a part of the BLA submission of albiglutide. At the time of BLA filing, the database cut-off date for the CV meta-analysis was June 8, 2012, when 4 studies were completed and the other 5 Phase 3 studies with a 3-year duration were ongoing but had at least 2-year data available. A group sequential approach using non-binding boundaries for controlling the type I error is pre-specified for a two-part testing procedure, of which the first analysis would be conducted at the initial BLA filing when approximately 90 unique subject events were available. If needed, a final assessment was planned to be conducted when all studies were completed.

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Table 1: Summary of Design Characteristics of the 9 Randomized Phase 2b/3 Trials Included in the CV Meta-Analysis

Trial	Treatment Arms	N	Albiglutide Dosage	Co-treatment					Duration
				Met	SU	Pio	Glim	Ins	
112753†	Placebo Sitagliptin Glimepiride Albiglutide	101 302 307 302	30mg weekly (uptitrated to 50mg weekly if needed)	X					3-year
112754†*	Insulin glargine Albiglutide	241 504	30mg weekly (uptitrated to 50mg weekly if needed)	X	X				3-year
112755 †	Placebo Albiglutide	151 150	30mg weekly	X		X			3-year
112756 †	Placebo Albiglutide	101 200	30mg weekly 30mg weekly (uptitrated to 50mg weekly at 12 weeks)						3-year
112757 †	Placebo Pioglitazone Albiglutide	115 277 271	30mg weekly (uptitrated to 50mg weekly if needed)	X	X		X		3-year
108486*	Lispro insulin Albiglutide	281 285	30mg weekly (uptitrated to 50mg weekly if needed)					X	1-year
114130 (renally Impaired)	Sitagliptin Albiglutide	246 249	30mg weekly (uptitrated to 50mg weekly if needed)	any combination of met, TZD, SU or none					1-year
114179*	Liraglutide Albiglutide	408 404	30mg weekly (uptitrated to 50mg weekly at 6 weeks)	any combination of met, TZD, SU					32 weeks
110932 (phase IIb)	Placebo Albiglutide	53 159	15mg weekly 30mg weekly 30mg biweekly						16 weeks

*: Open-label study †: 3-year studies ongoing at the time of BLA filing
Source: Created by reviewer.

2.2 Data Sources

The applicant submitted electronic documents and integrated cardiovascular safety datasets for the above 9 studies. The applicant's report on the meta-analysis was also used for comparison and verification purpose. BLA materials are archived in the CBER EDR. The below materials were utilized in the evaluation of CV safety.

Study Report \\cdsesub1\bla\ectd_submissions\stn125431\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\t-2-diabetes-mellitus\5353-rep-analys-data-more-one-stud\cv-meta-analysis\cv-meta-analysis-report.pdf

Analysis Plan Included in Appendix 17.1 of the Study Report

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Analysis Data Sets	
(Time-to-event)	\\cdsesub1\bla\ectd_submissions\stn125431\0000\m5\datasets\cv-meta-analysis\analysis\adam\datasets\adxetm.xpt
(Subject level)	\\cdsesub1\bla\ectd_submissions\stn125431\0000\m5\datasets\cv-meta-analysis\analysis\adam\datasets\adsl.xpt
(Exposure/Compliance)	\\cdsesub1\bla\ectd_submissions\stn125431\0000\m5\datasets\cv-meta-analysis\analysis\adam\datasets\adex.xpt
Define File	\\cdsesub1\bla\ectd_submissions\stn125431\0000\m5\datasets\cv-meta-analysis\analysis\adam\datasets\define.pdf

3 STATISTICAL EVALUATION

This review is focused on the meta-analysis of CV safety.

3.1 Data and Analysis Quality

Data and reports of this submission were submitted electronically. The data define file provides sufficient information about the variables included in each dataset. Using the submitted data, the reviewer was able to perform all analyses and reproduce the findings included in the CV meta-analysis study report.

3.2 Evaluation of Efficacy

This review does not evaluate efficacy submitted to the BLA. For a complete statistical evaluation of efficacy results, please refer to the review authored by Dr. Japobrata Choudhury.

3.3 Evaluation of Safety

Nine randomized trials were utilized to evaluate the association between albiglutide and CV safety, compared with other comparators. This included data from 1 Phase 2b trial (Study GLP110932) and 8 Phase 3 trials (Studies GLP112753, GLP112754, GLP112755, GLP112756, GLP112757, GLP108486, GLP114130, and GLP114179).

3.3.1 Study Design and Endpoints

3.3.1.1 Study Design

In order to allow for a meaningful comparison of CV event occurrence across treatment groups, studies included in the CV meta-analysis had to meet the following key requirements: enrolled subjects with T2DM, required repeat dosing, and included a control group treated with either

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placebo or active comparator. Based on these criteria, data from a total of 9 phase 2b/3 randomized and controlled clinical trials were integrated for the meta-analysis (see Table 1).

Study GLP112753 was a randomized, double-blind, placebo- and active-controlled, 4 parallel-group, multi-center, 3-year study to evaluate the efficacy and safety of a weekly SC injection of 30 mg of albiglutide (uptitrated to 50 mg weekly if needed) in combination with metformin as compared with metformin + sitagliptin, metformin + glimepiride, and metformin + placebo among subjects with T2DM whose glycemia was not adequately controlled with their current regimen of metformin. Approximately 1000 subjects were randomly assigned to each of the 4 treatment groups in a 3:3:3:1 ratio with metformin + placebo as the smaller group. At the data cut-off date of initial BLA filing, study GLP112753 was still ongoing and included at least 2-year data for safety analysis.

Study GLP112754 was a randomized, open-label, 2 parallel-group, multi-center, 3-year study to evaluate the efficacy and safety of a weekly SC injection of 30 mg of albiglutide (uptitrated to 50 mg weekly if needed) compared with insulin glargine in subjects with T2DM who were inadequately controlled on their current regimen of metformin alone or metformin + sulfonylurea (SU). Approximately 750 subjects were randomly assigned to each of the 2 treatment groups in a 2:1 ratio with insulin glargine as the smaller group. At the data cut-off date of initial BLA filing, study GLP112754 was still ongoing and included at least 2-year data for safety analysis.

Study GLP112755 was a randomized, double-blind, placebo-controlled, 2 parallel-group, multi-center, 3-year study to evaluate the efficacy and safety of a weekly SC injection of 30 mg of albiglutide in combination with pioglitazone (with or without metformin) compared with pioglitazone (with or without metformin) among subjects with a historical diagnosis of T2DM whose glycemia was inadequately controlled on their current regimen of pioglitazone alone or metformin + pioglitazone. Approximately 300 subjects were randomly assigned to each of the 2 treatment groups in a 1:1 ratio. At the data cut-off date of initial BLA filing, study GLP112755 was still ongoing and included at least 2-year data for safety analysis.

Study GLP112756 was a randomized, double-blind, placebo-controlled, 3 parallel-group, multi-center study, 3-year to evaluate the efficacy and safety of a weekly SC injection of 30 mg or 50 mg of albiglutide in subjects with T2DM whose glycemia was inadequately controlled on their current regimen of diet and exercise and who had received less than 7 contiguous days of treatment with any antidiabetic therapy within the 3 months before screening. There were 2 albiglutide treatment groups, one in which the albiglutide dose remained fixed at 30 mg weekly and the other in which the albiglutide 30 mg weekly dose was titrated to 50 mg weekly at 12 weeks, to be compared with the matching placebo group. A total of 315 subjects were randomly assigned to each of the 3 treatment groups in a 1:1:1 ratio. At the data cut-off date of initial BLA filing, study GLP112756 was still ongoing and included at least 2-year data for safety analysis.

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Study GLP112757 was a randomized, double-blind, placebo- and active- controlled, 3 parallel-group, multi-center, 3-year study to evaluate the efficacy and safety of a weekly SC injection of 30 mg of albiglutide (uptitrated to 50 mg weekly if needed) in combination with metformin + glimepiride compared with metformin + glimepiride alone and metformin + glimepiride + pioglitazone in subjects with T2DM whose glycemia was inadequately controlled with their current regimen of metformin plus an SU. A total of 685 subjects were randomly assigned to each of the 3 treatment groups in a 5:5:2 ratio with the metformin + placebo add-on as the smaller group of about 100 subjects. At the data cut-off date of initial BLA filing, study GLP112756 was still ongoing and included at least 2-year data for safety analysis.

