SYNOPSIS OF RESEARCH REPORT [redacted]
(PROTOCOL BC21587)

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

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	A multi-center, double-blind, randomized, parallel group, placebo-controlled 12-week study to investigate glycemic parameters of efficacy, safety/ tolerability and pharmacokinetics of five dose levels of RO4998452 in patients with type 2 diabetes mellitus. Report No [redacted] /November 2010.		
INVESTIGATORS / CENTERS AND COUNTRIES	64 centers in 12 countries/regions (USA, Canada, Mexico, Brazil, Japan, Hong Kong, Russia, Romania, Latvia, Germany, Spain, and Australia)		
PERIOD OF TRIAL	January 22 – October 28, 2009	CLINICAL PHASE	2
OBJECTIVES	<u>Primary</u>: To determine the absolute change in hemoglobin A1c (HbA1c) concentration from baseline to the end of the treatment period compared to placebo. <u>Secondary</u>: To determine additional efficacy parameters, safety and tolerability following RO4998452 administration compared to placebo, including – the absolute change in fasting plasma glucose from baseline to the end of the treatment period – the glycemic response with additional parameters of glycemic control (such as mean daily blood glucose obtained from 7-point plasma glucose profile, fructosamine, meal tolerance test) – the tolerability and safety profile – the effects on body weight – the pharmacokinetics and the exposure-response relationship of RO4998452 including the influence of covariates (by a population analysis approach). <u>Exploratory</u>: To determine – the effects on feeling of hunger and thirst – the dose-response curve of RO4998452 on 24-h urinary glucose excretion		
STUDY DESIGN	Multi-center, randomized, double-blind, parallel fixed dose, placebo-controlled dose range-finding study		

<table>
<tr><td>NUMBER OF SUBJECTS</td><td>Planned: 300; total randomized: 398 (209 men, 189 women)<table><tr><td>Placebo</td><td>2.5 mg</td><td>5 mg</td><td>10 mg</td><td>20 mg</td><td>40 mg</td></tr><tr><td>N = 66</td><td>N = 67</td><td>N = 65</td><td>N = 66</td><td>N = 65</td><td>N = 69</td></tr></table></td></tr>
<tr><td>DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION</td><td>Male and female patients with type 2 diabetes, either (1) treated with diet and exercise and a stable dose of metformin (1.5 g - 3 g per day) or (2) treated with diet and exercise alone.
