SYNOPSIS

Name of Sponsor: ActivX Biosciences, Inc. and Kyorin Pharmaceutical Co., Ltd.

Name of Finished Product: KRP-104

Title of Study: A 24-Week, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Once-Daily KRP-104 in Subjects with Type 2 Diabetes with Inadequate Glycemic Control on Metformin Alone

Study Sites: 55 sites in Czech Republic, Guatemala, Poland, Russia, South Africa, and the US

Publication (reference): None

Study Period: 24 weeks

Initiation Date: 19 October 2009

Completion Date: 20 January 2011

Phase of Development: IIb

Study Objectives:

The primary objective of the study was to demonstrate the hemoglobin A_{1c} (HbA_{1c})-lowering effects of KRP-104 in subjects with type 2 diabetes inadequately controlled on metformin alone.

The secondary objectives of the study were the following:

- To assess the safety and tolerability of KRP-104 in subjects with type 2 diabetes inadequately controlled on metformin alone;
- To assess the fasting plasma glucose (FPG)-lowering effects of KRP-104 in subjects with type 2 diabetes inadequately controlled on metformin alone;
- To compare the HbA_{1c}-lowering effects of KRP-104 at 120 mg, 100 mg, 80 mg, 40 mg, and 20 mg once daily (QD);
- To assess the effects of KRP-104 on insulin, other glycemic parameters (homeostasis model of index beta cell function [HOMA-β] and homeostasis model of index of insulin resistance [HOMA-IR]), and body weight in subjects with type 2 diabetes inadequately controlled on metformin alone; and
- To assess the number and percentage of subjects requiring rescue therapy for elevated glucose.

Methodology:

This was an up to 37-week or longer, multi-national, randomized, double-blind, placebo-controlled study consisting of a screening period, an approximately 10-week metformin dose-adjustment/stabilization period (as applicable), a 2-week single-blind placebo run-in period, and a 24-week double-blind treatment period.

Screening Period (Visit 1 [Week -3 or Week -13]):

A screening visit (Visit 1) occurred for all subjects from approximately 3 to 13 weeks prior to randomization. At this visit, informed consent was obtained and subjects underwent a review of their medical history and had clinical laboratory assessments including HbA_{1c} and FPG performed.

Glycemic eligibility and management of the subject during the screening period was dependent on antidiabetic medication status at the screening visit (Visit 1) as follows:

If subjects were on a stable dose (≥10 weeks at the same dose) of metformin monotherapy (≥1500 mg/day or maximum tolerated dose), had an HbA_{1c} ≥7.0% and ≤10.5%, and FPG ≤240 mg/dL (13.3 mmol/L), and met all other eligibility criteria, they were entered directly into the single-blind placebo run-in period (Visit 3 [Week -2]).

If subjects were on metformin (≤1500 mg/day) and 1 other antidiabetic agent (excluding thiazolidinedione [TZD], insulin, or incretin therapies [dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptidase-1 (GLP-1) analogues]) and had an HbA_{1c} ≥6.8% and ≤10.0%, they returned in 1 week (Visit 2) to enter a 10-week, washout/metformin dose adjustment period to discontinue the other antidiabetic agent and adjust/stabilize their dose of metformin.

If subjects were not on antidiabetic therapy (for at least 3 months prior to Visit 1) or have not been on a stable dose of metformin monotherapy for 10 weeks and had an HbA_{1c} ≥8.0% and ≤11.0%, they returned in 1 week (Visit 2) to enter a 10-week, metformin dose adjustment period to optimize and stabilize the dose of metformin. Following optimization of the metformin dose, subjects must have been on a stable dose of metformin for 10 weeks prior to Visit 3 (Week -2).

Washout/Metformin Dose Adjustment/Stabilization Period (Visit 2 [Week -12]):

All subjects who were not on stable metformin monotherapy at Visit 1 and had met all eligibility criteria underwent a physical examination, had a 12-lead electrocardiogram (ECG) performed, and had a blood sample for FPG taken.

Subjects on metformin (≤1500 mg/day) and 1 other antidiabetic agent (excluding TZD, insulin, or incretin therapies [DPP-4 inhibitors, and GLP-1 analogues]) discontinued their other antidiabetic agent and increased their metformin dose as tolerated and as indicated to compensate for the withdrawal of the second agent.