Study GLP108486 was a randomized, open-label, active-controlled, 2 parallel-group, multi-center, 1-year study to evaluate the safety and efficacy of a weekly SC injection of 30 mg of albiglutide (uptitrated to 50 mg weekly if needed) in combination with insulin glargine compared with the combination of insulin glargine and preprandial lispro insulin in subjects with T2DM. Subjects with a historical diagnosis of T2DM who were inadequately controlled despite the use of insulin glargine or other intermediate- or long-acting insulins for □6 months but <5 years, with or without oral antidiabetic medications, who were unable to achieve a glycosylated hemoglobin value of <7% were recruited into the study. A total of 586 subjects were randomly assigned to each treatment group in a 1:1 ratio. Study GLP108486 was completed before the data cut-off date of initial BLA filing and its completion date is November 14, 2011.

Study GLP114130 was a randomized, double-blind, active-controlled, 2 parallel-group, multi-center, 1-year study to evaluate the efficacy and safety of a weekly SC injection of 30 mg of albiglutide (uptitrated to 50 mg weekly if needed) compared with sitagliptin. Subjects who were renally impaired with a historical diagnosis of T2DM and whose glycemia was inadequately controlled on their current regimen of diet and exercise or their antidiabetic therapy of metformin, TZD, SU, or any combination of these oral antidiabetic medications were recruited into the study. A total of 500 subjects were randomly assigned to each treatment group in a 1:1 ratio. Study GLP114130 was completed before the data cut-off date of initial BLA filing and its completion date is May 30, 2012.

Study GLP114179 was a randomized, open-label, multi-center, 2 parallel-group, 32-week study to evaluate the efficacy and safety of a weekly SC injection of 30 mg of albiglutide (uptitrated to 50 mg weekly if needed) compared with liraglutide. Subjects with a historical diagnosis of T2DM and whose glycemia was inadequately controlled on their current regimen of metformin, TZDs, SUs, or combination of these oral antidiabetics were recruited into the study. A total of 800 subjects were randomly assigned to each treatment group in a 1:1 ratio. Study GLP114179 was completed before the data cut-off date of initial BLA filing and its completion date is September 09, 2011.

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Study GLP110932 was a Phase IIb, randomized, double-blind, placebo-controlled, multi-center, 4 parallel-group, dose-ranging, 16-week, superiority study evaluating the dose response, efficacy and safety of 15 mg or 30 mg weekly and 30 mg every other week SC injections of albiglutide in Japanese subjects with T2DM. A total of 220 subjects were randomly assigned to each treatment group in a 1:1:1:1 ratio. Study GLP110932 was completed before the data cut-off date of initial BLA filing and its completion date is May 11, 2011.

3.3.1.2 Endpoints

The pre-specified primary endpoint for CV safety analysis is major adverse cardiovascular event (MACE+), defined as a composite endpoint consisting of

- CV death
- Myocardial infarction
- Stroke
- Hospitalization for unstable angina

The secondary endpoint is MACE which considers only the three components

- CV death
- Myocardial infarction
- Stroke

All CV events were collected and adjudicated using a thorough, consistent and prospective adjudication plan.

3.3.1.3 Adjudication Methods

Blinded cardiovascular events were adjudicated by an independent Clinical Endpoint Committee (CEC), according to a pre-specified adjudication plan defined in the CEC charter (finalized on May 9, 2012). The primary objective of the CEC was to adjudicate major adverse CV events (MACE+). Other events adjudicated by the CEC, that were not endpoints, included silent MIs, hospitalizations for other angina, hospitalizations for other chest pain, hospitalizations for heart failure, subdural/extradural hemorrhages, and non-CV deaths. In addition, the CEC reviewed all transient ischemic attacks and coronary revascularizations to check for any missed stroke, MIs, or unstable angina events. The CEC also reviewed all serious adverse events (SAEs) to check for any missed MACE+.

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3.3.2 Statistical Methodologies

In this BLA application, the applicant submitted 9 randomized Phase 2b and Phase 3 trials in the clinical development program of albiglutide conducted in subjects with T2DM. All data as of the cut-off date (June 08, 2012) are included in this integrated analysis of CV safety. The BLA submission included a statistical analysis plan (SAP) which was finalized on May 31, 2012 with documented pre-specified statistical methods.

The combined CV meta-analysis datasets were the basis for summaries, analyses and presentation of CV safety evaluation.

3.3.2.1 Controlling of Type I Error

In the SAP, a group sequential testing strategy was pre-specified to control the overall Type I error rate to demonstrate albiglutide did not exhibit an excess amount of risk relative to comparators with a hazard ratio (HR) risk margin of 1.8 based on the MACE+ primary CV endpoint. Per the SAP, the following hypothesis for adjudicated MACE+ would be tested at the time of the initial BLA filing as well as at the end of all the studies:

H0: HR $\geq$ 1.8; vs.

Ha: HR < 1.8

The group sequential approach allows an early evaluation of CV safety at the time of BLA filing with approximately 90 adjudicated MACE+ events while accumulating more events to the end of the studies. With the Type I error adjustment, the applicant planned to perform the first formal statistical analysis with about 90 events to calculate the estimated HR using a 2-sided 97.55% CI. If the upper bound of the 2-sided 97.55% CI was less than 1.8, it would provide evidence of CV safety of albiglutide with a risk margin of 1.8 for the BLA filing. If with 90 events, the upper bound of the 2-sided 97.55% CI for HR was above 1.8, the final analysis was to be performed when all the studies were completed using a 2-sided 97.45% CI.

3.3.2.2 Analysis Methods

3.3.2.2.1 Analysis Populations and Event Ascertainment

The evaluation of CV risk utilizes an analysis population that is defined as the CV event (CVE) safety population, which consists of all randomized subjects who received at least 1 dose of study drug. It was pre-specified in the SAP that the CVE safety population will be used through the entire report of the cardiovascular risk meta-analysis. All analyses reported in this review are based on the CVE population unless specified otherwise.

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For the analysis of first occurrence of MACE+ events, two different censoring schemes are utilized for event ascertainment:

- On- study: Events occurred during the course of study, including the active treatment period and the follow-up period, were captured. On- study censoring scheme corresponds to total person-years of follow-up as defined in Section 3.3.3.

- On- treatment: Events occurred during the course of active treatment plus the following off-treatment period of 56 days were captured. On- treatment censoring scheme relates to total person-years of exposure (PYE).

3.3.2.2.2 Primary Comparison

All comparative analyses are between the randomized treatment groups. All albiglutide regimens are combined into one group, and all the comparators are combined into the pooled all comparator group.

The primary comparison was the incidence rate and relative hazard of the first occurrence of adjudicated MACE+ for albiglutide versus combined all comparators.

The pre-specified primary analysis is based upon time-to-event methods for MACE+. If a subject experienced multiple events of interest, only the event that occurred first while on study will be included in the analysis. The primary analysis method was a Cox proportional hazards regression model stratified by trial with a fixed effect for treatment to estimate the hazard ratio and corresponding 97.55% confidence interval of albiglutide group versus the pooled all comparator group. Trials with no events on both arms are excluded from the Cox regression analysis.

In this review, as a sensitivity analysis, stratified Mantel-Haenszel (M-H) estimates of the overall risk ratio (RR) (Sensitivity Analysis 1) and risk difference (RD) (Sensitivity Analysis 2) are calculated along with the associated 97.55% confidence interval using trial as a stratification factor. The RD method makes use of all trials including trials with no events of interest.

3.3.2.2.3 Secondary Comparison

As pre-specified in the SAP, similar time-to-event analysis was performed separately for the following comparisons,

- Albiglutide vs. active comparators

- Albiglutide vs. placebo comparators

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Studies with active comparators were grouped for the comparison of albiglutide vs. active comparators. Similarly, studies with placebo control were grouped for the comparison of albiglutide vs. placebo. Studies with both active control and placebo were included in both comparisons. These comparisons report a 97.55% confidence intervals of the stratified hazard ratio.

