2 SYNOPSIS

Name of Sponsor/Company: Akros Pharma Inc.	**Individual Study Table Referring to Part of the Dossier:**	***(For National Authority Use Only)***
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Title of Study: A **P**hase II, **R**andomized, D**O**uble-Blind, Placebo-Controlled, Multi-Center, Parallel Group Study Evaluating the Efficacy, Safety, and Tolerability of JTT-130 Administered Twice Daily for 24 Weeks in Treatment-Naïve, **M**etformin Only, or Metformin Plus Sulfonylurea-Treated **O**bese **T**ype 2 Diab**E**tic Patients (PROMOTE)

Investigators: See Appendix 16.1.4 for a complete list of Investigators.

Study Centers: 73 study centers (58 study centers in the US and 15 study centers in the rest of world [ROW])

Publication (reference): none

Study Period: 08 June 2009 through 07 May 2010 **Phase of Development:** 2

Objectives:

Primary:

The primary objective of this study was to investigate the change in glycosylated hemoglobin (HbA1c) levels in obese patients with type 2 diabetes with JTT-130 twice daily (BID) compared to placebo after 24 weeks of treatment.

Secondary:

Secondary objectives of this study included the following:

- To investigate the weight loss effect of JTT-130 BID compared to placebo in obese patients with type 2 diabetes after 24 weeks of treatment;
- To investigate the effect of JTT-130 BID compared to placebo on ancillary efficacy measures (e.g., fasting plasma glucose [FPG], plasma insulin, serum lipid parameters, and waist circumference) in obese patients with type 2 diabetes; and
- To determine the safety and tolerability of JTT-130 BID in obese patients with type 2 diabetes throughout 24 weeks of treatment.

Methodology:

This randomized, double-blind, placebo-controlled, multi-center, parallel group study consisted of up to a 2-week Screening Period, a 2-week single-blind Placebo Run-in Period, a 24-week double-blind Treatment Period, and a 2-week Follow-up Period.

After signing informed consent, patients entered the Screening Period. In order to be eligible for the study, patients had to have a body mass index (BMI) ≥27 kg/m^2 and ≤45 kg/m^2, an HbA1c ≥7.0 % and ≤10.0%, and an FPG ≤280 mg/dL (15.5 mmol/L). Patients who did not have an FPG ≤280 mg/dL at the Screening Visit could return to the site on a subsequent day for one repeat measurement.

Upon completion of the Screening Period, patients entered the Placebo Run-in Period and were advised to follow a locally-accepted diet and exercise program for patients with type 2 diabetes. Patients received placebo BID for 2 weeks in a single-blind manner. In order to qualify for randomization to active treatment, a patient must have had a treatment compliance ratio of 80% to 120% during this period. Patients who had a weight gain >2% of their body weight during the Placebo Run-in Period were not eligible for randomization to active treatment.

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At the end of the Placebo Run-in Period, eligible patients were assigned randomly in a 1:1:1:1 ratio to receive 24 weeks of double-blind treatment with one of the following regimens: JTT-130 1 mg BID, JTT-130 3.5 mg BID, JTT-130 5 mg BID, or placebo BID. Randomization was stratified by region (US or ROW), baseline antidiabetic therapy (treatment naïve, metformin only, or metformin plus sulfonylurea), and HbA1c level at Visit 1 (HbA1c <8.5% or HbA1c ≥8.5%). Patients received the same treatment from randomization to the end of treatment (EOT). However, patients randomized to JTT-130 5 mg BID received JTT-130 2.5 mg BID for the first 2 weeks of the double-blind Treatment Period followed by up-titration to JTT-130 5 mg BID at Week 3.

The Follow-up Period of the study consisted of a Follow-up Visit approximately 2 weeks after the last dose of study medication.

Patients with persistent hyperglycemia or hypoglycemia may have been eligible for rescue therapy. Patients completed all EOT study assessments prior to the initiation of rescue therapy, but still continued in the study (i.e., continued to receive study medication and completed study visits and procedures according to the protocol).