Subjects not on antidiabetic therapy (for at least 3 months prior to Visit 1) started metformin at an appropriate dose.

Subjects who had not been on the same dose of metformin for 10 weeks, had a metformin dose assessment and adjustment, if appropriate, performed.

After discontinuation of other antidiabetic medication(s) and/or any adjustment of metformin therapy, the subject was contacted by phone or returned in 2 weeks for a metformin dose assessment (Visit 2.1). If no further adjustment of metformin was needed, the next visit for the subject was the single-blind placebo run-in visit (Visit 3 [Week -2]), approximately 8 weeks later. If further escalation in the dose of metformin was required, another dose adjustment occurred, followed by contact in 2 weeks to assess clinical and glycemic status, and the subject returned in approximately 10 weeks, from the time of the second dose adjustment, for the single-blind placebo run-in visit (Visit 3 [Week -2]). Subjects could therefore have additional clinic visits and/or phone contacts between Visit 2.1 and Visit 3, if further metformin dose adjustments were necessary to achieve a maximum daily dose of 1500 mg or the maximum tolerated dose for the subject. The interval between Visit 2 and Visit 3 could vary as required to adjust the dose of metformin and provide a period of 10 weeks at the final stable metformin dose prior to Visit 3 (Week -2).

Subjects entering the washout/metformin dose adjustment/stabilization period were dispensed and given instructions on the use of a home glucose monitor and were required to record daily glucose levels and any hypoglycemic episodes in the provided blood glucose journal. Instructions on self-monitored blood glucose results that necessitated clinic contact were also provided. Subjects were contacted by the clinic at regular intervals in regards to their glycemic status.

Single-Blind Placebo Run-in Period (Visit 3 [Week -2]):

For subjects who entered the study on stable metformin monotherapy, a physical examination and 12-lead ECG were performed at Visit 3 (Week -2). At this visit, these subjects were dispensed a home glucose monitor and given instructions on its use as was done for other subjects at Visit 2. The subjects were likewise required to record daily glucose levels in the provided blood glucose journal.

All subjects during the single-blind placebo run-in period took 2 tablets of study medication daily, before the morning meal. Subjects continued to take metformin at the same time(s) and total daily dose it was taken prior to the start of the single-blind placebo run-in period. Subjects used the home glucose monitors and recorded daily glucose levels in the provided blood glucose journal. All subjects were contacted by the clinic at Week -1 in regards to their glycemic status and study medication compliance. Subjects were instructed to contact the site if fasting glucose readings were $<$60 mg/dL (3.3 mmol/L) or $>$240 mg/dL (13.3 mmol/L). Subjects who reported 2 or more readings of fasting glucose $<$60 mg/dL (3.3 mmol/L) or $>$240 mg/dL

(13.3 mmol/L) within a week were required to come into the clinic and were evaluated for exclusion based on clinical assessment and/or central laboratory confirmation.

Double-Blind Treatment Period (Visit 4 through Visit 10 [Week 0 to Week 24]):

Subjects returned 2 weeks after entering the single-blind placebo run-in period to enter a 24-week treatment period. At this visit, subjects were assigned randomly in 1:1:1:1:1 ratio to KRP-104 100 mg QD, KRP-104 80 mg QD, KRP-104 40 mg QD, KRP-104 20 mg QD, or placebo. Subjects randomized to 20 mg QD underwent a blinded dosage increase to KRP-104 120 mg QD after 12 weeks of double-blind treatment. Randomization was stratified by use of the ClinTrak® Interactive Voice Response System. Stratification was by (1) stable metformin dose at screening (Visit 1) vs. metformin stabilization during the metformin dose adjustment/stabilization period and (2) Visit 3 (Week -2) HbA_{1c} <8.0% vs ≥8.0%.

All study visits occurred in the morning after a minimum of 10-hour overnight fast. Subjects were instructed to bring study medication and metformin with them on the days of clinic visits. Study medication was administered at the clinic after fasting blood samples were drawn.