3.3.2.2.4 Additional Reviewer Sensitivity Analysis

As of the 08 June 2012 data cut-off date for primary analysis, there was an imbalance in the numbers of events pending adjudication in the respective integrated groups (7 in albiglutide group and 1 in all comparators group). As a sensitivity analysis conducted by the applicant, data were included only for events adjudicated as MACE+ up to 2 months prior to the 08 June 2012 data cut-off date as there were no events pending adjudication in either treatment group at that time.

To study the impact of the imbalance in pending adjudication, this review calculated the M-H estimate of the overall risk ratio under a worst case scenario (Sensitivity Analysis 3) assuming all pending events in albiglitide group would be adjudicated as MACE+ and none in comparators group).

To further investigate the sensitivity of the primary analysis on the primary composite endpoint, this review also conducted sensitivity analyses under various scenarios. These various analyses included the following assessments,

- Assessment of the individual component of MACE+
- Primary and secondary comparisons based on the MACE endpoint
- Primary and secondary comparisons based on various censoring schemes (on-study, on-treatment + 56 days after treatment discontinuation)

3.3.3 Patient Disposition, Demographic and Baseline Characteristics

Among the 5,281 randomized subjects in the 9 phase 2b/3 trials, a total of 5,107 (96.7%) subjects received at least 1 dose of study drug and were therefore included in the CVE population. As shown in Table 2, among the 5,107 subjects in the CVE population, 2,524 (49.4%) subjects were randomized to receive albiglutide, while 2,583 (50.6%) subjects were randomized to receive active comparator drugs or placebo.

As summarized in Table 2, at the time of data cut-off, approximately 42.7% of subjects (1,077/2,524) had completed active treatment in the albiglutide group, while 26.7% of subjects (674/2,524) terminated their treatment earlier than planned and 30.6% (773/2,524) of the

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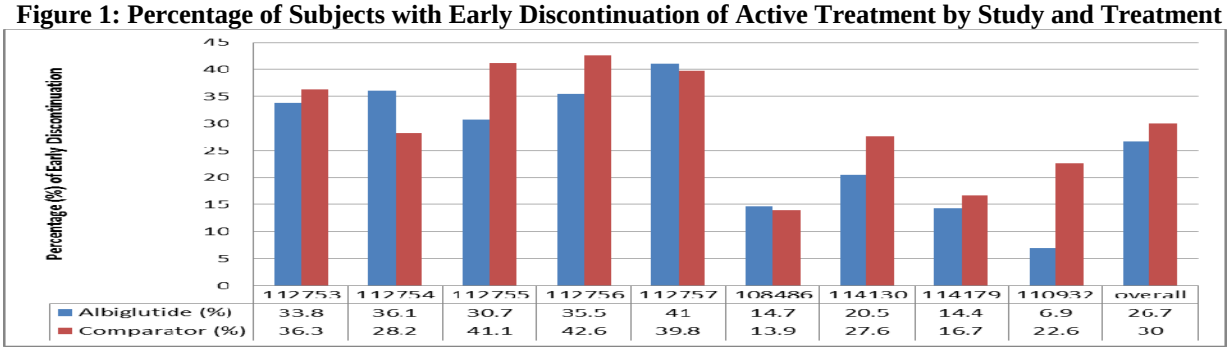
subjects were continuing their active treatment at the data cut-off date1. On average, the disposition of subjects (completed, continuing or discontinued active treatment) in the albiglutide group was not statistically significantly different than that of the combined comparator group with p-value = 0.34 (CMH test stratified by trial). As presented in Table 2, the percentage of subjects with premature discontinuation tended to be slightly higher in the comparators group (30.0%) than in the albiglutide group (26.7%). In general, the trials with a longer duration have higher drop-out rates compared to the trials with a shorter duration. As presented in Figure 1, there is some heterogeneity of treatment discontinuation rate across the trials: some trials had a higher drop-out rate on albiglutide group, while in some other trials, subjects randomized to comparator had a higher discontinuation rate. Overall, there was no statistically significant difference in discontinuation rates between the two pooled groups with p-value = 0.15 (CMH test stratified by trial).

Table 2: Subject Disposition

Disposition	Albiglutide	Comparator
All randomized	2600	2681
CVE safety population	2524 (100%)	2583 (100%)
Completed active treatment	1077 (42.7%)	943 (36.5%)
Continuing active treatment	773 (30.6%)	866 (33.5%)
Discontinued active treatment	674 (26.7%)	774 (30.0%)
Adverse event	201 (8.0%)	162 (6.3%)
Protocol violation	28 (1.1%)	35 (1.4%)
Non-compliance	58 (2.3%)	70 (2.7%)
Severe/repeated occurrence of hypoglycemia	3 (0.1%)	12 (0.5%)
Lost to follow-up	74 (2.9%)	95 (3.7%)
Withdraw by subject	255 (10.1%)	320 (12.4%)
Decision by investigator	23 (0.9%)	29 (1.1%)
Termination by sponsor	16 (0.6%)	33 (1.3%)
Other	16 (0.6%)	16 (0.6%)
Missing	0	2 (0.1%)

Source: Created by reviewer.

Figure 1: Percentage of Subjects with Early Discontinuation of Active Treatment by Study and Treatment



Source: Created by reviewer.

[1] This is due to the fact that 5 Phase 3 studies with a 3-year duration were ongoing at the date of data cut-off for CV meta-analysis. Each study had at least 2-year data included in the meta-analysis.

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For the analysis of first MACE+/MACE events, the person time of follow-up is calculated as follows:

- For subjects with any adjudicated events, the total number of days between the date of the first adjudicated event and the date of first dose plus 1.
- For subjects with no adjudicated event (e.g. subjects who were censored), equals to the number of days between the date of the last contact and the date of first dose plus 1.

To obtain the person years, the person time in days is divided by 365.25. Total person-years of follow-up is calculated as the sum of all person years for subjects in the integrated CVE population, i.e., it accounts for the total time on study before the first occurrences of interested CV events in the primary analysis population.

Table 3 provides a high level summary of the total number of subjects, total person-years of exposure (time on treatment) and total person-years of follow-up for the primary CV events for the two comparison groups, respectively.

Table 3: Treatment Exposure and Subjects Follow-up by Treatment Group (CVE)

	Albiglutide	Comparator
Sample Size (N)	2524	2583
Total Person Years of Exposure (PYE)	3646.7	3853.1
Total Person Years of Follow-up for MACE+	4214.7	4448.2

Source: Created by reviewer.

Based upon Table 4, demographic characteristics and baseline CV risk factors for the 5,107 subjects in the 9 trials included in the primary analysis were similar across the treatment groups. In the CVE population, there were slightly more male subjects than female subjects (53% versus 47%). Approximately 45% of subjects were White and about 25% were Hispanic, while 15% of subjects were Asian and about 13% were Black or African American. Almost 20% of subjects in the CVE were above 65 years of age, while the mean age was about 56 years. About 68% of subjects were from the U.S. About 65% of subjects had a body mass index (BMI) greater than 30 kg/m^2, while the mean BMI was about 32.3 kg/m^2. The mean duration of T2DM was 8.3 years with baseline insulin usage in 11% of the subjects. In the CVE population, approximately 9% of subjects had a prior history of ischemic cardiovascular disease. Furthermore, almost 70% of subjects had a history of hypertension and about 37% were current or former smoker. The mean baseline Hemoglobin A_{1c} (HbA_{1c}) of the CVE population is 8.2%.

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Table 4: Demographics and Baseline Characteristics by Treatment Group (CVE)

	Albiglutide (N = 2524)	Comparator (N = 2583)
Age± SD (years)	56±10	56±10
<65	80.9%	80.3%
65-74	17.0%	17.3%
>=75	2.1%	2.4%
Female	47.5%	47.2%
Race		
White	43.9%	45.7%
Black	14.0%	12.1%
Hispanic	23.1%	26.8%
Asian	16.8%	13.5%
Other	2.1%	1.9%
Region		
US	67.2%	68.8%
Europe	2.4%	2.2%
Asia	13.6%	9.8%
Rest of world	16.8%	19.2%
BMI± SD (kg/m²)	32.3±5.9	32.4±5.7
<25	9.4%	7.6%
25-30	26.0%	27.2%
30-35	29.7%	30.5%
>35	34.9%	34.7%
Hypertension	68.0%	69.1%
Prior CV disease	8.9%	8.9%
Baseline insulin usage	11.3%	10.9%
Duration of diabetes, yrs	8.3±6.3	8.2±6.3
HbA1c, %	8.2±0.9	8.2±0.9

Source: Created by reviewer.

