SYNOPSIS OF RESEARCH REPORT [redacted] (PROTOCOL BC22419)

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

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Final Clinical Study Report – BC22419 – Effects of 150 μg aleglitazar on renal function in patients with type 2 diabetes (T2D) and moderate renal impairment, as compared to pioglitazone (Actos®). Report number [redacted]. June 2013.
INVESTIGATORS / CENTERS AND COUNTRIES	Patients were enrolled at 62 sites in 13 countries: Australia (5), Hong Kong (3), Germany (8), Hungary (9), Italy (3), Romania (5), Russia (7), Slovakia (3), Brazil (4), Columbia (3), El Salvador (1), Mexico (8), Peru (3).
PUBLICATION (REFERENCE)	Abstracts: Ruilope LM, Hanefeld M, Lincoff AM, et al. Effects of aleglitazar on renal function in patients with stage 3 chronic kidney disease and type 2 diabetes. J Am Soc Nephrol 2012;23:1167 (Abstract). Malmberg K, Hanefeld M, Ruilope L, et al. Effects of aleglitazar on cardiovascular risk factors in patients with stage 3 chronic kidney disease and type 2 diabetes. J Am Coll Cardiol 2013;61(10_S):E1173.
PERIOD OF TRIAL	First Patient Randomized: 27 May 2010 Last Patient Randomized: 13 May 2011 Last Patient Last Visit: 05 July 2012
CLINICAL PHASE	II
OBJECTIVES	**Primary Objective** • To determine reversibility of the $eGFR_{MDRD}$ (estimated glomerular filtration rate [GFR] based on the abbreviated modification of diet in renal disease [MDRD] equation) decrease following 52 weeks of 150 µg aleglitazar treatment and 8 weeks follow up observation after the last study medication intake, in patients with T2D and moderate renal function impairment (chronic kidney disease [CKD] stage 3), in comparison with pioglitazone (Actos®) treatment. **Secondary Objectives** • To determine the effects of 52 weeks of 150 µg aleglitazar treatment on $eGFR_{MDRD}$, in patients with T2D and moderate renal function impairment (CKD stage 3). • To determine the effects of 150 µg aleglitazar treatment on lipid profile.

	Tertiary Objectives • To determine the effects of 52 weeks of 150 µg aleglitazar treatment on other markers of renal function (e.g. serum creatinine, eGFR using the Cockroft-Gault equation, cystatin C, urine albumin-creatinine ratio [UACR], tubular markers alpha glutathione S-transferase [α-GST] and N-acetyl-β-glucosaminidase [NAG], renin, and serum aldosterone). • To determine reversibility of other renal function marker changes after 8 weeks of follow up observation after the last study medication intake. • To determine the safety and tolerability (including glycemic control) of 150 µg aleglitazar over 52 weeks of treatment.
STUDY DESIGN	A multicenter, randomized, double-blind, active controlled, parallel group, renal function study with two treatment arms: 150 µg aleglitazar and 45 mg pioglitazone, added to the pre-existing antihyperglycemic therapy and/or to diet and exercise. Randomization was stratified according to $eGFR_{MDRD}$ (<45 or ≥ 45 mL/min/1.73m^2).
NUMBER OF SUBJECTS	Planned: 300 (150 per arm) Actual: 302 (150 aleglitazar vs. 152 pioglitazone)
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Patients with T2D and moderately impaired kidney function (CKD stage 3 [$eGFR_{MDRD} \geq 30$ to <60 mL/min/1.73m^2]), who were either drug naïve or were receiving treatment with monotherapy or a combination therapy of two antihyperglycemic medications which were stable for at least one month at the time of the screening visit.
TRIAL DRUG / STROKE (BATCH) No.	Aleglitazar batch numbers: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Aleglitazar 150 µg once daily for 52 weeks
REFERENCE DRUG / STROKE (BATCH) No.	Pioglitazone batch number: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Pioglitazone 45 mg once daily for 52 weeks
CRITERIA FOR EVALUATION	
ENDPOINTS:	**Primary Endpoint** • Percent change from baseline in the $eGFR_{MDRD}$ at the end of the follow-up period (8 weeks after treatment end) **Secondary Endpoints** • Absolute and percent change from baseline after 52 weeks of treatment in $eGFR_{MDRD}$ • Absolute change from baseline at the end of the follow-up period in $eGFR_{MDRD}$ • Absolute and percent change in the lipid profile parameters from baseline after 52 weeks of treatment: triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol, Total cholesterol/HDL-cholesterol ratio, Apolipoprotein (Apo) A1, Apo-B

