SYNOPSIS OF RESEARCH REPORT [redacted]
(PROTOCOL BP21850)

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

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Multi-center, randomized, double-blind, 5-arm parallel group, placebo-controlled 4-week study to investigate the safety, tolerability and efficacy of two doses each (near to maximum tolerated dose and lower dose) of RO5093151 (RO-151) administered twice daily (BID regimen) and RO5027838 (RO-838) administered once daily (QD regimen) in patients with type 2 diabetes mellitus (T2D) on a stable dose of metformin. Report No. [redacted] August 2010.		
INVESTIGATORS / CENTERS AND COUNTRIES	Five centers (two in Germany, one in Austria, and two in the USA)		
PERIOD OF TRIAL	March 3, 2009 to August 24, 2009	CLINICAL PHASE	IIa
OBJECTIVES	**Primary**: • To measure the effect of the two 11β-HSD1 inhibitors, RO-151 and RO-838, on mean daily plasma glucose (change from baseline at week 4) in T2D patients treated with a stable dose of metformin compared to placebo. **Secondary**: • To measure the effect of RO-151 and RO-838 on fasting plasma glucose (FPG), insulin, C-peptide, glucagon, HbA1c as well as β-cell function. • To evaluate the tolerability/safety of RO-151 and RO-838, including measurements of the function of the hypothalamic-pituitary-adrenal (HPA) axis. • To measure the effect of RO-151 and RO-838 on lipid parameters. • To measure the effect of RO-151 and RO-838 on arterial blood pressure and body weight. • To investigate, using a population analysis approach, the pharmacokinetics (PK) and the exposure-response relationship of RO-151 and RO-838 in the target population, including the influence of covariates such as age, gender and body weight. *These data will be reported separately.*		

	• To assess the systemic concentration of metformin in combination with RO-151 or RO-838 in patients
STUDY DESIGN	Multi-center, randomized, double-blind, 5-arm parallel group, placebo-controlled proof-of-principle study. To keep the study blinded and taking into account the BID versus QD dose regimen for RO-151 and RO-838, all patients took eight dosage units each day; four capsules and two tablets in the morning and two tablets in the evening.
NUMBER OF SUBJECTS	110 patients: • placebo: 21 patients • RO-151 5 mg BID (low dose RO-151): 24 patients • RO-151 200 mg BID (high dose RO-151): 20 patients • RO-838 50 mg QD (low dose RO-838): 21 patients • RO-838 200 mg QD (high dose RO-838): 24 patients
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Male and female patients with T2D on a stable dose of metformin, age 35-65 years, body mass index (BMI) 28 to 42 kg/m^2 inclusive, HbA1c ≥ 7.0% and ≤ 10.0% at screening.
TRIAL DRUG / STROKE (BATCH) No.	RO-151 tablets: • 5 mg (RO5093151/F02, batch number [redacted] • 100 mg (RO5093151/F04, batch number [redacted]) RO-838 capsules: • 50 mg (RO5027838/F04, batch number [redacted])
DOSE / ROUTE / REGIMEN / DURATION	RO-151 or RO-838 plus prescribed metformin therapy for 4 weeks: • RO-151 (5 mg BID or 200 mg BID) orally before breakfast and before dinner. • RO-838 (50 mg QD or 200 mg QD) orally before breakfast
REFERENCE DRUG / STROKE (BATCH) No.	Matching placebo to RO5093151 tablets: • placebo (RO5093151/F05, batch numbers [redacted]) Matching placebo to RO5027838 capsules: • placebo (RO5027838/F01, batch number [redacted])
DOSE / ROUTE / REGIMEN / DURATION	Matching placebo to RO-151 or RO-838 plus prescribed metformin therapy for 4 weeks: • placebo to RO-151 orally before breakfast and before dinner • Placebo to RO-838 orally before breakfast
CRITERIA FOR EVALUATION	
EFFICACY:	Primary efficacy endpoint: • Mean daily plasma glucose (assessed by a 9-point plasma glucose profile): absolute change from baseline (day -1) to day 27 of the treatment period. Secondary efficacy endpoints: • Fasting and postprandial plasma glucose, insulin, C-peptide and glucagon