Number of Patients:

Planned: 460 patients

Entered Placebo Run-in Period: 539 patients

Randomized: 496 patients

Completed Treatment: 377 patients

Discontinued: 119 patients

Diagnosis and Main Criteria for Inclusion: The study population consisted of male and female patients, 18 to 70 years of age, inclusive, with a stable body weight and BMI ≥27.0 kg/m^2 and ≤45.0 kg/m^2, who had type 2 diabetes (HbA1c ≥7.0% and ≤10.0%), and an FPG ≤280 mg/dL at Visit 1. Patients were either naïve with respect to hypoglycemic treatment or were receiving metformin alone (at least 1500 mg/day) or in combination with a sulfonylurea (at least half the maximum labeled daily dose or at the maximum tolerated dose).

Patients with triglycerides (TG) >500 mg/dL at Visit 1 or weight gain >2.0% between Visit 2 and Visit 3 were excluded from the study population.

Test Product, Dose, Mode of Administration, and Lot Number:

Test product: JTT-130
Dose: 1 mg (administered in the JTT-130 1 mg and 3.5 mg treatment groups)
Mode of administration: oral (tablet), BID, 30 minutes after the start of breakfast and dinner
Lot #: 622-1A

Test product: JTT-130
Dose: 2.5 mg (administered in the JTT-130 3.5 mg and 5 mg treatment group)
Mode of administration: oral (tablet), BID, 30 minutes after the start of breakfast and dinner
Lot #: 623-1A

Duration of Treatment: 24 weeks

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Reference Product, Dose, Mode of Administration, and Lot Number:

Reference product: Placebo
Dose: N/A (administered to all patients during the Placebo Run-in Period; during the double-blind Treatment Period, administered to the placebo and JTT-130 1 mg treatment groups for 24 weeks; and to the JTT-130 5 mg treatment group for 2 weeks)
Mode of administration: oral (tablet), BID, 30 minutes after the start of breakfast and dinner
Lot #: 621-1A

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint was change in HbA1c from baseline to EOT.

Secondary efficacy endpoints included the following:

- Percentage of patients achieving HbA1c <7.0% at EOT;
- Change in HbA1c from baseline to Weeks 4, 8, 12, 16, 20, and 24;
- Change and percent change in FPG and plasma insulin from baseline to Weeks 2, 4, 8, 12, 16, 20, 24, and EOT;
- Change and percent change in body weight from baseline to Weeks 2, 4, 8, 12, 16, 20, 24, and EOT;
- Percentage of patients achieving ≥5% body weight reduction from baseline to EOT;
- Change in BMI from baseline to Weeks 2, 4, 8, 12, 16, 20, 24, and EOT;
- Change and percent change in waist circumference from baseline to Weeks 12, 24, and EOT; and
- Change and percent change in serum lipid parameters (total cholesterol [TC], TG, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], very low-density lipoprotein cholesterol [VLDL-C], apolipoprotein B [ApoB], and apolipoprotein A1 [ApoA1]) from baseline to Weeks 12, 24, and EOT.

Exploratory efficacy endpoints included the following:

- Change and percent change in homeostasis model assessment of pancreatic β-cell function (HOMA-β) and homeostasis model assessment of insulin resistance (HOMA-IR) from baseline to Weeks 2, 4, 8, 12, 16, 20, 24, and EOT;
- Change and percent change in high-sensitivity C-reactive protein (hsCRP) from baseline to Weeks 12, 24, and EOT;
- Change and percent change in plasma glucagon from baseline to Weeks 12, 24, and EOT;
- Change and percent change in leptin from baseline to Weeks 12, 24, and EOT;
- Change and percent change in waist-hip ratio from baseline to Weeks 12, 24, and EOT; and
- Change and percent change in lipoprotein particles from baseline to Weeks 12, 24, and EOT.

Safety:

Safety assessments included adverse events, clinical laboratory evaluations (biochemistry, hematology, and urinalysis), fat-soluble vitamins (vitamins A, D, E, and K), coagulation (prothrombin time [PT], activated partial thromboplastin time [aPTT], and international normalized ratio [INR]), physical examinations, vital signs, and electrocardiograms (ECGs).

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Statistical Methods:

Efficacy:

Descriptive statistics (n, mean, standard deviation, minimum, maximum, and median) for all primary, secondary, and exploratory efficacy parameters for the Intent-to-Treat (ITT) Population were tabulated for the observed value at Screening, during the Placebo Run-in Period, at the visits during the double-blind Treatment Period, and at EOT. Descriptive statistics for the primary and key secondary and exploratory efficacy parameters for the Per-Protocol Population were also tabulated for the observed value at Screening, during the Placebo Run-in Period, at the visits during the double-blind Treatment Period, and at EOT. A summary of the changes from baseline in all efficacy parameters are presented at each visit during the double-blind Treatment Period and at EOT. A summary of the percent changes from baseline in all efficacy parameters except HbA1c and BMI are presented at each visit during the double-blind Treatment Period and at EOT.

