SYNOPSIS OF RESEARCH REPORT [redacted]
(PROTOCOL BM18102)

COMPANY: NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Abbreviated Clinical Study Report – Protocol BM18102. A multicenter, double-blind, randomized, placebo controlled, dose ranging phase 2 study to investigate efficacy, safety, tolerability and pharmacokinetics of the DPP-IV inhibitor RO0730699 in patients with type 2 diabetes. Report No. [redacted]. November 2006.		
INVESTIGATORS / CENTERS AND COUNTRIES	33 centers in eight countries (USA, Mexico, Romania, Bulgaria, Latvia, Estonia, Lithuania, and Costa Rica).		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	18 May 2005 – 29 March 2006	CLINICAL PHASE	II
OBJECTIVES	**Primary**: to determine the doses of RO0730699 which, when compared to placebo, are efficacious, safe and tolerable in patients with type 2 diabetes. **Secondary**: to investigate, by a population analysis approach, the pharmacokinetics and the exposure-response relationship of RO0730699 in the target population.		
STUDY DESIGN	Double-blind, placebo-controlled, randomized, multicenter study in type 2 diabetic patients with four phases (screening, 4-week washout/ placebo run-in, 12-week treatment, and follow-up). Stratification based on severity of disease (HbA1c <8.5% or ≥ 8.5%) and pre-study treatment (drug naïve or pre-treated).		
NUMBER OF SUBJECTS	• 792 patients screened. • 649 patients entered into 4-week placebo run-in/washout. • 291 patients randomized to treatment (four RO0730699 arms and one placebo arm)		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Type 2 diabetes (drug naïve or pre-treated with monotherapy or combination therapy), BMI ≤ 40 kg/m^2, age 18-75 years and: • HbA1c ≤ 10.0% at screening AND ≥ 7.0% and ≤ 10.0% at pre-randomization visit • FPG > 7.0 mmol/L (126 mg/dL) and ≤ 13.3 mmol/L (240 mg/dL) at pre-randomization visit		
TRIAL DRUG / STROKE (BATCH) No.	100 mg RO0730699 capsules: [redacted] 200 mg RO0730699 capsules: [redacted] 400 mg RO0730699 capsules: [redacted]		
DOSE / ROUTE / REGIMEN / DURATION	RO0730699 (100 mg b.i.d., 200 mg b.i.d., 400 mg qd., or 400 mg b.i.d.) administered orally 10 minutes before food intake for 12 weeks. In all groups, three tablets in the morning and three tablets in the evening were taken in order to keep the blinding (evening dose of the 400 mg qd arm was placebo).		

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REFERENCE DRUG / STROKE (BATCH) No.	Placebo to 100 mg RO0730699: [redacted] Placebo to 200 mg: [redacted] Placebo to 400 mg: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Placebo administered orally twice daily (three tablets morning, three tablets evening) 10 minutes before food intake for 12 weeks.
CRITERIA FOR EVALUATION	
EFFICACY:	**Primary endpoint**: • Absolute change in HbA1c from baseline to the end of treatment **Secondary endpoints:** • Absolute change in FPG from baseline to the end of treatment • Response rate (patients with HbA1c < 7.0% at the end of treatment or a reduction in HbA1c ≥ 0.7% from baseline) • Absolute/relative change from baseline to the end of treatment in insulin sensitivity (HOMA-S), β-cell-function (HOMA-B), lipid profile (triglycerides, total cholesterol, HDL, LDL, non-HDL, LDL/HDL ratio) **Mixed liquid meal test (MLMT):** • Relative change from baseline of AUE and/or E_{max} for MLMT parameters • Absolute change in mean value for MLMT parameters • Absolute/relative change in insulin sensitivity (insulin sensitivity index [ISI]) from baseline to the end of treatment
PHARMACOKINETICS:	To be reported separately.
SAFETY:	Adverse events, vital signs, clinical laboratory tests, body weight, waist/hip ratio, electrocardiogram (ECG).
STATISTICAL METHODS	**Efficacy** *Primary efficacy endpoint (absolute change of HbA1c from baseline at Week 12):* an analysis of covariance (ANCOVA) with treatment, region and pre-study treatment as fixed factors and HbA1c at baseline as covariate was performed. Each RO0730699 dose regimen was compared against placebo, and the null-hypothesis was used to test whether the mean differences exceeded 0%. The nominal one-sided significance level alpha = 0.025 was applied for each of the pairwise comparisons. Hypotheses were tested with the following hierarchical decision procedure: 400 mg b.i.d. vs. placebo, 200 mg b.i.d. vs. placebo, 400 mg qd vs. placbeo, and finally 100 mg b.i.d. vs. placebo.

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An ANCOVA was used to calculate least squares means of the difference from baseline and 95% confidence intervals at each timepoint. The placebo-corrected difference from baseline at Week 12 was also calculated.
Secondary efficacy endpoints: as above in an exploratory manner.
Safety
All data are presented by individual patient listings and summary tables as appropriate. No statistical testing was performed.