During the double-blind treatment period, all subjects took 2 tablets of study medication (KRP-104 20 mg QD [2 × 10 mg tablets], KRP-104 40 mg QD [30 mg tablet and 10 mg tablet], KRP-104 80 mg QD [50 mg tablet and 30 mg tablet], KRP-104 100 mg QD [2 × 50 mg tablets], and placebo [2 × placebo tablets]) daily before the morning meal for the first 12 weeks of treatment and 4 tablets of study medication (KRP-104 40 mg QD [30 mg tablet, 10 mg tablet, and 2 × placebo tablets], KRP-104 80 mg QD [50 mg tablet, 30 mg tablet, and 2 × placebo tablets], KRP-104 100 mg QD [2 × 50 mg tablets and 2 × placebo tablets], KRP-104 120 mg QD [4 × 30 mg tablets], and placebo [4 × placebo tablets]) daily before the morning meal for the second 12 weeks of treatment. Subjects continued to take their stable dose of metformin at the same time it was taken prior to the start of the single-blind placebo run-in period except on days of clinic visits, when the morning dose of metformin was administered with the midday meal.

After randomization (Week 0 [Visit 4]), subjects returned for clinic visits at Week 4 (Visit 5), Week 8 (Visit 6), Week 12 (Visit 7), Week 16 (Visit 8), Week 20 (Visit 9), and Week 24 (Visit 10). A safety follow-up telephone call occurred approximately 2 weeks later at Week 26.

During the double-blind treatment period, subjects continued to use their home glucose monitors and were instructed to record fasting glucose levels in their blood glucose journal on a schedule prescribed by their study physician based on the individual subject risk of hyperglycemia or hypoglycemia, but at least once a week (eg, every Tuesday). In addition to self-monitored blood glucose readings, subjects also recorded episodes of symptomatic hypoglycemia in their blood glucose journals for review at clinic visits. Subjects were instructed to contact the site if fasting glucose readings were

>240 mg/dL (13.3 mmol/L) until Visit 6 (Week 8) and >220 mg/dL (12.2 mmol/L) thereafter, or <60 mg/dL (3.3 mmol/L) not attributable to an incidental cause. Subjects who reported 2 or more readings of fasting glucose meeting these criteria within a week or experienced symptoms of hypoglycemia requiring assistance (severe hypoglycemic episode) were required to come into the clinic and be evaluated for rescue/discontinuation based on clinical assessment and/or central laboratory confirmation.

During the double-blind treatment period, the following specific criteria defined the guidance for discontinuation for study medication or rescue therapy for FPG:

Definition of Hyperglycemia:

- Up to Week 8: FPG >240 mg/dL (13.3 mmol/L);
- After Week 8: FPG >220 mg/dL (12.2 mmol/L); or
- Rescue or discontinuation for elevated glucose was based on 2 or more self-monitored blood glucose readings above the defined limit within a 1-week period and confirmed by a determination by the central laboratory, or on 2 consecutive readings above the defined limit by the central laboratory.

Definition of Hypoglycemia

- Persistent hypoglycemia: blood glucose <60 mg/dL (3.3 mmol/L) as assessed by the central laboratory or by self-monitoring; severe if present with symptoms requiring assistance (severe hypoglycemic episode) and no obvious explanation (eg, increased physical activity, illness, and/or skipped meal).
- Rescue or discontinuation for hypoglycemia was based on 2 or more self-monitoring blood glucose readings <60 mg/dL (3.3 mmol/L) within a 1-week period and confirmed by a determination by the central laboratory. In the opinion of the Investigator, the occurrence of persistent symptoms of hypoglycemia in the absence of confirmatory laboratory values may also warrant rescue or discontinuation from the study.

Subjects who met per-protocol glycemic criteria for rescue or discontinuation were eligible to receive additional antihyperglycemic medication (excluding incretin therapies [DPP-4 inhibitors and GLP-1 analogues]) or a reduction in metformin dose and continue participating in the study. Subjects underwent all rescue visit procedures and were registered with a call to add-on therapy or a reduction in metformin dose as appropriate. The subject continued in the study and completed all remaining scheduled visits.

If a subject could not be controlled on rescue therapy and continued to meet glycemic criteria for rescue/discontinuation, the subject completed an early withdrawal visit and was discontinued from the study.