The comparisons of JTT-130 5 mg BID, JTT-130 3.5 mg BID, and JTT-130 1 mg BID with placebo were to be carried out on a 2.5% level of significance (one-sided) using a step-down procedure.

The primary efficacy analysis of change in HbA1c from baseline to EOT was performed using the ITT Population. An analysis of covariance (ANCOVA) model was applied to the change in HbA1c from baseline to EOT. The ANCOVA model used treatment, region, baseline antidiabetic medications, and HbA1c strata at Screening (Visit 1) as factors and HbA1c at baseline (Visit 3) as the covariate. The least-squares (LS) mean estimates from the model along with a two-sided 95% confidence interval were tabulated for placebo and all JTT-130 doses. The differences between the LS mean estimates of each JTT-130 active dose and placebo, the p-values from the pairwise t-tests in the model, and a two-sided 95% confidence interval were tabulated. A similar analysis of change in HbA1c from baseline to EOT was conducted for the Per-Protocol Population.

Analysis of the responder rate of patients with HbA1c levels <7.0% at EOT was conducted for the ITT Population and the Per-Protocol Population. A logistic regression model with treatment, region, baseline antidiabetic medications, strata of HbA1c at Screening (Visit 1), and baseline HbA1c as factors was applied to compare the responder rates of JTT-130 active doses to placebo.

Analysis of the responder rate of patients with body weight reduction ≥5% at EOT was conducted for the ITT Population and the Per-Protocol Population. A logistic regression model with treatment, region, baseline antidiabetic medications, strata of HbA1c at Screening (Visit 1), and baseline HbA1c as factors and baseline body weight as the covariate was applied to compare the responder rates of JTT-130 active doses to placebo.

The ANCOVA model for the primary efficacy analysis was applied to all other secondary efficacy parameters as well as all exploratory efficacy parameters for the ITT Population and the Per-Protocol Population.

Safety:

Adverse events were summarized separately for pre-treatment adverse events and for treatment-emergent adverse events (TEAEs). Pre-treatment adverse events were defined as adverse events with an onset date prior to the first dose date of double-blind study medication. Treatment-emergent adverse events were defined as adverse events with an onset date on or after the date of the first dose of double-blind study medication (or adverse events that started prior to the initiation of study medication but worsened with double-blind treatment) up to and including 7 days after the date of the last dose of double-blind treatment.

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Pre-treatment adverse events are summarized by system organ class and preferred term for each treatment group. An overall summary is provided for TEAEs. Summaries of TEAEs by system organ class, preferred term, severity, and causality of TEAE percentage are provided by treatment group. Drug-related TEAEs are summarized by system organ class and preferred term for each treatment group.

Observed results and change from baseline results for hematology, serum biochemistry, continuous urinalysis tests, vital signs, and ECG parameters are summarized by visit and treatment group. Frequency and percentage of discrete urinalysis tests are also presented by visit and treatment group.

The number and percentage of patients with treatment-emergent potentially clinically significant abnormal laboratory values, vital sign measurements, and ECG results at any post-baseline visit are summarized by treatment group. Listings of all treatment-emergent potentially clinically significant abnormal values are provided.

Summary - Results:

Efficacy:

Table S1 presents the results for change in HbA1c from baseline to EOT for the ITT Population. The LS mean change in HbA1c from baseline to EOT was 0.03% for the placebo group, -0.24% for the JTT-130 1 mg BID group, -0.41% for the JTT-130 3.5 mg BID group, and -0.56% for the JTT-130 5 mg BID group. The differences in LS mean change in HbA1c between each JTT-130 treatment and placebo were statistically significant.

