Drug substance(s):	Candesartan cilexetil	**SYNOPSIS**	
Study code:	SH-AHM-0045_EC556 (Study 45, DIRECT-Prevent 1)		
Date:	15 December 2008		

Effects of candesartan cilexetil (candesartan) on diabetic retinopathy in type 1 diabetic patients without retinopathy

Study center(s): The DIRECT Programme involved 309 centers 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

First subject enrolled in the DIRECT Programme 8 June 2001

Last subject completed the DIRECT Programme 16 April 2008

Phase of development

Therapeutic confirmatory (III)

This study is 1 out of 3 studies 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 incidence of diabetic retinopathy in normotensive, normoalbuminuric type 1 diabetic patients without retinopathy.

The secondary objective was to determine whether candesartan, compared to placebo, 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 design study. It consisted of a 4 to 14-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 subject population and sample size: The study entry criteria specified enrollment of patients 18 to 50 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 15 years and who required continuous insulin treatment within 1 year of diagnosis of diabetes, and stabilized diabetic therapy within the prior 6 months. Patients had no history of retinopathy, with a retinal photograph grading level =10/10 on the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale. Eligibility criteria also specified sitting systolic/diastolic blood pressure (SBP/DBP) ≤130/≤85 mmHg. Thirteen hundred patients were planned to be randomized in this study.

Investigational product and comparator: 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 in appearance 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 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 year) and up to a maximum of 6 years.

Criteria for evaluation (main variables)

Efficacy:: The primary efficacy variable was time from randomization to the first occurrence of a retinopathy event. An event was defined as a 2-step or greater increase in the ETDRS severity scale, from 10/10 at the enrollment visit to any retinal photograph taken after the randomization visit. Two steps were defined as either a 1-step change in each eye or as a 2-step change in one eye only. An additional measure of effect was the distribution of all changes in the ETDRS severity scale from baseline to end of study.

Other efficacy variables included change from baseline in glycosylated hemoglobin (HbA1c) and in serum cholesterol.

A post-hoc analysis redefined a retinopathy event as a ≥3-step change (rather than ≥2-step change) in the ETDRS scale.

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, 2-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 (CI) using a proportional hazards model for interval-censored data (Alioum and Commenges 1996). Additional measures of treatment included the distribution of the number of steps change in the ETDRS severity scale from baseline to end of treatment (Wilcoxon-Mann-Whitney test) with odds and 95% CIs**.** Rate of change in UAER was analyzed in an ANCOVA model, as was change in HbA1c and change in serum lipids**.**

Additional post-hoc analyses considered the primary measure of effect analyses but with a retinopathy event defined as a ≥3 step change in ETDRS severity scale.

Patient population: A total of 1421 patients were randomized in this study, 711 to candesartan and 710 to placebo. Altogether 198 patients discontinued (106 on candesartan and 92 on placebo) and 1223 patients completed the study (605 on candesartan and 618 on placebo). The intention to treat (ITT) population included all 1421 randomized patients and the safety population included 1420 patients.

The majority of the study population was Caucasian (97%), mean age was 30 years (range 18 to 54 years) and there were slightly more men than women. The mean duration of diabetes was 7 years. Mean HbA1c at baseline was 8.0% in the candesartan and 8.2% in the placebo group (range 4.7 to 17.9%). The mean SBP/DBP at baseline was 116/72 mmHg for both the candesartan and placebo groups.

Efficacy results: The primary analysis of the cumulative incidence of retinopathy events, using interval censored data, showed a trend towards a reduction of the incidence of diabetic retinopathy with candesartan, compared to placebo, although the difference was not statistically significant (p=0.0508), with an unadjusted hazard ratio of 0.821 (95% CI 0.673-1.001).

The distribution of step changes on the ETDRS severity scale from baseline to end of study showed a statistically significant difference in favor of candesartan (p=0.0048), indicating a possible treatment effect. Expressed as an odds, the change in the ETDRS severity scale from baseline to last visit was 1.1648 (95% CI: 1.0476-1.2950) times more likely to be in a direction favoring candesartan. A post-hoc analysis using a ≥3 step change in the ETDRS severity scale as the definition for a retinopathy event also indicated a difference in favor of candesartan in the time to event analyses (p=0.0034) with a corresponding unadjusted hazard ratio of 0.647 (95% CI: 0.483-0.868).

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.

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 (2.6 and 2.7 mmHg, respectively) in the candesartan than in the placebo group.

Safety results: The mean (median) duration of treatment was 4.0 (4.4) years in the candesartan group and 4.1 (4.4) years in the placebo group. Mean (median) time in the study was 4.6 (4.7) years in the candesartan group and 4.7 (4.7) years in the placebo group. At the Final Visit, 78% of the candesartan patients were receiving the 32 mg dose of candesartan and 81% of placebo patients were receiving the corresponding placebo dose.

Table S 1 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 illnesses expected for this population.

Table S 1 Number (%) of patients who had an adverse event in any category (safety population)

Study 45 (DIRECT-Prevent 1)	During treatment		During study	
Category of AE	**Candesartan (N=710)**	**Placebo (N=710)**	**Candesartan (N=710)**	**Placebo (N=710)**
Any AE	505 (71.1%)	517 (72.8%)	512 (72.1%)	524 (73.8%)
Any SAE	102 (14.4%)	112 (15.8%)	121 (17.0%)	128 (18.0%)
SAE leading to death	6 (0.9%)	4 (0.6%)	7 (1.0%)	5 (0.7%)
SAE not leading to death	98 (13.8%)	111 (15.6%)	117 (16.5%)	127 (17.9%)
AE leading to temporary or permanent discontinuation[a]	64 (9.0%)	69 (9.7%)	68 (9.6%)	71 (10.0%)
AE leading to temporary discontinuations of IP	46 (6.5%)	54 (7.6%)	50 (7.0%)	57 (8.0%)
AE leading to permanent discontinuations of IP	22 (3.1%)	18 (2.5%)	22 (3.1%)	18 (2.5%)
AE leading to dose reduction[a]	94 (13.2%)	61 (8.6%)	94 (13.2%)	62 (8.7%)

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 or dose reduction 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.
AE Adverse event. SAE Serious adverse event. IP Investigational Product

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