Online-Only Supplementary Material

(Diabetes Care 2020 | https://doi.org/10.2337/dc19-2316)

Impact of a Weekly Glucagon-Like Peptide 1 Receptor Agonist, Albiglutide, on Glycemic Control and on Reducing Prandial Insulin Use in Type 2 Diabetes Inadequately Controlled on Multiple Insulin Therapy: A Randomized Trial

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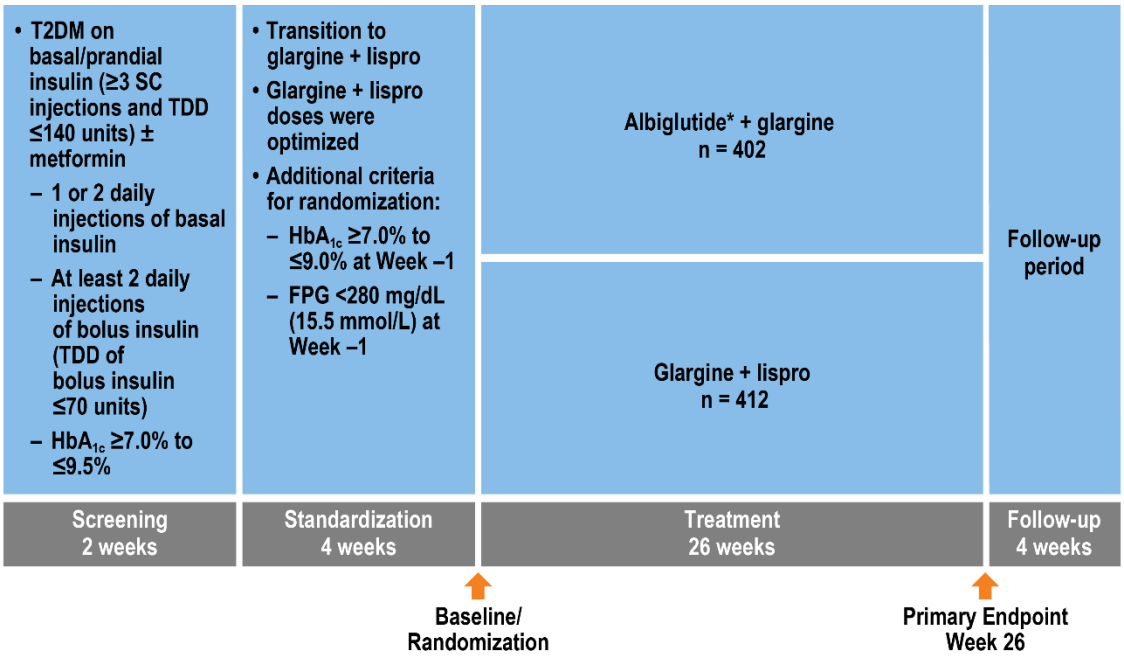
Supplementary Fig 1. Study Design.



FPG denotes fasting plasma glucose, HbA_{1c} glycated hemoglobin, SC subcutaneous, TDD total daily dose, T2DM type 2 diabetes mellitus

*At Baseline/Randomization, albiglutide was started at 30 mg once weekly with uptitration to albiglutide 50 mg once weekly at Week 4. Subjects randomly assigned to this treatment group were to reduce lispro by 50% at Baseline/Randomization, followed by complete (100%) discontinuation of lispro at Week 4

Randomized treatment assignment was done via the interactive voice response system, and randomization was implemented based on a sequestered fixed randomization schedule. Site personnel received a randomization notification indicating the unique subject identifier, the treatment assignment, and the date and time of randomization.

Each subject number was a unique identifier and once assigned was not reassigned.

Key amendments made to the study protocol:

- Included details of sensitivity analyses to assess the impact of missing data for the noninferiority test.
- Introduced additional flexibility into glycemic eligibility criteria at Screening and to the process for transitioning subjects from their prior basal-bolus insulin therapy to insulin glargine and insulin lispro at the beginning of the Standardization Period, as well as providing additional flexibility to the investigator when adjusting insulin glargine and insulin lispro.
- Included information to further mitigate the potential risk of hypoglycaemia, as well as enhance subject education and training pertaining to hypoglycaemic events.

Supplemental Data: Inclusion and Exclusion Criteria.

