

## Supplementary Appendix 2

This appendix has been provided by the authors to give readers additional information about their work.

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Clinical Research & Development

Nateglinide (Starlix®)/DJN608B

Protocol DJN608B2302

**A multinational, randomized, double-blind, placebo-controlled, forced-titration, 2 x 2 factorial design study of the efficacy and safety of long term administration of nateglinide and valsartan in the prevention of diabetes and cardiovascular outcomes in subjects with impaired glucose tolerance (IGT)**

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## List of abbreviations

ac	Before meals
ACE-I	Angiotensin-converting enzyme inhibitor
ALT	Alanine aminotransferase
ARB	Angiotension II receptor blocker
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CHD	Coronary heart disease
CRF	Case Report/Record Form
CS&E	Clinical Safety and Epidemiology
CVD	Cardiovascular disease
CRO	Contract Research Organization
DSMB	Data and Safety Monitory Board
ECG	Electrocardiogram
FPFV	First-patient first-visit
FPG	Fasting Plasma Glucose
HbA <sub>1c</sub>	Glycated hemoglobin A <sub>1c</sub>
IEC	Independent Ethics Committee
IGT	Impaired glucose tolerance (FPG < 7.0 mmol/L, 2hrOGTT > 7.8 mmol/L < 11.1 mmol/L)
IRB	Institutional Review Board
IVRS	Interactive voice response system
LATAM	Latin America group of countries
LDH	Lactate dehydrogenase
LPFV	Last-patient first-visit
MI	Myocardial infarction
NYHA	New York Heart Association
o.d.	Once a day
2hr OGTT	Oral glucose tolerance test (in this protocol, evaluation of blood glucose 2 hrs after oral administration of a 75 gram equivalent of glucose)
PTCA	Percutaneous transluminal coronary angioplasty
p.o.	By mouth
RF	Risk factor for a major cardiovascular event
SAE	Serious Adverse Event
SGOT	Serum glutamate-oxalacetate transaminase= AST
SGPT	Serum glutamate-pyruvate transaminase= ALT
SOP	Standard operating procedure
VAS	Visual analogue scale

## 1 Introduction

The strong association between increased glycemia and increased risk of cardiovascular complications, together with the high socio-economic burden of diabetes mellitus makes the concept of preventing diabetes very attractive (1-6). Persons with impaired glucose tolerance are at high risk for developing clinical diabetes and cardiovascular disease (7). By definition, persons with impaired glucose tolerance have higher than normal (but not diabetic) glucose responses to an oral glucose challenge and, in most cases, manifest an impairment in early insulin secretion as well (8). The impairment in early insulin secretion is thought to play a key role in the progression of impaired glucose tolerance to diabetes (8).

There is growing evidence that changes in life-style including exercise and dietary habits can reduce the risk of progression to diabetes in subjects with impaired glucose tolerance (9-12). However, despite these encouraging findings diet and exercise are not fully effective and cannot be implemented in all clinical settings. Therefore, the unmet medical need to prevent diabetes remains high.

Nateglinide is a D-phenylalanine derivative with insulinotropic activity. Its major known effect is exerted directly on pancreatic  $\beta$ -cell  $K^+$  ATP-channels and results in membrane depolarization, entry of extracellular calcium and insulin exocytosis. Nateglinide is indicated for the treatment of Type 2 diabetes mellitus as monotherapy and/or in combination with metformin. The safety and tolerability of nateglinide 30 mg, 60 mg, and 120 mg a.c. was assessed, in comparison to placebo, in subjects with impaired glucose tolerance (2 hr post-glucose challenge  $> 7.8$  mmol/L and FPG  $< 7$  mmol/L). Nateglinide 30 mg a.c. was well tolerated and induced a physiological insulin secretion pattern in subjects with IGM. Nateglinide 60 mg a.c. was associated with a low incidence of confirmed hypoglycemia. The incidence of confirmed hypoglycemia was considerably higher with nateglinide 120 mg a.c. therapy. All doses of nateglinide decreased peak glucose concentrations by  $\geq 1$  mmol/L between 40 and 60 minutes.

Recent studies suggest that the angiotensin converting enzyme inhibitors ramipril and captopril decrease the incidence of diabetes (13, 14). The mechanism for this is not known, but drugs in this class have been shown in some studies to improve the peripheral action of insulin. There are relatively few studies examining whether angiotensin II receptor blockers (ARB) have similar effects on insulin sensitivity, however, losartan has been shown to improve insulin action by almost 30% in patients with mild-to-moderate hypertension (15). ARBs, through blockade of the effects of angiotensin II may, therefore, act to improve insulin resistance, the second major metabolic defect underlying the development of diabetes. Studies also indicate that inhibition of angiotensin II decreases the incidence of cardiovascular events in high-risk populations. These benefits are thought to be mediated by lower blood pressure and through direct vascular effects.

Valsartan is the S-enantiomer of N-Valeryl-N-[[2'-(1H tetrazol-5-yl) biphenyl-4-yl] methyl]-valine and is a specific angiotensin II antagonist acting on the  $AT_1$  receptor subtype. Valsartan 40 mg, 80 mg and 160 mg o.d. is indicated in the treatment of hypertension. In a recently completed trial in patients with chronic congestive heart failure (NYHA Class II – IV), valsartan (40 – 160 mg b.i.d.) had a neutral effect on mortality, however significantly

reduced the risk for a first morbid event, a composite of death, hospitalization for congestive heart failure, sudden death with resuscitation and need for i.v. inotropic and vasodilating therapy.

In this placebo-controlled trial, the effect of nateglinide and valsartan on progression to diabetes and prevention of cardiovascular morbidity and mortality events will be assessed in subjects with impaired glucose tolerance at increased risk of a cardiovascular event.

## 2 Study objectives

### Primary objectives:

- To evaluate the effect of long-term administration of nateglinide and valsartan on the progression to diabetes in subjects with impaired glucose tolerance (IGT) at increased risk of a cardiovascular event.
- To evaluate the effect of long-term administration of nateglinide and valsartan on cardiovascular morbidity and mortality, defined as a composite endpoint (extended CV endpoint) of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, revascularization procedure, and hospitalization for congestive heart failure or unstable angina. Data on the components of this composite endpoint will be collected for the entire duration of this trial.
- To evaluate the effect of long-term administration of nateglinide and valsartan on cardiovascular morbidity and mortality, defined as a composite endpoint (core CV endpoint) of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and hospitalization for congestive heart failure). Data on the components of this composite endpoint will be collected for the entire duration of this trial.

To address the study objectives regarding nateglinide the study aims to demonstrate at least one of the three primary clinical hypotheses for nateglinide:

- N1 Nateglinide will reduce the incidence of or delay the progression to diabetes in individuals with impaired glucose tolerance.
- N2 Nateglinide will reduce the incidence of or delay the occurrence of cardiovascular morbidity and mortality as measured by the extended CV endpoint in this at-risk population.
- N3 Nateglinide will reduce the incidence of or delay the occurrence of cardiovascular morbidity and mortality as measured by the core CV endpoint in this at-risk population.

To address the study objectives regarding valsartan the study aims to demonstrate at least one of the three primary clinical hypotheses for valsartan:

- V1 Valsartan will reduce the incidence of or delay the progression to diabetes in individuals with impaired glucose tolerance.
- V2 Valsartan will reduce the incidence of or delay the occurrence of cardiovascular morbidity and mortality as measured by the extended CV endpoint in this at-risk population.
- V3 Valsartan will reduce the incidence of or delay the occurrence of cardiovascular morbidity and mortality as measured by the core CV endpoint in this at-risk population.



### **3 Investigational plan**

#### **3.1 Overall study design**

This is a multinational, randomized, double-blind, placebo-controlled, forced-titration, 2 x 2 factorial design trial to assess the effect of nateglinide and valsartan on the prevention of diabetes and cardiovascular events in subjects with impaired glucose tolerance (2hr post-challenge glucose > 140 mg/dL/7.8 mmol/L but < 200 mg/dL/11.1 mmol/L and FPG ≥ 95 mg/dL/5.2 mmol/L but < 126 mg/dL/7.0 mmol/L) and increased risk for a cardiovascular event. The three primary efficacy endpoints of this study are time to progression to diabetes, time to first occurrence of an extended CV endpoint and time to first occurrence of a core CV endpoint. These three endpoints will be tested in parallel using a closed testing procedure for each drug. It is thus possible to achieve statistical significance for any one endpoint independent of the others.

Originally, two formal efficacy interim analyses were foreseen which were to take place when approximately 687 and 1031 subjects had had an extended CV endpoint, corresponding to 50% and 75% of the 1374 target subjects, respectively (Section 6.1.7 of the study protocol). A first formal interim analysis was performed in December 2005 with 412 patients (30% of the target subjects) having experienced an extended CV endpoint. The second efficacy interim analysis will not be conducted.

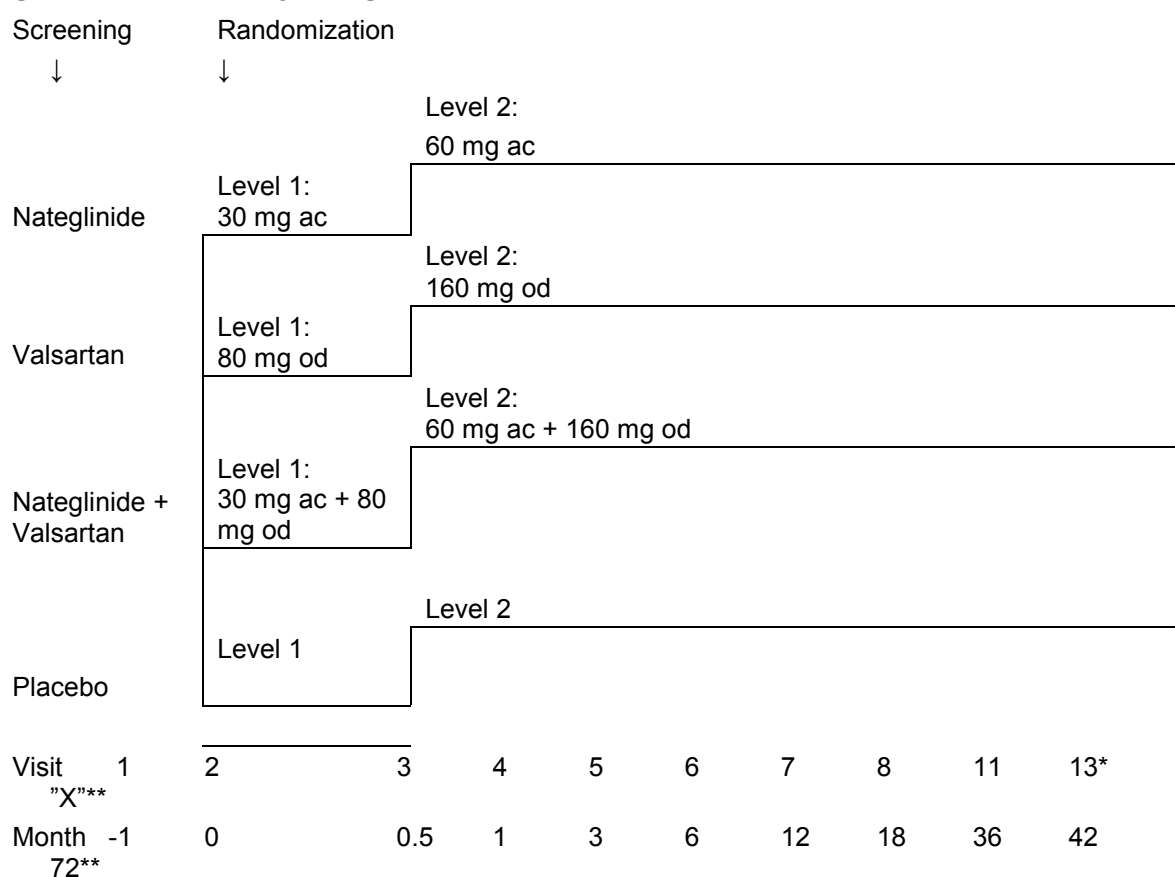
Approximately 9152 subjects from 800-900 centers in approximately 39 countries are to be randomized. Screening for eligibility will take place 1 month prior to treatment start and requires an oral glucose tolerance test (OGTT) to confirm eligibility. After receipt of the appropriate baseline data and cardiovascular disease status, eligible subjects will be randomly assigned to one of the four treatment groups (ratio 1:1:1:1), i.e. nateglinide 60 mg ac, valsartan 160 mg od, the combination of nateglinide 60 mg ac and valsartan 160 mg od, or placebo, using a computerized interactive voice response system (IVRS).

Study accrual is expected to require approximately 18 months. A total of 1374 patients with an extended CV endpoint are required. A total duration of follow-up of 5 years and 9 months after FPFV is anticipated under the original protocol assumptions. Based on the observed CV event rate at the time of Amendment No. 5, the projected total duration of the trial is approximately 8 years.

A diagram of the study design is shown below with times indicated relative to treatment start:

**Figure 1**

**Study design schematic**



\* Visit 12 has been eliminated.

\*\*The duration and visit number are approximate, depending on the patient accrual rate, length of patient accrual, and observed event rate.

At Visit 1, eligible subjects will enter a treatment-free run-in period for up to 4 weeks. At randomization (Visit 2) subjects will be assigned to either nateglinide 30 mg before meals, valsartan 80 mg once daily, the combination of nateglinide 30 mg before meals and valsartan 80 mg once daily or placebo, respectively. After 2 weeks of treatment (Visit 3), subjects will be uptitrated to receive either nateglinide 60 mg before meals, valsartan 160 mg once daily, the combination of nateglinide 60 mg before meals and valsartan 160 mg once daily or placebo, respectively. Subjects not tolerating the higher dose (Level 2) will be downtitrated to receive Level 1. Subjects not tolerating the lower dose (Level 1) will have a treatment interruption. Starting at Visit 3 and throughout the study an attempt should be made to reach the highest dose level (Level 2), if medically acceptable. Following each change in dose level or reinitiation of treatment, tolerability will be assessed after 2 weeks of exposure. In subjects either currently on or who are initiated on an ACE inhibitor, potassium and creatinine testing will be performed locally.

FPG will be measured semi-annually starting at Visit 6 (Month 6) and continuing through visit 11 (month 36). Thereafter FPG will be performed annually through the termination of the trial (as part of OGTT).

### **3.1.1 Monitoring Committees**

Several committees will be responsible for the management of the study and monitoring of the safety of the study subjects.

#### **3.1.1.1 Executive/Steering Committee**

The Executive Board is part of the Steering Committee. The role of the Executive Board is to disseminate information to the Steering Committee. The Executive Board leads the team in the performance of its functions and resolves issues not requiring full Steering Committee input or issues where there are differences of opinion within the Steering Committee. The Executive/Steering Committee is blinded to all information regarding treatment assignments while the trial is ongoing.

The main functions of the Executive/Steering Committee include: Review and approve all protocol amendments and substudies; review of study progress and transmission of information to the individual investigators; acting on recommendations of the DSMB and Endpoint Committee; review and approval of publications/presentations.

#### **3.1.1.2 Data and Safety Monitoring Board**

The Data and Safety Monitoring Board is a committee independent of Novartis. This board has the following responsibilities: overseeing the welfare of patients enrolled in the trial; reviewing the protocol and interim analysis plan; reviewing safety, efficacy, protocol compliance and trial progress at specified intervals and ad hoc if requested by the Executive/Steering Committees; making recommendations to the Executive/Steering Committees about any problems or potential problems. Although the DSMB will independently decide on appropriate procedures, the stopping rules specified in the design of the protocol will be considered when reviewing efficacy and safety data. Any major recommendation, e.g. amending the protocol or stopping the trial, must be reviewed and ratified by the Executive/Steering Committee prior to its enactment.

#### **3.1.1.3 Endpoint Committees**

The Endpoint Committees will not include any Novartis personnel. The members may not participate directly in the conduct of this trial.

The Cardiovascular Endpoint Committee will have the following responsibilities: to agree on the standard classifications and definitions of cardiovascular endpoints that will be used for the adjudication; to provide an independent and blinded assessment of the cardiovascular efficacy endpoints as defined in the protocol, based on the standardized classification and definitions. The decisions made by the Cardiovascular Endpoint Committee will be considered final and will form the basis of all analyses for health authority submissions and publications. The Cardiovascular Endpoint Committee will conduct this adjudication according to Standard Operating Procedures jointly developed and agreed to by the Committee and the sponsor.

The Diabetes Endpoint Adjudication Committee (DEAC) will have the following responsibilities: jointly with the sponsor it will develop Diabetes Endpoint Adjudication Charter for the adjudication of cases suggestive of diabetes but not meeting the formal,

laboratory test-based definition of progression to diabetes (Section 3.5.3 of the study protocol). The Diabetes Endpoint Adjudication Committee will be responsible for an independent and blinded assessment of all suspected cases of diabetes.

The DEAC will base their decision upon review of glucose levels from local laboratories, information on use of glucose lowering medication, and patient profiles which are based on the CRF data.

Committee members will review each case independently and indicate whether the subject should be considered as being diabetic (Yes/No) and, if yes, provide a date of onset to diabetes. A 2/3 majority votes are required (for both parameters) for the final decision. In the case where the decision did not achieve majority vote, the committee must confer to discuss the case for final judgment.

The decisions made by the Diabetes Endpoint Committee will be considered final. Cases adjudicated as 'progression to diabetes' will be counted for the primary diabetes endpoint along with the cases defined by the central laboratory results.