	• Oral glucose tolerance test (OGTT) parameters (C_{max} and AUC of plasma glucose, insulin, C-peptide and glucagon), applied OGTT indices (IGI30, IGI15, CGI15, CGI30, ISIEST, MCREST, Matsuda Index), and oral glucose insulin sensitivity (OGIS) after an OGTT at week 4 • Body weight, BMI and waist-to-hip ratio • Lipid profile • Insulin sesitivity (HOMA-IR) and β-cell function (HOMA-B) • HbA1c • Bio- and inflammatory markers (adiponectin, hsCRP, intact pro-insulin) • 24 hour ambulatory blood pressure monitoring (ABPM)
PHARMACOKINETICS:	• RO-151 and RO-838 concentrations in plasma. • Metformin concentrations with and without RO-151 and RO-838 (concentration ratios based on values at 1.5 hours on day 28 vs. 1.5 hours on day -2/-1).
SAFETY:	• Adverse events (AEs), safety laboratory tests, 12-lead electrocardiograms (ECG), vital signs (including semi-supine and orthostatic blood pressure), physical examinations (including a CNS/neurological exam to test speech, ataxia, and unsteadiness), and measurement of HPA axis function (24-h cortisol profile in plasma/serum and urine, ACTH stimulation test, androgen profile in plasma/serum, urinary metabolites). Since total urine volumes were not obtained for either data set, analysis of the urinary metabolite data is restricted to relative changes in 11β-HSD1, 11β-HSD2 activity, total glucocorticoid excretion, and androgen metabolite excretion.
STATISTICAL METHODS	**Efficacy** A mixed model analysis of variance (ANOVA) was used to estimate the effects of the high and low doses of RO-151 and RO-838 on the primary endpoint. Point estimates and 95% confidence intervals (CIs) were calculated using contrasts from the ANOVA. Similar analyses were undertaken for the secondary efficacy parameters although no formal hypothesis testing was performed. Exploratory Bayesian posterior probabilities for 'weak' and 'strong' trends for reduction in mean daily plasma glucose at week 4 were also calculated. **Pharmacokinetics** Metformin concentration ratios (1.5 hours on day 28 versus 1.5 hours on day -1) were compared between treatment arms using an ANOVA model. In addition, an analysis of covariance (ANCOVA) model was used to investigate the dependence on

treatment of the relationship between the change from baseline in metformin concentrations and the baseline value.

Safety

All data are summarized descriptively as appropriate. For some HPA axis function tests (cortisol and androgen profiles), an ANOVA was applied.

METHODOLOGY:

The study consisted of a screening period (up to 3 weeks), a 4-week pre-randomization period (for washout of oral anti-hyperglycemic and weight-lowering medications other than metformin), a 4-week double-blind treatment period, and a follow-up visit. The total study duration for any one patient was up to 13 weeks. All 12 visits were on an out-patient basis except visit 3 (pre-randomization; telephone), visit 6 (baseline; on-site) and visit 11 (end of treatment; on-site). The efficacy, PK and safety of RO-151 and RO-838 were assessed throughout the study.

EFFICACY RESULTS:

The study failed to show treatment-related improvements in mean daily blood glucose in patients who received RO-151 or RO-838. No statistically significant or clinically relevant placebo-corrected reductions from baseline were observed for either compound (Table 1).

Table 1 Mean Daily Plasma Glucose (mg/dL): Placebo-Corrected Absolute Change from Baseline at Week 4 (LS Mean and 95% CI) (ITT Population)

Absolute Change from Baseline in Area under the Curve of 9 Point Profile
Baseline Used as Covariate - Violations of Code 103 Included
Estimated Absolute Differences
AUCTYPE=Total

Comparison	Estimated Difference	--- Conf. Int. --- Lower Limit	Upper Limit	Confidence Level	p-Value
RO5027838 50 MG QD vs Placebo	-7.06	-25.49	11.37	0.95	0.449
RO5027838 200 MG QD vs Placebo	-1.35	-18.86	16.16	0.95	0.879
RO5093151 5 MG BID vs Placebo	1.43	-16.17	19.04	0.95	0.872
RO5093151 200 MG BID vs Placebo	1.33	-17.00	19.66	0.95	0.886
RO5027838 200 vs 50 MG	5.71	-12.17	23.59	0.95	0.527
RO5093151 200 MG vs 5 MG	-0.11	-18.02	17.81	0.95	0.991

Code 103: More than 3AM and Bedtime Sample Missing on either Day
Program: $PROD/cdpt7234/bp21850/creana_PD_9PGLU.sas Output: 9PGLU_ACHGE.out
15JAN10, 17:34, abtm1
$PROD/cdpt7234/bp21850, pgm: creana_PD_9PGLU.sas, 15JAN10 17:34, abtm1

The study also failed to show statistically significant or clinically relevant treatment-related improvements in fasting and postprandial (meal challenge and OGTT) blood glucose, insulin, C-peptide, and glucagon.

Neither compound showed a clear improvement in insulin sensitivity. In the high dose RO-151 group, however, related parameters including OGTT insulin and C-peptide AUC and C_{max}, HOMA-IR, OGIS, the Matsuda index, pro-insulin, and the insulinogenic indices ISIest and MCRest all showed trends for improvement. Data from two outlier patients with high fasting insulin concentrations at baseline may have contributed to these trends, particularly for HOMA-IR.

In the analysis of inflammatory biomarkers, negative effects were observed at the end of treatment for both compounds on adiponectin and in the low dose RO-838 group only for hsCRP.

Analysis of lipid profiles at baseline and week 4 failed to show evidence of consistent treatment related improvements in lipids for either compound.. For some parameters, including triglycerides and VLDL cholesterol, a negative effect of RO-838 was observed compared to placebo, particularly at the high dose.

