SYNOPSIS OF RESEARCH REPORT [redacted]
(PROTOCOL BM18106)

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 BM18106:** Multicenter, double-blind, randomized, placebo controlled, dose ranging phase 2 study to investigate efficacy, safety, tolerability and pharmacokinetics of the DPP-IV inhibitor ROO730699 in patients with type 2 diabetes, who are treated with a stable dose of metformin. Report No. [redacted]. December 2006.		
INVESTIGATORS / CENTERS AND COUNTRIES	31 centers in five countries (Germany, USA, Australia, Canada, Italy)		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	2 May 2005 - 19 June 2006	CLINICAL PHASE	II
OBJECTIVES	• **Primary objective**: To determine the doses of RO0730699 which, when added to metformin, are efficacious, safe and tolerable compared to metformin alone in patients with type 2 diabetes. • **Secondary objective**: 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. Stratification based on severity of disease (HbA1c <8.5% or ≥ 8.5%).		
NUMBER OF SUBJECTS	218 patients were randomized to treatment: • placebo + metformin: 53 patients • 100 mg b.i.d. RO0730699 + metformin: 56 patients • 200 mg b.i.d. RO0730699 + metformin: 53 patients • 400 mg b.i.d. RO0730699 + metformin: 56 patients		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	• Type 2 diabetes, BMI ≤ 40 kg/m2, age 18-75 years. • Treated with the maximum tolerated dose of metformin (minimum 1500 mg/day, maximum not higher than recommended in label) for at least 3 months before screening. • At screening: HbA1c ≥ 7.0% and ≤ 10.0%; FPG > 7.0 mmol/L (126 mg/dL) and ≤ 13.3 mmol/L (240 mg/dL).		
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 administered orally twice daily (100 mg b.i.d., 200 mg b.i.d., or 400 mg b.i.d.) 10 minutes before food intake for 16 weeks. In all groups, three tablets in the morning and three tablets in the evening were taken to keep the blinding.		
REFERENCE DRUG / STROKE (BATCH) No.	Placebo to 100 mg RO0730699: [redacted] Placebo to 200 mg: [redacted]		

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	[redacted] Placebo to 400 mg: [redacted] Metformin: same as before study start.
DOSE / ROUTE / REGIMEN / DURATION	Placebo: Administration same as RO0730699 (ie, orally, twice daily for 16 weeks). Metformin: same as before study start (minimum 1500 mg/day, maximum not higher than recommended in label).
CRITERIA FOR EVALUATION	

EFFICACY:	**Primary endpoint:**
	• Absolute change in HbA_{1c} from baseline to end of treatment
	Secondary endpoints:
	• Absolute change in FPG from baseline to end of treatment
	• HbA1c response rate (patients with HbA1c < 7.0% at end of treatment or a drop in HbA1c ≥ 0.7% from baseline)
	• Absolute and relative change from baseline to 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)
	• For the MLMT parameters (glucose, insulin, glucagon, GLP-1 [active] and GIP [active]) and DPP-IV activity:
	  • Relative change of AUE and/or Emax from baseline to end of treatment
	  • Absolute change of the mean from baseline to end of treatment.
	• Insulin sensitivity index: absolute and relative change from baseline to end of treatment.

PHARMACOKINETICS:	To be reported separately.
SAFETY:	Adverse events, clinical laboratory tests, vital signs, body weight, waist/hip ratio, ECG
STATISTICAL METHODS	**Efficacy** *Primary endpoint (absolute change in HbA1c from baseline at Week 16):* Using the Intent to Treat population (ITT) and the last observation carried forward (LOCF) approach, an analysis of covariance (ANCOVA) with treatment and region as fixed factors and HbA1c at baseline as covariate was performed. Each RO0730699 dose regimen was compared against placebo, and the nullhypothesis 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.

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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 16 was also calculated. *Secondary endpoints:* As above, but in an exploratory manner. **Safety** All data are presented by individual patient listings and summary tables as appropriate. No statistical testing was performed.

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METHODOLOGY:

The screening visit was conducted a maximum of 2 weeks before randomization. Eligible patients were placed on a diet and exercise plan according to recommendations from the investigator.
At randomization, patients were randomly assigned to receive a dose of 100 mg b.i.d., 200 mg b.i.d., or 400 mg b.i.d. RO0730699 or placebo in addition to their current stable dose of metformin for 16 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 (CNS) effects. Patients returned to the study site at Week 2, 4, 8, 12, and 16 for the evaluation of pharmacokinetics (Weeks 4, 8 and 16 only), efficacy and safety. A mixed liquid meal test (MLMT) was performed at a limited number of study sites. A final follow-up visit was conducted between 5 and 14 days after the last study medication intake.