## **3.2 Discussion of design**

### **Trial design**

The double-blind, randomized, placebo-controlled, parallel design has been shown to reduce bias in comparing different treatment regimens with respect to efficacy and safety. Three primary endpoints will be tested using a closed testing procedure separately for each of the two investigational drugs. This closed testing procedure splits the overall level one-sided alpha of 2.5% asymmetrically between time to progression to diabetes and time to first occurrence of the two cardiovascular endpoints, allocating one-sided 0.5% to the progression to diabetes endpoint and one-sided 2% to the extended and core CV endpoints, equally split between the cardiovascular endpoints (Section 6.1.5.1 of the study protocol).

The total trial duration is event-driven. A total of 1374 subjects with an extended CV endpoint are required for statistical analysis (a total duration of follow-up of 5 years and 9 months after FPFV is anticipated under the original protocol assumptions). Based on the observed CV event rate at the time of Amendment No. 5, the projected total duration of the trial is approximately 8 years.

Besides statistical considerations for an asymmetrical alpha allocation (event rate and treatment effect are assumed to be larger for progression to diabetes, which results in considerable larger statistical power than for the cardiovascular endpoints), the proposed closed testing procedure also seems justified from a scientific perspective since it is possible to achieve statistical significance for each individual endpoint alone.

The factorial design allows for efficient use of number of patients foreseen in one study to establish the efficacy of nateglinide and valsartan, as well as for exploration of the two drug effects in combination in supportive analyses.

## **Dose and dose interval**

A pre-prandial dosing of nateglinide has been shown to be efficacious and safe in subjects with impaired glucose tolerance. A once daily dosing of valsartan has been shown to be safe in normotensive subjects.

Titration is used: (i) to uptitrate the majority of subjects to the high dose of nateglinide 60 mg ac and valsartan 160 mg od and thus theoretically maximize the number of responders to both drugs; (ii) to allow subjects with problems tolerating the high dose to remain in the trial under presumed therapeutic doses; and (iii) to allow gradual exposure to the nateglinide 60 mg ac and valsartan 160 mg od dose.

## **Population**

The target population for treatment are subjects with impaired glucose tolerance and increased risk for cardiovascular events. Impaired glucose tolerance is characterized by higher than normal fasting and 2 h post-challenge glucose values which however are lower than in diabetic patients. Subjects with impaired glucose tolerance are at increased risk to develop diabetes. Subjects entering the trial also have either a cardiovascular risk factor or disease which can result in cardiovascular complications, including death.

The protocol's inclusion/exclusion criteria define this high risk population.

## **Controls/comparators**

It is not expected that placebo will have an effect on glucose metabolism or cardiovascular morbidity and mortality. The inclusion of a placebo treatment arm will allow for a direct, concurrent comparison of nateglinide and valsartan and placebo, respectively, which should provide an objective measure for the effectiveness of each drug.

## **Blinding**

Patients and investigators will be blinded during the double-blind treatment period. In addition, the treatment codes will remain blinded to all Novartis (or other contracted) personnel involved in monitoring the trial until after the database is locked for final analysis. These blinding conditions will reduce the chance of introducing bias during data collection and monitoring.

## **Measures**

The efficacy of nateglinide and valsartan will be determined using validated measures of diagnosis of diabetes, i.e. OGTT and/or fasting glucose levels as well as adjudication of suspected cases of diabetes; occurrence of cardiovascular morbidity/mortality events with adjudication of each event; and selected biochemical parameters. The health economics assessments performed in this trial will be used to provide economic data and will be described in a separate trial protocol and reported separately.

### **3.3 Study population**

#### **3.3.1 Patient population**

Male and female subjects with impaired glucose tolerance on OGTT screening and  $\geq 1$  cardiovascular risk factor(s) (RF) or  $\geq 1$  cardiovascular disease (CVD) conditions are eligible to participate. Approximately 2288 subjects will be randomized per treatment group. A discussion of sample size calculations can be found in Section 6 (Statistical Methods).

Eligible subjects are defined by the following inclusion and exclusion criteria assessed during the screening period. No deviations from the inclusion/exclusion criteria will be allowed.

#### **3.3.2 Inclusion and exclusion criteria**

##### **Inclusion criteria**

- Written informed consent to participate in this study.
- Males and females. Females must be surgically sterile or postmenopausal.
- Age 50 years or older
- Presence of RF(s) (see Table 1) or CVD(s) (see Table 2) at Visit 1
  - age 50 to 54 years - 1 or more CVD(s)
  - age 55 years and older - 1 or more RF(s) or 1 or more CVD(s)
- FPG  $\geq 95$  mg/dL (5.3 mmol/L) and less than 126 mg/dL (7.0 mmol/L) at Visit 1
- 2hr post-challenge glucose (after a 75-g OGTT)  $\geq 140$  mg/dL (7.8 mmol/L) but less than 200 mg/dL (11.1 mmol/L) at Visit 1
- Ability and willingness to comply with all study requirements

**Table 1 Cardiovascular risk factors (RFs)**

<ul style="list-style-type: none"><li>• Family history of premature CHD (definite myocardial infarction or sudden death before 55 years of age in father or other male first-degree relative, or before 65 years of age in mother or other female first-degree relative)</li><li>• Current cigarette smoking (defined as smoking at least 10 cigarettes/day on a regular basis for at least 5 years prior to inclusion in the study; if the patient has quit smoking, s/he will be considered a smoker if she/he stopped less than 12 months before inclusion)</li><li>• Hypertension (&gt;140mm Hg systolic or 90mm Hg diastolic or on anti-hypertensive medication)</li><li>• Low HDL cholesterol (&lt;40 mg/dL [1.0 mmol/L])</li><li>• High LDL (<math>\geq</math> 160 mg/dL [4.1 mmol/L]) or high non-HDL (<math>\geq</math>190 mg/dL [4.9 mmol/L]) if triglycerides are &gt;200 mg/dL (2.3 mmol/L) or on lipid-lowering therapy.</li><li>• Left ventricular hypertrophy with strain pattern defined as per ECG (Sokolow and Lyon criteria or Cornell criteria)</li><li>• Known microalbuminuria (&gt;30 mg/g creatinine)</li></ul>
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**Table 2 Cardiovascular Diseases (CVD)**

<ul style="list-style-type: none"><li>• Previous myocardial infarction (&gt;1 month ago)</li><li>• Stable angina or unstable angina (&gt;1 month ago) each with documented multivessel coronary disease; &gt;50% stenosis in at least two major coronary arteries, or positive stress test</li><li>• Multivessel PTCA &gt;1 month ago</li><li>• Multivessel CABG &gt; 4 years ago or with angina</li><li>• Previous limb bypass surgery or percutaneous angioplasty</li><li>• Previous non-traumatic limb or foot amputation</li><li>• History of intermittent claudication with ankle:arm blood pressure ratio of <math>\leq</math> 0.80 in at least one side</li><li>• Significant peripheral stenosis (&gt;50%) documented by angiography</li><li>• Stroke of atherosclerotic origin &gt;1 month ago</li></ul>
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### Exclusion criteria

- Failure to provide written informed consent
- Evidence of hepatic disease defined as SGOT or SGPT  $\geq$  2 times the upper limit of normal at Visit 1
- Renal failure with a serum creatinine >2.5 mg/dL (221  $\mu$ mol/L) at Visit 1
- Clinically significant laboratory abnormalities that may interfere with the assessment of safety and/or efficacy of the study drug, other than hyperglycemia, hyperinsulinemia, and glycosuria.
- Patients requiring thyroid hormone replacement who have been on their current medication dosage for less than 3 months prior to month –1.
- History of malignancy including leukemia or lymphoma (but not basal cell skin cancer) within the last 5 years

- Patients on an ACE inhibitor for hypertension who are unable or unwilling to discontinue the medication under supervision of their physician at least four weeks prior to screening and during the full course of double-blind treatment. A subject may be washed out from an ACE inhibitor only, if in the investigator's opinion, it is in the best interest of the subject and/or the subject has been intolerant to the ACE inhibitor. For those patients taken off an ACE inhibitor with the intent to enter the patient in the study, written informed consent will be obtained at the time of discontinuation of medication (at least 4 weeks prior to the screening visit). It is the physician's responsibility to appropriately monitor the patient during this period.
- Note – more details on the use of ACE inhibitors are provided in Section 3.4.7.
- Patients on an ARB who are unable or unwilling to discontinue the medication under supervision of their physician at least four weeks prior to screening and during the full course of double-blind treatment. A subject may be washed out from an ARB only, if in the investigator's opinion, it is in the best interest of the subject. For those patients taken off an ARB with the intent to enter the patient in the study, written informed consent will be obtained at the time of discontinuation of medication (at least 4 weeks prior to the screening visit). It is the physician's responsibility to appropriately monitor the patient during this period.
- Use of oral antidiabetics or insulin within the last 5 years
- History of clinically significant autoimmune disorders such as Systemic Lupus Erythematosus
- History of active substance or alcohol abuse within the last year
- Known hypersensitivity or contraindication to nateglinide or valsartan
- History of noncompliance to medical regimens and/or patients who are considered potentially unreliable
- Previous investigational drug treatment within the past month, unless local health authorities mandate a longer period
- Congestive heart failure NYHA Class 3 or 4
- Presence of any concomitant condition which, in the opinion of the investigator or the sponsor, could interfere with the interpretation of efficacy and safety data gathered in this trial.
- Chronic (> 7 days) concomitant use of oral corticosteroids within 1 month prior to screening
- Myocardial infarction, diagnosis of stable or unstable angina, multivessel PTCA or CABG, limb bypass surgery or percutaneous angioplasty, non traumatic limb or foot amputation, or stroke of atherosclerotic origin within 4 weeks prior to Visit 1 and the time period between Visit 1 and Visit 2

### 3.3.3 Interruption of treatment

All randomized patients, including patients who have achieved a glycemic and/or non-fatal cardiovascular endpoint, should remain on trial treatment (Treatment A, Treatment B) until death or trial end. The following conditions may be reasons to interrupt the trial treatment:



- the patient decides it is in his/her best interest (i.e., patient unwilling to take medication)
- the investigator considers it advisable or in the patient's best interest
- adverse experience(s)
- abnormal laboratory value(s)

Each treatment (Treatment A, Treatment B) can be interrupted individually. The reason for treatment interruption will be collected. If study treatment is interrupted, every effort must be made to reinstate treatment as soon as possible and medically acceptable. Reinstatement of trial treatment is not subject to a time limit and may occur after days, weeks, months, or even years. The number of attempts to re-initiate is also not limited. When treatment is re-initiated, it is not necessary to begin with the lowest dose level. At the investigator's discretion, re-initiation of trial treatment may start with the last dose level. Patients with a treatment interruption should continue the protocol visit schedule and comply with all study procedures, except treatment dispense.

### **3.4 Treatments**

Novartis will supply all study medication.

#### **3.4.1 Investigational therapy and reference therapy**

##### **Nateglinide or matching placebo**

Nateglinide or matching placebo will be labeled as Treatment A. Nateglinide 30 mg (Level 1), nateglinide 60 mg (Level 2) or matching placebo will be provided as a tablet.

Subjects will be instructed to take one tablet 1-30 minutes before each main meal of the day. The tablet should be taken with a glass of water. If a meal is missed, the subject should not take a tablet. On the day of the visit no medication should be taken until the visit has been completed. After the visit has been completed, the subject will be instructed to resume intake of the newly dispensed medication.

##### **Valsartan or matching placebo**

Valsartan or matching placebo will be labeled as Treatment B. Valsartan 80 mg (Level 1), valsartan 160 mg (Level 2) or matching placebo will be provided as capsules.

Subjects will be instructed to take one capsule daily in the morning with the exception of the day of the visit where the dose has to be withheld until the visit has been completed. After the visit has been completed, the subject will be instructed to resume intake of the newly dispensed medication.

#### **3.4.2 Treatment schedule**

At Visit 1, eligible subjects will enter a treatment-free run-in period for up to 4 weeks. At randomization (Visit 2) subjects will be assigned to either nateglinide 30 mg before meals, valsartan 80 mg once daily, the combination of nateglinide 30 mg before meals and valsartan 80 mg once daily or placebo. After 2 weeks of treatment (Visit 3), subjects will be uptitrated to receive either nateglinide 60 mg before meals, valsartan 160 once daily, the combination of

nateglinide 60 mg before meals and valsartan 160 mg once daily or placebo, respectively. The criteria for titration are given below. Subjects not tolerating the higher dose (Level 2) will be downtitrated to receive Level 1. Subjects not tolerating the lower dose (Level 1) will have a treatment interruption. Starting at Visit 3 and throughout the study an attempt should be made to reach the highest dose level (Level 2), if medically acceptable. Following each increase in dose level or reinitiation of treatment, tolerability must be assessed after 2 weeks of exposure. In patients either currently on or who are initiated on an ACE inhibitor, potassium and creatinine testing will be performed locally.

The patient should not take the morning dose of either medication or eat breakfast on the day of a scheduled study visit.

### 3.4.3 Criteria for titration

The following titration criteria must be followed:

#### Treatment A (nateglinide or matching placebo)

At Visit 3 (Month 0.5) and every visit thereafter, titration to the higher dose level will be done if the following criteria are met:

- No incidence of symptoms of Grade 1 hypoglycemia more than 2 within a week and no episode of Grade 2 hypoglycemia (as defined in Section 3.5.4).
- At any visit, patients with symptoms of Grade 1 hypoglycemia more than 2 within a week or one or more episode(s) of Grade 2 hypoglycemia must be downtitrated or discontinued from trial treatment, in case of dose Level 1.
- Following each uptitration or reinitiation of treatment, tolerability must be assessed after 2 weeks of exposure.

#### Treatment B (valsartan or matching placebo)

At Visit 3 (Month 0.5) and every visit thereafter, titration to the higher dose level will be done if the following criterion is met:

- No incidence of symptoms of hypotension (syncope, faintness, orthostatic dizziness).
- At any visit, patients with symptoms of hypotension (syncope, faintness, orthostatic dizziness) must be downtitrated or discontinued from trial treatment in case of dose Level 1. In patients who are treated with other anti-hypertensive medications, the investigator should consider adjusting these medications first, if possible and appropriate.
- Following each uptitration or reinitiation of treatment, tolerability must be assessed after 2 weeks of exposure. In patients either currently on or who are initiated on an ACE inhibitor, potassium and creatinine testing will be performed locally.

### 3.4.4 Packaging

All medication will be packaged in bottles. Each bottle will be labeled indicating the treatment letter (Treatment A, Treatment B) and the dose level (Level 1, Level 2). In addition, each bottle label will bear a unique drug number. All bottle labels will be in the local language and comply with legal regulations for each country and bear the storage conditions.

Each site will be provided with two stocks of medication:

- (i) One stock will be for Visit 2 (Month 0) and 3 (Month 0.5) containing Treatment A and B, and Level 1 and 2, respectively. At Visit 2 (randomization) only Level 1 medication will be dispensed.
- (ii) A second stock will be for Visit 4 (Month 1), 6 (Month 6) and every visit thereafter or in the event of a dose level change containing Treatment A and B, and Level 1 and 2, respectively.

### **3.4.5 Treatment assignment**

#### **Subject Number**

At Visit 1, each individual will receive a unique subject identification number. The subject identification number is composed of two parts. The first part is the center number, assigned to the center by the sponsor, and the last part is the subject number, which is sequentially assigned by the center to patients as they enter the study. For example, the third patient enrolled in Center 35 would be identified as 0035-0003. Once assigned, subject numbers must not be reused.

Subjects may be re-screened only one time and after approval by Novartis. Re-screened subjects must provide a new informed consent and will be assigned a new subject number.

#### **Randomization**

At randomization (Visit 2, Month 0), eligible subjects will be assigned to one (Treatment A and Treatment B) of the four treatment groups (ratio 1:1:1:1) via an Interactive Voice Response System (IVRS). A patient will be considered randomized when the subject number is entered into the IVR system and the phone call is completed.

At Visit 2 (randomization), 3, 4, 6 and every visit thereafter, trial treatment will be assigned via an IVRS.

### **3.4.6 Blinding**

The double-blinding of the randomized study medication will be maintained by the use of identical placebo and active tablets and capsules for nateglinide and valsartan, respectively.

Randomization will be performed by Novartis Drug Supply Management or by the IVRS vendor using a validated system that automates the random assignment of treatment groups to randomization numbers. The randomization scheme will be reviewed by the Quality Assurance Biostatistics Group in Novartis Medical Information Processing and Statistics Department and locked by them after approval.

Randomization data are kept strictly confidential; accessible only to authorized persons, until the time of unblinding. At the conclusion of the trial, the occurrence of any emergency code breaks will be determined from IVRS and unused drug supplies to Novartis. Only when the study has been completed, the data file verified, and the protocol violations determined will the drug codes be broken and made available for data analysis.

For details of the emergency procedure for unblinding of individual patients in cases of emergency see Section 8.1.2.

### **3.4.7 Concomitant therapy**

Every effort should be made to achieve recommended target levels for co-existing medical conditions throughout the duration of the study. Concomitant medications should be continued throughout the study if not mentioned under the exclusion criteria. The patient must be instructed not to take any additional medication (including over-the-counter medications) without informing the investigator. All concomitant medications taken throughout the trial will be recorded in the source documents. The use of selected classes of concomitant medication during the trial will be recorded on the Concomitant Medication CRF.

#### **Progression to Diabetes**

During the study, subjects may progress to diabetes and require additional therapy for glycemic control. All subjects who have progressed to diabetes should be monitored and the following treatment algorithm should be used for additional glycemic control:

Step 1: Intensified lifestyle intervention including diet and exercise

Step 2: Addition of metformin

Step 3: Addition of a second non-insulin secretagogue oral antidiabetic therapy (e.g. thiazolidinedione) or bedtime insulin.