Inclusion criteria

1. Male or female, aged 18 to 75 years (inclusive at the time of Screening) with type 2 diabetes mellitus
2. HbA_{1c} ≥7.0% and ≤9.5% (≥53 and ≤80 mmol/mol) at Screening. If the first screening HbA_{1c} does not meet the eligibility criterion, the HbA_{1c} value may be checked up to two times during Screening, and if the average of these determinations meets the criterion, the patient may be eligible for further participation in the study
3. Currently treated with a basal-prandial insulin regimen (with or without metformin) for at least 3 months before Screening. The patient must be taking the following:
   - Basal insulin (one or two daily injections of neutral protamine Hagedorn insulin, insulin glargine, insulin detemir, or insulin degludec)

   AND
   - Prandial insulin (at least two injections of regular insulin, insulin glulisine, insulin aspart, or insulin lispro) with a total daily dose of prandial insulin ≤70 units
   - In addition, the total daily dose of insulin must be ≤140 units
   - If taking metformin, a stable dose for at least 8 weeks before Screening
     Note: Patient should not have received any other antihyperglycemic agent within 30 days before Screening (eg, GLP-1 receptor agonist, dipeptidyl peptidase-IV inhibitor, sulfonylurea, meglitinide, sodium-glucose transporter 2 inhibitor, or thiazolidinedione). Patients receiving commercially available premixed basal and prandial insulin are not eligible for this study
4. Fasting C-peptide ≥0.8 ng/mL (≥0.26 nmol/L). If the fasting C-peptide is <0.8 ng/mL (<0.26 nmol/L) but stimulated C-peptide 90 minutes after a standardized mixed meal is ≥1.5 ng/mL (≥0.5 nmol/L), the patient may be eligible for further participation in the study
   Note: Plasma glucose will also be measured 90 minutes after the standardized mixed meal; if the concurrent plasma glucose collected 90 minutes after the standardized mixed meal is not ≥144.0 mg/dL (≥8.0 mmol/L), the stimulated C-peptide test may be repeated during an unscheduled visit.
5. Body mass index ≤40.0 kg/m^2
6. Thyroid-stimulating hormone level is normal or clinically euthyroid as demonstrated by further thyroid tests (eg, free T4)
7. Female patients of childbearing potential (ie, not surgically sterile and/or not postmenopausal) must be practicing adequate contraception (as defined below) for the duration of participation in the study including the 4-week posttreatment Follow-up Period:
   - Abstinence from penile-vaginal intercourse, when this is the female's preferred and usual lifestyle
   - Oral contraceptive, either combined or progestogen alone. For patients participating at sites in Germany; progestogen-only pills are only

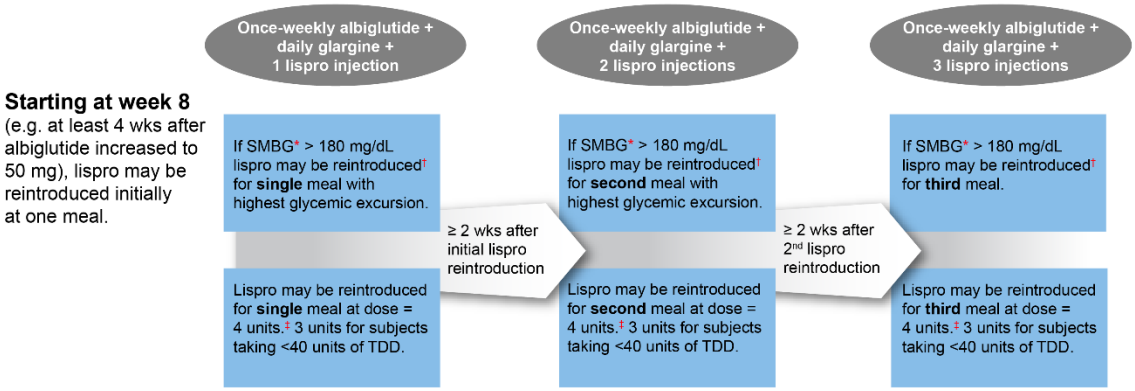
acceptable if they have a Pearl Index of less than 1.0 (eg, those containing 75 µg desogestrel
    - Injectable progestogen
    - Implants of etonogestrel or levonorgestrel
    - Estrogenic vaginal ring
    - Percutaneous contraceptive patches
    - Intrauterine device or intrauterine system that has a failure rate of less than 1% per year when used consistently and correctly as stated in the product label
    - Male partner sterilization before the female patient's entry into the study, and this male is the sole partner for that patient. The information on the male sterility can come from the site personnel's review of the female patient's medical records, medical examination of the patient and/or semen analysis, or interview with the female patient on her male partner's medical history
    - Male condom combined with a female diaphragm, either with or without a vaginal spermicide (foam, gel, film, cream, or suppository)
8. Willing and able to comply with all study procedures including performance of frequent self-monitored blood glucose profiles and use of an e-diary according to the protocol
9. Willing and able to provide written informed consent after a thorough explanation of the study by the investigator or designee, which will include the opportunity for the patients to ask questions
10. Suitable for participation in a treat-to-target study, including intensified basal-prandial insulin therapy utilizing the prespecified glycemic targets defined in the protocol