Tertiary Endpoints

- Absolute and percent change from baseline after 52 weeks of treatment of: serum cystatin C, serum creatinine, aldosterone, renin, UACR, sodium excretion, tubular markers α-GST and NAG
- Absolute and percent change from baseline after 52 weeks of treatment and 8 weeks of follow-up of: serum cystatin C, serum creatinine, aldosterone, renin, UACR, sodium excretion, tubular markers α-GST and NAG
- Time to first occurrence of any component of the triple composite renal endpoint:
  - End-stage renal disease (defined as requirement of long-term dialysis or renal transplant)
  - Doubling of serum creatinine from baseline (defined as the first serum creatinine value that was twice the baseline value, subsequently confirmed at least 4 weeks after the date of the first doubled post-baseline measurement)
  - Confirmed (within 2 weeks) 50% increase of serum creatinine from the baseline value, subsequently leading to a treatment discontinuation (prior to the next scheduled visit) according to protocol stopping rule
- Time to first occurrence of any component of the double composite renal endpoint:
  - End-stage renal disease (defined as requirement of long-term dialysis or renal transplant)
  - Any doubling of serum creatinine from baseline during the treatment phase (irrespective of whether it was confirmed or not)
- Time to first occurrence of each of the four individual components of both composite renal endpoints
- Progression or regression of albumin excretion (UACR) (based on shifts between categories of normo-, micro-, or macroalbuminuria) from baseline to end of treatment
- Progression or regression of albumin excretion (UACR) (based on shifts between categories of normo-, micro-, or macroalbuminuria) from baseline to end of follow-up
- Acute dialysis requirement and incidence of acute renal failure

Safety Endpoints

Change from baseline after 52 weeks of treatment of:

- Glycosylated hemoglobin A1c (HbA1c) (including responder analysis)
- Fasting plasma glucose (FPG)
- Fasting plasma insulin (FPI)
- C-peptide
- Homeostasis model assessment of insulin sensitivity (HOMA-IR)

	• Homeostasis model assessment of beta-cell function (HOMA-B)
PHARMACODYNAMICS/ PHARMACOKINETICS:	A summary of aleglitazar concentrations over time is provided.
SAFETY:	Adverse events (AEs), laboratory parameters, electrocardiograms (ECG), echocardiography, vital signs, body weight, adjudication of cardiovascular (CV) events.
STATISTICAL METHODS	**Primary Endpoint** A linear model was constructed with percent change from baseline in $eGFR_{MDRD}$ at the end of the follow-up period as the dependent variable. The model included centered baseline $eGFR_{MDRD}$ as a covariate and treatment group, region, $eGFR_{MDRD}$ stratum (stratification using measurement at baseline), UACR stratum (stratification using measurement at baseline), and the interaction between the $eGFR_{MDRD}$ stratum and UACR stratum as fixed effects. The model was also used to provide least-squares (LS) mean point estimates and corresponding 95% confidence intervals (CIs) for the change from baseline at end of follow-up period for both treatment groups, together with the estimated difference in this endpoint between the two groups. Non-inferiority was concluded if the lower bound of the two-sided 95% CI exceeds -7.5%. **Secondary Endpoints** Analyses corresponding to those described for the primary endpoint were performed using absolute or percent change from baseline as the dependent variable in the ANCOVA model. The 95% CIs for the LS mean value for each treatment group, as well as for the estimated difference between treatment groups, were calculated. As these analyses were considered exploratory, no formal testing of significance was performed for the secondary endpoints. The last observation carried forward (LOCF) principle was applied to missing data.

