SUPPLEMENTARY DATA

Harmony 6 Study Investigators

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SUPPLEMENTAL METHODS

Full Inclusion/exclusion criteria (key inclusion criteria appear in the full manuscript)

Patients eligible for enrolment in the study must have met all of the following criteria.

1. Male or female, aged 18–75 years, inclusive, with a historical diagnosis of type 2 diabetes mellitus who is currently treated with insulin glargine or other intermediate- or long-acting insulin, with or without oral antidiabetic medications but who is experiencing inadequate glycaemic control and who is willing and capable of participating in a regimen of intensive insulin administration. A patient who has been on an intermediate- or long-acting insulin for ≥6 months but <5 years, and in spite of dosage adjustments based on home blood glucose monitoring, is unable to achieve a glycated haemoglobin A_{1c} (HbA_{1c}) of <7%. These patients must be capable and willing to transition from a simple basal insulin regimen to an intensified regimen
2. Body mass index ≥20 kg/m^2 and ≤45 kg/m^2
3. Fasting C-peptide ≥0.8 ng/mL (≥0.26 nmol/L)
4. HbA_{1c} between 7.0% and 10.5%, inclusive, at visit 5 (week −1). The HbA_{1c} value may be checked up to 4 times, and if the average of these determinations meets the criterion, the patient may be randomly assigned to treatment
5. For the regular use of other medications, it is preferred that the patients are receiving a stable dose for at least 4 weeks before screening; however, as necessary during the run-in period and the treatment period, prescription or over-the-counter medications are allowed and may be adjusted by the investigator to optimise treatment (eg, increase or decrease of medication to treat blood pressure or hyperlipidemia in accordance with accepted local medical practice and relevant guidance documents)
6. Use of oral or systemically injected glucocorticoids is generally not allowed within 3 months before randomisation; however, short courses of oral steroids (single dose or multiple doses for up to 2 days) may be permitted provided these cases are discussed with the medical monitor. Inhaled, intra-articular, and topical corticosteroids are allowed
7. Hemoglobin ≥11 g/dL (≥110 g/L) for male patients and ≥10 g/dL (≥100 g/L) for female patients
8. Creatinine clearance >60 mL/min (calculated using the Cockcroft-Gault formula)
9. Thyroid-stimulating hormone level is normal or clinically euthyroid as demonstrated by further thyroid tests (eg, T_4, T_3, thyroid-binding globulin)
10. Female patients of childbearing potential (ie, not surgically sterile and/or not postmenopausal) must be practicing adequate contraception. Methods of adequate contraception include the following: abstinence, injectable progestogen, implants of levonorgestrel, estrogenic vaginal ring, percutaneous contraceptive patches, intrauterine device or intrauterine system, male partner sterilisation (vasectomy with documentation of azoospermia) before the female patient's entry into the study and this male partner is the sole partner for that patient, double-barrier method (condom and occlusive cap plus nonoxynol-9), or oral contraceptives in combination with a second method of contraception (eg, condom and occlusive cap). Adequate contraception must be practiced for the duration of participation in the study including the 8-week posttreatment follow-up period
11. Able and willing to monitor his or her own blood glucose concentrations with a home glucose monitor as per the protocol recommendations of self-administration

12. No major illness or debility that in the investigator's opinion prohibits the patient from actively participating in their diabetes management and completing the study
13. Able and willing to provide written informed consent

Patients meeting any of the following criteria must not be enrolled in the study.