Exclusion criteria

1. Type 1 diabetes mellitus
2. History of cancer that has not been in full remission for at least 3 years before Screening. (A history of squamous cell or basal cell carcinoma of the skin or treated cervical intra-epithelial neoplasia I or II is allowed)
3. Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2
4. Current symptomatic biliary disease or history of acute or chronic pancreatitis
5. Severe gastroparesis (ie, requiring regular therapy within 6 months before Screening)
6. History of significant gastrointestinal (GI) surgery that, in the opinion of the investigator, is likely to significantly affect upper GI or pancreatic function (eg, gastric bypass and banding, antrectomy, Roux-en-Y bypass, gastric vagotomy, small bowel resection, or surgeries thought to significantly affect upper GI function)
7. History of hypoglycemia unawareness (ie, the absence of autonomic warning symptoms before the development of neuroglycopenic symptoms such as blurred vision, difficulty speaking, feeling faint, difficulty thinking, and confusion)

8. Diabetic complications (eg, active proliferative retinopathy or severe diabetic neuropathy) or any other clinically significant abnormality (including a psychiatric disorder) that, in the opinion of the investigator, may pose additional risk in administering the investigational product
9. Clinically significant cardiovascular and/or cerebrovascular disease within 3 months before Screening including, but not limited to, the following:
    - Stroke or transient ischemic attack
    - Acute coronary syndrome (myocardial infarction or unstable angina not responsive to nitroglycerin)
    - Cardiac surgery or percutaneous coronary procedure
10. Any history of New York Heart Association class III or IV heart failure
11. Alanine aminotransferase (ALT) >2.5 × upper limit of normal (ULN) or bilirubin >1.5 × ULN (isolated bilirubin >1.5 × ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
12. Unstable liver disease (as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice), cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). (Chronic stable hepatitis B and C are acceptable if patient otherwise meets entry criteria and is not on active antiviral treatment [eg, presence of hepatitis B surface antigen or positive hepatitis C test result within 3 months of Screening])
13. Hemoglobin <11 g/dL (<110 g/L) for male patients and <10 g/dL (<100 g/L) for female patients at Screening
14. Estimated glomerular filtration rate ≤30 mL/min/1.73 m^2 (calculated using the Modification of Diet in Renal Disease formula) at Screening
    Note: As the use of metformin in patients with varying degrees of renal function may differ from country to country, use of metformin should be in accordance with the metformin product label within the participating country
15. Fasting triglyceride level >750 mg/dL (>8.48 mmol/L) at Screening
16. Hemoglobinopathy that may affect proper interpretation of HbA_{1c}
17. Known allergy to albiglutide or any product components (including yeast and human albumin), any other GLP-1 analogue, insulin, or other study medication's excipients OR other contraindications (per the prescribing information) for the use of potential study medications (eg, insulin glargine, insulin lispro)
18. Use of oral or systemically injected glucocorticoids within the 3 months before randomization or high likelihood of a requirement for prolonged treatment (>1 week) in the 6 months following randomization. However, short courses of oral steroids (single dose or multiple doses for up to 7 days) may be permitted provided these cases are discussed with the medical monitor. Inhaled, intra-articular, epidural, and topical corticosteroids are allowed
19. Female patient is pregnant (confirmed by laboratory testing) or lactating
20. Receipt of any investigational drug within the 30 days or five half-lives, whichever is longer, before Screening, a history of receipt of an investigational antihyperglycemic agent within the 3 months before randomization, or receipt of albiglutide in previous studies

Supplementary Fig. 2. Reintroducing Insulin Lispro for Albiglutide-Treated Participants.



* Mean of measurements (taken before lunch, dinner, or bedtime) from the last 3 available days (at least 2 of which are consecutive) in week before the next study visit/telephone contact. If measurements from 3 days (at least 2 of which are consecutive) are not available, the dose adjustment should be delayed until the next scheduled study visit/telephone contact; unless in the investigator's judgment, a dose adjustment is warranted. The subject should be retrained on the importance of SMBG measurements.