Thiazolidinediones alone or in combination with other antidiabetic agents can cause fluid retention, which may exacerbate or lead to heart failure. Patients should be closely observed for any signs and symptoms of heart failure.

The co-administration of nateglinide and a sulfonylurea or repaglinide is not permitted.

#### **Treatment of Hypertension**

If a patient has or develops hypertension, treatment with a diuretic and a calcium channel blocker is recommended.

For patients with pre-existing hypertension, angiotensin receptor blockers and angiotensin converting enzyme inhibitors must be discontinued at least four weeks prior to Visit 1. Angiotensin II receptor blockers must not be prescribed throughout the trial. If the patient develops symptomatic hypotension on the study drug, consideration should be given to adjusting the dose of concomitant anti-hypertensives, if possible and appropriate, before down-titrating the study drug.

#### **Use of angiotensin converting enzyme inhibitors**

At trial start and during the trial, ACEI's are permitted if used for the treatment of coronary artery disease, left ventricular dysfunction, macroalbuminuria, peripheral arterial disease, stroke and transient ischemic attack (TIA). Use of ACEI's for the treatment of patients who develop diabetes during the trial is also permitted.

The use of ACEI's for the treatment of uncomplicated hypertension at trial start and during the trial is not recommended.

### **3.4.8 Treatment compliance**

At Visit 2 and thereafter, patients will be instructed to return all medication bottles to the study site at each visit. Records of the amount of study medication and medication numbers dispensed and returned at each visit, and intervals between visits, will be kept in the patient's source documentation. Drug accountability will be reviewed by the field monitor during site visits and at the completion of the trial.

Dispense of medication (dose level for Treatment A/B) will be captured via IVRS; interruptions of treatment will be recorded on the CRF.

## **3.5 Visit schedule and assessments**

### **3.5.1 Visit schedule**

A minimum of twelve visits are scheduled to be performed in this trial over a period of approximately 72 months. Additional visits will be scheduled as needed (i.e., confirmation of progression of diabetes [refer to Section 3.5.2]).

At Visit 1 (Month -1) subjects will be screened and, if eligible, will enter up to a 4 week treatment-free run-in period. Visit 1 information other than laboratory measurements will be collected using IVRS (for details see Section 3.5.5). Once all results from Visit 1 assessments are available, the investigator will document the decision to randomize or discontinue from screening the subject using IVRS. Randomization will be at Visit 2 (Month 0) and post-randomization visits will be 2 and 4 weeks, 3 and 6 months, and then every 6 months thereafter.

Starting at Visit 2, patient data will be collected using a CRF. Deviations of  $\pm 1$  week between the Month 0 and Month 6 visits are acceptable. Deviations of  $\pm 2$  weeks between visits at Month 6 and thereafter are acceptable. However, every effort must be made to restore the visit schedule. Since the study duration is dependent on the total number of events reported rather than the individual treatment duration of a specific subject, the follow-up period of 6 years during treatment is an estimate for planning purposes. When the target number of cardiovascular events is reached, all patients will be scheduled to have their final study visit.

Visits will be scheduled between 7:00 AM and 10:00 AM. Patients should be instructed not to take the morning dose of either drug until the visit has been completed. Patient should not eat or drink anything (except water) overnight prior to each scheduled laboratory evaluation. If the patient has not fasted, the collection of laboratory evaluations must be rescheduled to obtain laboratory values in the fasting state.

A summary of evaluations by visit is given in Table 3; details of assessment are given in Sections 3.5.3 to 3.5.5.

**Table 3 Evaluation schedule**

Examination	S	BL	0.5	1	3	(Visit 6-11)		(visit 11)	(visit 13 onwards)**		Final Visit <sup>a</sup>
						Every 6 months	Every 12 months	Month 36	Every 6 months	Every 12 months	
Informed consent	X										
Inclusion/exclusion criteria	X										
Medical history	X	X									
Concomitant Medications/ Significant Non-drug Therapies	X	X	X	X	X	X		X	X		X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X						X	X		X	X
Waist circumference	X						X	X		X	X
ECG		X						X			X
Occurrence of a CV endpoint			X	X	X	X		X	X		X
FPG						X		X		X <sup>h</sup>	
HbA <sub>1c</sub> <sup>e</sup>		X					X <sup>g</sup>	X <sup>g</sup>		X <sup>g</sup>	X
OGTT <sup>c,e</sup> (incl. FPG)	X						X	X		X <sup>h</sup>	X
Biomarker sample		X					Only yr1				X
Pharmacogenetic sample*		X									
Safety laboratory tests											
Chemistry	X		☒ <sup>d</sup>	☒ <sup>d</sup>			X	X		X	X
Hematology	X						X	X		X	X
Urinalysis	X <sup>f</sup>						X	X		X	X
Adverse events			X	X	X	X		X	X		X
Access IVRS	X	X	X	X		X		X	X		
Life-style intervention counseling		X	X	X	X	X		X	X		
Life-style conduct assessment		X	X	X	X	X		X	X		X
Health economics assessment		X				X		X	X		X
Study treatment dispensed		X	X	X		X		X	X		
Study treatment returned			X	X		X		X	X		X

<sup>a</sup> final visit in case of death or trial end

<sup>b</sup> (deleted)

<sup>c</sup> OGTT also ad hoc to confirm an endpoint.

<sup>d</sup> In patients on ACE inhibitors, potassium and creatinine testing performed locally

<sup>e</sup> HbA<sub>1c</sub> will be measured at time point 0 minutes of positive, confirmatory OGTT

<sup>f</sup> Spot urine albumin and creatinine will be analyzed for eligible patients, only

<sup>g</sup> only in patients who progressed to diabetes

<sup>h</sup> For patients who have progressed to diabetes and have had an FPG  $\geq$  300 mg/dL (16.7 mmol/L), an annual OGTT is no longer required; an FPG, however, should still be performed.

\* Pharmacogenetic assessment is also detailed in the Sub-study 1 Protocol for countries where this assessment is required to be separate from the core protocol

\*\* Visit 12 has been eliminated.

### 3.5.2 Discontinuation from the study

A patient will be only discontinued from the study prior to trial end in case of death. Unblinding of trial treatment is not a reason for discontinuation from the study.

In cases where the patient has withdrawn consent to visit/contact the investigator, at least vital status, as a matter of public record in most countries, must be followed at every scheduled visit until trial end or patient's death, if known. Patients who withdrew the consent to visit/contact the investigator can re-enter the trial. A second informed consent should be obtained. The re-entry into the trial is not subject to a time limit; it may occur after days, weeks, months or even years.

Patients who are considered lost to follow-up at one point in time will remain in the study until trial end or patient's death, if known. At every scheduled visit until trial end or patient's death, if known, every possible effort should be made to contact the patient (or patient's relatives) to obtain visit information. At least vital status information, as a matter of public record in most countries, must be followed at every scheduled visit to the end of the study.

### 3.5.3 Efficacy assessment

Efficacy assessments will be performed at every visit following randomization.

#### Primary endpoint: time to progression to diabetes (V1, N1)

In order to assess patients' diabetic condition the following procedure must be followed: When a patient has an FPG  $\geq$  126 mg/dL (7.0 mmol/L) or a 2hr post-challenge glucose  $\geq$  200 mg/dL (11.1 mmol/L) during the trial, a repeat OGTT should be performed as soon as possible (on a different day), preferably within 4 weeks (28 days) but not later than 12 weeks (84 days) after the day of the initial laboratory assessment indicative of diabetes. If, for whatever reason, a repeat OGTT cannot be performed, at least an FPG should be performed at that time.

The progression to diabetes endpoint is defined through (a) an algorithm based on central laboratory measurements of FPG and/or 2hr OGTT, or (b) adjudication by the Diabetes Endpoint Adjudication Committee as follows:

1. Endpoint definition based on laboratory tests: FPG  $\geq$  126 mg/dL (7.0 mmol/L) or a 2hr post-challenge glucose (OGTT)  $\geq$  200 mg/dL (11.1 mmol/L) during two consecutive valid measurements that are within 12 weeks ( $\leq$  84 days) but at least one day apart. The time to progression to diabetes is defined as the time of the original measurement (subsequently confirmed) of an FPG  $\geq$  126 mg/dL (7.0 mmol/L) or a 2hr post-challenge glucose  $\geq$  200 mg/dL (11.1 mmol/L).
2. Adjudication by the Diabetes Endpoint Adjudication Committee: progression to diabetes may be confirmed by the Committee in cases suggestive of diabetes but where above laboratory test-based definition does not hold (e.g. due to missing central laboratory measurements or repeat tests outside the 12-week time limit). E.g., the Committee will adjudicate cases where diabetes has been diagnosed by a primary care physician (possibly based on local laboratory assessments) and/or where anti-diabetic medication has been initiated; adjudication also includes deciding on the time to progression to diabetes. Details of adjudication are provided in a Diabetes Endpoint Adjudication Charter to be followed by the Committee.

An HbA<sub>1c</sub> measurement cannot replace an FPG or a 2hr post-challenge glucose to confirm progression to diabetes.

### **Primary endpoint: extended CV endpoint (V2, N2)**

This primary endpoint is defined as the time to first occurrence of a cardiovascular morbidity/mortality event (including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, revascularization procedure, hospitalization for congestive heart failure, hospitalization for unstable angina). Occurrence of a suspected morbidity/mortality endpoint will be reported by the investigator and adjudicated by the Cardiovascular Endpoint Committee. Only Adjudication Committee-confirmed events can be considered for this primary endpoint.

### **Primary endpoint: core CV endpoint (V3, N3)**

This primary endpoint is defined as the time to first occurrence of a cardiovascular morbidity/mortality event (cardiovascular death, myocardial infarction, stroke or hospitalization for congestive heart failure). Occurrence of a suspected morbidity/mortality endpoint will be reported by the investigator and adjudicated by the Cardiovascular Endpoint Committee. Only Adjudication Committee-confirmed events can be considered for this primary endpoint.

### **Documentation of cardiovascular endpoints**

All cardiovascular endpoints and fatal events will be processed by completing an Assessment of Endpoint Form and forwarding all relevant documentation to the Cardiovascular Endpoint Committee. Please, refer to the Cardiovascular Endpoint Manual for more details.

The cardiovascular mortality and morbidity endpoints of this study will also be documented and processed as serious adverse events (SAE) and reported to Novartis CS&E, as outlined in Section 8.1.



### **3.5.4 Safety assessments**

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry (including liver enzymes) and urine values, regular measurement of vital signs and the performance of physical examinations and ECG.

#### **Adverse events**

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded in the patient's source documents and CRF and followed as appropriate.

An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug(s) (or therapy) even if the event is not considered to be related to study drug (or therapy). Study drug (or therapy) includes the drug (or therapy) under evaluation, and any reference or placebo drug (or therapy) given during any phase of the trial.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment. Adverse events occurring before starting study treatment but after signing the informed consent form are recorded on the Medical History/Current Medical Conditions Case Report Form. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms or require therapy, and are recorded on the Adverse Events Case Report Form under the signs, symptoms or diagnosis associated with them.

As far as possible, each adverse event will also be described by:

1. its duration (start and end dates),
2. the severity grade (mild, moderate, severe)
3. its relationship to the study drug (suspected / not suspected),
4. the action(s) taken and, as relevant, the outcome.

Examples of the severity grade, relationship to study drug and actions taken, as presented in the case report form are provided in Section 8.1.3, Instructions for completing Adverse Event Case Report Forms.

#### **Pre-defined safety and tolerability parameters**

The following pre-defined safety and tolerability conditions are known side effects of valsartan and nateglinide and will be recorded on the CRF.

##### **Valsartan**

##### **Hypotension**

Hypotension is defined as the mean of 2 sitting diastolic or systolic blood pressure measurements of < 60 mm Hg or < 100 mm Hg, respectively.

### **Orthostatic hypotension**

Orthostatic hypotension is defined as a decrease in diastolic or systolic blood pressure upon changing from sitting to standing of  $\geq 10$  mm Hg or  $\geq 20$  mm Hg, respectively.

### **Symptomatic hypotension**

Symptomatic hypotension is defined as persistent symptoms such as dizziness, faintness, presyncope etc. Symptoms are expected to lessen in severity or completely resolve after downtitration or discontinuation of trial treatment or reduction in dose of concomitant antihypertensive treatment.

### **Orthostatic symptomatic hypotension**

Orthostatic symptomatic hypotension is defined as the occurrence of symptoms such as dizziness, faintness, presyncope etc. upon changing from sitting to standing. Symptoms are expected to lessen severity or completely resolve after downtitration or discontinuation of trial treatment or reduction in dose of concomitant antihypertensive treatment.

### **Nateglinide**

#### **Symptoms suggestive of hypoglycemia**

Symptoms suggestive of hypoglycemia are defined as adrenergic (e.g., tachycardia, palpitations, shakiness) or cholinergic (e.g., sweating) defense symptoms or neurologic symptoms (e.g., inability to concentrate, dizziness, hunger, blurred vision, obvious impairment of motor function, confusion or inappropriate behavior but still alert enough to seek self-treatment) which reverse after intake of carbohydrates.

#### **Confirmed hypoglycemia**

Confirmed hypoglycemia is defined as plasma glucose  $< 3.3$  mmol/L (60 mg/dL) and symptoms suggestive of hypoglycemia.

All subjects from a subset of trial sites will be provided with glucometers.

The occurrence of symptoms suggestive of hypoglycemia and confirmed hypoglycemia should be recorded on a diary.

#### **Grading and treatment of hypoglycemia**

At the Month 0 visit, patient education regarding hypoglycemic symptoms and treatment should occur, and this information should be reviewed throughout the study as necessary. Additionally, patients should be instructed in the specific hypoglycemia monitoring tools to be used in this study. This education should include:

- Review of Table 4 Grading and treatment of symptomatic and suspected hypoglycemia and use of other instructional material as appropriate, in order to explain possible triggers of hypoglycemia (e.g., strenuous exercise, delayed meals),

identify the symptoms of hypoglycemia, and initiate appropriate treatment for events (symptomatic or asymptomatic).

**Table 4 Grading and treatment of symptomatic and suspected hypoglycemia**

Grade	Clinical Signs and Symptoms	Treatment
1	THE SUBJECT DOES NOT REQUIRE THE ASSISTANCE OF ANOTHER PERSON Adrenergic (e.g., tachycardia, palpitations, shakiness) or cholinergic (e.g., sweating) defense symptoms or the neurologic symptoms (e.g., inability to concentrate, dizziness, hunger, blurred vision, obvious impairment of motor function, confusion or inappropriate behavior but still alert enough to seek self-treatment).	Approximately 10-15 grams (g) of carbohydrate, in the form of glucose tablets (5 g each) or gel (30 g tube) should be given for grade 1 symptomatic hypoglycemia and/or an asymptomatic fingerstick <b>plasma</b> sugar of < 3.3 mmol/L (< 60 mg/dL). Alternatively, 100-150 mL (4-6 oz) of orange juice or regular cola can be used. If the cause of hypoglycemia is a missed meal or strenuous exercise, then 20-30 g of carbohydrate should be given. Hypoglycemic reactions that occur during the night should be treated initially with 10-15 g of carbohydrate followed by a longer-acting mixture of carbohydrate and protein, e.g., 100-200 mL (4-8 oz) milk plus a few crackers. This is intended to prevent further hypoglycemia during the night.
2	THE SUBJECT REQUIRES THE ASSISTANCE OF ANOTHER PERSON Episode resulting in coma, seizure, or significant neurologic impairment so that the subject is unable to initiate self-treatment or requires the assistance of another person.	Notify appropriate emergency medical services including the investigational site. The investigational center must have intravenous glucose (25-50 mL of a 50% solution) to treat severe events. This is a serious adverse event and the procedures outlined for serious adverse events in the adverse event section must be followed (Grade 2).

- Instructions that the patient should carry a card (to be provided by the study center) indicating that he/she is participating in a research study. This card will indicate the name and the phone number of the investigational site to be contacted in case of an emergency, including any episode of suspected hypoglycemia requiring the assistance of another person.
1. Treat the event as appropriate (see Table 4).
  2. Record the event in the study diary, including any relevant associated information, time of occurrence in relation to the last medication and to the last meal intake, the treatment used and the response to it.
- Additionally, if a patient performs measurements of glucose, he/she should record all glucose values.
  - Return the Study Diary with the study medication at the next scheduled visit.

A qualified person must review diary entries with the patient at each visit to determine if the signs and symptoms are consistent with hypoglycemia.

Any occurrence of Grade 2 hypoglycemia must be considered a Serious Adverse Event and the procedures outlined in Section 8.1.1, Instructions for rapid notification of serious adverse events must be followed.

## Serious adverse events

Information about all serious adverse events will be collected and recorded on the CRF and the Serious Adverse Event Report Form. Each serious adverse event must also be reported to Novartis within 24 hours of learning of its occurrence. A serious adverse event is an undesirable sign, symptom or medical condition which:

1. is fatal or life-threatening
2. requires or prolongs hospitalization
3. results in persistent or significant disability/incapacity.
4. constitutes a congenital anomaly or a birth defect
5. are medically significant, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Events not considered to be serious adverse events are hospitalizations for the:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

In the unlikely event that in this study a pregnancy occurs, study medication should be stopped immediately and this event must be reported to Novartis within 24 hours of learning of its occurrence. The Novartis Clinical Safety & Epidemiology Department (CS&E) will then monitor the pregnancy. For detailed instructions about completing and returning Serious Adverse Event Report Forms to Novartis refer to Section 8.1.1, Instructions for rapid notification of serious adverse events.

## Laboratory evaluations

All laboratory samples will be sent to a central laboratory for analysis, unless logistically contraindicated. Local (regional) labs will be utilized as necessary. All tests will be conducted in accordance with GLP principles following individual standard operating procedures.