3.3.4 Results and Conclusions

As described in Section 3.3.1.2, the pre-specified primary endpoint is MACE+. Table 5 provides the trial-level detail of first-occurrence of on-study MACE+ and its individual components, broken down by treatment groups.

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Table 5: Summary of First MACE+ by Study, Treatment Group and Type of Events (CVE, on-study)

Trial	Treatment	N	MACE+ n(%)*	MI n(%)*	Stroke n(%)*	CV Death n(%)*	Hosp. for UA n(%)*
112753	Placebo	101	3(3.0)	2 (2.0)	-	1(1.0)	-
	Sitagliptin	302	3(1.0)	1(0.3)	-	1(0.3)	1(0.3)
	Glimepiride	307	2(0.6)	1(0.3)	1(0.3)	-	1(0.3)
	Albiglutide	302	10(3.3)	5 (1.6)	3(1.0)	2(0.7)	-
112754	Insulin glargine	241	8(3.3)	4(1.6)	-	3(1.2)	3(1.2)
	Albiglutide	504	11(2.2)	5(1.0)	3(0.6)	3(0.6)	3(0.6)
112755	Placebo	151	4(2.6)	3(2.0)	-	1(0.7)	-
	Albiglutide	150	2(1.3)	1(0.7)	-	1(0.7)	-
112756	Placebo	101	3(3.0)	3(3.0)	1(1.0)	-	-
	Albiglutide	200	2(1.0)	2(1.0)	-	-	-
112757	Placebo	115	3(2.6)	1(0.9)	1(0.9)	-	1(0.9)
	Pioglitazone	277	4(1.4)	2(0.7)	2(0.7)	-	-
	Albiglutide	271	4(1.5)	2(0.7)	-	1(0.4)	1(0.4)
108486	Lispro insulin	281	2(0.7)	-	-	-	2(0.7)
	Albiglutide	285	5(1.7)	3(1.0)	2(0.7)	1(0.3)	-
114130	Sitagliptin	246	7(2.8)	2(0.8)	4(1.6)	3(1.2)	-
	Albiglutide	249	7(2.8)	2(0.8)	3(1.2)	2(0.8)	-
114179	Liraglutide	408	7(1.7)	3(0.7)	1(0.2)	3(0.7)	-
	Albiglutide	404	3(0.7)	-	1(0.2)	2(0.5)	-
110932	Placebo	53	1(1.9)	-	1(1.9)	-	-
	Albiglutide	159	0(0.0)	-	-	-	-

*: The number of unique subjects experienced first occurrence of MACE+ and its components, respectively. The counts of individual components don't necessarily add up to that of MACE+ since one subject may have experienced more than one component events.
Source: Created by reviewer.

3.3.4.1 Primary Comparison (Albiglutide vs. All Comparators)

Per the SAP, the primary comparison is between the albiglutide group and the combined all comparators group for the incidence of MACE+ during the course of the study (on-study: including the follow-up period after treatment discontinuation). Below in Table 6, the primary analysis results are presented for MACE+, along with the sensitivity analysis results including Mantel-Haenszel RR and RD. Sensitivity analysis results to study the impact of imbalanced number of pending adjudication at the data cut-off are also presented.

The presented results were comparable between the stratified Cox regression and Mantel-Haenszel methods. Both methods found the incidence of the primary composite endpoint to be slightly lower in the albiglutide group compared to the comparators group. The upper bound of

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the corresponding 97.55% CI for the HR and RR exclude the risk margin of 1.8. When studying the impact of the imbalanced pending adjudication, the applicant's analysis result using an earlier data cut-off date of April 8, 2012 shows a similar result to that of primary analysis with an upper bound of 1.63. In the reviewer's sensitivity analysis under the worst case scenario, the point estimate of M-H RR is slightly greater than 1 and the upper bound of its 97.55% CI is 1.65.

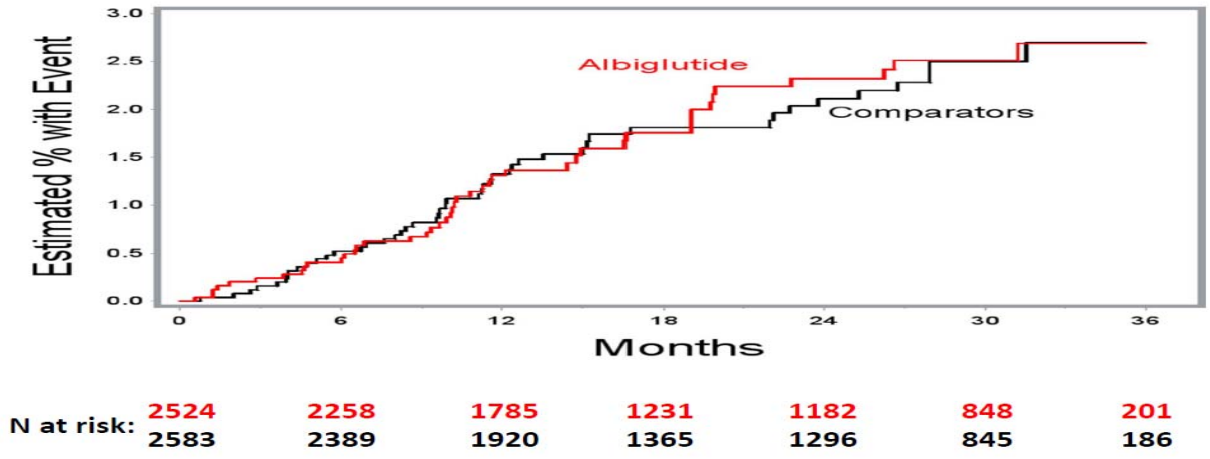
Table 6: Primary/Sensitivity Analysis Results for MACE+ (CVE, On-Study)

		Albiglutide (*N* = 2524)	**Comparator** (*N* = 2583)
Primary			
Cut-off: 06/08/2012	Events/PY [IR*]	44/4214.7 [10.4]	47/4448.2 [10.6]
	HR (97.55% CI)†	**0.93 (0.55, 1.58)**	
Sensitivity (Sponsor)			
Cut-off: 04/08/2012	Events/PY [IR*]	44/4155.0 [10.6]	46/4383.2 [10.5]
(no pending adjudication)	HR (97.55% CI)†	0.96 (0.57, 1.63)	
Sensitivity Analysis ‡			
1. Risk Ratio	M-H RR (97.55% CI)	0.94 (0.60, 1.48)	
2. Risk Difference	M-H RD (97.55% CI)	-0.11% (-1.04%, 0.81%)	
3. Worst Case[1]	M-H RR (97.55% CI)	1.07 (0.69, 1.65)	

*: Per 1,000 PY. †: Cox proportional hazards model stratified by trial.
‡: Refer to Section 3.3.2.2.2 and 3.3.2.2.4 for the details of the Sensitivity Analysis 1-3.
[1]: Assuming all 7 pending events occurred on 6 unique subjects in albiglitide group would be adjudicated as MACE+ and none in comparator group. This analysis is to study the impact of the imbalanced number of pending adjudication between albiglutide and comparators group.
Source: Created by reviewer.

Based on the Kaplan Meier (K-M) method, the cumulative probability of developing a CV-related event as measured by MACE+ (on-study) is shown in Figure 2. For MACE+ the K-M plot shows that the two curves are close to each other throughout the study period.

Figure 2: Kaplan-Meier Plot of Time to First MACE+ (CVE, on- study)



Source: Created by reviewer.