† According to investigator clinical judgment.

‡ Per investigator clinical judgment as appropriate for patient, lispro may be further titrated per titration algorithm.

SMBG denotes self-monitored blood glucose, TDD total daily dose of insulin.
SMBG >180 mg/dL is equal to >10.0 mmol/L.

Note: The algorithm for reintroduction of insulin lispro should apply in the majority of circumstances; however, as the intent of glycemia management is to individualize treatment goals to achieve a target HbA_{1c} level as close to normal as possible without significant hypoglycemia or other adverse effects of treatment, the investigator was allowed to use his/her judgment in determining benefit/risk of further insulin dose adjustment and modification, accordingly. In the event an individual experienced significant evidence of hyperglycemia (eg, symptoms of polyuria and polydipsia and laboratory evidence of hyperglycemia) and the investigator determined that further dose adjustment with insulin was not in the best interest of the individual and that the individual required rescue with another antihyperglycemic medication, the individual was to be discontinued from the study and the appropriate rescue therapy initiated. Additionally, individuals not achieving a predefined threshold for glycemic control (confirmed FPG ≤270 mg/dL [15.0 mmol/L]) at any time within at least 8 weeks after randomization could be considered for study withdrawal based on the discretion of the investigator and the medical monitor.

Supplementary Table 1. Titration Algorithm for Recommended Lispro Dose Adjustment.

Plasma glucose before lunch and dinner, and before bedtime*		Adjustment of lispro (U)†
mg/dL	mmol/L	
≤99 without obvious explanation	≤5.5 without obvious explanation	−2‡ For a dose >50 U, consider a 5%−10% dose reduction at the discretion of the investigator
100 – 119 = target	5.6 – 6.6 = target	No adjustment
120 – 139	6.7 – 7.7	+2
140 – 179	7.8 – 9.9	+3
≥180	≥10.0	+4
If severe hypoglycemia (requiring assistance) or any other clinically significant hypoglycemia was documented since the last dose adjustment		Decrease insulin dose at the investigator's discretion (ie, 10%−15%)

U denotes units.

*Mean of measurements from the last 3 available days (at least two of which are consecutive) in the week before the next study visit/telephone contact. If measurements from the last 3 available days (at least two of which are consecutive) are not available, the dose adjustment should be delayed until the next scheduled study visit/telephone contact, unless in the investigator's judgment, a dose adjustment is warranted at that time.

†Modified based on the insulin titration algorithms in the BEGIN basal-prandial type 2 study[1] and other published treat-to-target studies.[2-5]

‡For patients with an SMPG value <70 mg/dL (<3.9 mmol/L) without obvious explanation, lispro may be stopped at the investigator's discretion.

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Supplementary Table 2. Titration Algorithm for Recommended Glargine Dose Adjustment.

Before breakfast plasma glucose*		Adjustment of glargine (U)†
mg/dL	**mmol/L**	
<56‡	<3.1‡	−4 For a dose >50 U, consider 10% dose reduction
56 – 69‡	3.1 – 3.8‡	−2 For a dose >50 U, consider 5% dose reduction
70 – 79	3.9 – 4.4	−1
80 – 109 = target	4.5 – 6.0 = target	No adjustment
110 – 139	6.1 – 7.7	+2
140 – 179	7.8 – 9.9	+4
≥180	≥10.0	+6
If severe hypoglycemia (requiring assistance) or any other clinically significant hypoglycemia (eg, nocturnal hypoglycemia) was documented since the last dose adjustment		Decrease insulin dose 10%−15%, at the investigator's discretion

U denotes units.

*Mean of measurements from the last 3 available days (at least two of which are consecutive) in the week before the next study visit/telephone contact. If measurements from the last 3 available days (at least two of which are consecutive) are not available, the dose adjustment should be delayed until the next scheduled study visit/telephone contact; unless in the investigator's judgment, a dose adjustment is warranted.

†Modified based on the insulin titration algorithms in the BEGIN basal-prandial type 2 study[1] and other published treat-to-target studies.[2-5]

‡Investigator may defer adjustment if there is an obvious reason for the low value, such as a missed meal.

Supplemental Data: Prespecified Hierarchical Testing.