The central (or local) laboratory will use standardized normal value ranges, utilize the same methods and references for methodology and will supply the sponsor with their internal quality control methods and external evaluations of methods and certification.

Laboratory results will be forwarded to the investigator and sponsor for review. The investigator should retain all laboratory results in the patient's source documents.

Notable ranges for selected laboratory tests are provided in Appendix 3.

## Hematology

Includes hematocrit, hemoglobin, platelet count, erythrocyte count, total leukocyte count. These parameters will be measured Visit 1 (one measurement must be available prior to randomization), annually thereafter and at the final visit.

## Blood chemistry

A fasting venous blood sample will be obtained for analysis of creatinine, SGOT (ALT), SGPT (AST), alkaline phosphatase, LDH, triglycerides, total cholesterol, potassium, sodium, calcium, chloride, BUN, total protein. All tests will be measured at Visit 1 (one measurement must be available prior to randomization), annually thereafter and at the final visit with the exception of LDL and HDL cholesterol which will be measured at Visit 1, Visit 11 (Month 36) and at the final visit, only.

Creatinine and potassium should be measured in patients already receiving an ACE inhibitor or who are initiated on an ACE inhibitor during the course of the study. Creatinine and potassium levels will be assessed at the local laboratory during the initial titration phase at Visit 3 (Week 2) and 4 (Week 4), and after 2 weeks of exposure to the higher dose in the event the patient has his/her initial titration after Visit 3.

## Fasting Plasma Glucose (FPG)

FPG will be measured at Visit 1 and at the final visit, respectively (as part of OGTT), and semi-annually from visit 6-11. Thereafter FPG will be measured annually (as part of OGTT).

For patients who have progressed to diabetes and have had an FPG  $\geq$  300 mg/dL (16.7 mmol/L), an annual OGTT is no longer required; an FPG, however, should still be performed. An annual OGTT is still required for all patients with FPG < 300 mg/dL (16.7 mmol/L).

## HbA<sub>1c</sub>

Blood samples for HbA<sub>1c</sub> will be collected at baseline (visit 2) and at the final study visit. In addition, HbA<sub>1c</sub> will be measured in subjects with positive, confirmatory OGTT and annually thereafter in patients who have progressed to diabetes.

## Urine measurements

Samples for spot urine albumin and creatinine will be taken at Visit 1 and analyzed for eligible patients, only (one measurement must be available prior to randomization). Following randomization, spot urine albumin and creatinine will be measured annually and at the final visit.

## Vital signs

Notable ranges for vital signs are provided in Appendix 3.

## Height

Height will be measured at Visit 1.

### **Pulse rate**

Pulse rate will be measured at each visit once in the sitting position after 5 minutes resting followed by one measurement in the standing position after at least 2 minutes of equilibration. Pulse rate will be measured for 30 seconds and before blood pressure measurements.

### **Blood pressure**

Systolic and diastolic blood pressure will be measured at each visit using a validated device (two measurements in the sitting position after 5 minutes resting followed by one measurement in the standing position after at least 2 minutes of equilibration). Blood pressure will be measured by the same clinician using the same device on the patient's dominant arm. The measurements should always be carried out at the same time of the day and prior to the intake of the morning doses.

### **Body weight**

Body weight will be measured to the nearest 0.1 kilogram in indoor clothing but without shoes at each visit using the same scale.

### **Waist circumference**

Waist circumference (the minimum circumference of the waist above the iliac crest) will be measured at Visit 1, yearly thereafter and at the final visit.

### **Physical examination**

A physical examination will be performed at Visit 1, yearly thereafter and at the final visit. Physical examination evaluations should include general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and neurological (including sensory) examinations. Information about the physical examination must be present in the source documentation at the study site. Significant findings present prior to randomization will be entered in the Relevant Medical History/Current Medical Conditions Case Report Form at Visit 2. Significant findings made after the start of the study which meet the definition of a pre-defined or serious adverse event (as defined in Section 3.5.4) will be recorded on the Adverse Event Case Report Form.

### **Electrocardiogram**

A standard 12 lead electrocardiogram (ECG) must be obtained at Visit 2, Month 36, and at the final visit.

### **3.5.5 Other assessments**

#### **Screening visit (Visit 1) information**

The following information will be collected at Visit 1: demographics, vital signs, waist circumference, concomitant medication, medical history. In addition, laboratory measurements will be performed. All information except medical history, concomitant

medication, and laboratory measurements will be collected using IVRS. Also, the decision to randomize or discontinue the subject from screening, including the reason for discontinuation, will be recorded using IVRS. All Visit 1 screening information will be transferred from IVRS to the trial database.

### 2hr OGTT (with FPG, post-prandial glucose)

Subjects have to be fasting at each OGTT assessment. A fasting and 2hr post-challenge glucose evaluation is required at Visit 1 to confirm eligibility of screened subjects. Post-randomization OGTT will be performed at Visit 7 (Month 12), annually thereafter, and at the final visit (for exceptions see below). Repeat OGTT to confirm a glycemic endpoint will be performed as soon as possible (on a different day), preferably within 4 weeks ( $\leq 28$  days) but no later than 12 weeks ( $\leq 84$  days) following the day of the initial laboratory assessment that indicates diabetes. If, for whatever reason, a repeat OGTT cannot be performed, at least an FPG should be performed at that time.

For patients who have progressed to diabetes and have had an FPG  $\geq 300$  mg/dL (16.7 mmol/L), an annual OGTT is no longer required; an FPG, however, should still be performed. An annual OGTT is still required for all patients with FPG  $< 300$  mg/dL.

In patients who have progressed to diabetes HbA<sub>1c</sub> will be measured at time point 0 minutes of positive, confirmatory OGTT and annually thereafter.

Patients who achieved a confirmed glycemic endpoint must withhold the morning dose of any antidiabetic treatment, in addition to the study medication, prior to each subsequent OGTT assessment.

The OGTT must initiate (0 minute sample) no later than 10:00 a.m.

Subjects are given a 75 gram glucose-equivalent oral glucose challenge. The glucose solution is centrally provided to all centers. A venous sample will be taken 2 hours post-challenge to evaluate glucose levels (see table below).

**Table 5** OGTT assessment

	Time (minutes) Post Glucose Administration	
	0+	120
75 g glucose	X	
Plasma glucose	X	X
HbA <sub>1c</sub> ++	X	

### Life-style intervention education

At Visit 2 and every visit thereafter, patients will receive counseling on diet and physical activity as treatment to prevent diabetes. Counseling will include review of an education brochure. The assessment of physical activity will include the use of pedometers. Pedometers will be dispensed to a subset of patients based on practical considerations. At Visit 2 and every visit thereafter, information on life-style conduct, including physical activity and diet habits, will be assessed.

## Health economics assessment

Health economics assessments will be performed at Visit 2, every 6 months thereafter and at the final visit. The assessment will include information on hospitalization (diagnosis, admission, discharge date), medical care in addition to this protocol, and the patient's health state using a visual analogue scale (VAS).

The VAS forms provided in the CRF will be in English only. However laminated VAS forms in local languages will be available to each center separately. Patients should read the instructions on the laminated forms, in their native language, prior to completing the VAS form in the CRF by drawing a line through the VAS to indicate their health status on the day of the visit. The investigator should then record the VAS score in the appropriate space provided.

The analysis of health economic parameters will be reported separately.

## Pharmacogenetic assessments

The pharmacogenetic assessment is also detailed in the Substudy 1 Protocol for countries where this assessment is required to be separate from the core protocol.

In order to begin to study the effects of human genetic variation on drug responses, it is planned to conduct exploratory pharmacogenetics research studies as a part of this protocol. The objective is to identify genetic factors related to impaired glucose tolerance and cardiovascular disorders that may predict response to treatment with nateglinide and/or valsartan and/or predict the subject's relative susceptibility to drug-drug interactions or serious side effects. The goal of these exploratory research studies is to find genetic markers that will identify persons with impaired glucose tolerance and cardiovascular disorders who will have the best possible response to nateglinide and/or valsartan or to identify persons who will have fewer side effects in order to maximize the benefit of the study drugs. This is not a genetic testing project since we are not trying to identify genetic information to determine risk of diseases that are not present during the study, alter clinical care or make or change a diagnosis. This research study is focused on studying the role genes play in impaired glucose tolerance and cardiovascular disorders and the responses of subjects to nateglinide and valsartan as described below.

It is planned to study polymorphisms in genes that are linked to the etiology of impaired glucose tolerance and cardiovascular disorders, those related to drug action, and those in drug metabolism genes, including any not yet currently identified, that may become important in the future as the human genome project moves toward completion. Polymorphisms related to type 2 diabetes mellitus may include Gly40Ser in the glucagon receptor (GCGR) gene, Thr130Ile in the hepatocyte nuclear factor 4 alpha (HNF4  $\alpha$ ) gene and Asn130Asn in the solute carrier family 2 member 4 (GLUT-4) gene. Variants in drug metabolism genes may include the A-209G in the promoter of CYP3A4 and Arg144Cys and Ile359Leu in CYP2C9. Polymorphisms related to cardiovascular disorders may include Glu298Asp in the endothelial nitric oxide synthase (eNOS) gene, I/D in the angiotensin I converting enzyme (ACE) gene, and Met325Thr and Thr174Met in the angiotensinogen (AGT) gene. Potential variants in the angiotensin receptor (AGTR1) include 3'UTR A1166C.



To obtain sufficient DNA for pharmacogenetic studies, a single 12 ml blood sample will be drawn at Visit 3 from each subject who agrees, in writing, to participate in pharmacogenetic evaluations. The blood is collected into two 6 ml plastic EDTA-containing tubes, which are gently inverted several times to prevent clotting. The tubes are transferred on the day of sampling by Express Mail at ambient temperature to the Central Laboratory. DNA extraction, relabeling, and storage at  $-70^{\circ}\text{C}$  will be done by Covance. It is intended that only one 12 ml sample will be taken once from the patient for these studies. However, in the event of loss or damage to the original or missed withdrawal at Visit 3, subjects may be requested to provide another blood sample.

The extracted DNA is given a new unique bar-code number by Covance. The sample extraction information is transferred electronically into a secured Novartis database separate from the clinical trial database. The blood sample and any DNA derived from the sample may be stored for up to 15 years to research scientific questions related to nateglinide, valsartan, impaired glucose tolerance, diabetes mellitus, metabolic disorders, and cardiovascular disorders. This research study is focused on studying the role genes play in impaired glucose tolerance and cardiovascular disorders and the responses of subjects to nateglinide and valsartan. Since nateglinide and valsartan may be developed for other diseases, and Novartis may develop new drugs for impaired glucose tolerance, diabetes mellitus, and cardiovascular disorders, the genetic information and samples may be used for other impaired glucose tolerance, diabetes mellitus, cardiovascular disorder, nateglinide, and valsartan-related drug research and development. If the sponsor desires to expand from this restricted scope of research, the sponsor will first seek approval from the IRB/EC.”

At the end of the storage period, any remaining blood sample will be destroyed according to standard biohazard procedures. Any remaining DNA will be destroyed according to chemical waste disposal procedures.

### **Biomarker assessments**

Insulin, pro-insulin and other predictors of diabetes and cardiovascular disease (e.g. high sensitivity C-reactive protein) will be measured in all subjects subsequently enrolled. The parameters to be measured would be restricted to those that would lead to a better understanding of the pathophysiology of diabetes and cardiovascular disease, prediction of the development of these conditions or responses to treatment. For these measurements 12 ml of blood will be obtained at baseline, 12 months and at the final visit. Plasma and serum aliquots will be frozen until the time of analysis.

#### **3.5.6 Drug levels and pharmacokinetic assessments**

No pharmacokinetic assessments are planned.

## **4 Protocol amendments, other changes in study conduct**

### **4.1 Protocol amendments**

Any changes to the protocol will be made in the form of an amendment

## **4.2 Other changes in study conduct**

Changes in study conduct are not permitted without an amendment to the protocol. Any unforeseen deviations in study conduct will be recorded in the clinical study report.

## **5 Data management**

### **5.1 Data collection**

Selected Visit 1 information will be collected using IVRS. Starting at Visit 2 investigators must enter the information required by the protocol onto the Novartis Case Report Forms (CRFs) that are printed on 3-part, no carbon required (NCR) paper. Field monitors will review the IVRS printouts and CRFs for completeness and accuracy, and instruct site personnel to make any required corrections or additions. The CRFs are forwarded to the Novartis Medical Documents Reception Center or designee by field monitors or by the investigational site, one copy being retained at the investigational site. Once the CRFs are received by Novartis or designee, their receipt is recorded, the original copy is placed in Central Files and the NCR copy is forwarded to the responsible medical data management staff for processing. If CRFs are sent directly to Novartis or designee by investigational sites, they are reviewed prior to data entry.

### **5.2 Database management and quality control**

Visit 1 information will be transferred from IVRS into the trial database. Data items from the CRFs are entered into the study database using double data entry with electronic verification.

Subsequently, the information entered into the database is systematically checked by Data Management staff, using error messages printed from validation programs and database listings. Obvious errors will be corrected by Novartis personnel or designee. Other errors or omissions will be entered on Data Query Forms, which will be returned to the investigational site for resolution. A copy of the signed Data Query Form is to be kept with the CRFs, and once the original is received at Novartis or designee the resolutions will be entered into the database. Quality control audits of all key safety and efficacy data in the database will be made after entering data from each visit.

Concomitant medications entered into the database will be coded using a WHO Drug Reference List. Coexistent diseases and adverse events will be coded using MEDDRA.

Laboratory samples will be processed through a central laboratory, and the results will be sent electronically to Novartis or designee.

When the database has been declared to be complete and accurate, the database will be locked and unblinded. Any changes to the database after that time can only be made by joint written agreement between the Clinical Trial Leader, the Trial Statistician and the Data Manager.

## 6 Statistical methods

### 6.1 Statistical methods

The primary efficacy parameters of this study are time to progression to diabetes and time to first occurrence of an extended and time to first occurrence of a core CV endpoint. These three endpoints will be tested in parallel using a closed testing procedure for each drug. It is thus possible to achieve statistical significance for any one endpoint independent of the others (under sensible assumptions; see below).

The closed testing procedure proposed combines weighted Bonferroni and weighted trimmed Simes (Hochberg) tests. Progression to diabetes and the cardiovascular endpoints are always tested asymmetrically, with a 1:4 weight allocation, respectively. The two cardiovascular endpoints are equally weighted as (i) they are equally important, and (ii) the impact of the treatment effect differences between extended and core CV endpoints (assumed to be larger for the core CV endpoint which in turn is less frequent than the extended CV endpoint) on the power of statistical tests is unclear. The trimmed Simes (Hochberg) test is applied to the pairwise intersection hypotheses and the intersection of the cardiovascular endpoints hypotheses in the 3-way (global) intersection hypothesis. In case of independent or positively correlated test statistics, the Simes (Hochberg) test for two hypotheses allows rejection a) if one of the tests is “significant” at its individually allocated level (e.g. nominal alpha levels of 0.01 and 0.04), or b) if both tests are “significant” at the sum of the individual levels (i.e., 0.05 in above example).

In this study it can be safely assumed that the test statistics related to the extended and core CV endpoints are non-negatively correlated. A negative correlation between the test statistics relative to the progression to diabetes and cardiovascular endpoints cannot be ruled out, however. On the other hand, relevant (particularly statistically significant) treatment differences for both the diabetes and CV endpoints but in favor of different treatments will have a rather low likelihood. Otherwise this study would certainly not have been done and use of the trimmed Simes test would not be recommendable.

When there is possibly a negative correlation between the (one-sided) test statistics a trimmed version of the (asymmetric) Simes test controls the overall type I error  $\alpha$  as follows: reject the intersection hypothesis  $H_A \cap H_B$  if (a)  $p_A < \alpha$  &  $p_B < \alpha$ , or (b)  $p_A < \alpha_A$  &  $\underline{p_B < 1 - \alpha_B}$ , or (c)  $\underline{p_A < 1 - \alpha_A}$  &  $p_B < \alpha_B$ , where  $\alpha = \alpha_A + \alpha_B$ , and  $p_A$  and  $p_B$  are one-sided p-values related to the individual hypotheses  $H_A$  and  $H_B$ . The underlined conditions are additional requirements and can be considered rather mild as the rejection of an individual hypothesis relative to one endpoint would fail only if there were a (statistically significantly) strong effect of the other endpoint in the opposite direction. As argued above, the odds of such a finding in this trial are very low and also the overall conclusions from this trial would be inconclusive anyway.

The closed testing strategy with seven intersection hypotheses for the three primary endpoints is summarized in Table 6. As described it is only valid if no interim analysis was performed. Its modification to account for the interim efficacy analysis performed in December 2005 is detailed in Section 6.1.7.