METHODOLOGY:

The study consisted of four periods: screening, 4-week washout/ placebo run-in, 12-week treatment, and follow-up.
The screening period was as short as possible and up to a maximum of two weeks. For eligible patients, an individualized diet and exercise plan was implemented on the basis of recommendations from the investigator.
During the 4-week placebo run-in/wash-out period, patients took three placebo tablets in the morning and three placebo tablets in the evening, 10 minutes before food intake. Any oral antihyperglycemic medication was stopped before the start of this phase. A pre-randomization visit was conducted between five and two days before the end of the period (Day -5 to Day -2) to determine whether the final HbA1c and fasting plasma glucose (FPG) inclusion criteria had been met.
Upon completion of the placebo run-in/wash-out period, eligible patients were randomly assigned to receive a dose of 100 mg b.i.d., 200 mg b.i.d., 400 mg qd or 400 mg b.i.d. RO0730699 or placebo for 12 weeks. Blood samples were collected at 30 and 45 minutes post-dose on Day 1 in order to determine peak plasma exposure of RO0730699 in relation to any potential central nervous system effects. Patients returned to the study site at Week 2, 4, 8, and 12 for the evaluation of pharmacokinetics (Weeks 4, 8 and 12 only), efficacy and safety. A MLMT was performed at a limited number of study sites in order to assess the effect of RO0730699 on postprandial glucose, insulin, glucagon, dipeptidyl peptidase IV (DPP-IV), glucagon-like peptide-1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP), and on whole body insulin sensitivity.
A final follow-up visit was conducted between 5 and 14 days after the last study medication intake.

EFFICACY RESULTS:

Compared to baseline, the HbA1c values in the placebo group were increased at the end of treatment by 0.5% (absolute change) because the 4-week period for washout of previous BSLM was not long enough for the attainment of stable HbA1c values at baseline. Therefore, in this clinical study report, analyses of the efficacy of RO0730699 based on changes relative to placebo are considered to be more meaningful than those based on changes relative to baseline.
RO0730699 significantly improved both fasting and postprandial blood glucose control. Compared to placebo, statistically significant reductions in HbA1c (the primary parameter) were observed following 12-week treatment with RO0730699 at doses of 200 mg b.i.d. (placebo-corrected LSmean change from baseline -0.508%, $p=0.0052$), 400 mg qd (-0.790%, $p=0.0052$) and 400 mg b.i.d. (-0.928%, $p<0.0001$).
Statistically significant improvements were also seen at the end of treatment at the 400 mg b.i.d. dose for FPG (placebo-corrected LS mean -1.969 mmol/L, $p=0.0002$) and β-cell function (HOMA B; $p=0.0093$). No effects were seen on fasting insulin, C-peptide or glucagon.
In a 4 hour MLMT, the activity of DPP-IV decreased with increasing doses of RO0730699, which lead to clear increases in postprandial active GLP-1 at all doses of RO0730699 tested whereas increases in GIP

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were seen only at the 400 mg qd and 400 mg b.i.d. RO0730699 doses. Compared to placebo, dose related improvements in postprandial glucose and insulin were seen. No clear dose response was apparent for glucagon, but glucagon concentrations were decreased compared to placebo in all RO0730699 treatment groups.
A slight improvement in insulin sensitivity (based on the Matsuda formula) was observed during the MLMT at Week 12 at all doses of RO0730699 (mean relative change from baseline 15.15% to 28.61% vs. 10.76% in placebo). Likewise, a dose response was observed for adiponectin (an indicator of insulin sensitivity) with a statistically significant increase at Week 12 compared to placebo in the 400 mg b.i.d. group ($p<0.0001$). However, no effect of RO0730699 was observed at any dose on HOMA-S.
No effects were seen at any dose on lipids.

SAFETY RESULTS:

RO0730699 was well tolerated in this study at all doses tested. Adverse events during the active treatment phase were relatively low in number (34% to 45% for active, 46% placebo) with no events showing a dose response. The most frequently reported MedDRA-defined body systems were infections (18% placebo vs. 10%-22% RO0730699 groups) and gastrointestinal disorders (12% placebo vs. 9%-14% RO0730699 treatment groups).
Three patients, including two in the placebo group (pancreatitis, appendicitis) and one in the 400 mg b.i.d. group (cholecystitis), experienced a serious adverse event; all three events were considered to be unrelated to trial treatment. Five patients, including one in the placebo group and four in three of the RO0730699 treatment groups (100 mg b.i.d., 200 mg b.i.d., 400 mg b.i.d.), experienced a severe adverse event. Seven patients, including two in the placebo group and five in three of the RO0730699 treatment groups (100 mg b.i.d., 200 mg b.i.d., 400 mg b.i.d.), experienced adverse events that led to premature withdrawal. There were no deaths, no CNS signals, and only one case of hypoglycemia (linked to alcohol ingestion). Extensive ECG monitoring (pre- and post-dose) during the study did not show any indication of QTc prolongation at any dose tested. There were also no clinically relevant effects seen on any laboratory parameter, vital signs or anthropometric measurements such as body weight and waist:hip ratio.

CONCLUSIONS:

In this Phase II study in type 2 diabetic patients, 12 week treatment with RO0730699 resulted in clear inhibition of DPP-IV activity. This lead to statistically significant improvements in HbA1c (the primary parameter) compared to placebo at doses 200 mg b.i.d, 400 mg qd, and 400 mg b.i.d. Statistically significant beneficial effects were also observed on FPG, β-cell function (HOMA-B), and adiponectin at the 400 mg b.i.d. dose. All doses tested (100-400 mg b.i.d.) were well tolerated with no safety signals identified.