1. History of cancer, other than squamous cell or basal cell carcinoma of the skin, that has not been in full remission for at least 3 years before screening. (A history of treated cervical intraepithelial neoplasia I or cervical intraepithelial neoplasia II is allowed)
2. History of treated diabetic gastroparesis
3. Current ongoing symptomatic biliary disease or history of pancreatitis
4. History of significant gastrointestinal surgery, including gastric bypass and banding, antrectomy, Roux-en-Y bypass, gastric vagotomy, small-bowel resection, or surgeries thought to significantly affect upper gastrointestinal function
5. Recent (as defined below) clinically significant cardiovascular and/or cerebrovascular disease, including but not limited to the following.
    - Previous history of stroke or transient ischemic attack within 1 month before screening. However, patients who are deemed clinically stable by the investigator may be enrolled 1 month after the cerebrovascular event
    - Acute coronary syndrome, which includes the following
        - Documented myocardial infarction within the 2 months before screening and during the period up until receiving the first dose of study medication
        - Any cardiac surgery including percutaneous transluminal coronary angioplasty, coronary stent placement, or coronary artery bypass graft surgery within the 2 months before screening and during the period up until receiving the first dose of study medication
        - Unstable angina not responsive to nitroglycerine within the 2 months before screening and during the period up until receiving the first dose of study medication
    - Unstable cardiac rhythm; however, as an example, controlled atrial fibrillation is allowed
    - Current or history of heart failure (New York Heart Association class I–IV). Note: investigators must consult the approved product labelling for thiazolidinedione (TZD) in their country to determine a patients' eligibility to participate in this study if they are currently taking a TZD
    - Resting systolic pressure is >160 mm Hg and/or diastolic pressure >100 mm Hg. If the patient's systolic blood pressure is >160 mm Hg or the patient's diastolic blood pressure is >100 mm Hg at screening, the blood pressure readings may be repeated at 5-minute intervals for a total of three determinations. If the averages of the systolic or diastolic pressure readings still do not meet the criteria, the patient can be treated and rescreened. It is preferred that patients be on a stable dose of medication for at least 4 weeks before being rescreened; however, when stable, they may be rescreened at the discretion of the investigator. Should a patient not meet this criterion on visit 6 (first dose of study medication following the randomisation visit), the patient may continue in the study at the discretion of the investigator with the understanding that the patient's hypertension will be monitored and treated in accordance with accepted local medical practice and relevant guidance documents
    - QTc interval (Fridericia) >470 ms confirmed by a central reader at screening
6. History of stroke or other central nervous system disorder that would negatively impact the patient's ability to participate in a program of intensive insulin management (eg, physically or mentally incapable of performing home blood glucose monitoring or administering and/or adjusting insulin dosage)
7. Haemoglobinopathy that may affect determination of HbA_{1c}
8. History of HIV infection
9. History of total bilirubin >1.5 × upper limit of normal (ULN) unless the patient has a previously known history of Gilbert syndrome and a fractionated bilirubin that shows conjugated bilirubin <35% of total bilirubin
10. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 × ULN
11. Fasting triglyceride level >850 mg/dL at screening or week −1 (visit 5). If the patient's triglyceride level is >500 mg/dL at screening and week −1, the patient is excluded. If the patient meets the aforementioned exclusion criteria for triglycerides, the patient can be treated and rescreened. Treated patients must be on a stable dose of medication for at least 4 weeks before being rescreened
12. Acute symptomatic (within 3 months before screening) infection with hepatitis B or hepatitis C; however, patients with past or chronic hepatitis B or hepatitis C are allowed provided the requirements for ALT, AST, and total bilirubin are met
13. History of a psychiatric disorder that will affect the patient's ability to participate in the study

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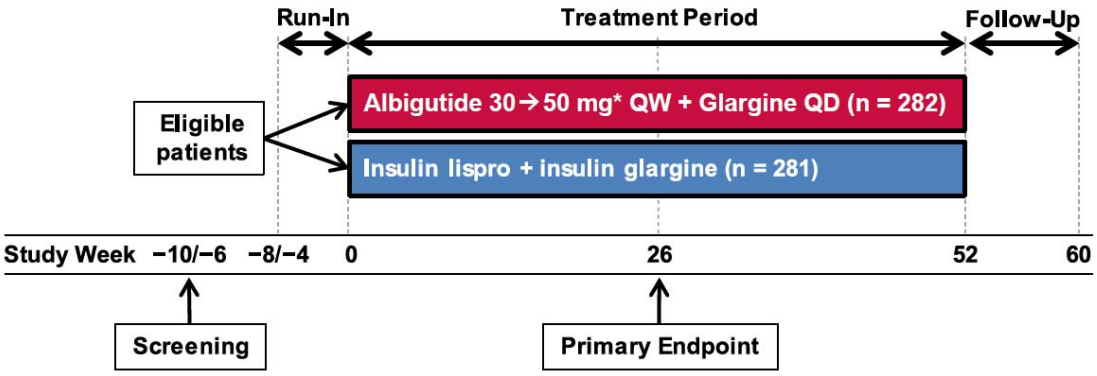
14. History of alcohol or substance abuse within 1 year before screening
15. Positive urine drug screen at screening, unless the patient is taking a medically approved medication for which a positive drug screen simply verifies the use of this medication
16. Hypoglycaemia unawareness that has impaired cognitive function and required outside assistance
17. Female patient is pregnant (confirmed by laboratory testing), lactating, or <6 weeks postpartum
18. Known allergy to any GLP-1 analogue, insulin, other study medication excipients, excipients of albiglutide, or Baker's yeast
19. Receipt of any investigational drug within the 30 days, or 5 half-lives whichever is longer, before screening or a history of receipt of an investigational antidiabetic drug within the 3 months before randomisation or receipt of albiglutide in previous studies
20. Current use of any GLP-1 analogue
21. History of type 1 diabetes mellitus, diabetic complications (eg, active proliferative retinopathy or severe diabetic neuropathy) that in the opinion of the investigator would preclude effective participation in the study, or a history of ketoacidosis or hyperosmolar coma
22. Contraindications (as per the prescribing information) for the use of either background or potential randomised study medications (eg, insulin glargine or lispro)
23. History or family history of medullary carcinoma
24. History or family history of multiple endocrine neoplasia type 2

Supplementary Figure 1. Study Design.