**Table 6 Closed testing strategy for the three primary endpoints**

Endpoint	In order for the endpoint to be statistically significant, the following intersection hypotheses must be rejected	
Progression to diabetes	$PD \cap CE \cap CC$ ; $PD \cap CE$ ; $PD \cap CC$ ; $PD \cap \square \cap \square$	
Extended CV endpoint	$PD \cap CE \cap CC$ ; $PD \cap CE$ ; $CE \cap CC$ ; $CE$	
Core CV endpoint	$PD \cap CE \cap CC$ ; $PD \cap CC$ ; $CE \cap CC$ ; $CC$	
Intersection hypothesis	One-sided tests applied (weights in parentheses)	Requirement for rejection (nominal p-values (*))
$PD \cap CE \cap CC$	Weighted Bonferroni for PD (0.2) and the intersection hypothesis $CE \cap CC$ (0.8); unweighted trimmed Simes for CE (0.5) and CC (0.5)	$p_{PD} < .005$ or $p_{CE} < .01$ & $p_{CC} < .99$ or $p_{CC} < .01$ & $p_{CE} < .99$ or $p_{CE} < .02$ & $p_{CC} < .02$
$PD \cap CE$	Weighted trimmed Simes for PD (0.2) and CE (0.8)	$p_{PD} < .005$ & $p_{CE} < .98$ or $p_{CE} < .02$ & $p_{PD} < .995$ or $p_{PD} < .025$ & $p_{CE} < .025$
$PD \cap CC$	Weighted trimmed Simes for PD (0.2) and CC (0.8)	$p_{PD} < .005$ & $p_{CC} < .98$ or $p_{CC} < .02$ & $p_{PD} < .995$ or $p_{PD} < .025$ & $p_{CC} < .025$
$CE \cap CC$	Unweighted trimmed Simes for CE (0.5) and CC (0.5)	$p_{CE} < .0125$ & $p_{CC} < .9875$ or $p_{CC} < .0125$ & $p_{CE} < .9875$ or $p_{CE} < .025$ & $p_{CC} < .025$
PD		$p_{PD} < .025$
CE		$p_{CE} < .025$
CC		$p_{CC} < .025$
<b>Characteristics of procedure (summary)</b>	<ul style="list-style-type: none"> <li>- All three endpoints are primary endpoints</li> <li>- PD on the one hand and CE / CC on the other hand are always tested using a 1:4 weight allocation</li> <li>- CE and CC are weighted equally</li> <li>- tests are one-sided</li> <li>- Simes procedure has been modified (through trimming) in order to preserve the type I error under any correlation between the test statistics</li> </ul>	
<b>Notation:</b>	<b>Null hypothesis associated with</b>	
PD	Progression to diabetes	
CE	Extended CV endpoint	
CC	Core CV endpoint	

(\*) To account for the interim efficacy analysis already performed, the (one-sided) alpha level of this testing procedure at the final analysis will be less than 0.025; this is detailed in Section 6.1.7

The following example may help to understand the closed testing procedure. In order to claim that there is a positive effect on the core CV endpoint, say, all four intersection hypotheses involving this endpoint must be rejected, namely  $H_{CC} \cap H_{CE} \cap H_{PD}$ ,  $H_{CC} \cap H_{CE}$ ,  $H_{CC} \cap H_{PD}$ ,

and  $H_{CC}$ . Now let's suppose that the p-values  $p_{CC}$ ,  $p_{CE}$  and  $p_{PD}$  relative to  $H_{CC}$ ,  $H_{CE}$  and  $H_{PD}$ , respectively, are 0.0096, 0.0188, and 0.1583, say. From the right-hand column in above table we see that (1)  $H_{CC} \cap H_{CE} \cap H_{PD}$  can be rejected as the condition  $p_{CC} < .01$  &  $p_{CE} < .99$  is fulfilled, (2)  $H_{CC} \cap H_{CE}$  can be rejected as the condition  $p_{CC} < .0125$  &  $p_{CE} < .9875$  is fulfilled, (3)  $H_{CC} \cap H_{PD}$  can be rejected as the condition  $p_{CC} < .02$  &  $p_{PD} < .995$  is fulfilled, and (4)  $H_{CC}$  can be rejected as the condition  $p_{CC} < .025$  holds. One can therefore conclude that there is a statistically significant between-treatment group difference as to the core CV endpoint. With above p-values the very same statement holds for the extended CV endpoint, but not for progression to diabetes.

Time to progression to diabetes will be analyzed using a discrete time proportional odds model. Time to first cardiovascular event (in days) for both the extended and core CV endpoints will be analyzed using a logrank statistic. The trial will be stopped and the final analysis performed when 1374 patients have had an Adjudication Committee-confirmed extended CV endpoint.

Tests will be performed separately for both valsartan and nateglinide, unless stated otherwise. The primary tests will be for the main effect of an experimental treatment (i.e. nateglinide or valsartan), stratified for the other treatment (i.e. valsartan or nateglinide) and for CVD at baseline.

Formal efficacy interim analyses were foreseen at two time-points during the trial. A first efficacy interim analysis was performed in December 2005; the second one will be dropped (see Sections 3.1 and 6.1.7).

Additional exploratory efficacy endpoints will also be analyzed.

Demographic and baseline characteristics, exposure to study medication, concomitant medication and safety information will be presented primarily in descriptive tables using summary statistics. Summaries will be by treatment groups (i.e. four groups included).

Baseline is either the measurement at Visit 2, or the last measurement prior to Visit 2 if no Visit 2 value is available. HbA1c will also be measured at baseline (Visit 2).

### **6.1.1 Populations**

The primary efficacy analysis will be based on the intent to treat (ITT) population. This population will consist of all randomized patients. Patients will be classified into the treatment groups they were assigned to by the IVR system.

Analyses will also be done for the per protocol (PP) population. This population will consist of all patients in the ITT population without major deviations from the protocol. "Major deviations" will be defined under blinded conditions. The safety analyzable (or safety) population will contain all randomized patients who had at least one post-baseline safety measurement.

### **6.1.2 Background and demographic characteristics**

Baseline demographic and background data will be summarized by treatment group using contingency tables for the qualitative variables (sex, race, age group and body mass index group; established cardiovascular disease at baseline yes/no) and the mean, standard

deviation, median, minimum and maximum for the quantitative variables (age, height, body mass index, waist circumference). Body mass index (BMI) will be calculated from the collected variables height and weight. ( $BMI = \text{weight} / \text{height}^2$ , where weight is in kg and height is in m.)

Summaries and listings will use the ITT population.

Baseline comparability among the four treatment groups for demographic variables (as described above) and baseline efficacy variables (HbA<sub>1c</sub>, FPG, 2-hr post-OGTT glucose value) will be examined using the Cochran-Mantel-Haenszel test for qualitative variables and an F-test for quantitative variables. These p-values are provided for descriptive purposes, and are not to be considered to define any formal basis for determining factors which should be included in statistical analysis models.

### **6.1.3 Study medication**

Duration in the trial, as well as duration on study treatment (i.e. excluding interruptions) will be summarized by drug (or matching placebo) for the four treatment groups. The number of patients on each dose level of nateglinide and valsartan (and number of patients who have discontinued study medication) will be presented at each visit.

### **6.1.4 Concomitant therapy**

Prior medications and significant non-drug therapies (as coded using the WHO dictionary) will be summarized by treatment group. Listings will be presented by treatment group and patient number.

The specified concomitant medications (see section 3.4.7 of this protocol) will be summarized and listed overall by preferred term and treatment group, and at each visit by type of medication and treatment group.

Summary statistics will be presented by treatment group and visit for the evaluation of lifestyle conduct (see Section 3.5.5).

### **6.1.5 Efficacy evaluation**

#### **6.1.5.1 Primary efficacy analysis**

There will be three primary variables in the study:

- Time to progression to diabetes (on a discrete time scale)
- Time to first extended cardiovascular endpoint after randomization (in days since randomization)
- Time to first core cardiovascular endpoint after randomization (in days since randomization)

These variables will be analyzed using a closed testing procedure for each drug. The three endpoints will be tested in a parallel manner for each drug (Table 6). There will be unequal weights for tests of the progression to diabetes and the cardiovascular endpoints.

Due to the discrete nature in which time to diagnosis of diabetes is measured (every six months for fasting glucose from visits 6-11, every twelve months for post-prandial glucose), a score test will be used based on a discrete time proportional odds model (Cox's [16] model for discrete time data, discussed also in [17]) for the effect of nateglinide (valsartan) stratified for valsartan (nateglinide) and history of cardiovascular disease at baseline (yes/no – see section 3.3.2 for a definition). This model is analogous to TIES = DISCRETE in the SAS® procedure PHREG.

For the first three years in study the time intervals used in the model will be defined by the six-monthly study visit period of the visit at which it was detected (in line with the definition of progression to diabetes (Section 3.5.3), a confirmatory measurement has to take place at a repeat visit). If progression was detected at an unscheduled visit (or defined by the diabetes adjudication process), it will be assigned to the next regular six-monthly visit. After three years FPG/OGTT assessment intervals are yearly.

For the endpoints 'time to first extended/core cardiovascular event', the effect of nateglinide (valsartan) will be tested using a logrank statistic, stratified for valsartan (nateglinide) and for history of cardiovascular disease at baseline (yes/no). That is, a score test will be implemented, with TIES = EXACT in the SAS® procedure PHREG. If not otherwise stated, all efficacy analyses will be performed on the ITT population.

Progression to diabetes and cardiovascular endpoints are defined as in Section 3.5.3 of the protocol.

The six null hypotheses will be:

- N1 There is no difference between the nateglinide and non-nateglinide treated groups in time to progression to diabetes.
- N2 There is no difference between the nateglinide and non-nateglinide treated groups in time to first extended cardiovascular endpoint.
- N3 There is no difference between the nateglinide and non-nateglinide treated groups in time to first core cardiovascular endpoint.
- V1 There is no difference between the valsartan and non-valsartan treated groups in time to progression to diabetes.
- V2 There is no difference between the valsartan and non-valsartan treated groups in time to first extended cardiovascular endpoint.
- V3 There is no difference between the valsartan and non-valsartan treated groups in time to first core cardiovascular endpoint.

Testing will be done using the closed testing procedure described in Section 6.1, Table 6, using a 2.5% one-sided alpha level. Nateglinide or valsartan will be declared superior to non-nateglinide/non-valsartan for a primary endpoint if the respective intersection hypotheses (see Table 6) can be rejected in favor of the experimental drug using the adjustment criteria as specified in Section 6.1.7 "Interim analyses".

The interaction effect of nateglinide and valsartan will be tested in separate models that include an interaction term. For the progression to diabetes, this will be done by a discrete time proportional odds model. For the cardiovascular endpoints, a standard Cox models (on a continuous time scale) will be applied, using a TIES=EXACT option in SAS. In each of these

models, the two treatment effects, and history of cardiovascular disease at baseline will be fitted as covariates, in addition to the interaction term.

Two-sided 95% confidence intervals of the hazard ratio will be presented for each of the primary comparisons.

This factorial trial is testing two drugs, and therefore can be considered a combination of two trials into one. The combined type I error probability of two independent trials (one for each drug, each using 5% alpha-level) is 9.75%. As the overall type I error of this trial will be exactly the same, a 5% alpha-level will be used for each of the two experimental treatments.

The primary analysis will be on the ITT population, but the models will also be performed as supportive analysis for the per-protocol population.

Confidence intervals will be calculated for the hazard ratio in two-group treatment comparisons of the two monotherapies vs. placebo, combination therapy vs. placebo, and combination therapy vs. the two monotherapies.

Another sensitivity analysis will be performed for the ITT population, in which time after the permanent discontinuation of study treatment will be considered as censored.

The impact of baseline and demographic characteristics on the primary outcomes will be explored. The factors to be explored (individually or in the same model) will include:

- Country
- Fasting plasma glucose at baseline
- 2-hr prandial glucose at baseline
- Age at baseline
- Sex
- Race
- Body mass index at baseline
- Waist circumference at baseline

The methodology used for these explorations will be the same as that used for exploration of the interaction of nateglinide and valsartan, with the factor(s) to be explored in the model instead of the interaction term.

Subgroup analyses will be performed for patients with and without established CHD at baseline, male and female patients, by race, age group, low and high body mass index, low/high fasting glucose at baseline, and low/high post-prandial glucose at baseline, patients taking ACE-inhibitors at baseline, and patients with hypertension at baseline.

Supportive analyses will be presented on the glucose results at the end of the withdrawal period: Change from baseline (week 0) in fasting glucose and in post-prandial (2hr) glucose will be tested for each drug by means of a general linear model. Center, baseline value, history of CVD at baseline (yes/no), and the two experimental treatment effects will be the variables in the model. Summary statistics will be presented by treatment group for the glucose values at baseline and at the end of treatment.



The final analysis is foreseen to be performed (event-driven, not time-driven) when 1374 patients have experienced an Adjudication Committee-confirmed extended CV endpoint.

Kaplan-Meier plots of the event rates by treatment group will be presented for each primary endpoint.

### **6.1.5.2 Exploratory efficacy analyses**

The following additional exploratory analyses will be performed:

- Time to first occurrence of each of the individual components of the extended cardiovascular endpoint
- Time to all cause death
- Time to first cardiovascular-related hospitalization
- Time to first extended CV endpoint including suspected events which were not Committee-confirmed, i.e., including investigator reports of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, revascularization procedure, hospitalization for congestive heart failure, or hospitalization for unstable angina which were not confirmed by the Cardiovascular Adjudication Committee
- Time to first core CV endpoint including suspected events which were not Committee-confirmed, i.e., including investigator reports of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for congestive heart failure which were not confirmed by the Cardiovascular Adjudication Committee

A logrank test, set up in the same way as for the primary cardiovascular endpoint, will be performed for these analyses.

Additional exploratory analyses for renal function will be performed using a discrete time proportional odds model (the same method employed for the primary endpoint of diabetes progression):

- Time to development of microalbuminuria (for subjects without albuminuria at baseline; microalbuminuria is defined as urine albumin/creatinine ratio  $> 30$  mg/g, confirmed by a second measurement)
- Time to progression from microalbuminuria at baseline to macroalbuminuria (urine albumin/creatinine ratio  $> 300$  mg/g, confirmed by a second measurement)
- Time to two-fold increase from baseline in serum creatinine (confirmed by a second measurement), endstage renal disease (renal transplant, dialysis), or renal death

Confirmatory measurements for renal function related variables must take place within one year after the first measurement.

Descriptive statistics and Kaplan-Meier plots will be presented for all time to event variables.

The effect of excluding Adjudication Committee-confirmed events from the progression to diabetes endpoint will also be explored; the analysis of this endpoint will parallel the progression to diabetes endpoint analyses:

- Time to progression to diabetes excluding Adjudication Committee-confirmed cases not meeting laboratory test-based definition, i.e., the cases described in Section 3.5.3, Primary endpoint: time to progression to diabetes, (b).

Exploratory analyses will also be performed using general linear models to test each of the two experimental treatments, these include:

- Indices of hyperglycemia
  - Change from baseline at study endpoint in fasting plasma glucose
  - Change from baseline at study endpoint in 2hr post-OGTT plasma glucose value
  - Change from baseline at study endpoint in HbA<sub>1c</sub>
- Change from baseline in body weight

The covariates in the linear models will be center, baseline value, history of CVD at baseline (yes/no), and the two experimental treatment effects. Small centers may be pooled for the analysis. The exact specification of the pooling algorithm will be defined under blinded conditions. Study endpoint is defined as last post-baseline observation carried forward.

Summary statistics for change from baseline will be presented for the indices of hyperglycemia both at study endpoint and by time period. Time windows will be used to assign study visits to time periods.

#### **6.1.6 Safety evaluation**

The assessment of safety will be based mainly on the frequency of all adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g. electrocardiogram, vital signs, special tests) will be considered as appropriate.

Adverse events will be summarized by presenting, for each treatment group, the number and percentage of patients having any adverse event, having an adverse event in each body system and having each individual adverse event. Any other information collected (e.g. severity or relatedness to study medication) will be listed as appropriate.

For the subset of patients at prospectively defined study centers who will be dispensed glucometers, the number and percentage with confirmed hypoglycemic events (plasma glucose < 3.3 mmol/l) will be presented. The number and percentage of patients with any events suggestive of hypoglycemia will also be presented for this subset, in order to be able to put the number of confirmed vs. suggestive events into a perspective. Patients who were dispensed glucometers at the investigator's discretion (i.e. not from the pre-defined centers) will not be shown in this summary.

Laboratory data will be summarized by presenting shift tables using extended normal ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values (means, medians, standard deviations, ranges) and by the flagging of notable values in data listings.

Data from other tests (e.g. electrocardiogram or vital signs) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate.

Unless otherwise indicated, the safety population will be used for the safety analyses.

### 6.1.7 Interim analyses

Originally, two formal efficacy interim analyses were foreseen which were to take place when approximately 687 and 1031 subjects had had an extended CV endpoint, corresponding to 50% and 75% of the 1374 target subjects, respectively.

The first formal efficacy interim analysis was performed in December 2005 (approximately 4 years after study start) with an information fraction of 0.3 (412 patients with an extended CV endpoint). The analysis was brought forward (i.e., not awaiting the 0.5 information fraction) mainly for the following reasons (it is noted that there is no protocol amendment reflecting this change in trial conduct):

- due to a lower-than-expected CV event rate there was the expectation of the study lasting longer (originally, the trial was projected to last 5 years and 9 months; the ). It was considered undesirable to continue a trial with low likelihood for a positive outcome;
- only the first interim analysis foresaw a futility analysis to allow stopping the study early in case of low probability of success;
- with possibly increased hazards of CV events in later phases of the study the timing of second interim and final analyses would possibly be very close to each other and also close to the first interim analysis if this were done with 50% of the target CV events; a quick follow-up of interim and final analyses was not considered desirable.

The second efficacy interim analysis will not be conducted. The rationale is as follows: in the light of adopting the third primary efficacy endpoint (Sections 2 and 6.1.5.1) there was concern over the complication for properly spending the Type I error in case of a second efficacy interim analyses. Though technically feasible, a closed testing procedure for multiple endpoints with several interim analyses based on an alpha-spending function approach is not a standard procedure and statistically complex. In order to simplify the statistical methodology and make the statistical approach more acceptable to regulatory authorities, the Executive Committee recommended to drop the second formal efficacy interim analysis. The DSMB endorsed the recommendation.