After demonstration of noninferiority, superiority of the albiglutide+glargine group against the lispro+glargine group was tested in a step-down sequential manner at a 2-sided significance level of 0.05 in the following order, as specified in the reporting and RAP:

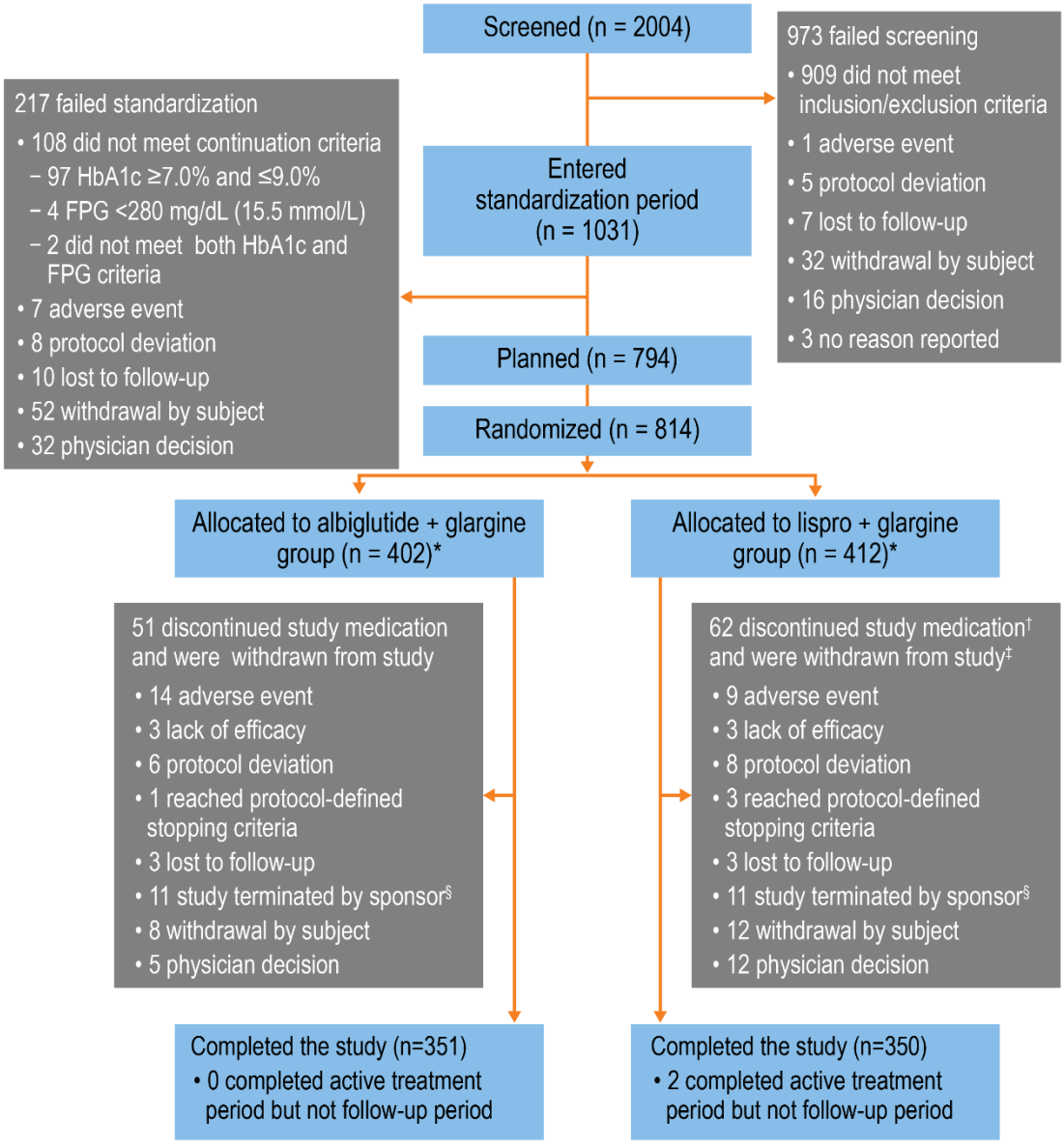
1. Percentage of subjects with severe or documented symptomatic hypoglycemia through Week 26
2. Change from baseline in body weight at Week 26
3. Total daily insulin dose at Week 26
4. HbA_{1c} change from baseline at Week 26

Supplementary Table 3. Analysis Methods for Secondary End Points.