Table S1: Change in HbA1c (%) From Baseline to End of Treatment – ITT Population

Parameter Statistics	**Placebo BID (N = 124)**	**JTT-130 1 mg BID (N = 120)**	**JTT-130 3.5 mg BID (N = 122)**	**JTT-130 5 mg BID (N = 122)**
n [1]	118	120	118	120
Baseline				
Mean (SD)	8.04 (0.872)	8.00 (0.929)	8.09 (0.778)	8.04 (0.795)
End of Treatment [2]				
Mean (SD)	8.14 (1.211)	7.83 (1.244)	7.74 (1.068)	7.53 (0.808)
Change from Baseline				
Mean (SD)	0.10 (1.002)	-0.17 (0.878)	-0.36 (0.848)	-0.50 (0.760)
LS Mean (SE) [3]	0.03 (0.095)	-0.24 (0.093)	-0.41 (0.093)	-0.56 (0.092)
95% CI [3]	(-0.15 , 0.22)	(-0.43 , -0.06)	(-0.59 , -0.22)	(-0.74 , -0.38)
		Difference in Change from Baseline [3]		
Treatment Comparison		**LS Mean**	**95% CI**	**p-value**
JTT-130 5 mg BID vs. Placebo BID		-0.60	(-0.82 , -0.38)	<0.0001
JTT-130 3.5 mg BID vs. Placebo BID		-0.44	(-0.66 , -0.22)	<0.0001
JTT-130 1 mg BID vs. Placebo BID		-0.28	(-0.50 , -0.06)	0.0131

1. n is the number of patients with values at both baseline and end of treatment.
2. End of treatment is the last visit before study completion, discontinuation from double-blind treatment period, or prior to rescue medication and no more than 14 days after the last dose of study medication.
3. LS mean, SE, 95% CI, and p-value are from an ANCOVA model with treatment, region, baseline antidiabetic medications, and HbA1c strata at Screening as factors and baseline HbA1c value as the covariate.

ANCOVA = analysis of covariance; BID = twice daily; CI = confidence interval; HbA1c = glycosylated hemoglobin; LS = least squares; SD = standard deviation; SE = standard error.

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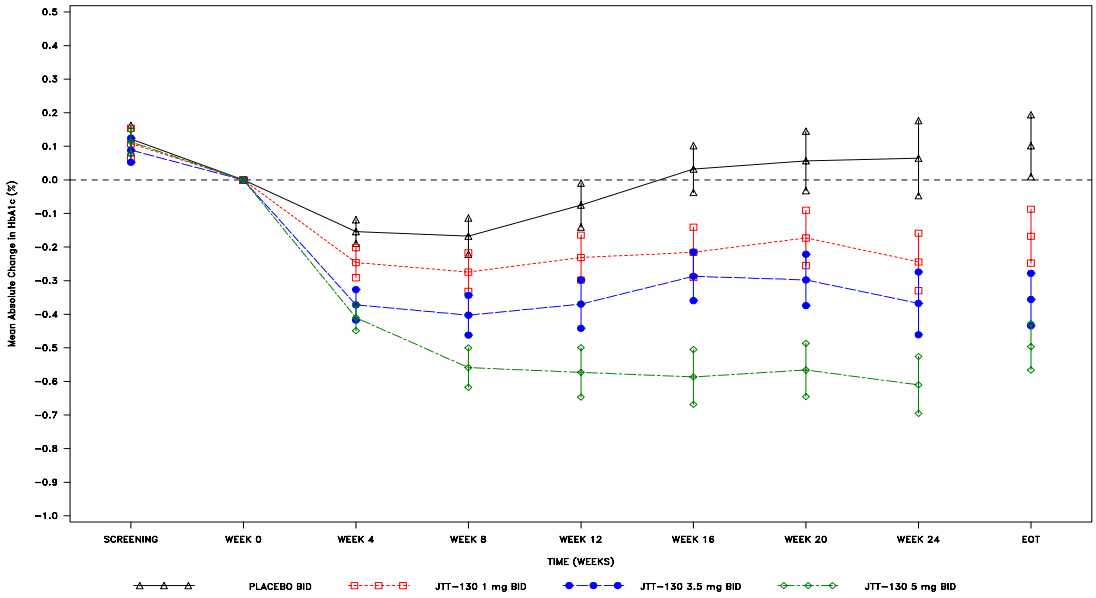
Figure S1 shows the mean change in HbA1c from baseline to each study visit along with standard error for the ITT Population. Dose-related treatment effects on HbA1c were observed at all time points after baseline. The treatment comparisons of JTT-130 5 mg BID and JTT-130 3.5 mg BID with placebo for mean change in HbA1c were statistically significant at all time points. The difference in LS mean change in HbA1c between JTT-130 1 mg BID and placebo was statistically significant at Week 16, Week 20, and Week 24.