METHODOLOGY

Patients providing informed consent were screened within 2 weeks prior to enrolment. Those fulfilling the entry criteria were randomized 1:1 to treatment with either aleglitazar 150 μg once daily or pioglitazone 45 mg once daily. The total duration of study treatment was 52 weeks followed by an 8-week off-treatment observation period. Throughout the study duration, patients pretreated with antihyperglycemic medication continued to take this medication. A diet and exercise plan to control body weight was implemented for each patient at screening.

An independent Clinical Events Committee provided blinded assessment of pre-defined clinical endpoints or events.

RESULTS: ENDPOINT ANALYSES

The percentage change in $eGFR_{MDRD}$ from baseline to the end of follow-up was -2.7% for aleglitazar and -3.4% for pioglitazone. The treatment difference in $eGFR_{MDRD}$ at the end of follow-up (primary endpoint) was 0·77% (95% CI, –4·5%, 6·0%), with lower 95% CI above −7.5%, thus establishing non-inferiority of aleglitazar to pioglitazone. The primary endpoint was met, irrespective of the analysis population studied. Subgroup analysis of $eGFR_{MDRD}$ by $eGFR_{MDRD}$ stratum at baseline ($eGFR_{MDRD}$ < 45 or ≥45 mL/min/1.73 m^2) showed a similar pattern of changes in both strata.

For the key secondary endpoint of percent change in $eGFR_{MDRD}$ from baseline to the end of treatment (i.e. after 52 weeks of treatment), a greater reduction was observed for aleglitazar than for pioglitazone, -15.0% (95% CI, –19.1%, –10.8%) and -5.4% (95% CI, -9.6%, -1.2%), respectively.

The changes in lipid secondary endpoints from baseline to the end of 52 weeks of treatment between aleglitazar and pioglitazone were consistently superior ($p < 0.05$) following treatment with aleglitazar compared with pioglitazone. A similar decrease in HbA1c was observed for both aleglitazar and pioglitazone after 52 weeks of treatment.

Table: Overview of Key Endpoints (LOCF) (FAS)

Parameter	Aleglitazar 150 μg (N = 149)	Pioglitazone 45 mg (N = 148)	Treatment difference (95% CI), p-value*
Primary Endpoint			
$eGFR_{MDRD}$ at EOF: % LSmean change (95% CI)	n=140 –2·7% (–7·7, 2·4)	n=132 –3·4% (–8·5, 1·7)	0·77% (–4·5, 6·0) p = 0·77
Key Secondary Endpoints			
$eGFR_{MDRD}$ mL/min/1.73m^2 at EOF: abs LSmean change (95% CI)	n=140 -1.6 (-3.6, 0.36)	n=132 -1.7 (-3.7, 0.3)	0.11 (-1.9, 2.2) p = 0.92
$eGFR_{MDRD}$ at EOT: % LSmean change (95% CI)	n=148 –15·0% (–19·1, –10·8)	n=147 –5·4% (–9·6, –1·2)	–9.5% (-13.8, -5.3) p < 0.001
$eGFR_{MDRD}$ mL/min/1.73m^2 at EOT: abs LSmean change (95% CI)	n=148 -7.3 (-8.9, -5.6)	n=147 -2.8 (-4.5, -1.2)	–4.4 (-6.1, -2.8) p < 0.001
Triglycerides at EOT: % LSmean change (95% CI)	n=142 –33.6% (–41.1, –26.1)	n=140 –14.1% (–21.7, –6.5)	–19.5% (–27.3, –11.7) p < 0.001
HDL-C at EOT: % LSmean change (95% CI)	n=142 22.0% (17.4, 26.6)	n=140 11.6% (6.9, 16.3)	10.4% (5.5, 15.2) p < 0.001
LDL-C[§] at EOT: % LSmean change (95% CI)	n=142 –7.3% (–13.2, –1.0)	n=141 –0.3% (–6.8, 6.6)	–7.0% (–13.2, –0.4) p = 0.039

[§] Analyses performed on log-transformed scale; * p-value calculated for a difference from zero in change from baseline between treatment groups; EOF end of follow-up; EOT end of treatment; LS least squares.