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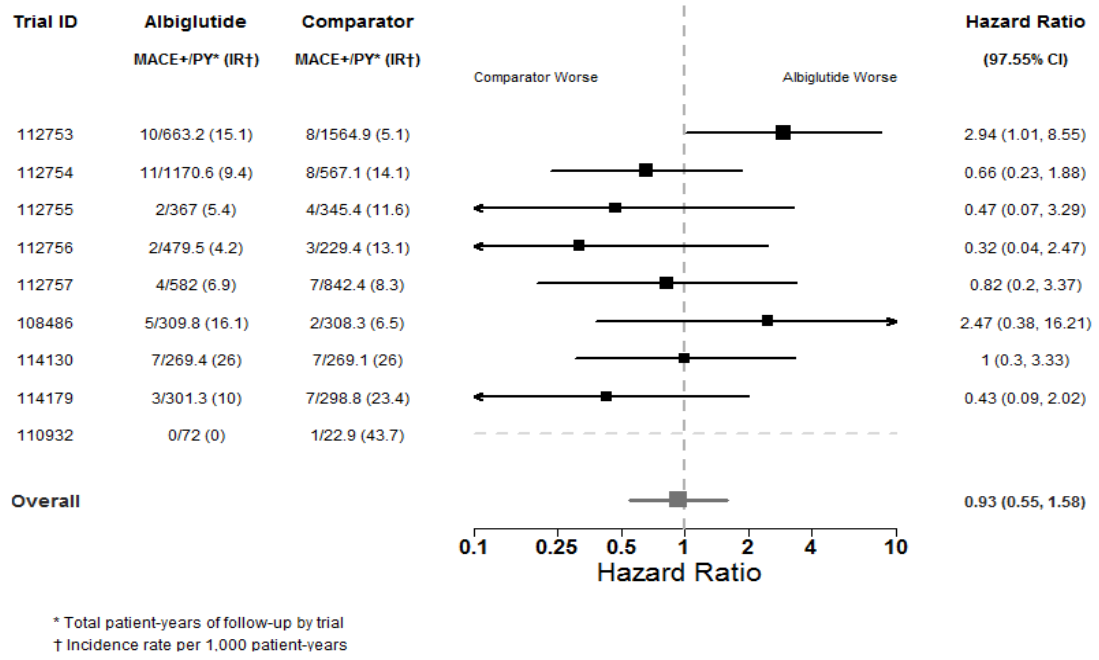
The forest plot of the hazard ratios of the MACE+ composite endpoint (on-study) is presented in Figure 3 for the primary comparison. Trials are ordered by the planned duration of treatment (trials with the longest planned duration are presented on the top of the figure and trials with the shortest planned duration are presented at the bottom of the figure). The individual hazard ratio and the corresponding 97.55% CI of each trial calculated from a Cox regression model are shown, where the size of the symbol for each hazard ratio corresponds to the size of the trial. As with the result of the primary analysis, the overall HR and its 97.55% CI are shown at the bottom. In the forest plot only trials where MACE+ events were observed on both treatment arms include a point estimate for the hazard ratio and the corresponding 97.55% CI.

Among the 9 randomized trials, Study GLP112753 was the only one showing statistically significant difference between albiglutide and comparators. For this study, the individual HR of albiglutide compared to comparators was 2.94 with a wide 97.55% CI of (1.01, 8.55), which is marginally significant. Study GLP112753 is a 3-year study with the longest patient-years of follow-up among all the 9 trials, accounting for 20% of all the observed primary CV events (18 out of 91). However, there was no notable difference between the study design and population of GLP112753 and other trials included in the meta-analysis. Considering the small number of MACE+ events (10 on albiglutide and 8 on comparators) occurred in this single trial and the assessment of nine trials individually with no multiplicity correction, it is hard to exclude the possibility of a chance finding of the significant result for this trial.

Figure 3: Forest Plot of Time-to-Event Analysis of MACE+ (CVE, On-study)



Source: Created by reviewer.

Reference ID: 3367015

3.3.4.2 Secondary Comparisons

For the secondary comparisons, studies with active comparators were grouped for albiglutide vs. active comparators comparison, while studies with placebo control were grouped for albiglutide vs. placebo comparison. Studies with both active control and placebo were included in both comparisons. The pre-specified primary analysis was the Cox proportional hazards (CPH) model stratified by trial with treatment as a fixed effect. Similar analyses were conducted for the secondary comparisons for MACE+ and MACE endpoints, respectively (Table 7 and Table 8), accounting for various censoring schemes (on-study, on-treatment + 56 days).

Table 7: CPH Analysis Results for MACE+

	On-study		On-treatment + 56 Days	
	Albiglutide	**Comparator**	**Albiglutide**	**Comparator**
All Comparators				
MACE+/N	44/2524	47/2583	39/2524	41/2583
HR (97.55% CI)	-	0.93 (0.55, 1.58)	-	0.92 (0.52, 1.61)
Placebo				
MACE+/N	18/1082	14/521	16/1082	11/521
HR (97.55% CI)	-	0.57 (0.25, 1.27)	-	0.62 (0.26, 1.49)
Active Comparators				
MACE+/N	40/2062	33/2015	35/2062	30/2015
HR (97.55% CI)	-	1.17 (0.66, 2.10)	-	1.11 (0.59, 2.05)

Source: Created by reviewer.

Table 8: CPH Analysis Results for MACE

	On-study		On-treatment + 56 Days	
	Albiglutide	**Comparator**	**Albiglutide**	**Comparator**
All Comparators				
MACE/N	40/2524	42/2583	36/2524	38/2583
HR (97.55% CI)	-	0.97 (0.55, 1.69)	-	0.93 (0.52, 1.68)
Placebo				
MACE/N	17/1082	13/521	15/1082	11/521
HR (97.55% CI)	-	0.58 (0.25, 1.34)	-	0.58 (0.24, 1.42)
Active Comparators				
MACE/N	36/2062	29/2015	32/2062	27/2015
HR (97.55% CI)	-	1.24 (0.66, 2.31)	-	1.16(0.60, 2.23)

Source: Created by reviewer.

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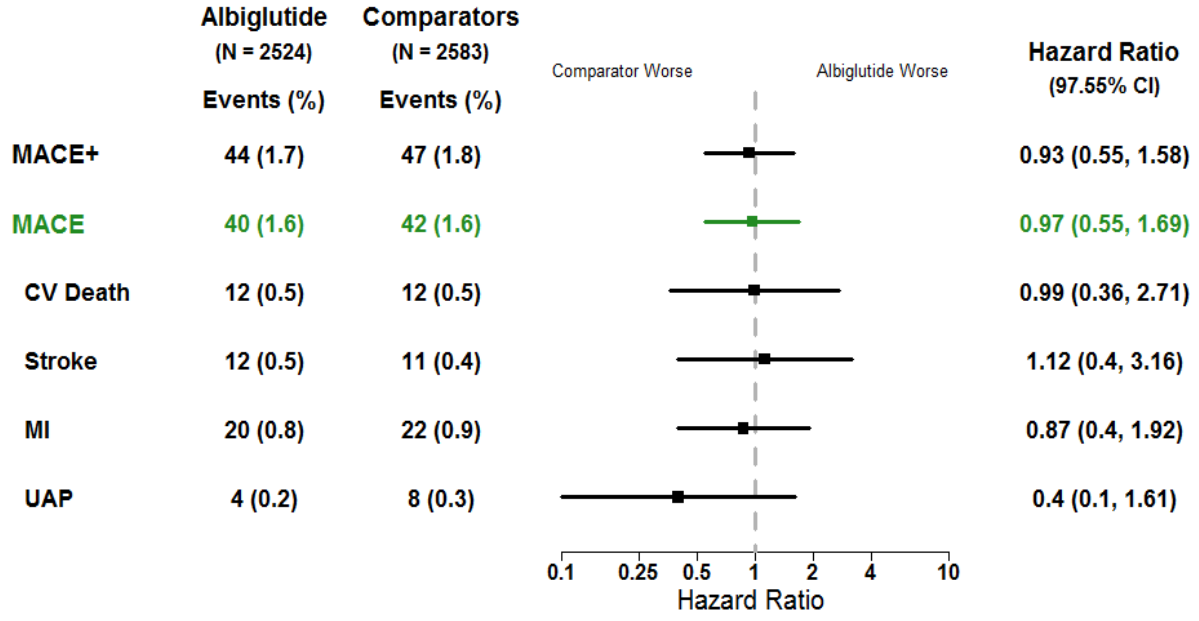
The results utilizing the stricter endpoint MACE are generally consistent with those of MACE+, with a slightly wider CI due to the smaller number of events. The findings of on-study and on-treatment analysis are consistent. The HR estimates comparing albiglutide to placebo and active comparators have the point estimates in opposite directions. However, with limited number of events in each comparison, none of the comparisons show a significant effect with wide confidence intervals that overlap.