Figure S1: Mean Change in HbA1c (%) From Baseline to Each Visit – ITT Population



BID = twice daily; EOT = end of treatment; HbA1c = glycosylated hemoglobin.

The percentage of patients with HbA1c <7.0% at EOT was 15.3% with placebo treatment, 25.0% with JTT-130 1 mg BID treatment, 27.1% with JTT-130 3.5 mg BID treatment, and 28.3% with JTT-130 5 mg BID treatment. Treatment with JTT-130 5 mg BID and JTT-130 3.5 mg BID resulted in a significantly higher proportion of patients with HbA1c <7.0% than placebo.

Dose-related treatment effects on FPG were observed at all time points. The LS mean change in FPG from baseline to EOT was 11.5 mg/dL for the placebo group, 5.1 mg/dL for the JTT-130 1 mg BID group, 2.3 mg/dL for the JTT-130 3.5 mg BID group, and -7.3 mg/dL for the JTT-130 5 mg BID group. The difference in LS mean change in FPG between JTT-130 5 mg BID and placebo was statistically significant at all time points.

The LS mean change in plasma insulin from baseline to EOT was 0.8 µIU/mL for the placebo group, 2.0 µIU/mL for the JTT-130 1 mg BID group, 0.6 µIU/mL for the JTT-130 3.5 mg BID group, and -0.7 µIU/mL for the JTT-130 5 mg BID group. The difference in LS mean change in plasma insulin between JTT-130 5 mg BID and placebo was not statistically significant.

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For each JTT-130 treatment group, mean body weight progressively decreased from baseline to Week 24. The LS mean change in body weight from baseline to EOT was -0.3 kg for the placebo group, -1.9 kg for the JTT-130 1 mg BID group, -2.5 kg for the JTT-130 3.5 mg BID group, and -2.7 kg for the JTT-130 5 mg BID group. The LS mean percent change in body weight from baseline to EOT was -0.3% for the placebo group, -1.9% for the JTT-130 1 mg BID group, -2.6% for the JTT-130 3.5 mg BID group, and -2.7% for the JTT-130 5 mg BID group (i.e., same effect on body weight with JTT-130 3.5 mg BID and JTT-130 5 mg BID). The differences in LS mean change and LS mean percent change in body weight between each JTT-130 treatment and placebo were statistically significant at all time points.

The percentage of patients with ≥5% body weight reduction from baseline to EOT was 5.6% with placebo treatment, 12.5% with JTT-130 1 mg BID treatment, 20.5% with JTT-130 3.5 mg BID treatment, and 21.5% with JTT-130 5 mg BID treatment. Treatment with JTT-130 5 mg BID and JTT-130 3.5 mg BID resulted in a significantly higher proportion of patients with ≥5% body weight reduction than placebo.

For each JTT-130 treatment group, mean change in BMI progressively decreased from baseline to Week 24. The LS mean change in BMI from baseline to EOT was -0.1 kg/m^2 for the placebo group, -0.7 kg/m^2 for the JTT-130 1 mg BID group, -0.9 kg/m^2 for the JTT-130 3.5 mg BID group, and -1.0 kg/m^2 for the JTT-130 5 mg BID group. The differences in LS mean change in BMI between each JTT-130 treatment and placebo were statistically significant at all time points.

The LS mean change in waist circumference from baseline to EOT was -1.0 cm for the placebo group, -1.8 cm for the JTT-130 1 mg BID group, -2.5 cm for the JTT-130 3.5 mg BID group, and -2.4 cm for the JTT-130 5 mg BID group. The treatment comparisons of JTT-130 5 mg BID and JTT-130 3.5 mg BID with placebo for mean change in waist circumference were statistically significant at EOT.

The LS mean percent change in LDL-C from baseline to EOT was 8.7% for the placebo group, 1.8% for the JTT-130 1 mg BID group, -2.7% for the JTT-130 3.5 mg BID group, and -9.5% for the JTT-130 5 mg BID group. The difference in LS mean percent change in LDL-C between JTT-130 5 mg BID and placebo was statistically significant at EOT (-18.2%; $p<0.0001$).