It is noted that the first interim efficacy analysis performed in December 2005 adhered to the original study protocol which stipulated: “The stopping criteria for efficacy will be based on an O'Brien-Fleming alpha-spending approach, combined with a hierarchical testing procedure (see Working Protocol (incorporating Amendments 1 to 4), released on 3-Mar-2004). It is planned to use O'Brien-Fleming boundaries as calculated by EAST2000®. For the alpha-spending, it will be assumed that the number of patients with adjudicated events for the final analysis of the cardiovascular endpoint (this is now to read extended CV endpoint) is 1374”.

The 0.3 information fraction reached at the first interim analysis corresponds to an “(one-sided) alpha spent” less than 0.00005 (EAST® software). The final analysis can therefore be performed at an (one-sided) alpha level of 0.02495 which is just the difference between the commonly-used alpha level (i.e., a one-sided 0.025) and “alpha spent”. Due to the Bonferroni inequality this is a conservative approach regardless of the timing of the final analysis and the number of extended CV endpoints that have occurred at the time of final data cut-off (unless the results of the first interim analysis were known and would trigger the timing of the final analysis). The final analysis therefore resembles the analysis of a fixed sample study (in this

case: an event-driven study with a fixed number of events) only that it is performed at a reduced significance level.

In summary, the final analysis will use in the closed testing procedure detailed in Table 6 at a one-sided alpha level of 0.02495, both for the valsartan and nateglinide comparisons.

Recommendation from the DSMB to stop the trial will be reviewed and ratified by the Executive/Steering Committee. In its recommendation the DSMB may take into account ethical considerations as well as a potential need for further clarification of the robustness of the results observed.

If the trial continues, assignment of study treatment (i.e. both nateglinide and valsartan) should be continued as randomized, unless the results would ethically mandate a change regarding one of the two treatments.

If changes to the interim analysis plan are instituted at the request of the DSMB, statistical significance criteria will be determined using the O'Brien Fleming spending function approach.

Additional safety interim reviews will be performed (without formal testing being performed) as per the DSMB's request. It is planned that such safety reviews will be performed twice per calendar year.

#### **6.1.8 Other topics**

Not applicable

### **6.2 Sample size and power considerations**

The original sample size calculation is based on an event rate of 4% (i.e. 4% of the population experiencing at least one event) per year for the extended cardiovascular endpoints in the placebo group. This assumption is based on risk score calculation for baseline characteristics of early patients recruited into NAVIGATOR. A reduction in the annual hazard rate of 20% under treatment is considered clinically significant. An accrual time of 18 months, and further four-year, three month follow-up was used for the sample size calculation. This will give a total trial duration of five years and nine months from first patient first visit (which can vary if event rates are not as expected, as the timing of the final analyses will be driven by the number of patients with events). The reductions in hazard (under treatment) as compared to patients receiving placebo was assumed to be 20% for both nateglinide and valsartan monotherapy.

For the combination group, the effect size in comparison to placebo is 36%, assuming the effects of the two drugs are independent. Although there is no known drug-drug interaction between valsartan and nateglinide, an effect size of this magnitude is ambitious. The sample size calculation was therefore based on a "subadditivity / 75% additivity of effects" approach, assuming an effect size of 32% on cardiovascular outcome of the two drugs in combination. The treatment discontinuation rate was assumed to be 30% over five years, corresponding to approximately 6.9% per annum. While patients on treatment were assumed to have the full effect (i.e. 20% reduction of hazard rate if in the monotherapy group), it was assumed that patients who discontinued treatment would have only  $\frac{1}{4}$  of the treatment effect remaining as

carry-over effect. Furthermore, it was expected that 75% of the patients who discontinued treatment could be followed up for events. The remaining 25% would comprise patients completely lost to follow-up, patients who die (without reaching a primary endpoint), and those for whom events are unintentionally not reported by the investigator.

Based on these assumptions, a total of 9152 patients will provide 90% testwise power to detect a treatment difference in the extended cardiovascular endpoint.

For the glycemic primary endpoint, it is assumed that 6% of the placebo IGT patients will progress to diabetes each year. This assumption was obtained using progression rates observed in recently reported studies [20,21] and considering the existence of lifestyle advice as background therapy for all patients in NAVIGATOR. Treatment effects were expected to be 25% reduction in the hazard for progression to diabetes in each monotherapy group (nateglinide or valsartan) and 39.1% reduction in the nateglinide-valsartan combination group (consistent with the “75% additivity” approach as used for the cardiovascular endpoint). Using the same expectations for the effect of treatment discontinuation as for the cardiovascular outcome, there will be greater than 99% testwise power to detect a treatment difference in time to progression to diabetes.

These power calculations, and the calculation of 1374 patients with extended cardiovascular endpoints at the end of the trial, were performed using a generic SAS program, which was crosschecked against the results obtained from nQuery advisor® version 4.1 (for the extreme cases, and by use of approximate “average” hazards for the pooled groups over the whole trial) and against simulation results.

Table 7 shows the effects of the changes to the testing procedure on power under the protocol assumptions about treatment effects. However, the closed testing procedure would provide a more robust performance under scenarios in which the effect size for the extended CV endpoint is smaller and the effect size is as large or larger for the core CV endpoint.

**Table 7 Power comparison between hierarchical and closed testing procedure (based on 10,000 simulations)**

Assumed hazard reduction			Test procedure	Power				
Progression to diabetes	Core CV endpoint	Extended CV endpoint		Progression to diabetes	Any endpoint significant	Extended CV endpoint	Core CV endpoint	Any CV endpoint significant
20%	16%	16%	Hierarchical	90.0%	90.0%	90.0%	NA	90.0%
			Closed	>99.9%	>99.9%	85.8%	67.1%	86.6%

### 6.3 Pharmacogenetic data analysis

The pharmacogenetic data analysis is also detailed in the Substudy 1 Protocol for countries where this assessment is required to be separate from the core protocol.

These exploratory pharmacogenetic studies are designed to investigate the association between genotypes and phenotypes. Neither genotypes nor phenotypes are pre-specified for this investigation. Hence, all statistical analysis to be performed will be considered exploratory. Summary statistics, performed by the pharmacogenetics group, will be provided as appropriate and the correlation between the genotype and phenotype will be assessed. Other statistical methods used in genetic studies may be used for exploring the relationship, if

applicable. Due to multiple comparisons of unspecified hypotheses, results of applied test procedures will serve illustrative purposes only.

If the numbers of subjects enrolled in the study are too small to complete proper statistical analyses, these data will be combined, as appropriate, with those from other studies to enlarge the data set for analysis.

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## **8 Procedures and instructions**

### **8.1 Special safety-related procedures**

#### **8.1.1 Instructions for rapid notification of serious adverse events**

##### **8.1.1.1 Reporting responsibility**

Any serious adverse event occurring in a patient after providing informed consent and until 4 weeks after stopping the trial must be reported. The period after discontinuing study drug may be extended if there is a strong suspicion that the drug has not yet been eliminated. All serious adverse events must also be reported for the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

Each serious adverse event (but not pregnancies) must be reported by the investigator to Novartis within 24 hours of learning of its occurrence, even if it is not felt to be treatment-related. Follow-up information about a previously reported serious adverse event must also be reported to Novartis within 24 hours of receiving it. If the serious adverse event has not been previously documented (new occurrence) and it is thought to be related to study drug (or therapy), the Medical Safety Expert of the Clinical Safety & Epidemiology (CS&E) Department may contact the investigator to obtain further information. If warranted, an investigator notification may be issued, to inform all investigators involved in any study with the same drug (or therapy) that this serious adverse event has been reported.

##### **8.1.1.2 Reporting procedures**

The investigator must complete the Serious Adverse Event Report Form in English, assess the relationship to study treatment and send the completed form by fax within 24 hours to the local Novartis Clinical Safety & Epidemiology (CS&E) Department (for trials monitored by Novartis) OR to the relevant Contract Research Organization (CRO). The CRO or local CS&E department, after ensuring that the form is accurately and fully completed, must then fax it to the central Novartis CS&E Department within 2 to 3 calendar days for deaths or life-threatening events and 5 calendar days for other serious adverse events. The original and the duplicate copies of the Serious Adverse Event Form, and the fax confirmation sheet must be kept with the case report forms at the study site. The monitor will collect a copy of the Serious Adverse Event Form and deliver it to Novartis.

Follow-up information is sent to the same person that sent the original Serious Adverse Event Form, re-stating the date of the original report. Either a new Serious Adverse Event Form is sent (stating that this is a follow-up), or the original one is resent (with the new information highlighted and a new date provided). The follow-up should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or discontinued study participation. The form and fax confirmation sheet must be retained. Pregnancy, although not itself a serious adverse event, should also be reported by completing a Clinical Trial Pregnancy form and faxing to Novartis CSE. Pregnancy follow-up should describe the outcome of the pregnancy, including any

voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects.

### **8.1.1.3 Contact persons and numbers**

The telephone and telefax numbers of the contact persons in the local Clinical Research (CR) department, at the Clinical Research Organization (CRO) and in the local department of Clinical Safety and Epidemiology (CS&E), specific to the site, are listed in the investigator folder provided to each site.

### **8.1.2 Emergency procedure for unblinding**

For blinded studies using IVRS the code break is performed using the IVR System both the respective monitor for the site and the Clinical Trial Leader will be immediately informed of any code break event. Upon calling the system the investigator receives details of the drug treatment for the specified patient and receives a fax confirming this. The IVR System Emergency unblinding must not be used for any reason, other than an emergency. When the investigator contacts the system to unblind a patient he/she must note the date, time and reason for unblinding and retain this information with the case report form documentation. The system will automatically inform Novartis of any unblinding event.

### **8.1.3 Instructions for completing adverse event case report forms**

All adverse events are to be reported on an Adverse Event Case Report Form. Refer to the Case Report Form or to the Case Report Form Completion Guideline for details.

## **8.2 Administrative procedures**

### **8.2.1 Changes to the protocol**

Any change or addition to this protocol requires a written protocol amendment that must be approved by Novartis and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study, require additional approval by the IRB/IEC/REB of all centers, and, in some countries, by the regulatory authority. A copy of the written approval of the IRB/IEC/REB, which becomes part of the protocol, must be given to the Novartis monitor. Examples of amendments requiring such approval are:

1. an increase in drug dosage or duration of exposure of subjects
2. a significant change in the study design (e.g. addition or deletion of a control group)
3. an increase in the number of invasive procedures to which subjects are exposed
4. addition or deletion of a test procedure for safety monitoring.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Novartis in the interests of preserving the safety of all subjects included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented by him/her for safety reasons Novartis should be notified and the IRB/IEC/REB at the center should be informed within 10 working days.

Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB/IEC/REB approval but the IRB/IEC/REB of each center must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB/IEC/REB approval that can be treated as administrative amendments include:

1. changes in the staff used to monitor trials (e.g. Novartis staff versus a CRO)
2. minor changes in the packaging or labeling of study drug.

### **8.2.2 Monitoring procedures**

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative (or designated CRO representative) will review the protocol and case report forms (CRFs) with the investigators and their staff. During the study the field monitor will visit the site regularly, to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and also to ensure that study medication is being stored, dispensed and accounted for according to specifications. Key trial personnel must be available to assist the field monitor during these visits.

The investigator must give the monitor access to relevant hospital or clinical records, to confirm their consistency with the CRF entries. No information in these records about the identity of the subjects will leave the study center. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs and the recording of primary efficacy and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

### **8.2.3 Recording of data and retention of documents**

The investigator must complete the CRFs and transmit the data as instructed by Novartis at study initiation and must store a copy of the CRF with other study documents, e.g. the protocol, the investigators' brochure and any protocol amendments, in a secure place. All entries to the CRFs must be made as described in the Case Report Form Completion Guideline or as instructed by Novartis at study initiation.

Data on subjects collected on CRFs during the trial will be documented in an anonymous fashion and the subject will only be identified by the subject number, and by his/her initials if also required. If, as an exception, it is necessary for safety or regulatory reasons to identify the subject, both Novartis and the investigator are bound to keep this information confidential.

The investigator must maintain source documents for each patient in the study, consisting of all demographic and medical information, including laboratory data, electrocardiograms, etc, and keep a copy of the signed informed consent form. All information on CRFs must be traceable to these source documents kept in the patient's file. Data without a written or electronic record will be defined before trial start and will be recorded directly on the CRFs, which will be documented as being the source data.

Essential documents, as listed below, must be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after

discontinuing clinical development or after the last marketing approval). Novartis will notify the investigator(s)/institution(s) when the study-related records are no longer required. The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

1. IRB/IEC/REB approvals for the study protocol and all amendments
2. all source documents and laboratory records
3. CRF copies
4. patients' informed consent forms (with study number and title of trial)
5. FDA form 1572 (as required)
6. any other pertinent study document.

#### **8.2.4 Auditing procedures**

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance Unit exists within Novartis. This unit conducts audits of clinical research activities in accordance with internal SOPs to evaluate compliance with the principles of Good Clinical Practice. A regulatory authority may also wish to conduct an inspection (during the study or even after its completion). If an inspection is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

#### **8.2.5 Handling of study medication**

All study medication will be supplied to the principal investigator by Novartis. Drug supplies must be kept in an appropriate, secure area (e.g. locked cabinet) and stored according to the conditions specified on the drug labels. The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger, a copy of which must be given to Novartis at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time.

All drug supplies are to be used only for this protocol and not for any other purpose. The investigator must not destroy any drug labels, or any partly-used or unused drug supply. At the conclusion of the study, and, as appropriate during the course of the study, the investigator will return all used and unused drug containers, drug labels and a copy of the completed drug disposition form to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

#### **8.2.6 Publication of results**

Any formal presentation or publication of data from this trial will be considered as a joint publication by the investigator(s) and appropriate Novartis personnel. Authorship will be determined by mutual agreement. For multicenter studies, it is mandatory that the first publication is based on data from all centers, analyzed as stipulated in the protocol, by Novartis statisticians, and not by the investigators. Investigators participating in multicenter studies agree not to present data gathered from one center or a small group of centers before the full publication, unless formally agreed to by all other investigators and Novartis.

Novartis must receive copies of any intended communication in advance of publication (at least 15 working days for an abstract or oral presentation and 45 working days for a journal

submission). Novartis will review the communications for accuracy (thus avoiding potential discrepancies with submissions to health authorities), verify that confidential information is not being inadvertently divulged and provide any relevant supplementary information.

### **8.2.7 Disclosure and confidentiality**

By signing the protocol, the investigator agrees to keep all information provided by Novartis in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Novartis (protocols, investigators' brochures, CRFs and other material) will be stored appropriately to ensure their confidentiality. The information provided by Novartis to the investigator may not be disclosed to others without direct written authorization from Novartis, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

### **8.2.8 Discontinuation of study**

Novartis reserves the right to discontinue any study under the conditions specified in the clinical trial agreement.

## **8.3 Ethics and Good Clinical Practice**

This study must be carried out in compliance with the protocol and in accordance with Novartis standard operating procedures. These are designed to ensure adherence to Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

### **8.3.1 Institutional Review Board/Independent Ethics Committee**

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. The name and occupation of the chairman and the members of the IRB/IEC/REB must be supplied to Novartis. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

### **8.3.2 Informed consent**

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If written consent is not possible, oral consent can be obtained if witnessed by a signed statement from one or more persons not involved in the study, mentioning why the patient was unable to sign the form. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval. Novartis supplies a proposed informed consent form, which complies with regulatory requirements and is considered appropriate for the study. Any changes to the proposed consent form suggested by the Investigator must be agreed to by Novartis before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC/REB approval.

### **8.3.3 Declaration of Helsinki**

The investigator must conduct the trial in accordance with the Declaration of Helsinki. A copy of the Declaration of Helsinki is provided in the investigator folder at each site.

World Medical Association Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects.

Adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and as revised by the World Medical Assembly in Tokyo, Japan in 1975, in Venice, Italy in 1983, in Hong Kong in 1989 and the 48th General Assembly in Somerset West, Republic of South Africa, 1996.

### **Introduction**

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The Purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

## **I. Basic Principles**

Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

## **II. Medical Research Combined with Professional Care (Clinical Research)**

In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

In any medical study, every patient--including those of a control group, if any--should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I,2).



The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

### **III. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-Clinical Biomedical Research)**

In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

The subjects should be volunteers--either healthy persons or patients for whom the experimental design is not related to the patient's illness.

The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

#### **8.4 Preserving confidentiality of pharmacogenetic data**

The preservation of confidentiality of pharmacogenetic data is also detailed in the Substudy 1 Protocol for countries where this assessment is required to be separate from the core protocol.

To protect the research subject against the risk of loss of confidentiality, all DNA samples will be marked with a unique code number and all genetic assay results will have a different unique bar code from the DNA. This information is stored in an anonymous fashion in two different secured computer databases, one containing the DNA sample codes and the other with the genetic information to maximize confidentiality.

Results of these studies are for research purposes only and since they are not expected to benefit the subject directly or to alter their treatment course, these results will not be placed in their medical record and will not be made available to the subject, members of their family, their personal physician, or other third parties except as specified below.

Unless required by law or regulatory authorities for the purpose of verifying information obtained from this study, only Novartis Pharmaceuticals Corporation (the sponsor) and its authorized personnel and agents will have access to the confidential genetic data. Novartis will not collect or maintain data which identifies the subject by name. The investigator will collect and maintain that information. The results and other information from this study may be submitted to the FDA and governmental agencies in other countries where the Study Drugs may be considered for approval; however, the subject will be identified by initials and subject study number only. The lead investigators for this study may have access to the bar-coded genetic information for purposes of data analysis and publication. Individual subjects will not be identified in any reports or publications resulting from this study. Because of the need to give these parties access to this information, absolute confidentiality cannot be guaranteed.