Duration of Treatment: This was an up to 37-week or longer study, with subjects being treated with study medication for 26 weeks (2 week placebo run-in, 24 weeks of active treatment).

Number of Subjects:

Synopsis Table 1: Summary of Subject Disposition – All Subjects

Disposition	Placebo (N = 81) n (%)	KRP-104 40 mg (N = 81) n (%)	KRP-104 80 mg (N = 80) n (%)	KRP-104 100 mg (N = 81) n (%)	KRP-104 20 mg/ 120 mg (N = 80) n (%)	Total (N = 403) n (%)
Subject who were screened						795 (100.0)
Primary reason for termination prior to randomization						392 (49.3)
Did not meet inclusion/exclusion criteria						357 (44.9)
Adverse event						3 (0.4)
Subject lost to follow-up						8 (1.0)
Subject withdrew consent						20 (2.5)
Pregnancy						1 (0.1)
Others						3 (0.4)
Subjects who were randomized	81 (100.0)	81 (100.0)	80 (100.0)	81 (100.0)	80 (100.0)	403 (100.0)
Subjects who completed the study	70 (86.4)	74 (91.4)	73 (91.3)	76 (93.8)	75 (93.8)	368 (91.3)
Subjects who early terminated from the study	11 (13.6)	7 (8.6)	7 (8.8)	5 (6.2)	5 (6.3)	35 (8.7)
Withdrew consent	4 (4.9)	2 (2.5)	1 (1.3)	3 (3.7)	1 (1.3)	11 (2.7)
Adverse event	3 (3.7)	1 (1.2)	2 (2.5)	0 (0.0)	1 (1.3)	7 (1.7)
Excluded concomitant medication	0 (0.0)	0 (0.0)	1 (1.3)	0 (0.0)	1 (1.3)	2 (0.5)
Rescue failure	0 (0.0)	1 (1.2)	1 (1.3)	0 (0.0)	0 (0.0)	2 (0.5)
Investigator judgment	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Lost to follow-up	2 (2.5)	2 (2.5)	2 (2.5)	1 (1.2)	0 (0.0)	7 (1.7)
Protocol deviation/ violation	0 (0.0)	1 (1.2)	0 (0.0)	1 (1.2)	0 (0.0)	2 (0.5)
Other	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.5)	3 (0.7)

Diagnosis and Main Criteria for Inclusion:

The population for this study consisted of men and women of non-childbearing potential (or who were using an acceptable double-barrier method of contraception including intrauterine devices), between the ages of 18 years and 75 years, inclusive, with a diagnosis of type 2 diabetes, a body mass index ≥20 kg/m^2 and ≤48 kg/m^2, on a stable dose of metformin monotherapy (≥1500 mg/day or maximum tolerated dose and unchanged for ≥10 weeks prior to placebo run-in), have an FPG ≤240 mg/dL (13.3 mmol/L), alanine aminotransferase, aspartate aminotransferase, or creatine phosphokinase ≤2 × the upper limit of normal, and serum creatinine >1.5 mg/dL (132.6 µmol/L) for males and 1.4 mg/dL (123.8 µmol/L) for females.

At Screening, subjects were to be 1 of the following:

- On a stable dose (≥10 weeks at the same dose) of metformin monotherapy (≥1500 mg/day or maximum tolerated dose) and had an HbA_{1c} ≥7.0% and ≤10.5%;
- On metformin (≤1500 mg/day) and 1 other antidiabetic agent (excluding TZD, insulin, or incretin therapies [DPP-4 inhibitors and GLP-1 analogues]) and had an HbA_{1c} ≥6.8% and ≤10.0%; or
- Not on antidiabetic therapy (for at least 3 months prior to Visit 1) or had not been on a stable dose of metformin monotherapy for 10 weeks and had an HbA_{1c} ≥8.0% and ≤11.0%.

Subjects also had to have an FPG <240 mg/dL (also assessed at Visit 3 [Week -2] and by fingerstick at Visit 4 [Week 0]).