An LS mean percent decrease in TC was also observed with JTT-130 5 mg BID and only a slight LS mean percent increase was observed with JTT-130 3.5 mg BID; LS mean percent increase in TC was observed with JTT-130 1 mg BID and placebo. Mean percent increases in TG, HDL-C, VLDL-C, and ApoA1 were observed with all treatments. Dose-related changes in ApoB were observed with JTT-130 treatment relative to placebo. The treatment comparisons of JTT-130 5 mg BID and placebo for percent changes in TC, LDL-C, ApoB, and ApoA1 were statistically significant at EOT. The treatment comparisons of JTT-130 3.5 mg with placebo for percent changes in TC, LDL-C, and ApoA1 were statistically significant at EOT.

Least-squares mean percent decreases in total low-density lipoprotein particle (LDL-P) concentration were observed with each JTT-130 treatment while a mean percent increase was observed with placebo. A mean percent decrease in small LDL-P concentration was observed with JTT-130 5 mg BID while mean percent increases were observed with the other treatments. The treatment comparisons of JTT-130 5 mg BID with placebo for percent changes in total LDL-P concentration and small LDL-P concentration were statistically significant.

The LS mean changes in the exploratory efficacy variables of HOMA-β, HOMA-IR, plasma glucagon, and waist-hip ratio, and the LS mean percent changes in leptin and hsCRP with JTT-130 were not statistically different from placebo.

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For each JTT-130 treatment group, the mean trough plasma concentration of metabolite M1 at Week 12 was similar to the concentration at Week 24. For the subset of patients who provided pharmacokinetic blood samples, the mean trough plasma metabolite M1 concentrations at both time points were approximately five-fold higher with JTT-130 5 mg BID treatment (29.96 nmol/L and 22.28 nmol/L) and JTT-130 3.5 mg BID treatment (26.44 nmol/L and 25.86 nmol/L) than with JTT-130 1 mg BID treatment (5.84 nmol/L and 6.04 nmol/L). In all three dose groups, the variability in trough plasma metabolite M1 concentrations was large.

Safety:

In total, 357 patients had a TEAE. The overall incidence of TEAEs was similar across the JTT-130 groups: 64.0% in the placebo group, 73.2% in the JTT-130 1 mg BID group, 78.9% in the JTT-130 3.5 mg BID group, and 73.2% in the JTT-130 5 mg BID group (i.e., the rates were comparable across the JTT-130 treatment groups). The incidence of drug-related TEAEs was 18.4% in the placebo group, 25.2% in the JTT-130 1 mg BID group, 43.1% in the JTT-130 3.5 mg BID group, and 42.3% in the JTT-130 5 mg BID group (i.e., similar in the JTT-130 3.5 mg BID group and JTT-130 5 mg BID group).

No patients died during the study. In total, 15 patients in the Safety Population had a treatment-emergent serious adverse event (SAE). The incidence of treatment-emergent SAEs was 2.4% in the placebo group, 4.1% in the JTT-130 1 mg BID group, 2.4% in the JTT-130 3.5 mg BID group, and 3.3% in the JTT-130 5 mg BID group. One patient in the Safety Population (in the placebo group) had an SAE prior to the first dose of study medication. In addition, 3 patients had an SAE during the Placebo Run-in Period and were not randomized to treatment. One patient (in the placebo group) had 3 drug-related SAEs. No dose-related trends in the incidence or severity of treatment-related SAEs were observed.

The percentages of patients who discontinued study medication due to a TEAE in the JTT-130 3.5 mg BID group (11.4%) and JTT-130 5 mg BID group (12.2%) were similar and higher than the percentages of patients who discontinued study medication due to a TEAE in the JTT-130 1 mg BID group (3.3%) and placebo group (5.6%). In total, 30 patients discontinued study medication due to a drug-related TEAE: 3 (2.4%) patients in the placebo group, 3 (2.4%) patients in the JTT-130 1 mg BID group, 10 (8.1%) patients in the JTT-130 3.5 mg BID group, and 14 (11.4%) patients in the JTT-130 5 mg BID group.