EFFICACY RESULTS:

The addition of 400 mg b.i.d. RO0730699 to a stable dose of metformin for 16 weeks resulted in an absolute HbA1c change from baseline (LS mean) of -0.567%. Since the mean HbA1c at baseline in this group was 7.87%, the magnitude of the effect was in the range expected. However, a decrease in HbA1c from baseline was also observed in the placebo group (LS mean -0.227%), with the result that the placebo-corrected LS mean estimate in the 400 mg b.i.d. group was only -0.339%. The difference from placebo reached statistical significance, but was less than has been reported previously for other DPP-IV inhibitors. Placebo-corrected improvements in HbA1c at doses of 100 mg b.i.d. and 200 mg b.i.d. RO0730699 were not statistically significant.

The HbA1c response rates (ie, patients with HbA1c <7.0% or HbA1c reduction ≥0.7%) were higher in all RO0730699 groups (41.8% [100 mg b.i.d.], 44.2% [200 mg b.i.d.], 56.6% [400 mg b.i.d.]) compared to the placebo group (21.2%). However, the addition of RO0730699 to metformin did not appear to affect FPG, insulin sensitivity (HOMA-S), or β-cell function (HOMA B). Likewise, no clinically relevant effects were observed at any dose of RO0730699 on lipid profiles.

In a 4 hour MLMT at the end of treatment, dose-related deceases in DPP IV activity in the RO0730699 groups were associated with dose-related increases in postprandial active GLP-1. Improvements in postprandial glucose AUE at the end of treatment were slightly greater in the RO0730699 groups (-12.5% to -17.9%) than in the placebo group (-9.9%). Dose-related increases were also observed at Week 16 in the RO0730699 groups for mean insulin AUE (+5.14% to +13.40%) whereas a slight worsening from baseline was seen in the placebo group (-5.46%). Postprandial glucagon AUE did not show the expected dose related decrease in the RO0730699 groups and a positive effect on insulin sensitivity (based on the Matsuda formula) was not observed.

At the end of treatment, minor reductions in fasting insulin and glucagon were observed in the 400 mg b.i.d. group. The effect on glucagon was expected due to the mode of action of RO0730699, but the effect on insulin cannot be explained. In addition, small dose related reductions in fructosamine and a dose response for fibrinogen were seen. No clear effects of RO0730699 were seen on other fasting glycemic and inflammatory/cardiovascular biomarkers, including free fatty acid, adiponectin, high sensitive C-reactive protein and plasminogen activator inhibitor-1.

SAFETY RESULTS:

Overall, the addition of RO0730699 to a stable dose of metformin for 16 weeks was well tolerated at all doses tested. The proportion of patients who experienced one or more adverse events was similar in all groups (72% placebo vs. 66%-84% RO0730699 groups), with no sign of dose response to RO0730699.

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There were no CNS signals during the study. Nausea, which is a known side effect of metformin, occurred at a higher incidence in the 400 mg b.i.d. RO0730699 group (13%) compared to the other groups (5% 6%), but there was no relationship to C_{max} of RO0730699 and there were no reports of convulsions or EEG changes.

No events of concern were seen at a higher incidence in the RO0730699 groups or in the highest RO0730699 (400 mg b.i.d.) dose group. The only adverse event to show a clear increase in incidence in the RO0730699 groups compared to the placebo group was nasopharyngitis (13% 18% vs. 8%). The only events to occur at a higher incidence in the 400 mg b.i.d. group were nausea (discussed above) and pruritus (7% vs. 0%-2% [pruritus and generalized pruritus categories combined]).

There were no deaths or cases of hypoglycemia during the study, and extensive ECG monitoring (pre- and post-dose) did not show any indication of QTc prolongation at any RO0730699 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:

- The addition of RO0730699 to a stable dose of metformin for 16 weeks resulted in clear inhibition of DPP-IV activity at all doses tested (100 to 400 mg b.i.d.) with a statistically significant improvement in HbA1c (the primary parameter) at the highest dose only.
- The overall efficacy of RO0730699 at the end of treatment was less than expected. This may have been due, at least in part, to a relatively large effect of placebo in the placebo group as well as to a drop in exposure to RO0730699 towards the end of treatment.
- All RO0730699 doses tested were well tolerated with no safety signals identified.