Investigational Product and Comparator Information:

The following were supplied by Kyorin Pharmaceutical Co., Ltd.:

- KRP-104 50 mg tablets (Lot No. S987440, S987450, S987460);
- KRP-104 30 mg tablets (Lot No. S9174C0, S9174D0, S987420, S987430);
- KRP-104 10 mg tablets (Lot No. S917430, S917480); and
- Placebo, matching image of KRP-104 tablets (Lot No. S987410, S8Z7420, S8Z7430).

Metformin was obtained by prescription from the local pharmacy.

Criteria for Evaluation:

Efficacy

The primary efficacy variable was change in HbA_{1c} from baseline (Week 0) to Week 24.

The following secondary efficacy variables were assessed:

- Change in FPG from baseline to Week 24;
- Change in insulin, HOMA-β, and HOMA-IR from baseline to Week 24;
- Change in body weight from baseline to Week 24;
- Change in HbA_{1c}, FPG, insulin, HOMA-β, HOMA-IR, and body weight from baseline to each post-baseline study week;
- Number and percentage of subjects achieving HbA_{1c} <7.0% at each post-baseline visit; and
- Number and percentage of subjects requiring rescue therapy for elevated glucose.

Safety

Safety variables for assessment included adverse events, physical examinations, ECGs, vital signs, serum lipids, and safety laboratory tests (chemistry, hematology, and urinalysis).

Statistical Methods:

The primary efficacy parameter was change in HbA_{1c} from baseline (Week 0) to Week 24. If the Week 24 measurement was missing, the last valid post-baseline observation (LOCF) algorithm was applied to impute the missing Week 24 value. All efficacy data collected for a subject after the initiation of rescue therapy was excluded from the efficacy analyses.

The primary efficacy hypothesis was that at least 1 KRP-104 treatment group would result in a statistically significant reduction in mean HbA_{1c} at Week 24 with LOCF compared to the placebo group. The primary efficacy hypothesis was tested using linear contrasts from an analysis of covariance model with treatment and screening metformin status as factors and the baseline HbA_{1c} value as a covariate. Dunnett's adjustment was used to control type 1 error rate at α=0.05.

The primary efficacy analysis was based on the Intent-to-Treat (ITT) population.

One interim analysis was performed after all subjects completed the first 12 weeks of the study. All efficacy variables, including change from baseline, were summarized at each post-randomization timepoint through Week 12. Key safety variables, including adverse events and safety laboratory parameters were also summarized by treatment group. No inferential analyses were planned for the interim analysis and the interim analysis had no effect on the conduct of the study. The analyses were produced by an independent statistician not otherwise involved with the study. No individual subjects were unblinded to anyone but the independent statistician during this interim analysis.

Summary of Results:

Baseline Characteristics

In the Randomized population, all groups were well-balanced at baseline for key demographic characteristics. The mean age of the Randomized population at screening was 55.8 years, 64.3% were female, 69.0% were White. The mean weight was 85.30 kg. The mean BMI was 32.16 kg/m^2. The mean duration from diabetes diagnosis was 73.8 months. The mean HbA_{1c} was 8.07% and the mean FPG was 162.3 mg/dL. Approximately 64% of the randomized subjects entered the study on stable metformin monotherapy, 27% on combination therapy, and only 9% were naïve (or non-stable on metformin monotherapy).

Efficacy

In subjects with type 2 diabetes mellitus inadequately controlled on metformin alone, treatment for 24 weeks with KRP-104 80 mg, KRP-104 100 mg, and KRP-104 20/120 mg clinically and statistically significantly reduced HbA_{1c} compared to placebo treatment. The proportion of subjects achieving American Diabetes Association target HbA_{1c} (<7.0%) was significantly higher for all of the KRP-104 treatment groups compared to the placebo group.

