Drug substance(s):	Candesartan cilexetil	**SYNOPSIS**	
Study code:	SH-AHM-0046_EC557 (Study 46, DIRECT-Protect 1)		
Date:	11 December 2008		

Effects of candesartan cilexetil (candesartan) on diabetic retinopathy in type 1 diabetic patients with retinopathy

Study centre(s): The DIRECT Programme involved 309 centres in 30 countries.

Publications: Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials. Chaturvedi N, Porta M, Klein R, Orchard T, Fuller J, Parving HH, Bilous R, Sjølie AK, for the DIRECT Programme Study Group. Lancet 2008;372:1394-1402.

Study dates		**Phase of development**
First patient enrolled in DIRECT Programme	8 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 normotensive, normoalbuminuric type 1 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-centre, 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 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 18 to 55 years old with type 1 diabetes mellitus (hereafter referred to as diabetes) diagnosed before the age of 36 years and with a duration of at least 1 year but not more than 20 years and who required continuous insulin treatment within 1 year of diagnosis of diabetes, and stabilized diabetic therapy within the prior 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 sitting systolic/diastolic blood pressure (SBP/DBP) ≤130/≤85 mmHg. A total of 1850 patients were planned to be randomized for this study.

Investigational product and comparator(s): dosage, mode of administration and batch numbers: 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 experienced a clinically significant fall in blood pressure (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 (original protocol specified at least 3 years) and up to 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 the enrollment visit to any photograph taken after Visit 2 by at least 3 steps on the ETDRS severity scale. A 3-step change was 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 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 photography sets) in the ETDRS severity scale, from baseline to any retinal photograph taken after the randomization visit; 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 event of permanent discontinuation of study drug due to 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 a retinopathy progression event 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 (CI) using a proportional hazards model for interval-censored data (Alioum and Commenges 1996). A Wilcoxon-Mann-Whitney test was used to calculate the distributions of the number of steps change from baseline to end of treatment with odds and 95% CIs. The generalized log-rank test was also used for the secondary objectives 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 serum cholesterol.

Patient population: A total of 1905 patients were randomized in Study 46: 951 to candesartan and 954 to placebo. Altogether 297 patients discontinued (132 on candesartan and 165 on placebo) and 1608 patients completed the study (819 on candesartan and 789 on placebo). The intention to treat (ITT) population included all 1905 randomized patients and the safety population included 1902 patients.

Most patients were Caucasian (98%) and the mean age was 32 years (range 18 to 56 years). There were slightly more men than women (approximately 57.5% vs 42.5%). Few patients had a retinal photograph level above 35/35 on the ETDRS severity scale. More than half of the patients had a diabetes duration of 6 to 13 years and a third had a diabetes duration of 13 years or more at baseline. Mean HbA1c was 8.5% in both treatment groups (range 4.8% to 15.6%). The mean SBP/DBP at baseline was 117/74 mmHg for the candesartan group and 117/73 mmHg for the placebo group.

Efficacy results: The primary analysis of the time to a retinopathy progression event, could not establish that candesartan, compared to placebo, reduced the progression of diabetic retinopathy in normotensive, normoalbuminuric patients with type 1 diabetes and with mild to moderate non-proliferative retinopathy (p=0.8487, unadjusted hazard ratio (HR) 1.024, 95% CI 0.800-1.312).

The distribution of step changes on the ETDRS severity scale from baseline to end of study, did however show a difference in favor of candesartan (p=0.0264), indicating a possible treatment effect. Expressed as an odds, the change in the ETDRS severity scale from baseline to last visit was 1.1244 (95% CI: 1.0138-1.2470) times more likely to be in a direction favoring candesartan.

There was no difference in time to retinopathy regression between candesartan and placebo (p=0.9222), with an unadjusted HR of 1.012 (95% CI 0.800-1.279).

Twelve percent of patients in the candesartan and 11% in the placebo group developed CSME and/or PDR.

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 and there was no between treatment group difference. 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 (3.6 and 2.5 mmHg, respectively) in the candesartan than in the placebo group.

Safety results: Mean (median) duration of active treatment was 4.2 (4.5) years in the candesartan group and 4.3 (4.5.) years in the placebo group. Mean (median) time in the study was 4.7 (4.8) years in the candesartan group and 4.7 (4.8) years in the placebo group. At the Final Visit, 81% of the candesartan patients were receiving the 32 mg dose of candesartan and 87% of placebo patients were receiving the corresponding placebo dose.

Table S1 shows that the proportions of patients with any AEs, any SAEs, and AEs leading to temporary or permanent discontinuation of treatment were generally similar between the treatment groups. AEs leading to dose reduction were more frequent in the candesartan group and primarily due to hypotension. Most of the AEs reflected medical conditions or expected illnesses for this population.

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

Study 46 (DIRECT-Protect 1)	During treatment		During study	
Category of AE	Candesartan (N=951)	Placebo (N=951)	Candesartan (N=951)	Placebo (N=951)
Any AE	738 (77.6%)	721 (75.8%)	746 (78.4%)	732 (77.0%)
Any SAE	173 (18.2%)	161 (16.9%)	196 (20.6%)	182 (19.1%)
SAE leading to death	6 (0.6%)	7 (0.7%)	7 (0.7%)	8 (0.8%)
SAE not leading to death	167 (17.6%)	155 (16.3%)	190 (20.0%)	175 (18.4%)
AE leading to temporary or permanent discontinuation[a]	88 (9.3%)	74 (7.8%)	94 (9.9%)	75 (7.9%)
AE leading to temporary discontinuations of IP	74 (7.8%)	61 (6.4%)	78 (8.2%)	62 (6.5%)
AE leading to permanent discontinuations of IP	17 (1.8%)	16 (1.7%)	19 (2.0%)	16 (1.7%)
AE leading to dose reduction	106 (11.1%)	49 (5.2%)	106 (11.1%)	49 (5.2%)

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 were no laboratory test abnormality trends that were clinically significant.