Drug substance(s):	Candesartan cilexetil	**SYNOPSIS**	
Study code:	SH-AHM-0047_EC558 (Study 47, DIRECT-Protect 2)		
Date:	11 December 2008		

Effects of candesartan cilexetil (candesartan) on diabetic retinopathy in type 2 diabetic patients with retinopathy

Study Center(s)

The DIRECT Programme was conducted in 309 centers in 30 countries.

Publications:

Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised placebo-controlled trial. Sjølie AK, Klein R, Porta M, Orchard T, Fuller J, Parving HH, Bilous R, Chaturvedi N, for the DIRECT Programme Study Group. Lancet 2008;372:1385-1393.

Study dates		**Phase of development**
First patient enrolled in DIRECT Programme	08 June 2001	Therapeutic confirmatory (III)
Last patient completed DIRECT Programme	16 April 2008	

This study is 1 out of 3 in a clinical program comparing candesartan cilexetil (hereafter referred to as candesartan) versus placebo as to the effects on diabetic retinopathy.

Objectives: The primary objective of this study was to determine whether candesartan, compared to placebo reduced the progression of diabetic retinopathy in normoalbuminuric, type 2 diabetic patients with retinopathy.

The secondary objectives were to evaluate whether candesartan, compared to placebo, improved diabetic retinopathy (regression), reduced the incidence of clinically significant macular edema (CSME) and/or proliferative diabetic retinopathy (PDR) and, beneficially

influenced the rate of change in urinary albumin excretion rate (UAER). Other objectives were to compare candesartan and placebo with respect to: glycemic control; effects on serum cholesterol; and safety/tolerability.

Study design: This was an international, multi-center, double-blind, randomized, placebo-controlled, parallel group study which included a 4 to14-week single-blind placebo run-in period followed by a double-blind treatment period in which patients were randomly allocated to treatment with either candesartan or placebo in a 1:1 ratio.

Target patient population and sample size: The study entry criteria specified enrollment of patients 37 to 75 years of age with type 2 diabetes mellitus (hereafter referred to as diabetes), diagnosed at age 36 years or thereafter and with a duration of ≥1 year but not more than 20 years and who had no need for continuous treatment with insulin within the 1st year of diagnosis of diabetes, and stabilized diabetic therapy within the last 6 months. The presence of non-proliferative diabetic retinopathy was required (level ≥20/10 up to ≤47/47 on Early Treatment Diabetic Retinopathy Study [ETDRS] severity scale). Eligibility criteria also specified untreated resting mean blood pressure (BP) systolic/diastolic (SBP/DBP) ≤130/≤85 mmHg, or treated resting mean BP ≤160/≤90 mmHg on antihypertensive pharmacologic therapy, except for angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs). A total of 1700 patients were planned for this study.

Investigational product and comparator(s): dosage and mode of administration: The study drug was administered orally once daily in the morning. During the run-in period patients received 1 single-blind placebo tablet identical to the 16 mg candesartan tablet. During double-blind treatment, patients received 16 mg candesartan or placebo for 1 month, then the dose was doubled to 32 mg candesartan (given as two 16 mg tablets). If a patient had experienced a clinically significant fall in BP, the patient could remain on 16 mg. A further dose reduction to 8 mg was allowed, if higher doses were not tolerated.

Duration of treatment: Patients were treated in the double-blind period for at least 4 years (the original protocol specified at least 3 years) and up to a maximum of 6 years.

Criteria for evaluation (main variables):

Efficacy: The primary efficacy variable was time to progression of diabetic retinopathy, defined as a change (worsening) from enrollment visit to any photograph taken after the randomization visit by at least 3 steps in the ETDRS severity scale. Three steps were defined as a 1-step change in one eye and a 2-step change in the other eye or as a 3-step change in in one eye only.

Secondary variables included time to regression of diabetic retinopathy, defined as at least a 3-step improvement or a persistent 2-step improvement confirmed in 2 consecutive photographic sets, in the ETDRS severity scale, from baseline to any retinal photograph taken after randomization; change in the ETDRS severity scale from baseline to end of study, time to incident CSME and/or PDR; and rate of change in UAER. Other efficacy variables included change from baseline in glycosylated hemoglobin (HbA1c) and serum cholesterol.

Safety: Safety measures included reported adverse events (AEs), clinical laboratory values, blood pressure, heart rate, physical (including ophthalmologic) examinations, and tolerability (time to permanent discontinuation of study drug due to an AE, including death, at any time after the randomization visit).

Statistical methods: The comparison of treatments, testing for equal times to the first occurrence of an event (ie, 3-step or greater increase in EDTRS severity scale), employed a generalized log-rank test for interval-censored data to generate a p-value (Sun et al 2005). The size of the treatment effect was estimated along with the 95% confidence interval using a proportional hazards model for interval-censored data (Alioum and Commenges 1996). A Wilcoxon-Mann-Whitney test was used to analyze the distributions step changes from baseline to end of treatment; odds and 95% confidence intervals were also provided. The generalized log-rank test was also used for the secondary objective of regression of diabetic retinopathy and combined incidence of CSME/PDR. Rate of change in UAER was analyzed in an ANCOVA model, as was change in HbA1c and change in serum lipids.

Patient population: A total of 4717 patients enrolled into Study 47 and 1905 patients were randomized (951 to candesartan and 954 to placebo); the main reason for not being randomized was failure to meet eligibility criteria (2069 patients). Altogether 298 patients discontinued after randomization (144 on candesartan and 154 on placebo) and 1607 patients completed the study (807 on candesartan and 800 on placebo). The ITT population included all 1905 randomized patients and the safety population included 1902 patients.