The incidences of gastrointestinal disorders, the most common system organ class of TEAEs, increased in a dose-related manner. Most gastrointestinal disorders were mild or moderate in severity. The incidence of diarrhea was higher in the JTT-130 groups than in the placebo group and increased in a dose-related manner between the JTT-130 1 mg BID group and the 2 higher dose groups. The overall incidence of diarrhea decreased over time. In total, 24 patients discontinued study medication due to an adverse event of diarrhea: 1 patient in the placebo group, 1 patient in the JTT-130 1 mg BID group, 7 patients in the JTT-130 3.5 mg BID group, and 15 patients in the JTT-130 5 mg BID group. For the JTT-130 3.5 mg BID group and JTT-130 5 mg BID group, diarrhea was the most common adverse event leading to discontinuation of study medication. Other common gastrointestinal disorders included nausea (6.4% in the placebo group, 4.9% in the JTT-130 1 mg BID group, 8.9% in the JTT-130 3.5 mg BID group, and 8.1% in the JTT-130 5 mg BID group) and vomiting (1.6% in the placebo group, 4.1% in the JTT-130 1 mg BID group, 5.7% in the JTT-130 3.5 mg BID group, and 5.7% in the JTT-130 5 mg BID group). No patients had a TEAE of fecal incontinence or steatorrhea.

The incidence of hypoglycemia was low and similar for the treatment groups. No trends in the incidence of hypoglycemia were observed. No patients discontinued study medication due to hypoglycemia.

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Mean decreases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) from baseline to EOT were observed for each treatment group; however, the mean ALT and AST values for each group were still within the normal range at EOT. Four patients in the JTT-130 groups had potentially clinically significant increases in ALT, AST, and gamma-glutamyl transferase: 1 patient in the JTT-130 1 mg BID group, 2 patients in the JTT-130 3.5 mg BID group, and 1 patient in the JTT-130 5 mg BID group. None of these patients had potentially clinically significant increases in total bilirubin.

Mean values for coagulation parameters (INR, aPTT, and PT) at EOT were within normal ranges for each treatment group; no clinically significant or time-dependent trends were observed. No clinically significant changes in fat-soluble vitamins from baseline to EOT were observed. With the exception of vitamin D3, mean levels of fat-soluble vitamins were within normal ranges at EOT for each treatment group. For each treatment group, the mean levels of vitamin D3 were below the lower limit of normal at baseline and throughout the study. Mean decreases in vitamins D3 and E and mean increases in vitamin A were observed in each treatment group. Mean increases in vitamin K were observed in the JTT-130 1 mg BID group and JTT-130 3.5 mg BID group, while mean decreases were observed in the JTT-130 5 mg BID group and placebo group.

Overall, no clinically important differences among the treatment groups in mean changes in safety laboratory parameters, hematology parameters, vital signs, or ECG parameters from baseline to EOT were noted.

Conclusions:

On the basis of these results, JTT-130 appears to be safe and efficacious for the treatment of type 2 diabetes mellitus in obese patients.

- Treatment with JTT-130 5 mg BID, 3.5 mg BID, and 1 mg BID was effective in significantly reducing HbA1c, body weight, and LDL-C relative to placebo.
- Relative to placebo, the effect of JTT-130 treatment for up to 24 weeks on HbA1c was comparable in magnitude to that observed with dipeptidyl peptidase-4 (DPP-4) inhibitors and somewhat less than that associated with injectable glucagon-like peptide-1 (GLP-1) analogue therapy.
- The weight loss observed with JTT-130 treatment was comparable to the weight loss associated with GLP-1 agents, but superior to the historical experience with DPP-4 inhibitors, which are, on average, weight neutral.
- Treatment with JTT-130 also resulted in statistically significant and clinically meaningful improvements in FPG, BMI, waist circumference, and lipids.
- A dose-related increase in mean trough plasma concentrations of metabolite M1 was observed between the JTT-130 1 mg BID group and the 2 higher dose groups. For each treatment group, the mean trough plasma concentrations of metabolite M1 were similar at Week 12 and Week 24, indicating that the disposition of metabolite M1, and thus JTT-130, did not change over the 6-month treatment period.
- Dose-related increases in incidences of gastrointestinal disorders, namely diarrhea, were observed. However, the incidence and severity of diarrhea were similar in the JTT-130 3.5 mg BID group and JTT-130 5 mg BID group. Overall, the incidence of diarrhea was shown to decrease over time.
- No clinically meaningful differences in mean changes in safety laboratory parameters, hematology parameters, vital signs, or ECG parameters from baseline to EOT were observed among the treatment groups.
- Overall, JTT-130 demonstrated a favorable benefit/risk profile in obese patients with type 2 diabetes.

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