Synopsis Table 2: Mean Change in Hemoglobin A_{1c} (%) from Baseline to Week 24 with LOCF – Intent-to-Treat Population

Treatment	N [1]	Baseline [2] Mean (SD)	Week 24 (LOCF) [3] Mean (SD)	Change From Baseline	
				LS Mean (SE)	95% CI
Placebo	78	8.09 (1.073)	7.97 (1.310)	-0.09 (0.097)	(-0.28 , 0.10)
KRP-104 40 mg	79	8.10 (0.907)	7.65 (1.306)	-0.41 (0.097)	(-0.60 , -0.22)
KRP-104 80 mg	79	7.93 (0.900)	7.23 (1.131)	-0.70 (0.097)	(-0.89 , -0.51)
KRP-104 100 mg	80	8.08 (1.037)	7.35 (1.206)	-0.71 (0.096)	(-0.89 , -0.52)
KRP-104 20 mg/120 mg	79	8.11 (1.069)	7.35 (0.984)	-0.73 (0.097)	(-0.92 , -0.54)

Comparison	Difference in Change from Baseline		
	LS Mean (SE)	95% CI	p-value
KRP-104 40 mg vs. placebo [4]	-0.32 (0.136)	(-0.66 , 0.01)	0.0587
KRP-104 80 mg vs. placebo [4]	-0.61 (0.136)	(-0.94 , -0.28)	<0.0001
KRP-104 100 mg vs. placebo [4]	-0.62 (0.136)	(-0.95 , -0.28)	<0.0001
KRP-104 20 mg/120 mg vs. placebo [4]	-0.64 (0.136)	(-0.97 , -0.31)	<0.0001

1. N is the number of subjects with data at baseline and the specified visit.
2. Baseline is defined as the Week 0 (Visit 4) measurement. If the Week 0 measurement was missing, the last measurement prior to the first dose of study medication was used.
3. The Week 24 (LOCF) value was the measurement at the scheduled Week 24 visit. If missing, the LOCF imputation method was used.
4. LS means, SEs, CIs, and p-values are from linear contrasts of an ANCOVA model with treatment and screening metformin status (stabilization period required or stabilization period not required) as factors and the baseline value as a covariate.

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

After 24 weeks of treatment, a dose-related effect on HbA_{1c} was observed across the range of doses of KRP-104 (40 mg, 80 mg, 100 mg, and 120 mg) compared to placebo. The lowest dose at which the maximum effect on HbA_{1c} was observed was in the KRP-104 80 mg group. The effects on HbA_{1c} in the KRP-104 100 mg and KRP-104 20/120 mg groups were similar to the effects observed in the KRP-104 80 mg group. Because of the similar effects on the primary efficacy parameter observed in the KRP-104 80 mg, KRP-104 100 mg, and KRP-104 20/120 mg groups, the dose selection for studies going forward was determined to be KRP-104 80 mg QD.

Although median FPG changes from baseline were similar in all KRP-104 treatment groups (0.5, -11.5, -14.5, -11.0, and -12.5 mg/dL for placebo, KRP-104 40 mg, KRP-104 80 mg, KRP-104 100 mg, and KRP-104 20/120 mg, respectively) the FPG minimum to maximum ranges for most groups was wide and it was possible that a few outliers influenced the mean response. Median reductions in FPG were relatively consistent for all

KRP-104 dosages compared to placebo in both the LOCF and non-LOCF datasets and were more consistent with the observed HbA_{1c} effects.

Synopsis Table 3: Mean Change in Fasting Plasma Glucose (mg/dL) from Baseline to Week 24 LOCF – Intent-to-Treat Population

Treatment	N [1]	Baseline [2] Mean (SD)	Week 24 (LOCF) [3] Mean (SD)	Change From Baseline	
				LS Mean (SE)	95% CI
Placebo	78	163.4 (32.26)	164.8 (43.43)	2.04 (4.804)	(-7.41,11.49)
KRP-104 40 mg	79	169.0 (32.40)	160.5 (49.59)	-6.19 (4.818)	(-15.66,3.28)
KRP-104 80 mg	79	156.2 (29.98)	153.5 (52.39)	-3.97 (4.796)	(-13.41,5.46)
KRP-104 100 mg	80	161.8 (32.30)	152.4 (54.55)	-9.21 (4.749)	(-18.55,0.13)
KRP-104 20 mg/120 mg	79	162.1 (31.54)	146.8 (38.09)	-14.97 (4.783)	(-24.37,-5.57)