3.3.4.3 Assessment of the individual components of MACE+

To explore which cardiovascular event components of MACE+ contributed to the composite primary endpoint, the hazard ratio and corresponding 97.55% CI for each component was calculated using a stratified Cox regression model similar to that used in the primary analysis. Figure 4 presents a forest plot of these hazard ratios in reference to the hazard ratio for the composite primary endpoint. It can be observed in this figure that of the individual components comprising MACE+, CV death, myocardial infarction and stroke have HR point estimates around null, whereas unstable angina has a HR point estimate below 1 with a small number of events. Due to the same reason, the exclusion of UAP does NOT impact the results of strict MACE compared to MACE+. Note that none of the individual components of MACE+ demonstrated a statistically significant effect.

Figure 4: Forest Plot of Time-to-Event Analysis of MACE+ components (CVE, on-study)



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4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In the following sections, on-study analysis results for MACE+ are presented for specific subgroups. It should be noted that these analyses are exploratory in nature to assess general trends. There were no protocol-defined multiplicity corrections for subgroup analyses and as such results are presented using unadjusted nominal 95% confidence intervals for each of the subgroup analyses. Because of the small number of events which are likely to occur in subgroups, caution is advised when interpreting results of these subgroup analyses.

4.1 Gender, Age, Race and Geographic Region

Evaluations for gender, age, race and geographic region are presented in the paragraphs that follow. A forest plot combining all results is presented in Figure 5. All hazard ratios were calculated using Cox proportional hazards model stratified by trial.

4.1.1 Gender

Among the 5,107 subjects in the CVE population, 2,690 (52.7%) were male and 2,417 (47.3%) were female. Among the 91 subjects with MACE+ events, 64 were reported in male subjects and 27 were reported in female subjects.

Among male subjects, the risk of developing a MACE+ event was higher in the pooled comparators group than in the pooled albiglutide group, HR 0.81, 95% CI (0.47, 1.39). In contrast, among female subjects, the risk of developing a CV related events as measured by MACE+ is higher in the albiglutide group, HR 1.4, 95% CI (0.6, 3.27).

4.1.2 Age

Among the 5,107 subjects in the CVE population, 4,117 (80.6%) were younger than 65 years old, 876 (17.1%) were between 65 and 74 and 114 (2.2%) were older than 74. Among the 91 subjects with MACE+ events, 62 events were reported in subjects aged 64 years or younger, while 29 events were reported in subjects older than 64 years.

Among subjects aged 64 years or younger, the risk of developing a MACE+ events was lower in the albiglutide group than in the pooled all comparator group, HR 0.79, 95% CI (0.45, 1.39). Similarly, among subjects older than 74, the risk is lower in the albiglutide group, with a wider confidence interval due to smaller number of events, HR 0.69, 95% CI (0.19, 2.53). For those subjects aged in-between, the risk appeared to be higher in the albiglutide group, along with a wide confidence interval, HR 1.86, 95% CI (0.71, 4.82)

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4.1.3 Race

Among the 5,107 subjects in the CVE population, 2,290 (44.8%) were non-Hispanic White, 667 (13.1%) were Black, 1,275 (25%) were Hispanic, 772 (15.1%) were Asian, and 103 (2%) were subjects with other races. Among the 91 subjects with MACE+ events, 51 were reported in non-Hispanic White subjects, 15 were reported in Black subjects, 13 were reported in Hispanic subjects, 10 were reported in Asian subjects, and 2 was reported in a subject classified as other race.

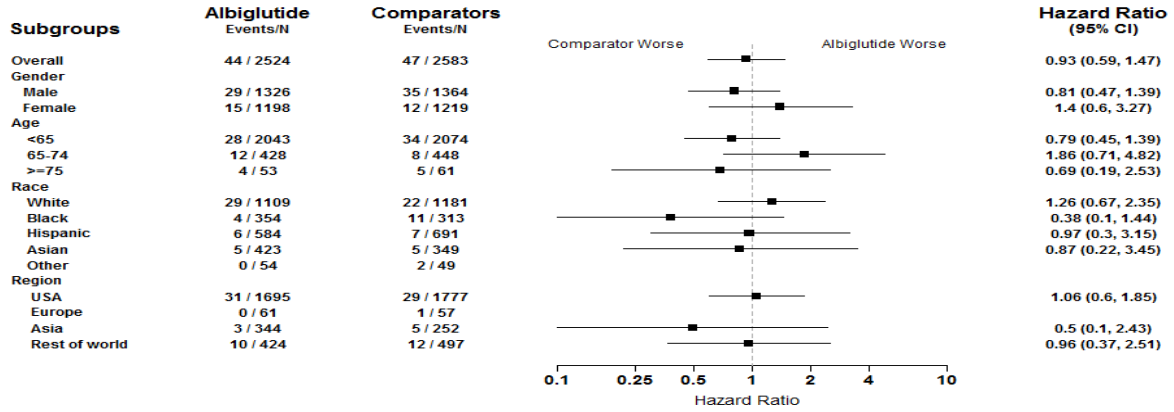
Among non-Hispanic White subjects, the risk of developing a CV related event as measured by MACE+ was higher in the pooled albiglutide group than in the pooled all comparator group, HR 1.26, 95% CI (0.67, 2.35). The effect is opposite among Black subjects - the risk was higher in the comparator group than in the albiglutide group, HR 0.38, 95% CI (0.1, 1.44). Among Hispanic and Asian subjects, the risk appeared to be slightly lower in the albiglutide group than in the comparators (Hispanic: HR 0.97, 95% CI (0.3, 3.15); Asian: (HR 0.87, 95% CI (0.22, 3.45)).

4.1.4 Region

Among the 5,107 subjects in the CVE population, 3,472 (68%) were randomized in the USA, 118 (2.3%) were randomized in Europe, 596 (11.7%) were randomized in Asia, and 921 (18%) were randomized in other regions. Among the 91 subjects with MACE+ events, 60 events were reported in US subjects, while one single event was reported in Europe, 8 events were reported in Asia, and 22 events were reported in other regions.

The HR estimate for US subjects is close to 1, HR 1.06, 95% CI (0.6, 1.85), as well as for the rest of world, HR 0.96, 95% CI (0.37, 2.51). Among Asia subjects, the risk of developing a MACE+ event is lower in the albiglutide group than in the comparator group, along with a wide confidence interval due to small number of events, HR 0.5, 95% CI (0.1, 2.43).

Figure 5: Forest Plot of Hazard Ratio of MACE+ by Baseline Demographics (CVE, On-study)



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4.2 Other Special/Subgroup Populations

4.2.1 Baseline CV Risk Factors and Diabetes History

To determine if the health history of the subjects had any impact on the risk of developing a CV event as determined by the primary composite endpoint MACE+, the baseline BMI (<30, >= 30), history of cardiovascular disease, and duration of diabetes, were evaluated. A forest plot combining all these subgroup analysis results is presented in Figure 6.

4.2.1.1 BMI

Among the 5,107 subjects in the CVE population, 1,790 (35%) had BMI < 30 kg/m^2 and 3,316 (65%) had BMI >= 30 kg/m^2. Among the 91 subjects with MACE+ events, 31 were reported in low BMI subjects and 60 were reported in high BMI subjects.

Among low BMI subjects, the risk of developing a MACE+ event was lower in the pooled albiglutide group than in the pooled comparator group, HR 0.81, 95% CI (0.37, 1.75). Among subjects with BMI >= 30 kg/m^2, the risk of developing a CV related events as measured by MACE+ is similar between the two groups, HR 1.01, 95% CI (0.57, 1.77).

4.2.1.2 Prior CV Disease

Among the 5,107 subjects in the CVE population, 454 (8.9%) had a history of cardiovascular disease. Among those subjects with prior CV disease, 30 experienced adjudicated MACE+ events during the course of clinical trials. Based on the time-to-event analysis in the CVE population for the incidence of MACE+, it was found that the two subgroups (with prior CV disease and no prior CV disease) both had a HR point estimate close to 1, while the subjects with CV history had a slightly higher risk for albiglutide group compared to comparators, HR 1.12, 95% CI (0.55, 2.28). For those who didn't have prior CV disease, the HR is lower than 1, HR 0.86, 95% CI (0.48, 1.54).