*Albiglutide could be uptitrated from 30 mg to 50 mg if prespecified glycemic targets were not met.

Directions on insulin lispro titration

- A preprandial lispro insulin dose adjustment will be made based on the average of the 2 previous day's home blood glucose monitoring results, checking before and 2 hours after breakfast, lunch, dinner, and bedtime such that there are 4 to 7 values per day for at least the 2 days before a visit to the study center. Specifically:
- Adjustment for breakfast preprandial lispro insulin is based on prelunch home blood glucose monitor readings
- Adjustment for lunch preprandial lispro insulin is based on predinner home blood glucose monitor readings
- Adjustment for dinner preprandial lispro insulin is based on bedtime home blood glucose monitor readings

The intent of the American Diabetes Association and the European Association for the Study of Diabetes consensus statement for the treatment of type 2 diabetes mellitus is to maintain fasting and preprandial glucose values in as close to a normal range as possible without untoward hypoglycemia [Nathan, 2008]. Given the potential for the adverse effects of hypoglycemia, it is recommended that:

- Preprandial capillary plasma glucose level be 80 to 130 mg/dL
- Peak (approximately 1 to 2 hours) postprandial capillary plasma glucose level be <180 mg/dL

It is anticipated that the subject will settle into a regimen of preprandial insulin before each meal with the dose contingent upon the planned carbohydrate caloric consumption, activity level, and the results of home blood glucose monitoring.

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Supplementary Table 1. Dose titration guidance for insulin glargine treatment

Mean of self-monitored FPG values from preceding 2 days, mmol/L	**Increase in insulin dose, IU/d**
≥10	8
7·7–9·9	6
6·7–7·6	4
5·6–6·6	2
FPG	Decrease in insulin dose at the investigator's discretion
FPG <3·3 mmol/L ± symptoms documented at any time during the preceding week	2–4
FPG <4·4 mmol/L average over preceding week	2–4
Severe hypoglycemia (requiring assistance) documented during preceding week	10%–15%

FPG = fasting plasma glucose.

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Pancreatitis adjudication committee process

An independent, blinded pancreatitis adjudication committee (PAC) was established for the review and prospective adjudication of suspected cases of pancreatitis reported during the phase 3 development program. The remit of the PAC included review of all reported adverse events (AEs) of pancreatitis, review of serious AEs to determine if adjudication for pancreatitis was warranted, and review of amylase and/or lipase measurements (≥3 × ULN), whether or not patients had signs or symptoms suspicious for pancreatitis. The criteria for assessing the probability of pancreatitis events suspicious for pancreatitis or as an abnormal amylase and/or lipase measurement (≥3 × ULN) are presented in Supplemental Table 2. In addition, the PAC identified that the most likely aetiology and contributing factors in the development of pancreatitis were based on careful consideration of all relevant data. Finally, the PAC made an assessment of relationship to study drug for cases that were considered definite, probable, or possible. This assessment could be definite, probable, possible, or unlikely alternative aetiology. Definite attribution to study drug was made in the case of positive challenge/rechallenge to study drug.

Supplementary Table 2. Criteria for assessing the probability of pancreatitis

Probability of pancreatitis	**Abdominal pain**	**Lipase >3 × ULN (or 300), and/or amylase >5 × ULN (or 1000)**	**Imaging: positive CT, MRI, or ultrasound (peripancreatic fluid/ pseudocyst/ necrosis)**
Definite	Positive	Positive	Positive
Probable	Positive	Negative	Positive
	Positive	Positive	Negative
	Negative	Positive	Positive
Possible (must meet laboratory or imaging criteria)	Negative	Positive	Negative
	Negative	Negative	Positive
Not diagnostic	Not specific	No laboratory data or data do not satisfy criteria	No laboratory data or data do not satisfy criteria
Not likely	Positive/negative	Negative	Negative

CT = computed tomography; MRI = magnetic resonance imaging; ULN = upper limit of normal.