The majority of the study population were Caucasians (96%) and the mean age was 57 years (range 37 to 76 years) with 34% of patients being in the age range of 59 to 68 years and 7% being 69 years of age or older. There were equal proportions of men and women in the study. Few patients had a retinal photograph level above 35/35 on the ETDRS severity scale at baseline. About a third of the patients had known diabetes for between 1 up to 6 years, and around half of the patients had a diabetes duration of 6 to 13 years. The mean HbA1c was 8.2% in both treatment groups (range 4.3% to 17.3%). The SBP/DBP at baseline in patients treated for hypertension at baseline was 139/79 mmHg in the candesartan and 139/80 mmHg in the placebo group. Mean baseline SBP/DBP in normotensive patients was 123/75 mmHg in the candesartan and 123/76 mmHg in the placebo group.

Efficacy results: There was no statistically significant difference in the progression of retinopathy between the candesartan and placebo groups, based on the time-to-event analysis for interval censored data (p=0.1994, unadjusted hazard ratio (HR) 0.870, 95% CI 0.704-1.076). However, the additional analysis of the distribution of step changes in the ETDRS severity scale from baseline to end of study favored candesartan (p=0.0032). Expressed as an odds, the change in the ETDRS severity scale from baseline to last visit was 1.1694 (95% CI: 1.0531-1.2985) times more likely to be in a direction favoring candesartan.

A higher rate of regression of retinopathy was observed in the candesartan than in the placebo group (p=0.0091, unadjusted HR 1.344; 95% CI 1.075-1.679). However, because of the specified closed, hierarchical analysis approach, it can not be concluded that candesartan improves retinopathy, since the primary analysis failed to show an effect of candesartan.

Twenty percent of patients developed CSME and/or PDR in both the candesartan and placebo treatment groups.

There was a small difference in rate of change in UAER from baseline to end of study, favoring candesartan compared to placebo, but the difference was not statistically significant.

When the analysis was repeated excluding UAER values from patients on rescue medication treatment (21.5% candesartan patients and 30.2% placebo patients), a small difference in favor of candesartan (p=0.003) was observed.

There was no notable change in the level of glycemic control (HbA1c) or serum cholesterol levels over the course of the study in either treatment group. Lower mean blood pressure in the candesartan group was evident around 6 months into the study. This difference was maintained over the course of the study. By the end of the study the estimated mean change from baseline for both SBP and DBP was lower (4.3/2.5 mmHg in patients treated for hypertension at baseline, 2.9/1.3 mmHg in patients not treated for hypertension at baseline) in the candesartan than in the placebo group.

Safety results: The mean (median) duration of treatment was 4.1 (4.5) years in the candesartan group and 4.1 (4.4.) years in the placebo group. The mean (median) time in the study was 4.5 (4.7) years in the candesartan group and 4.5 (4.6) years in the placebo group. At the Final Visit, 88% of the candesartan patients were receiving the 32 mg dose of candesartan and 89% of placebo patients were receiving the corresponding placebo dose.

Table S1 shows that the number of patients with AEs in any category were generally similar between the treatment groups. More candesartan patients had SAEs compared to placebo patients but individual SAEs generally occurred at similar rates. The higher number of patients who had dose reductions in the candesartan group was mainly due to hypotension; however, events of hypotension resulting in permanent discontinuations or SAEs were rare and occurred at similar rates in candesartan and placebo patients. Most of the AEs reflected medical conditions or expected illnesses for this population (mainly cardiovascular events and glycemic events).

Table S1 Number (%) of patients who had an adverse event in any category (Safety population)

Study 47 (DIRECT-Protect 2)	During treatment		During study	
Category of adverse event (AE)	**Candesartan (N=949)**	**Placebo (N=953)**	**Candesartan (N=949)**	**Placebo (N=953)**
Any AE	796 (83.9%)	786 (82.5%)	798 (84.1%)	788 (82.7%)
Any SAE	301 (31.7%)	267 (28.0%)	318 (33.5%)	277 (29.1%)
SAE leading to death	27 (2.9%)	27 (2.8%)	37 (3.9%)	35 (3.7%)
SAE not leading to death	284 (29.9%)	248 (26.0%)	299 (31.5%)	259 (27.2%)
AEs leading to temporary or permanent discontinuation	100 (10.5%)	104 (10.9%)	100 (10.5%)	105 (11.0%)
AE leading to temporary discontinuations of IP	69 (7.3%)	68 (7.1%)	70 (7.4%)	69 (7.2%)
AE leading to permanent discontinuations of IP	37 (3.9%)	42 (4.4%)	37 (3.9%)	42 (4.4%)
AE leading to dose reduction	79 (8.3%)	52 (5.5%)	80 (8.4%)	53 (5.6%)

Note: Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
'During Study' refers to the patient's entire study period, ie, includes AEs reported while on study treatment as well as during the period following discontinuation of study treatment.
'During Treatment' refers to the period of actual treatment with randomized study drug, ie, is a subset of the patients included in 'During Study'.
a The during treatment and during study columns differ slightly with respect to number of patients because patients who received wrong study medication (by error) were considered not to be on treatment but could have a discontinuation which is presented in the during study column only; on treatment status was determined from dose records, sometimes there were inconsistencies between dose records and AE records.
SAE Serious adverse event. IP Investigational Product.

There was a trend towards a lower risk of the composite cardiovascular outcome of cardiovascular death, non-fatal MI or non-fatal stroke reported as SAEs associated with candesartan (candesartan 4.8% and placebo 5.7%, respectively), but the finding was not statistically significant (log-rank p-value = 0.3964).

There were no laboratory test abnormality trends that were clinically significant.