Comparison	Difference in Change from Baseline		
	LS Mean (SE)	95% CI	p-value
KRP-104 40 mg vs. placebo [4]	-8.23 (6.736)	(-24.74 , 8.28)	0.5520
KRP-104 80 mg vs. placebo [4]	-6.02 (6.741)	(-22.54 , 10.51)	0.7829
KRP-104 100 mg vs. placebo [4]	-11.25 (6.704)	(-27.68 , 5.18)	0.2719
KRP-104 20 mg/120 mg vs. placebo [4]	-17.01 (6.724)	(-33.49 , -0.53)	0.0407

1. N is the number of subjects with data at baseline and the specified visit.
2. Baseline is defined as the Week 0 (Visit 4) measurement. If the Week 0 measurement was missing, the last measurement prior to the first dose of study medication was used.
3. The Week 24 (LOCF) value was the measurement at the scheduled Week 24 visit. If missing, the LOCF imputation method was used.
4. LS means, SEs, CIs, and p-values are from linear contrasts of an ANCOVA model with treatment and screening metformin status (stabilization period required or stabilization period not required) as factors and the baseline value as a covariate.

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

The proportion of subjects who required rescue therapy was not statistically significantly higher in the KRP-104 groups compared to placebo.

Subjects with baseline HbA_{1c} ≥median (median baseline HbA_{1c} was 7.9% for all randomized subjects) had larger numerical mean reductions in HbA_{1c} with KRP-104 treatment than subjects with baseline HbA_{1c} <median compared to placebo.

Mean changes in body weight were not clinically significant for KRP-104 treatment groups compared to placebo.

Safety

For subjects with type 2 diabetes mellitus, inadequately controlled on metformin alone, treatment with KRP-104 was generally well tolerated.

The overall incidence of treatment-emergent adverse events (TEAEs) as well as specific TEAEs reported was similar among the KRP-104 treated groups. Most of the TEAEs were mild or moderate in severity.

No subjects died during this study. A total of 11 subjects had a serious adverse event (SAE); none of the SAEs was considered by the Investigator to be related to study medication. A total of 6 subjects discontinued from the study due to an adverse event. Subject 016-003 in the KRP-104 80 mg group had concurrent drug-related adverse events of epigastric discomfort and

palpitations that led to discontinuations; no other adverse events leading to discontinuation were considered by the Investigator to be related to study medication.

No clinically significant treatment-associated trends in safety, laboratory, vital signs, ECG, or physical examination findings were observed.

Conclusions:

On the basis of these study results, the following conclusions can be made:

- In subjects with type 2 diabetes mellitus inadequately controlled on metformin alone, treatment for 24 weeks with KRP-104 80 mg, KRP-104 100 mg, or KRP-104 20/120 mg clinically and statistically significantly reduced HbA_{1c} levels compared with placebo treatment.
- A dose-related effect on HbA_{1c} was observed across the range of doses of KRP-104 (40 mg, 80 mg, 100 mg, and 20/120 mg) compared to placebo. The lowest dose group where the maximum effect on HbA_{1c} was observed was the KRP-104 80 mg group. Groups administered doses greater than KRP-104 80 mg QD achieved HbA_{1c} reductions comparable to those observed with KRP-104 80 mg QD after 12 weeks or 24 weeks of treatment. It appears that KRP-104 80 mg QD represents the best balance of safety and efficacy. Therefore, it was selected as the usual recommended clinical dose for Phase 3.
- Mean reductions of HbA_{1c} were greater in subjects with baseline HbA_{1c} levels $\geq$median for all KRP-104 treated groups than in the subgroups of subjects with baseline HbA_{1c} levels $<$median compared to placebo.
- Although median FPG reductions from baseline were similar in all KRP-104 treatment groups consistent with HbA_{1c} responses, a statistically significant mean change in FPG compared to placebo was observed only in the KRP-104 20/120 mg group.
- There were no clinically significant changes in body weight in any KRP-104 treatment group compared to placebo over 24 weeks of treatment.
- For subjects with type 2 diabetes mellitus, inadequately controlled on metformin alone, treatment with KRP-104 was generally well tolerated. No clinically significant treatment-associated trends in safety, laboratory, vital signs, ECG, or physical examination findings were observed.
- The overall incidences of TEAEs and specific TEAEs reported were similar among the KRP-104 treatment groups and the placebo group.

Date of the Report: 22 December 2011