4.2.1.3 Duration of Diabetes

Among the 5,107 subjects in the CVE population, 1,842 (36.1%) had a duration of diabetes less than 5 years, 1,629 (31.9%) had a duration between 5 years and 10 years, and 1,636 (32%) had been diabetics for at least 10 years. Among the 91 subjects with MACE+ events, 32 events were reported in subjects with shortest diabetes duration, while 21 events were reported in subjects with medium duration and 38 events were reported in subjects with longest duration.

It shows a trend of decreasing CV risk in albiglutide group compared with comparators group with the increasing duration of diabetes (<5 yrs: HR 1.44, 95% CI (0.64, 3.27); >=5 to < 10 yrs: HR 1.01, 95% CI (0.41, 2.48); >= 10 years: HR 0.61, 95% CI (0.3, 1.26)). However, the three CIs are all overlapping and none of them show a significant effect.

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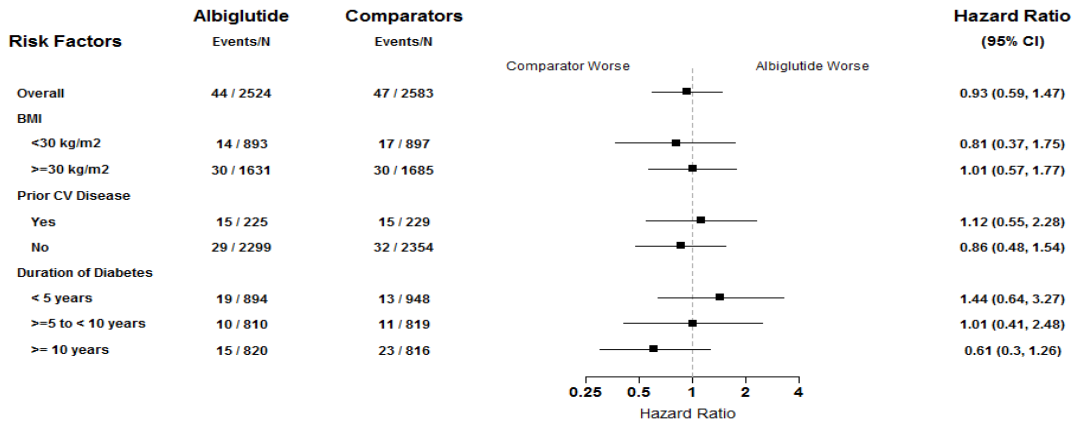
Figure 6: Forest Plot of Hazard Ratio of MACE+ by Baseline CV Risk Factors (CVE, On-study)



Source: Created by reviewer.

4.2.2 Trial Duration

An additional exploratory analysis was conducted to assess the effect of treatment duration using a trial level subgroup where trials were grouped into two sets (long-term trials defined as trials planned with 3 years of treatment, and short-term trials defined as those with a treatment duration less than 3 years). The five 3-year ongoing trials (Studies GLP112753, GLP112754, GLP112755, GLP112756, and GLP112757) and the four short-term trials (Studies GLP108486, GLP114130, GLP114179 and GLP110932) were grouped together to observe any difference in the incidence rates of the primary composite endpoint based on the duration of trial. Table 9 presents the results from the meta-analysis of these two subgroups. The HR estimates for these two subgroups are both less than 1 and the two CIs are overlapping for the most part. Therefore quantitatively, there is no notable effect of trial duration on the hazard ratio of the primary endpoint. In the primary forest plot (Figure 3), the trials are ordered by its duration thus the five 3-year studies are shown on the top. The forest plot does not show an obvious trend related to trial duration either, which is consistent with the quantitative exploratory analysis result.

Table 9: Sensitivity Analysis Result for MACE+ by Trial Duration (CVE, on-study)

Group by duration		**Albiglutide**	**Comparator**
3-year Studies			
	Events/PY [IR*]	29/3262.2 [8.9]	30/3549.1 [8.4]
	HR (95% CI)†	0.98 (0.54, 1.79)	
Other Studies			
	Events/PY [IR*]	15/952.5 [15.7]	17/899.1 [18.9]
	HR (95% CI)†	0.85 (0.42, 1.73)	

*: Per 1,000 PY. †: Cox proportional hazards model stratified by trial.

Source: Created by reviewer

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5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The primary agreed upon composite endpoint for CV safety evaluation was MACE+, comprised of hospitalization of unstable angina, myocardial infarction, stroke, and CV death. In this meta-analysis of CV risk, the agreed upon primary analysis was time-to-event analysis based on a stratified Cox proportional hazards model with trial as the stratification factor for the MACE+ endpoint. The primary comparison was between the combined albiglutide treatment group versus the all comparator group which consisted of various control arms including other anti-diabetic medications, basal insulin and placebo.

This meta-analysis is the first of a two-part group sequential testing strategy that was pre-specified to control the Type I error rate for ruling out an excess risk with respect to the 1.8 relative risk margin, as estimated by the hazard ratio, of the investigational agent compared to the control group at an overall one-sided 0.025 alpha-level. The planned group sequential testing strategy included the first formal meta-analysis test of the MACE+ endpoint using a one-sided alpha-level of 0.01225 (corresponding to a two-sided 97.55% CI). Per the FDA "Guidance for industry: Diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes" (December 2008), if the upper bound of the 97.55% CI was less than 1.8 then the meta-analysis for CV risk met the pre-marketing criteria for ruling out an 80% relative increase in CV risk. If the pre-marketing criteria were not met with the first analysis, a second analysis was planned to be tested at the one-sided alpha-level of .01245 at the end of albiglutide clinical program.

In the BLA submission, data from 9 randomized Phase 2b/3 trials were synthesized to evaluate the risk of developing a CV related event as measured by the primary composite MACE+ endpoint with a data cut-off date of June 08, 2012. The primary analysis was the incidence rate and relative hazard of the first occurrence of adjudicated MACE+ for albiglutide vs. all comparators. These analyses were also performed for MACE endpoint. Secondary comparisons were conducted for albiglutide vs. placebo and albiglutide vs. active comparators, respectively with MACE+ and MACE, as well as employing different censoring schemes (on-study, on-treatment + 56 days).

As a sensitivity analysis, the Mantel-Haenszel risk ratio and risk difference approach were also utilized to evaluate the CV risk using MACE+. The statistical methods applied to this application are similar to those used in other meta-analyses of CV risk for products intended to treat Type 2 diabetes mellitus which are felt to be sufficient in characterizing the CV risk. More details for the statistical methodologies used in this review are provided in Section 3.3.2.

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5.2 Collective Evidence

Based on the pooled data of 9 randomized phase 2b/3 trials, a total of 91 subjects experienced at least one adjudicated MACE+ event during the course of the studies, with 44 subjects in the pooled albiglutide group and 47 subjects in the pooled all comparator group. The incidence rate of MACE+ was 10.4 per 1,000 patient-years in the pooled albiglutide group, as compared to 10.6 per 1,000 patient-years in the pooled all comparator group. The estimated hazard ratio of albiglutide compared to all comparator was 0.93 with a 97.55% CI of (0.55, 1.58) for MACE+. Detailed analysis results are provided in Section 3.3.4.1.

Using the strict definition of MACE, a total of 82 subjects experienced at least one adjudicated MACE event, with 40 subjects reporting an event in the pooled albiglutide group and 42 subjects reporting an event in the pooled all comparator group. The estimated hazard ratio of albiglutide compared to all comparators was 0.97 with a 97.55% CI of (0.55, 1.69) for strict MACE. Detailed analysis results are provided in Section 3.3.4.2.

As shown in Section 3.3.4.1, the Mantel-Haenszel risk ratio and risk difference results are consistent with the primary analysis result based on the hazard ratio. Sensitivity analyses were also conducted to investigate the impact of imbalanced number of pending adjudication between the two comparison arms. The results are consistent with the result of primary analysis.

The difference between albiglutide and all comparators in developing a CV related event as measured by MACE+ was also evaluated in subgroups by age, gender, race, region, baseline risk factors and duration of treatment. Most of the subgroup analysis results were in the same direction as the overall result. Detailed results for subgroup analyses are provided in Section 4.