## Appendix 1A: Informed Consent

Protocol: CDJN608 Study B2302

TITLE: A multinational, randomized, double-blind, placebo-controlled, forced-titration, 2 x 2 factorial design study of the efficacy and safety of long term administration of nateglinide and valsartan in the prevention of diabetes and cardiovascular outcomes in subjects with impaired glucose tolerance (IGT).

INVESTIGATOR:

### Introduction

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. Do not sign this consent form unless you have received satisfactory answers to all of your questions.

### Purpose and Description of the Study

As a patient at risk for diabetes and heart disease, you are being invited to participate in this research study sponsored by Novartis Pharmaceuticals. The purpose of this study is to assess the efficacy and safety of long term administration of nateglinide and valsartan in the prevention of diabetes and cardiovascular disease.

Nateglinide (Starlix®) is a drug approved in many countries for the treatment of diabetes. Valsartan (Diovan®) is a drug approved in many countries for the treatment of hypertension (high blood pressure).

Approximately 9152 patients from 800-900 centers in 39 countries will take part in this study.

This study, from first visit to last visit, is approximately 6 years long with up to 18 visits for each patient.

You will be randomly assigned (by chance) to receive one of the following:

Nateglinide 60mg before meals + matching placebo once daily

Nateglinide 60mg before meals + Valsartan 160mg once daily

Matching placebo before meals + matching placebo once daily

Matching placebo before meals + Valsartan 160mg once daily

Placebo looks exactly like the other study tablets, but do not contain any medication. They do not affect blood sugar or blood pressure.

Placebos are given to ensure that neither you nor the study doctor will know what combination of study medication you are taking. This study is called “double-blind” because neither you nor the study doctor will know which combination of study medication you will receive: however, the doctor can get this information in case of an emergency.

You (and all other subjects) will take one of the above-mentioned combinations of medications. You will be given two types of medication bottles. Tablets from one bottle will be taken before meals. Capsules from the other bottle will be taken once daily. IT IS IMPORTANT THAT YOU TAKE YOUR MEDICATION AS DIRECTED BY THE STUDY DOCTOR.

### **Trial Procedures**

At the first visit to the office or clinic, you will be screened by the study doctor or one of the study staff to see if you can participate in the study. To be eligible for the remainder of the study you must have impaired glucose tolerance (that is, your blood sugar is higher than normal but not diabetic). After the initial visit, you will come to the office or clinic again for a minimum of twelve visits.

You will be asked not to eat or drink (water is allowed) overnight prior to each visit. At each visit (excluding visits 3, 4 and 5), blood will be taken through a needle in your vein for laboratory tests. For those who are currently taking additional heart medication (such as “ACE inhibitors”) blood will also be drawn at visits 3 and 4 for the purpose of laboratory testing.

At the first visit, the study doctor or a member of the study staff will ask you questions about your past health (illnesses or injuries) and diet. You will also have a physical examination. Also, at each visit, you will be weighed and have your blood pressure and heart rate measured. At each visit (excluding visits 3, 4 and 5), blood (approximately 1-6 teaspoon-full or 5 to 30 ml) will be taken through a needle in a vein for laboratory test. At visits 2, 7 and at end of trial additional blood (approximately 1-6 teaspoons-full or 5-30 ml) will be drawn and frozen for the measurement of biomarker parameters upon completion of the trial. A urine specimen will be collected 7 times during the study. At the second visit, you will have an electrocardiogram (ECG-a tracing of the electrical activity of the heart). The ECG will be repeated two more times during the study.

On all visits, the study staff will ask you how you have felt since the last visit. You will also receive information on diet and exercise to lower your risk of diabetes and heart disease and you may be asked to fill out some questions about your diet and exercise habits. You will be asked to wear a pedometer (a small battery operated device that measures the number of steps you take in a day) for 7 days up to 7 times during the study.

On the day you come to the office for your visit, you will not take your morning study medication at home. It will be given to you at the office after your laboratory tests are done.

In addition, at seven of the office visits, you will have a 2-hour oral glucose tolerance test. An additional 2-hour oral glucose tolerance test may be required. You will have blood (total amount approximately 2 teaspoon-full or approximately 10 ml) taken through a needle in your vein a total of two times during this test.

You will be asked to keep a diary of suspected hypoglycemic (low blood sugar) events. You may be provided a blood testing kit for you to check and record these occurrences.

## **Risks**

### **General**

During the collection of blood samples, you may experience pain and /or bruising at the site where the blood is drawn.

Trial medication must be taken only by the person for whom it has been prescribed, and it should be kept out of reach of children or others of limited capacity to read or understand.

### **Side effects – nateglinide**

Nateglinide is approved for treatment of diabetes. It is possible that treatment with nateglinide could lower your blood sugar too much. This could make you feel tired, dizzy, sweaty, and/or nauseated. In addition, it could cause your heart to feel as if it is racing. These signs and symptoms are referred to as hypoglycemia (low blood sugar). If such blood sugar changes persist, the study doctor may remove you from the study medication so that you can be treated with medication chosen by your own doctor. Untreated severe hypoglycemia could be life threatening.

### **Side effects – valsartan**

Valsartan is a vasodilator medication that has been shown to reduce blood pressure in patients with hypertension. The most frequently reported adverse experiences in patients with hypertension were headaches, dizziness, viral infection, upper respiratory tract infection, coughing, diarrhea and fatigue.

There is also a potential risk of developing low blood pressure as well as higher than normal levels of potassium and creatinine in the blood. Abnormalities in potassium could produce abnormalities in heart rhythm which could be life threatening. High creatinine levels may indicate abnormal kidney function.

If you are already receiving valsartan or a similar treatment, it will be withdrawn 4 weeks prior to study entry and during the full course of the study. If you are taking an angiotensin converting enzyme inhibitor for the treatment of hypertension, it will be withdrawn 4 weeks prior to study entry. Your doctor will inform you of the risks associated with the withdrawal.

You are expected to report all side effects promptly to the study doctor, should they occur. The study doctor is aware of the side effects, as well as the best methods for treating them. This includes reducing the dose of medication or interrupting treatment. The study doctor is prepared to handle any medical problem should it be necessary.

### **Alternative Treatment**

There is no medication currently approved to treat impaired glucose tolerance. Diet and exercise have been shown to have a positive effect on the progression to diabetes in subjects with impaired glucose tolerance. If you have questions about other medications and treatments for cardiovascular disease or diabetes, as well as information on diet and exercise,

ask Dr. XXXX for additional information. You do not have to participate in this study to receive treatment for your condition.

### **Benefits of treatment**

It is possible that no benefits to you will result from your participation in this study and that you may experience only side effects. However, you may also benefit from the treatment if the progression of impaired glucose tolerance to diabetes is slowed down. If the side effects of study therapy become intolerable, or if new scientific developments occur indicating that this treatment is no longer in your best interest, treatment will be stopped and other alternatives will be discussed with you. If your disease worsens to diabetes or if it becomes necessary to treat a worsening cardiovascular disease, other therapy will be discussed with you and may be commenced with your agreement. In this circumstance it is foreseen that study therapy will also continue in order to assess whether nateglinide and/or valsartan can reduce the amount of therapy required to bring your diabetes or cardiovascular disease under control.

Office visits and procedures related to the study and study medication will be provided at no charge to you.

### **Compensation**

Novartis will provide payment for reasonable, non-reimbursed medical expenses, including hospitalization, which you may incur as a direct result of the study drug or its administration in accordance with the Protocol, as determined by Novartis and the study doctor. Novartis will not provide payment for expenses that are in any way attributable to the negligence or misconduct of any person employed by or acting on behalf of the Institution or your failure to follow instructions. Novartis will not pay for medical expenses for injuries unrelated to the study drug, or which are in any way attributable to the natural course of any underlying disease or treatment process. No other type of compensation will be provided by Novartis.

You must notify the study doctor immediately of any research-related injury and the nature of the expenses to be covered. If you have any questions concerning the research or the availability of medical care or if you think you have experienced a research-related illness, injury or emergency, contact:

Investigator: «Investigator» Telephone: «Phone Number»

### **Participation**

Your decision to participate in this study is voluntary. If you decide not to enter the study, the quality of care you receive will not be affected. If you do enter, you can leave the study at any time without any loss of quality of care or any other penalty. However, you should enter the study only if your current plan is to continue in it until it ends (in about 6 years). If the study medication is interrupted you will be asked to continue with all remaining study visits to evaluate your condition. If you discontinue study participation (i.e., taking study medication and being seen at the clinic), you agree that data may be continued to be collected about your overall health. This data includes, but is not limited to, information on progression to diabetes, as well as your cardiovascular disease. This data will be collected every six months, until the

conclusion of the study. This information may be provided by you or someone who knows you.

You will be informed and asked to re-consent to participate in the trial if, during the course of this study, there are any significant new findings (from this or other studies) that might affect your continued willingness to participate.

If you want to leave the study, please talk to Dr. XXXX or one of his/her associates. A final visit will be done by the study doctor to ensure your ensuing medical health.

The study doctor can also stop your participation in the study at any time without your consent for any of the following reasons; if you fail to follow directions for participation in the study, if it appears harmful to you, if it is discovered at a later date that you do not meet the study requirements or if the study is cancelled.

Should you have any questions about your rights as a study patient, please contact:

XXXX (IRB) in XXXXXXXXXXX, XXXXXXXXXXX.

Ask to speak with a Research Subject Advocate at XXX.XXX.XXXX.

### **Confidentiality and Source Document Review**

Unless required by law, only the study doctor, the study team, Novartis Pharmaceuticals Corporation (the sponsor) and its authorized agents, the U.S. Food and Drug Administration (FDA), governmental agencies in other countries where the study drug may be considered for approval, and XXXXX (IRB) will have access to confidential data which identifies you by name. Because of the need to give these parties access to this information, absolute confidentiality cannot be guaranteed.

The results and other information from this study may be submitted to the FDA and governmental agencies in other countries where nateglinide or valsartan may be considered for approval in this new indication; however, you will be identified by initials and patient study number only. You will not be identified in any reports or publications resulting from this study.

### **Patient's Statement**

By signing this consent, I acknowledge that I have been informed of the methods and means of administration of the study medication to be used, the inconveniences, risks, benefits and adverse events that might occur from the procedures and the drug.

I certify that I have been given sufficient time to read and understand the above information. I also acknowledge that all technical language used in describing this research study has been explained to my satisfaction and I have received answers to all my questions. I also confirm that I have received a copy of this consent form. I understand that I am free to withdraw from the study at any time without loss of benefits or any other penalty.

I freely, without reservations, give my consent to serve as a patient in this study.

\_\_\_\_\_  
Name of Participant (printed)

\_\_\_\_\_  
Signature of Participant or Legal Representative

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Consent Presenter

\_\_\_\_\_  
Signature of Consent Presenter

\_\_\_\_\_  
Date

I or my representative have discussed the nature and purpose of this study, and the possible risks and benefits of participation, with the participant and/or legally authorized representative. I believe that the participant and/or his/her representative has been fully informed, using language which is understandable and appropriate, and has understood this explanation.

\_\_\_\_\_  
Signature of Principal Investigator

\_\_\_\_\_  
Date

Subject's Number \_\_\_\_\_

Subject's Initials \_\_\_\_\_

## Appendix 1B: Pharmacogenetics Informed Consent

The pharmacogenetics informed consent is also presented in the Substudy 1 Protocol for countries where this assessment is required to be separate from the core protocol.

Protocol: CDJN608B2302

TITLE: A multinational, randomized, double-blind, placebo-controlled, forced-titration, 2 x 2 factorial design study of the efficacy and safety of long term administration of nateglinide and valsartan in the prevention of diabetes and cardiovascular outcomes in subjects with impaired glucose tolerance (IGT).

### Introduction

I understand that I am being asked to provide one additional blood sample (about 2.5 teaspoonfuls or 12 ml) for the studies described below. DNA will be extracted from the blood sample so that my genetic information can be used to study whether my response to treatment with nateglinide and/or valsartan and any side effects that I may have developed are related to my genes. This area of research is called "pharmacogenetics" because we are striving to understand how genes influence the different responses people have to the same drug. The goal of these exploratory research studies is to find genetic markers that will identify persons with impaired glucose tolerance and cardiovascular disorders who will have the best possible response to nateglinide and/or valsartan or to identify persons who will have fewer side effects in order to maximize their benefit from nateglinide and valsartan.

### Trial Purpose and Conduct

This is an experimental research study designed specifically to evaluate the relationship of my individual genetic markers to any improvement in my condition seen with nateglinide and/or valsartan or to any adverse drug reactions that may arise during treatment. The use of my sample will be confined to research focused on pharmacogenetics. This is not a genetic testing project since we are not trying to identify genetic information to determine risk of diseases that are not present during the study. This research study is focused on studying the role genes play in impaired glucose tolerance and cardiovascular disorders and the responses of subjects to nateglinide and valsartan.

### Risks and Inconveniences

Risks associated with drawing blood may include pain, bruising, perforation or penetration of the needle through the vein leading to discoloration, bleeding from the site of the needle, puncture into the vein and the formation of a blood clot. I will contribute one additional blood sample during the CDJN608B2302 study for these genetic studies. It is intended that only one 18 ml blood sample will be drawn for these studies. I understand that in the case of loss or damage to the original blood sample, I may be asked to provide a second sample.

The privacy of the preliminary research information generated from my blood sample will be protected in accordance with the Confidentiality section below. If this information were released to me, my family, or third parties, there could potentially be adverse psychological



effects and/or undesired effects on my ability, or that of my family members, to obtain a job, or insurance. In order to minimize any such risks, and since the results of these studies are not expected to benefit me directly or to alter my treatment course, all genetic research information obtained from my blood sample will be kept confidential in accordance with the Confidentiality section below. As more is learned about the role of genes in the drug response to nateglinide and valsartan, new clinical studies will be needed to clarify our understanding of the implications of these genetic studies.

### **Potential Benefits**

I understand that participation in this study may not benefit me directly. Indirect benefits may include the possible advancement of medical knowledge so that scientists can find more effective and safer treatments for to prevent diabetes and cardiovascular disorders.

### **Confidentiality**

To protect me against the risk of loss of confidentiality, all DNA samples will be marked with a unique code number and all genetic assay results will have a different unique bar code from the DNA. This information is stored in an anonymous fashion in two different secured computer databases, one containing the DNA sample codes and the other with the genetic information to maximize confidentiality.

Since these studies are not expected to benefit me directly or to alter my treatment course, these results will not be placed in my medical record and will not be made available to me, members of my family, my personal physician, or other third parties except as specified below.

Unless required by law or regulatory authorities for the purpose of verifying information obtained from this study, only Novartis Pharmaceuticals Corporation (the sponsor) and its authorized personnel and agents will have access to my confidential genetic data. Novartis will not collect or maintain data which identifies me by name. The investigator will collect and maintain that information. The results and other information from this study may be submitted to the FDA and governmental agencies in other countries where the Study Drugs may be considered for approval; however, I will be identified by initials and subject study number only. The lead investigators for this study may have access to the bar-coded genetic information for purposes of data analysis and publication. I will not be identified in any reports or publications resulting from this study. Because of the need to give these parties access to this information, absolute confidentiality cannot be guaranteed.

### **Voluntary Participation**

My decision whether or not to participate is completely voluntary and will not affect me or my medical care. There is no penalty or loss of benefit to me (to which I would otherwise be entitled) if I choose not to participate or withdraw from the study. In particular, non-participation in this evaluation will in no way affect my ability to participate in the CDJN608B2302 research study.

## **Collection, Research and Storage of Genetic Material**

During the course of this study, the Study Doctor or members of his/her staff will take a 12ml (about 2.5 teaspoonfuls) sample of my blood. This sample and any DNA derived from the samples may be stored for up to 15 years to research scientific questions related to nateglinide, valsartan, impaired glucose tolerance, diabetes mellitus, metabolic disorders, and cardiovascular disorders. This research study is focused on studying the role genes play in impaired glucose tolerance and cardiovascular disorders and the responses of subjects to nateglinide and valsartan. Since nateglinide and valsartan may be developed for other diseases and Novartis may develop new drugs for my condition, my genetic information may be used for other impaired glucose tolerance, diabetes mellitus, cardiovascular disorder, nateglinide, and valsartan- related drug research and development.

I will continue to be the owner of the sample and retain the right to have the sample material destroyed at any time by contacting the Study Doctor. The Study Doctor will provide the Sponsor with the required study and subjects numbers, so that any remaining blood or DNA samples can be located and destroyed. The sponsor will be the exclusive owner of any data, discoveries or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at my request or at the end of the storage period. If a commercial product is developed from this research project, the commercial product will be owned by the Sponsor and I will not profit financially from such a product.

## **Compensation for Subject Injury**

Novartis will not provide payment for any medical expenses, which you may incur as a result of your participation in this study. No other type of compensation will be provided by Novartis.

You must notify the Study Doctor immediately of any research-related injury. If you have any questions concerning the availability of medical care or if you think you have experienced a research-related illness, injury or emergency, contact: investigator's name and phone and/or pager number.

By signing this form you have not given up any of the legal rights which you otherwise would have as a participant in a research study.

## **Questions About Research**

If you have any questions about the research or develop a research-related problem contact your Study Doctor, XXXXXXXXXXXX at (XXX) XXX-XXXX. During non-business hours, page the physician or nurse on-call at (XXX) XXX-XXXX. If you have any questions regarding your rights as a participant in this research study, please contact XXXXXX at XXX-XXXX.

## **Consent**

By signing this form, I acknowledge that I have read and I understand its contents and have asked and received a satisfactory response to each question I have concerning this investigational evaluation and I agree to participate.

I understand that I will receive a copy of this consent form.

I authorize the release of my medical records to the Sponsor, CRO if indicated, IRB/IEC, and regulatory authorities.