Source: efftgfrf_FAS, efftgfraf_FAS, efftgfrpt_FAS, efftgfrat_FAS, efftc4pttrig_FAS, efftc4pthdl_FAS, efftlrcldleot_FAS.

PHARMACODYNAMIC/ PHARMACOKINETIC RESULTS

Aleglitazar concentrations were assessed at pre-dose and at least 30 minutes after aleglitazar administration at Weeks 12, 16 and 26. Median values were similar at each week of measurement (i.e., pre-dose: median of 1.1 of 1.2 ng/mL; post dose: median of 20-21 ng/mL) and were in line with aleglitazar trough and peak concentrations seen in other studies after multiple dosing with aleglitazar.

SAFETY RESULTS

Overall, study treatments were generally well tolerated. The safety profile observed in the aleglitazar group of this study was consistent with the safety profile of aleglitazar characterized to date and there were no new safety concerns or toxicities identified. The proportion of patients who experienced at least one AE during the study was comparable between the groups, with the majority of patients having events that were mild to moderate in severity; severe AEs on-treatment were reported in 11% aleglitazar vs. 9% pioglitazone patients. Two deaths were reported in the aleglitazar group versus three deaths in the pioglitazone group during the study period. One patient who previously received aleglitazar died due to an unknown cause subsequent to withdrawal from the study for non-compliance (refused treatment). The proportion of patients with serious adverse events (SAEs) was balanced between the groups and the number of patients who prematurely discontinued study treatment due to an AE was 8% in the aleglitazar group compared with 5% in the pioglitazone group. During 8 weeks of follow-up, similar number of patients in both treatment arms experienced SAEs (3% aleglitazar vs. 2% pioglitazone).

Table: Overall Adverse Event Profile (Safety Analysis Population)

Type of Adverse Event	Aleglitazar 150 μg N=149 No. of Pts (%)	Pioglitazone 45 mg N=152 No. of Pts (%)
Any AE	100 (67)	103 (68)
Severe AEs	16 (11)	14 (9)
SAEs**	18 (12)	18 (12)
Deaths*	2 (1)	3 (2)
Withdrawals due to AE	12 (8)	8 (5)
AEs leading to dose interruption	5 (3)	7 (5)
Selected Adverse Events Related to the PPAR Class		
Peripheral edema	18 (12)	30 (20)
Congestive heart failure	5 (3)	3 (2)
Hypoglycemia	29 (20)	22 (15)
Malignancies	3 (2)	1 (1)
Renal adverse events	8 (5)	6 (4)
Hepatobiliary adverse events	2 (1)	3 (2)
Musculoskeletal adverse events	4 (3)	5 (3)
Fractures	3 (2)	2 (1)

Includes all AEs with onset from first dose of study drug through 1 day after last dose of study drug.

*Total number of deaths occurring on treatment and during 8 weeks of follow-up; one additional death occurred post follow-up (aleglitazar group, Day 362, last study drug intake on Day 134).

**SAEs on treatment; patients with SAEs during follow-up: 4 (3%) on aleglitazar vs. 3 (2%) on pioglitazone

Source: aet02_SAP, aet03i_SAP, aet02s_SAP, aelfu_SAP, aeldth_SAP, aet02w_SAP, aelm_SAP, aet01b1_SAP, aet01b2_SAP, aet01b3_SAP, aet01b4_SAP, aet01b5_SAP, aet01b6_SAP, aet01b7_SAP, aet01b8_SAP

CONCLUSIONS

In patients with T2D and moderately impaired kidney function (CKD stage 3), aleglitazar was associated with a greater decrease in eGFR compared with pioglitazone after 52 weeks of treatment (a difference of –9.5%), which returned towards baseline during the 8-week off-treatment follow-up period. The primary objective of this study, to show non-inferiority to pioglitazone in terms of reversibility of on-treatment GFR reduction, was met, with the mean change in eGFR from baseline to the end of follow-up being comparable between groups (a difference of 0.77%). Following 52 weeks of treatment, a superior lipid-modulation profile and similar effects on HbA1c were observed for aleglitazar when compared with pioglitazone. No major safety concerns or new toxicities were identified in this patient population during the study.