5.3 Conclusions and Recommendations

Based on the meta-analysis of the 9 randomized phase 2b/3 trials, the risk of developing a major adverse cardiovascular event, as measured by MACE+ (composite endpoint consisting of CV death, MI, stroke, and hospitalization of unstable angina) using on-study censoring scheme, was slightly lower in the pooled albiglutide group relative to the pooled all comparator group. Compared to the pooled all comparator group, the estimated hazard ratio of albiglutide is 0.93 with a 97.55% CI of (0.55, 1.58) (Table 10) as the first formal analysis of a pre-specified two-part group sequential strategy for controlling of Type 1 error.

In addition to the above approaches, several sensitivity/supportive analyses were conducted that explored strict MACE endpoint, incorporated different effect measures (risk difference and risk ratio), and examined various censoring schemes, secondary comparisons and subgroup analyses. While various scenarios resulted in different values of the effect estimates, these results are consistent with the primary finding.

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Table 10: Primary Analysis Result for MACE+ (CVE, on-study)

		Albiglutide	Comparator
		(*N* = 2524) [PY = 4214.7]	(*N* = 2583) [PY = 4448.2]
MACE+ Endpoint			
	Events [IR*]	44 [10.4]	47 [10.6]
	HR (97.55% CI)†	**0.93 (0.55, 1.58)**	

*: Per 1,000 PY. †: Cox proportional hazards model stratified by trial
Source: Created by reviewer.

Based upon the 1.8 risk margin set forth in the FDA Diabetes Guidance, the upper-bound of the alpha-adjusted 97.55% confidence interval of the hazard ratio meets the pre-marketing criteria for ruling out an 80% relative increase in CV risk.

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/s/

BO LI
09/03/2013

MATTHEW J SOUKUP
09/03/2013
Concur with review

ALOKA G CHAKRAVARTY
09/03/2013

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

BLA Number: 125431

Applicant: GlaxoSmithKline

Stamp Date: 01/19/2013

Drug Name: albiglutide for injection

NDA Type: Standard review

Electronic submission, CBER EDR http://cberedrweb.fda.gov:8080/esp/cberedr.jsp?folderObjId=0bbcaea681167203

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups	X			
4	Data sets in EDR are accessible and conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

No filing issues are noted at this time.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			The pre-marketing clinical development program for albiglutide has been prospectively designed to exclude excess CV risk.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			In the pivotal trials for efficacy, cardiovascular events were defined, collected and adjudicated in a consistent manner after the trials started. The pre-specified primary CV safety endpoint is adjudicated MACE+.
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit	X			

File name: StatisticsFilingChecklist_BLA125431

analyses across clinical trials in the NDA/BLA.				
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Background:
Albiglutide is a novel analogue of human glucagon-like peptide-1 (GLP-1) designed to retain the therapeutic actions of GLP-1 while having a greatly extended duration of action to treat type 2 diabetes mellitus (T2DM). Starting in 2009, several randomized, double-blind, placebo and active-controlled, multi- and parallel-group, multi-center studies were initiated to evaluate the efficacy and safety of a weekly SC injection of albiglutide alone or in combination with currently approved anti-diabetic therapy.

In accordance with most experts and with the recommendations of the FDA letter dated 08 November 2008 regarding cardiovascular (CV) risk, the December 2008 FDA Guidance for Industry [DHHS, 2008], and the EMA Guideline on the Clinical Investigation of Medicinal Products in the Treatment or Prevention of Diabetes [CHMP, 2012], the clinical development program for albiglutide has been designed to exclude excess CV risk during the prelicensure development of this anti-diabetic treatment.

The primary objective of the CV meta-analysis was to evaluate whether albiglutide alters the risk of CV events in subjects with T2DM relative to all comparators (placebo and active) that comprise the standard of care in the albiglutide Phase III program.

In the pivotal trials for efficacy, cardiovascular events were prospectively defined, collected and adjudicated in a consistent manner. The pre-specified primary CV safety endpoint is adjudicated MACE+ consisting of acute MI, stroke, CV death and hospitalization for unstable angina.

The primary comparison was the incidence rate and relative hazard of the first occurrence of adjudicated MACE+ for albiglutide vs. combined comparators.

Brief summary of clinical development program

CV events from a single Phase I study, 2 Phase II studies, and 9 Phase III studies underwent adjudication by the CEC. The key requirements for inclusion of data from studies in the meta-analysis were that the study enrolled subjects with T2DM, subjects received repeat dosing, and a control group was included.

The meta-analysis of CV safety included data from the following nine studies (Table 1):

- Five Phase III studies for which subject enrollment started in the first quarter of 2009 and continued for up to 3 years
- Three Phase III studies for which subject enrollment started in the first half of 2010
- One Japanese Phase IIb study for which subject enrollment started in the first

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quarter of 2010

At the time of the meta-analysis, the 5 Phase III studies with a 3-year duration were ongoing and have at least 2-year data available. At the time of the BLA filing, available CV data from all enrolled subjects from the 9 studies were used based upon a multiplicity adjusted sequential meta-analysis plan.

CV safety meta-analysis datasets and report are located at CBER EDR: BLA125431\0000\m5

Table 1 Studies Included in the CV Meta-analysis for the Albiglutide Clinical Development Program (Safety Population)

Protocol Number	Study Description	Treatment	Number of Subjects in Safety Population
Phase IIIa: First Wave of 5 Core Studies			
GLP112753	Add-on to metformin (3-year)	Placebo	101
		Sitagliptin	302
		Glimepiride	307
		Albiglutide	302
GLP112754*	Albiglutide vs insulin (3-year)	Insulin glargine	241
		Albiglutide	504
GLP112755	Add-on to TZD (+/- metformin) (3-year)	Placebo	151
		Albiglutide	150
GLP112756	Monotherapy (3-year)	Placebo	101
		Albiglutide	200
GLP112757	Add-on to metformin + SU (3-year)	Placebo	115
		Pioglitazone	277
		Albiglutide	271
Phase IIIa: Second Wave of 3 Studies			
GLP108486*	Add-on to basal insulin (1-year)	Lispro insulin	281
		Albiglutide	285
GLP114130	Renally impaired, albiglutide vs sitagliptin (1-year)	Sitagliptin	246
		Albiglutide	249
GLP114179*	Head to head with liraglutide (32-week)	Liraglutide	408
		Albiglutide	404
Phase IIb: Japan Study			
GLP110932	Proof of concept (Japan) (16-week)	Placebo	53
		Albiglutide	159
All Studies		All comparators	2583
		Albiglutide	2524

SU = sulfonylurea; TZD = thiazolidinedione
*: open-lable studies

Brief summary of CV meta-analysis at time of BLA filing

As of cut-off date 08 June 2012, 91 MACE+ events were positively adjudicated.

The incidence for first MACE+ was similar between the treatment groups (1.0 and 1.1 events per 100 person-years in the albiglutide and all comparators groups, respectively). The HR was 0.93, and the upper bound of the 2-sided CI was less than

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1.8 (97.55% CI: 0.55, 1.58; noninferiority p=0.0025). Note that the 97.55% CI is calculated due to multiplicity adjustment of group sequential approach. A final analysis is to be performed when all the studies are completed using a 2-sided 97.45% CI.

Bo Li	02-26-2013
Reviewing Statistician	Date
Mat Soukup	02-26-2013
Supervisor/Team Leader	Date

File name: StatisticsFilingChecklist_BLA125431

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BO LI
03/14/2013

MATTHEW J SOUKUP
03/14/2013

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NDA Number: 125431/000 **Applicant: Glaxo SmithKline, LLC** **Stamp Date: 1-14-13**

Drug Name: Albiglutide (proposed Eperzan™) **BLA Type: Standard** **Submission Date: 1-11-13**

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Studies Submitted

STUDY GLP112753
STUDY GLP112754
STUDY GLP112755
STUDY GLP112756
STUDY GLP112757
STUDY GLP108486
STUDY GLP114179
STUDY GLP114130

Studies to be Reviewed

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.				**No comments**
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	*			

Further Information Request in 74-day letter

* The sponsor has done sensitivity analyses as mentioned in the protocol. Depending on the overall results, this reviewer may request additional sensitivity analyses.

Japobrata Choudhury, Ph.D. 2-27-12

Reviewing Statistician Date

Jon T. Sahlroot, Ph.D.

Supervisor/Team Leader Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JAPOBRATA CHOUDHURY
03/08/2013

JON T SAHLROOT
03/08/2013