Secondary End Point	Analysis Method
Proportion of participants treated with once-weekly albiglutide who were able to replace prandial insulin without the reintroduction of insulin lispro	Estimated using a 95% CI
FPG and body weight	Analyzed using a similar MMRM used for the primary end point, with the corresponding baseline value as a covariate
Change over time in HbA_{1c} and daily insulin use	Summarized descriptively
Binary secondary end points (achieving HbA_{1c} targets and occurrence of hypoglycemia)	Compared between groups using Cochran-Mantel-Haenszel test, adjusting for baseline HbA_{1c} stratum, age group, current use of metformin, and region

FPG denotes fasting plasma glucose, MMRM mixed-effects model with repeated measures.

Supplementary Fig. 3. CONSORT Diagram.



The first subject was initiated on 21-Nov-2014 and the last subject completed on 24-Jul-2017

*One participant randomized to the albiglutide+glargine arm was mistakenly not dispensed albiglutide and was only dispensed lispro and glargine; the participant was analyzed for efficacy according to randomized treatment and for safety according to the actual treatment received. One participant randomized to the albiglutide+glargine arm was not treated with study drug and was excluded from the Safety population.

†Among 113 participants who discontinued study treatment, only one participant randomized to lispro+glargine continued in the study for the remaining scheduled visits and the follow-up visit instead of just the follow-up visit.

‡One participant randomized to lispro+glargine withdrew from the study after Week 16, but was mistakenly reported as "completed the study." This participant was from one site in Europe closed by study sponsor due to significant good clinical practice noncompliance.

§Participants withdrawn from the study with reason "Study terminated by sponsor" are participants from one site in Europe closed by study sponsor due to significant good clinical practice noncompliance. The study was not terminated.

Supplementary Table 4. TRIM-Diabetes Questionnaire Individual Domain Scores*.

	Albiglutide + Glargine (n=402)	Lispro + Glargine (n=412)
Treatment burden domain score, mean±SD		
Participants (n)	347	350
Baseline	64.8±22.1	67.1±20.4
Week 26	68.2±21.9	67.5±21.5
Change from baseline	3.5±20.7	0.4±22.2
LS mean difference (95% CI)	1.66 (-1.12, 4.44); *P* = 0.241	
Daily life domain score, mean±SD		
Participants (n)	345	347
Baseline	76.8±19.0	75.8±20.2
Week 26	79.3±18.5	76.9±18.6
Change from baseline	2.6±19.6	1.1±20.6
LS mean difference (95% CI)	2.16 (-0.29, 4.61); *P* = 0.083	
Diabetes management domain score, mean±SD		
Participants (n)	345	347
Baseline	61.9±21.5	62.2±20.9
Week 26	68.2±20.7	61.4±20.4
Change from baseline	6.3±21.7	-0.73±20.9
LS mean difference (95% CI)	7.16 (4.49, 9.83); *P* <0.0001	
Compliance domain score, mean±SD		
Participants (n)	345	347
Baseline	78.8±17.5	79.2±17.1
Week 26	83.2±16.0	78.8±17.7

Change from baseline	4.4±18.6	-0.4±16.8
LS mean difference (95% CI)	4.91 (2.72, 7.10); *P* <0.0001	
Psychological health domain score, mean±SD		
Participants (n)	347	349
Baseline	78.7±18.6	81.3±16.5
Week 26	83.5±16.0	83.4±17.3
Change from baseline	4.9±16.1	2.2±15.6
LS mean difference (95% CI)	1.49 (-0.54, 3.52); *P* = 0.150	

*TRIM-Diabetes total and domain scores range from 0 to 100 with higher scores indicative of better experienced health state (less negative impact).

Supplementary Table 5. Overview of Adverse Events of Special Interest (Safety Population).

	Albiglutide + Glargine (n=400)	Lispro + Glargine (n=413)
	n (%)	n (%)
Cardiovascular events	7 (1.8)	9 (2.2)
Pancreatitis*	1 (0.3)	0
Thyroid adverse events	1 (0.3)	0
Any gastrointestinal events	102 (25.5)	53 (12.8)
Diarrhea	31 (7.8)	18 (4.4)
Nausea	37 (9.3)	7 (1.7)
Vomiting	19 (4.8)	4 (1.0)
Systemic allergic reactions – by CMQ	27 (6.8)	36 (8.7)
Injection-site reactions	8 (2.0)	1 (0.2)
Malignant neoplasm – by CMQ	2 (0.5)	2 (0.5)
Renal events	1 (0.3)	1 (0.2)

For each level of summarization, a participant is counted once if the participant reported one or more events. Percentages are based on the number of participants in each treatment group.
CMQ, Customized MedDRA Query.
*Confirmed acute pancreatitis by independent pancreatitis adjudication committee.
†"Thyroid AE" was a single report of goiter.

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