Both compounds showed a trend for improvement in HbA1c at week 4, with the largest placebo-corrected effect observed in the low dose RO-151 group (placebo-corrected LS mean -0.37% [95% CI: -0.75, 0.01], p=0.053). Statistical significance was not reached for either compound.

Both compounds also showed a trend for improvement in body weight, particularly in the RO-151 groups. LS mean estimates of the change in body weight at week 4 were -0.28 kg in the placebo group ($p>0.05$) and ranged from -0.86 to -1.67 kg in the active treatment groups (all $p<0.05$). After correcting for placebo, the change from baseline at week 4 reached statistical significance only in the high dose RO-151 group (LS mean -1.39 kg [95% CI -2.54, -0.23], p=0.019). The decreases in body weight were reflected in changes in BMI but not in waist-hip-ratio.

In the 24 hour ABPM, neither compound had a clear and consistent clinically relevant effect on ABPM SBP, DBP, heart rate, or pulse pressure. A trend for decrease was observed for day, night and combined 24 hour SBP recordings in the low dose RO-151 group, but this was not replicated in the high dose group.

PHARMACOKINETIC RESULTS:

No effects of RO-151 or RO-838 were observed on serum metformin concentrations.

SAFETY RESULTS:

RO-838 and RO-151 were well tolerated in this study. The incidence of patients with at least one AE was not different across groups; 38% of patients in the placebo group and 33% to 45% of patients in the four active treatment groups (Table 2). The AE profiles in the RO-838 and low dose RO-151 groups were similar to the profile in the placebo group. In the high dose RO-151 group, slightly higher incidences of headache and certain gastrointestinal (GI) disorders (nausea, diarrhoea, and vomiting) were reported. The majority of AEs in all groups were of mild intensity, transient in nature, and resolved without sequelae. One patient in the low dose RO-151 group experienced hypoglycemia. There were no SAEs, no withdrawals due to an AE, and no deaths.

No clinically relevant effects on laboratory safety parameters were identified for RO-151 or RO-838. Slight increases from baseline within normal limits in mean GGT and alkaline phosphatase were observed in the RO-838 groups, but the changes are not considered to be clinically relevant.

Compared to baseline and placebo, a trend for increase was observed in the high dose RO-838 group only for semi supine SBP and, to a lesser extent, DBP. No detectable trends were observed in the other active treatment groups. No clinically relevant effects of RO-151 or RO-838 were observed on semi-supine heart rate, orthostatic vital signs, ECG parameters, or neurological assessments.

In the HPA axis function tests, up-regulation of the HPA axis in the RO-151 groups with sustained elevation of ACTH secretion was likely due to a slightly increased susceptibility of the adrenal gland to stimulation of the HPA axis and an increase in adrenal androgen precursors in both sexes, especially in females. No signs of upregulation of the HPA axis were observed in the RO-838 groups.

Table 2 Overview of Adverse Events (Safety Population)

	Placebo	RO5027838		RO5093151	
	N=21 No. (%)	50 mg QD N=21 No. (%)	200 mg QD N=24 No. (%)	5 mg BID N=24 No. (%)	200 mg BID N=20 No. (%)
All body systems					
Total patients with ≥ 1AE	8 (38)	9 (43)	10 (42)	8 (33)	9 (45)
Total no. AEs	14	18	14	18	26
Serious AE	-	-	-	-	-
Withdrawal due to AE	-	- [a]	-	-	-
Death	-	-	-	-	-
Related AE [b]	3 (14)	4 (19)	6 (25)	4 (17)	5 (25)
Hypoglycemia	-	-	-	1 (4)	-

a One patient in the low dose RO-838 group ([redacted] was withdrawn from the study due to insufficient therapeutic response (identified by a mild hyperglycemic event).
b Remote, possible or probable.

CONCLUSIONS:

The results of this phase IIa proof-of-principle study in T2D patients on a stable dose of metformin failed to demonstrate that treatment with RO-151 or RO-838 for 4 weeks is effective at lowering mean daily blood glucose. Likewise, despite clear inhibitory effects of both compounds on 11ß-HSD1 activity (RO-151 more than RO-838), neither compound was shown to be effective at improving fasting or postprandial blood glucose, insulin sensitivity, or fasting blood lipids. Trends for improvements in insulin-related parameters (high dose RO-151), HbA1c (RO-151 more than RO-838), body weight (RO-151 more than RO-838) and blood pressure profiles (low dose RO-151) require further investigation.

Neither compound appeared to have an effect on serum metformin concentrations.

RO-151 and RO-838 were well tolerated in this study, with both compounds showing a safety profile that was similar to placebo. The only effect of potential clinical relevance for RO-151 was an up-regulation of the HPA axis, with sustained elevation of ACTH secretion leading to an increase in adrenal androgen precursors in both sexes, particularly in females. For RO-838, the only effect of potential clinical relevance was a trend for increasing SBP/DBP in the high dose group, which was more evident in the clinic than with the more robust 24 hour ABPM readings.