Supplementary Table 3. Descriptive statistics for populations excluding patients who continued a sulfonylurea: Focus on efficacy

	Albiglutide	Lispro
HbA_{1c}		
N	265[2]	264[2]
Baseline, %	8.48	8.43
Change from baseline[1], %	-0.84	-0.70
Weight		
N	268[3]	265[3]
Baseline, kg	91.7	91.4
Change from baseline[1], kg	-0.6	0.9

[1] Descriptive summary

[2] Includes the ITT population for HbA_{1c} excluding 14 patients in each arm who continued SU use

[3] Includes the ITT population for weight excluding 14 patients in the albiglutide arm and 15 subjects in the lispro arm who continued SU use

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Supplementary Table 4. Hypoglycemia as a function of SU use

	Patients who discontinued SU use		Patients who continued SU use	
	Albiglutide	Lispro	Albiglutide	Lispro
	n (%) # of Events/Rate[1]		n (%) # of Events/Rate[1]	
n	270[2]	266[2]	15[3]	15[3]
Any hypoglycemic event[4]	71 (26.3) 221/ 0.3	111(41.7) 554/ 0.5	4 (26.7) 27/0.4	5 (33.3) 10/0.5
Severe	0 0	3 (1.1) 3/ 0.01	0 0	0 0
Documented symptomatic	48 (17.8) 161/ 0.2	90 (33.8) 427/ 0.4	2 (13.3) 19/0.2	2 (13.3) 4/0.2
Asymptomatic	21 (7.8) 32/ 0.1	25 (9.4%) 47/ 0.1	3 (20) 8/0.3	2 (13.3) 4/0.2
Probable symptomatic	7 (2.6) 8/ 0.03	7 (2.6) 18/ 0.03	0 0	1 (6.7) 1 /0.1
Relative	12 (4.4) 20/ 0.06	15 (5.6) 40/ 0.07	0 0	1 (6.7) 1 /0.1

[1] Event rate per patient-year.
[2] Includes the safety population excluding 15 patients in each arm who continued SU use
[3] Includes the 15 patients who continued on SU in the safety arm
[4] Patients with more than one hypoglycemic event were counted in all severity categories reported

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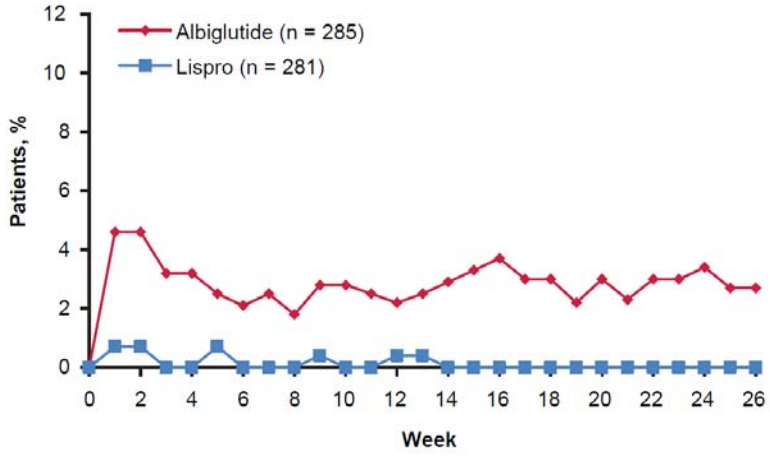
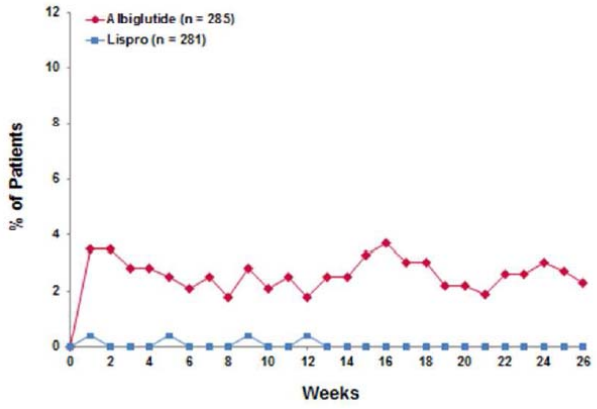
Supplementary Figure 2. On-therapy events over time*: (A) nausea or vomiting, (B) nausea, and (C) vomiting

(A)



(B)



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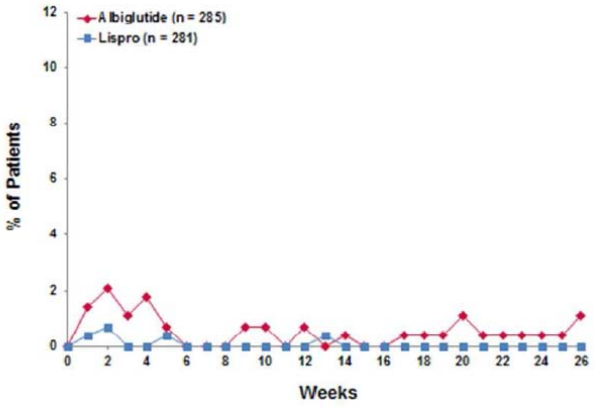

*The denominator used for percentages was the number of subjects considered on therapy for that particular time point. An event may have been counted in multiple weeks depending on its duration. If a subject experienced more than 1 GI AE within a week, the subject was counted only once.