By signing this form, I have not waived any of the legal rights which I otherwise would have as a participant in a research study.

**Signatures**

\_\_\_\_\_  
Name of Participant (printed)

\_\_\_\_\_  
Signature of Participant or Legal Representative

\_\_\_\_\_  
Date

\_\_\_\_\_  
Name of Consent Presenter

\_\_\_\_\_  
Signature of Consent Presenter

\_\_\_\_\_  
Date

I or my representative have discussed the nature and purpose of this study, and the possible risks and benefits of participation, with the participant and/or legally authorized representative. I believe that the participant and/or his/her representative has been fully informed, using language which is understandable and appropriate, and has understood this explanation.

\_\_\_\_\_  
Signature of Principal Investigator

\_\_\_\_\_  
Date

Subject's Number \_\_\_\_\_

Subject's Initials \_\_\_\_\_

## **Appendix 1C: Informed Consent for patients with more than 18 study visit**

Protocol: CDJN608B2302

TITLE: A multinational, randomized, double-blind, placebo-controlled, forced-titration, 2 x 2 factorial design study of the efficacy and safety of long term administration of nateglinide and valsartan in the prevention of diabetes and cardiovascular outcomes in subjects with impaired glucose tolerance (IGT).

### **Introduction**

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. Do not sign this consent form unless you have received satisfactory answers to all of your questions.

You are currently participating in the NAVIGATOR study that started in January 2002. More than 9,000 patients from approximately 700 centers in 40 countries were enrolled in this study.

In order to achieve adequate results and draw meaningful conclusions, the study requires to have an adequate time of study treatment and follow-up for the individual patients in the study.

Originally, you have agreed to participate in this trial with up to 18 study visits which at that time was anticipated to be sufficient.

However, during the course of the study it has turned out that in order to complete the NAVIGATOR protocol with meaningful results the trial will need to be continued beyond its original timelines. Therefore, you are now asked to consent to an additional 4 regular study visits and a separate final close-out visit. Dependent on when you actually entered the study this may also be less additional visits for you.

The overall duration of the NAVIGATOR trial is not exactly predictable at this moment. Your study doctor will be able to discuss that with you.

### **Purpose and Description of the Study**

As a patient at risk for diabetes and heart disease, you were invited to participate in this research study sponsored by Novartis. The purpose of this study is to assess the efficacy and safety of long term administration of nateglinide and valsartan in the prevention of diabetes and cardiovascular disease.

Nateglinide (Starlix®) is a drug approved in many countries for the treatment of diabetes. Valsartan (Diovan®) is a drug approved in many countries for the treatment of hypertension (high blood pressure).

At the beginning of the study you were randomly assigned (by chance) to receive one of the following:

- Nateglinide 60mg before meals + matching placebo once daily
- Nateglinide 60mg before meals + Valsartan 160mg once daily
- Matching placebo before meals + matching placebo once daily
- Matching placebo before meals + Valsartan 160mg once daily

Placebos look exactly like the other study tablets, but do not contain any medication. They do not affect blood sugar or blood pressure.

Placebos are given to ensure that neither you nor the study doctor will know what combination of study medication you are taking. This study is called “double-blind” because neither you nor the study doctor will know which combination of study medication you will receive. However, the doctor can get this information in case of an emergency.

You (and all other subjects) are taking one of the above-mentioned combinations of medications. You are given two types of medication bottles. Tablets from one bottle will be taken before meals. Capsules from the other bottle will be taken once daily.

**IT IS IMPORTANT THAT YOU TAKE YOUR MEDICATION AS DIRECTED BY THE STUDY DOCTOR.**

### **Trial Procedures**

During the additional study visit (every six months) the same assessments and procedures will be done as on previous study visits.

At each visit, you will be weighed and have your blood pressure and heart rate measured.

On all visits, the study staff will also ask you how you have felt since the last visit. You will receive information on diet and exercise to lower your risk of diabetes and heart disease and you may be asked to fill out some questions about your diet and exercise habits. You may be asked to wear a pedometer (a small battery operated device that measures the number of steps you take in a day) for 7 days prior to an annual visit.

At the annual visits and at the end of the study, blood (approximately 1-6 teaspoon-full or 5 to 30 ml) will be taken through a needle in a vein for laboratory test and a urine specimen will be collected.

In addition, at the annual visits and at the end of the study, you will have a 2-hour oral glucose tolerance test. An additional 2-hour oral glucose tolerance test may be required to confirm the results. For that purpose you will be asked to drink a glucose solution and you will have blood (total amount approximately 2 teaspoon-full or approximately 10 ml) taken through a needle in your vein two times during this test.

Additional procedures will be performed at the end of the study. You will have an electrocardiogram (ECG, a tracing of the electrical activity of the heart). Additional blood (approximately 1-6 teaspoons-full or 5-30 ml) will be drawn and frozen for the measurement of biomarker parameters upon completion of the trial.

You will be asked not to eat or drink (water is allowed) overnight prior to each visit.

On the day you come to the office for your visit, you will not take your morning study medication at home. It will be given to you at the office after your assessments are done.

You will be asked to keep a diary of suspected hypoglycemic (low blood sugar) events. You may be provided a blood testing kit for you to check and record these occurrences.

## **Risks and inconveniences**

### **General**

Trial medication must be taken only by the person for whom it has been prescribed, and it should be kept out of reach of children or others of limited capacity to read or understand.

During the collection of blood samples, you may experience pain and/or bruising at the site where the blood is drawn.

In rare instances where a nurse, a doctor, or laboratory technician, sustains an exposure to your blood by needle stick, cut or splash to mucosa or damaged skin, it may be necessary to test your blood for Hepatitis B and C and HIV, to enable that person to receive appropriate counseling, monitoring and treatment if necessary. The study doctor will offer you the information relevant to your health and advise you on the next steps. Confidentiality of your data will be respected at all times.

### **Side effects – nateglinide**

Nateglinide is approved for treatment of diabetes. It is possible that treatment with nateglinide could lower your blood sugar too much. This could make you feel tired, dizzy, sweaty, and/or nauseated. In addition, it could cause your heart to feel as if it is racing. These signs and symptoms are referred to as hypoglycemia (low blood sugar). If you develop these symptoms, the study doctor should be contacted who will advise what to do in such circumstances. If these symptoms occurs too frequently or are severe, the study doctor may remove you from the study medication so that you can be treated with medication chosen by your own doctor. Untreated severe hypoglycemia could be life threatening.

### **Side effects – valsartan**

Valsartan is a vasodilator medication that has been shown to reduce blood pressure in patients with hypertension. The most frequently reported adverse experiences in patients with hypertension were headaches, dizziness, viral infection, upper respiratory tract infection, coughing, diarrhea, rhinitis, sinusitis, pharyngitis and arthralgia.

Other less frequently reported drug reactions that have been observed in clinical studies included chest pain, fatigue, palpitation, itching, skin rash, tingling sensation, anorexia, impotence, muscle pain or ache, muscle cramps, shortness of breath, and vomiting.

There is also a potential risk of developing low blood pressure as well as higher than normal levels of potassium. Abnormalities in potassium could produce abnormalities in heart rhythm which could be life threatening. Infrequent cases of liver enzymes elevation (including hepatitis) have been reported which are mostly asymptomatic and have improved spontaneously. High creatinine levels may indicate abnormal kidney function. Very rare

cases of swelling around the throat muscles causing difficulties in breathing (angioedema) have been observed.

You are expected to report all side effects promptly to the study doctor, should they occur. The study doctor is aware of the side effects, as well as the best methods for treating them. This includes reducing the dose of medication or interrupting treatment. The study doctor is prepared to handle any medical problem should it be necessary.

### **Alternative Treatment**

There is no medication currently approved to treat impaired glucose tolerance. Diet and exercise have been shown to have a positive effect on the progression to diabetes in subjects with impaired glucose tolerance. If you have questions about other medications and treatments for cardiovascular disease or diabetes, as well as information on diet and exercise, ask investigator for additional information. You do not have to continue in this study to receive treatment for your condition.

### **Benefits of treatment**

It is possible that no benefits to you will result from your continuation in this study and that you may experience only side effects. However, you may also benefit from the treatment if the progression of impaired glucose tolerance to diabetes is slowed down. If the side effects of study therapy become intolerable, or if new scientific developments occur indicating that this treatment is no longer in your best interest, treatment will be stopped and other alternatives will be discussed with you. If your disease worsens to diabetes or if it becomes necessary to treat a worsening cardiovascular disease, other therapy will be discussed with you and may be commenced with your agreement. In this circumstance it is foreseen that study therapy will also continue in order to assess whether nateglinide and/or valsartan can reduce the amount of therapy required to bring your diabetes or cardiovascular disease under control.

Office visits and procedures related to the study and study medication will be provided at no charge to you.

### **Compensation**

Novartis will provide payment for reasonable, non-reimbursed medical expenses, including hospitalization, which you may incur as a direct result of the study drug or its administration in accordance with the Protocol, as determined by Novartis and the study doctor. Novartis will not provide payment for expenses that are in any way attributable to the negligence or misconduct of any person employed by or acting on behalf of the Institution or your failure to follow instructions. Novartis will not pay for medical expenses for injuries unrelated to the study drug, or which are in any way attributable to the natural course of any underlying disease or treatment process. No other type of compensation will be provided by Novartis.

You must notify the study doctor immediately of any research-related injury and the nature of the expenses to be covered. If you have any questions concerning the research or the availability of medical care or if you think you have experienced a research-related illness, injury or emergency, contact:

Investigator: (Investigator).

Telephone: (Phone number).

If you have any questions about your rights as a participant in a research study, you may contact the following neutral individual:

(Enter here the name / address affiliation / phone number of a third party, usually the ethics committee/IRB chair or patient ombudsman of the hospital.)

### **Participation/continuation**

Your decision to continue in this study is voluntary. If you decide not to continue in the study, the quality of care you receive will not be affected. If you do continue, you can discontinue study treatment or leave the study at any time without any loss of quality of care or any other penalty. If the study medication is interrupted you will be asked to continue with all remaining study visits to evaluate your condition. If you discontinue taking study medication and you are not coming back for regular clinic visits, you agree that data may be continued to be collected about your overall health. This data includes, but is not limited to, information on progression to diabetes, as well as your cardiovascular disease. This data will be collected every six months, until the conclusion of the study. This information may be provided by you or someone who knows you.

You will be informed and asked to re-consent to participate in the trial if, during the course of this study, there are any significant new findings (from this or other studies) that might affect your continued willingness to participate.

If you decide to leave the study you should tell the study doctor or study staff. A final visit will be done by the study doctor to ensure your ensuing medical health.

The study doctor can also stop your participation in the study at any time without your consent for any of the following reasons: if you fail to follow directions for participation in the study, if it appears harmful to you, if it is discovered at a later date that you do not meet the study requirements or if the study is discontinued.

### **Confidentiality**

For purposes of this study, (Institution) and (Investigator) will use medical information collected or created as part of the study, such as medical records and test results, that identifies you by name or in another way. Your consent to participate in the study means you agree that (Institution) and (Investigator) may obtain your medical information that they request for study purposes from your physicians and your other health care providers. You are also agreeing that (Institution) and (Investigator) may use and share this information with the parties described below. In addition, you agree that, during the study, you may not have access to some of your medical information obtained or created as part of this study. You will be allowed to access this information once the study is finished.

Unless required by law, (Institution) and (Investigator) will share this medical information only with the Study Team and other professionals involved in the Study, Novartis (the study sponsor) and its authorized agents, the US Food and Drug Administration (FDA), governmental agencies in other countries where the study drug may be considered for



approval, and the Ethics Committee/Institutional Review Board. The purpose for using and sharing this information with these parties is to perform the study and to ensure the accuracy of the study data. Because of the need to give these parties access to this information, absolute confidentiality cannot be guaranteed.

You have the right to cancel this consent at any time by giving written notice to (Investigator). If you cancel this consent, then (Institution) and (Investigator) will no longer use or disclose your medical information, unless it is necessary to do so to preserve the scientific integrity of the study. However, canceling this consent will not affect previous uses and disclosures and your medical information would not be removed from the study records.

If you fail to give your consent by signing this document, or if you cancel your consent later, then you will not be eligible to continue in this study and will not receive any treatment provided as part of the study. Unless and until you do cancel the consent, it will remain valid and effective.

The results and other information from this study may be submitted to the FDA and governmental agencies in other countries where the drugs may be considered for approval; however, you will be identified by initials and patient study number only. You will not be identified in any reports or publications resulting from this study.

### Sample signature page

Protocol number: CDJN608B2302.

Protocol title: A multinational, randomized, double-blind, placebo-controlled, forced-titration, 2 x 2 factorial design study of the efficacy and safety of long term administration of nateglinide and valsartan in the prevention of diabetes and cardiovascular outcomes in subjects with impaired glucose tolerance (IGT).

By signing this consent, I acknowledge that I have been informed of the methods and means of administration of the study medication to be used, the inconveniences, risks, benefits and adverse events that might occur from the procedures and the drug.

I certify that I have been given sufficient time to read and understand the above information. I also acknowledge that all technical language used in describing this research study has been explained to my satisfaction and I have received answers to all my questions. I also confirm that I have received a copy of this consent form. I understand that I am free to withdraw from the study at any time without loss of benefits or any other penalty.

I authorize the release of my medical records to the Sponsor, IRB/IEC, and regulatory authorities.

I freely, without reservations, give my consent to continue as a patient in this study.

\_\_\_\_\_  
type/print name

Patient

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
type/print name

Legal representative  
(legally authorized to act  
as personal  
representative to sign for  
[name of patient])

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
type/print name

Investigator

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

\_\_\_\_\_  
type/print name

Name of presenter  
(who resented/explained  
the document)

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

**Appendix 2: Study Diary**

Novartis PHARMACEUTICALS CORPORATION: Blood Sugar Testing Diary PLEASE RETURN THIS DIARY TO THE CLINIC ON YOUR NEXT SCHEDULED VISIT DATE Study : CDJN608 B2302																			
Subject Initials _____		Issued Visit: _____			Next Visit : _____														
Center :				Subject:					Issue date:					Next Visit date:					
										day	mont	year				day	mo	yea	
										h				nth	r				
Blood Sugar Testing Diary																			
OCCURRENCES OF SUSPECTED HYPOGLYCEMIA (LOW BLOOD SUGAR)																			
List Symptoms (include duration)	Surrounding Circumstances	Date Day/month/ year	Time of Day	Blood Sugar Test Result	Time of Last Meal	Date of Last Dose day/month/ year	Time of Last Dose	Type of Treatmen t	Time to Recovery										
		/ /	AM _____ PM _____	Not done Yes _____	AM _____ PM _____	/ /	AM _____ PM _____												
		/ /	AM _____ PM _____	Not done Yes _____	AM _____ PM _____	/ /	AM _____ PM _____												
		/ /	AM _____ PM _____	Not done Yes _____	AM _____ PM _____	/ /	AM _____ PM _____												
		/ /	AM _____ PM _____	Not done Yes _____	AM _____ PM _____	/ /	AM _____ PM _____												

The actual diary will have extra rows to record suspected hypoglycemia events.  
At every visit a sheet will be distributed for each week between visits.

### Appendix 3: Notable ranges for selected laboratory tests and measurements of vital signs

Results that meet the below mentioned criteria need to be commented on by the investigator on the CRF.

#### Laboratory notable range criteria:

Laboratory variables:	Notable Abnormalities	
	Standard Units	SI Units
<b>HEMATOLOGY</b>		
Hemoglobin	≤ 11.5 (m), 9.5 (f) g/d	≤ 7.1 (m), 5.9 (f) mmol/l
Hematocrit	≤ 37 (m), 32(f) %	≤ 37 (m), 32 (f) %
Erythrocytes	≤ 4 (m), 3.5 (f) 10 <sup>6</sup> /mm <sup>3</sup> ≥ 7 (m), 6.5 (f) 10 <sup>6</sup> /mm <sup>3</sup>	≤ 4 (m), 3.5 (f) 10 <sup>12</sup> /L ≥ 7 (m), 6.5 (f) 10 <sup>12</sup> /L
Leukocytes	≤ 2.8 ≥ 16 10 <sup>3</sup> mm <sup>3</sup>	≤ 2.8 ≥ 16 10 <sup>9</sup> /l
<b>BIOCHEMISTRY</b>		
Alkaline Phosphatase	≥ 3 x ULN	≥ 3 x ULN
ALT (SGPT)	≥ 3 x ULN	≥ 3 x ULN
AST (SGOT)	≥ 3 x ULN	≥ 3 x ULN
BUN	≥ 40 mg/dl	≥ 14.2 mmol/l
Creatinine	> 2.5 mg/dl	> 221 μmol/l
Fasting Plasma Glucose	≤ 45 or ≥ 250 mg/dl	≤ 2.5 or ≥ 13.2 mmol/l
Potassium	≤ 3.0 or ≥ 6.0 mEq/l	≤ 3.0 or ≥ 6.0 mmol/l
Sodium	≤ 115 or ≥ 160 mEq/l	≤ 115 or ≥ 160 mmol/l
Total Cholesterol	≥ 350 mg/dl	≥ 9.1 mmol/l

m = male f = female

**Vital signs notable range criteria:**

Vital Signs		Notable Abnormalities or Change Since the Previous Visit
Pulse (beats per minute)		< 40 or > 160 or increase/decrease > 50 since the previous visit
Blood Pressure (mmHg)	Systolic	< 60 or > 210 or increase/decrease > 50 since the previous visit
	Diastolic	< 40 or > 130 or increase/decrease > 30 since the previous visit
Weight (kg)		< 30 or > 220 or increase/decrease > 10% since the previous visit