Screening HbA1c ≥ 7.0%, ≤ 10.0%; BMI > 22 kg/m^2, ≤ 45 kg/ m^2</td></tr>
<tr><td>TRIAL DRUG / STROKE (BATCH) No.</td><td>RO4998452 capsules of dose strengths 2.5, 10, 20 mg</td></tr>
<tr><td>DOSE / ROUTE / REGIMEN / DURATION</td><td>2.5, 5, 10, 20, or 40 mg RO4998452 orally once daily (before breakfast) for 12 weeks</td></tr>
<tr><td>REFERENCE DRUG / STROKE (BATCH) No.</td><td>Matching placebo capsules</td></tr>
<tr><td>DOSE / ROUTE / REGIMEN / DURATION</td><td>Daily oral doses for 12 weeks</td></tr>
<tr><td>CRITERIA FOR EVALUATION</td><td></td></tr>
<tr><td>EFFICACY:</td><td>Primary: absolute change in HbA1c from baseline to the end of the treatment period.
Secondary: absolute change from baseline to the end of the treatment period for fasting plasma glucose, mean daily glucose concentration (obtained from 7-point profile assessed by the patients at home), fructosamine concentration, HOMA-IR index, meal tolerance test (0-3 h glucose AUC, 0-3 h insulin AUC, 0-3 h urinary glucose excretion), body weight, waist to hip ratio, abdominal circumference, proportion of patients successfully treated to target (last HbA1c value under treatment < 7%; ≤ 6.5%).
Exploratory: Feelings of hunger and thirst (visual analogue scale), 24-h urinary glucose excretion.</td></tr>
<tr><td>PHARMACODYNAMICS:</td><td>Total proinsulin, glucagon, C-peptide, free fatty acids, fructosamine, fibrinogen, adiponectin, 7-point glucose profile (patient self-assessment)</td></tr>
<tr><td>PHARMACOKINETICS:</td><td>Apparent clearance, apparent volume of distribution (V/F) for RO4998452 and metabolites, as appropriate. PK model to be developed based on data from this and other studies.</td></tr>
<tr><td>SAFETY:</td><td>Adverse events, vital signs, ECG, laboratory tests, adjudication of cardiovascular and cerebrovascular adverse events</td></tr>
<tr><td>STATISTICAL METHODS</td><td>Analysis of covariance with previous treatment, geographical region and the corresponding baseline value as covariables for HbA1c and for secondary efficacy parameters as appropriate
Summaries and listings for adverse events, laboratory test results</td></tr>
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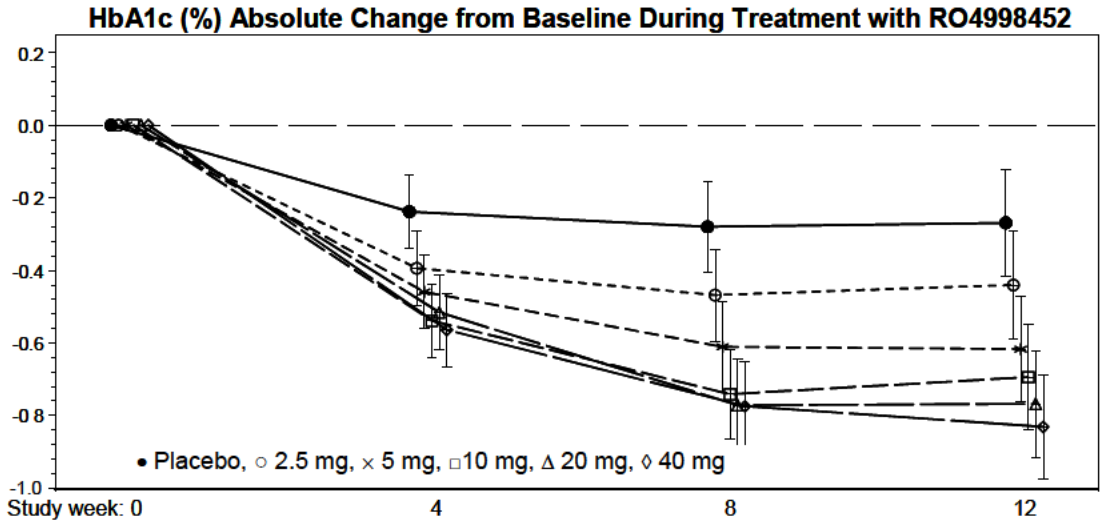
METHODOLOGY:

Eligible patients were instructed to follow a diet and exercise plan. After a 4-week single-blind placebo run-in phase, patients were assigned to one of 6 treatment arms (placebo, or 2.5, 5, 10, 20, or 40 mg RO4998452). Patients were not hospitalized, but returned to the clinic at regular intervals and were provided with a home glucose monitoring device.

EFFICACY RESULTS:

Treatment with RO4998452 for 12 weeks resulted in a dose dependent reduction of mean HbA1c up to -0.83% and in a statistically significant difference to placebo, except for the lowest dose of 2.5 mg (difference to placebo -0.56% at 40 mg dose, see figure and table below). Secondary efficacy parameters, such as mean fasting plasma glucose, fructosamine concentration, and body weight, also improved dose dependently during treatment with RO4998452. The proportion of patients treated to the target value of HbA1c < 7% at the end of the treatment period increased in a dose-dependent manner (from 17.2% in the 2.5 mg arm to 40.9% in the 40 mg arm).



Parameter	Placebo N = 65	RO4998452 2.5 mg N = 64	RO4998452 5 mg N = 65	RO4998452 10 mg N = 66	RO4998452 20 mg N = 64	RO4998452 40 mg N = 66
Primary Efficacy Endpoint						
HbA1c (%)	-0.27	-0.44	-0.62	-0.69	-0.77	-0.83
Placebo corrected		-0.17	-0.35 [a]	-0.43 [b]	-0.50 [b]	-0.56 [b]
Secondary Efficacy Endpoints						
Fasting plasma glucose (mmol/L)	-0.50	-0.02	-0.64	-1.04	-0.94	-1.42
Placebo corrected		0.48	-0.14	-0.54	-0.43	-0.92
Mean daily glucose concentration (mmol/L)	-0.28	-0.56	-0.80	-1.06	-0.88	-1.30
Placebo corrected		-0.28	-0.52	-0.78	-0.60	-1.02
Fructosamine concentration (µmol/L)	-0.37	-11.20	-12.99	-16.71	-18.76	-20.62
Placebo corrected		-10.83	-12.62	-16.34	-18.39	-20.25
Meal tolerance test: 0-3h mean glucose concentration (mmol/L)	-0.66	-1.69	-2.15	-2.35	-2.44	-2.88
Placebo corrected		-1.04	-1.49	-1.69	-1.79	-2.23
Body weight (kg)	-0.7	-1.6	-1.9	-2.2	-2.6	-2.8
Placebo corrected		-0.8	-1.1	-1.5	-1.8	-2.1
Proportion of patients treated to target HbA1c < 7% (%)	13.8 %	17.2 %	23.1 %	24.2 %	34.4 %	40.9 %
Placebo corrected		3.3 %	9.2 %	10.4 %	20.5 %	27.1 %
Proportion of patients treated to target HbA1c < 6.5% (%)	3.1 %	6.3 %	9.2 %	6.1 %	10.9 %	16.7 %
Placebo corrected		3.2 %	6.2 %	3.0 %	7.9 %	13.6 %

[a] unadjusted p-value 0.0005.
[b] unadjusted p-value < 0.0001.

PHARMACODYNAMIC RESULTS:

A clear dose response was observed for mean fructosamine concentrations and for the 0-3h mean glucose concentration of the meal tolerance test, which is linked to the dose-dependent improvement of the pre-meal fasting plasma glucose. Mean daily glucose levels as monitored by the patients showed a trend to a dose-dependent reduction. Other PD parameters showed little change with no clear dose-dependent trend.

PHARMACOKINETIC RESULTS:

Presented in separate report.

SAFETY RESULTS:

Daily oral doses of RO4998452 for 12 weeks were well tolerated. The incidence of AEs was comparable between active treatment arms and placebo, see table below. There were no deaths and no treatment-related SAEs. The rate of withdrawals due to AEs was low (1-2 patients per treatment arm [≤ 3%]) and comparable between active treatment groups and placebo. Treatment with RO4998452 did not increase the incidence of hypoglycemia, urinary or genital tract infection, or cardiovascular events relative to placebo. There were no clinically relevant findings for vital signs, ECGs, or laboratory safety tests.

Overview of Safety of Treatment with RO4998452 for 12 Weeks						
Event	Placebo N = 66 No. (%)	2.5 mg N = 66 No. (%)	5 mg N = 65 No. (%)	10 mg N = 66 No. (%)	20 mg N = 64 No. (%)	40 mg N = 67 No. (%)
Number of patients with at least one Adverse Event	25 (37.9)	24 (36.4)	30 (46.2)	25 (37.9)	23 (35.9)	31 (46.3)
Hypoglycemic Episode	2 (3.0)	1 (1.5)	0 (-)	2 (3.0)	0 (-)	0 (-)
Cardiovascular/ Cerebrovascular Event	3 (4.5)	0 (-)	1 (1.5)	1 (1.5)	1 (1.6)	0 (-)
Urogenital Infection	2 (3.0)	1 (1.5)	5 (7.7)	2 (3.0)	2 (3.1)	3 (4.5)
Polyuria	0 (-)	1 (1.5)	0 (-)	4 (6.2)	1 (1.6)	3 (4.5)
Serious Adverse Event	1 (1.5)	2 (3.0)	0 (-)	0 (-)	0 (-)	1 (1.5)
AE Withdrawals	2 (3.0)	1 (1.5)	0 (-)	2 (3.0)	0 (-)	1 (1.5)

CONCLUSIONS:

This 12-week study met its primary efficacy endpoint showing a statistically significant reduction of HbA1c from baseline at the end of treatment for RO4998452 doses of ≥ 5 mg with a maximum decrease of 0.56% in the 40 mg arm relative to placebo. In addition, secondary glycemic parameters and body weight showed a dose-dependent improvement. Administration of RO4998452 doses ranging from 2.5 to 40 mg once daily for 12 weeks was well tolerated. No new clinical safety concerns were identified in addition to the known fungal genital infections reported with other SGLT2 inhibitors in development.