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| *Document title* | **Study Clinical Report Synopsis** |
| *Study title* | **A one-year multicentre, international, randomised, double-blind study with comparison of benfluorex (150 mg bid or 150 mg tid) *versus* pioglitazone (30 mg od or 45 mg od) in combination with sulfonylurea administered orally for the treatment of type 2 diabetes.** |
| *Study drug* | **S 00780 Benfluorex (Mediator®, Mediaxal®, Lipascor®)** |
| *Studied indication* | **Type II Diabetes** |
| *Development phase* | **Phase III** |
| *Protocol code* | **CL3-00780-148** |
| *Study initiation date* | **24 January 2006** |
| *Study completion date* | **15 January 2009** |
| *Main coordinator* | [redacted] **France** |
| *Sponsor* | **Institut de Recherches Internationales Servier (I.R.I.S.)<br>50 Rue Carnot<br>92284 Suresnes Cedex -France** |
| *Responsible medical officer* | [redacted] |
| *GCP* | **This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents.** |
| *Date of the report* | **Final version of 17 December 2010** |

**~~CONFIDENTIAL~~**

## 2. SYNOPSIS

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| **Name of Company:**<br>**I.R.I.S.**<br>**6 place des Pleiades**<br>**92415 Courbevoie - France** | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
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**Title of study:**
A one-year multicentre, international, randomised, double-blind study with comparison of benfluorex (150 mg bid or 150 mg tid) *versus* pioglitazone (30 mg o.d. or 45 mg o.d.) in combination with sulfonylurea administered orally for the treatment of type 2 diabetes.
Protocol No.: CL3-00780-148
Eudra CT number: 2005-004798-60

**International coordinator**: [redacted]rance

**Study centres:**
Multicentre study involving 8 countries (5 countries initially planned, increased by Amendment No. 4). 196 centres included at least 1 patient: Argentina: 11 centres – 100 patients, Czechia: 8 centres – 54 patients, France: 125 centres – 257 patients, Germany: 17 centres – 138 patients, India: 9 centres – 131 patients, Romania: 5 centres – 37 patients, South Africa: 10 centres – 76 patients, Tunisia: 11 centres – 54 patients.

**Publication (reference):** Not applicable

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| **Studied period:**<br>Initiation date: 24 January 2006<br>Completion date: 15 January 2009 | **Phase of development of the study:** III |

**Objectives:**
The purpose of this study was to compare the efficacy and the safety profile of benfluorex and pioglitazone in type 2 diabetic patients, not optimally controlled on sulfonylurea, over 1 year.
The **primary objective** was to demonstrate the non-inferiority of the combination sulfonylurea plus benfluorex compared to the combination sulfonylurea plus pioglitazone on the evolution of HbA1c.
Both benfluorex and pioglitazone were administered at optimal dosage for the treatment of type 2 diabetic patients insufficiently controlled on sulfonylurea monotherapy.
The **main secondary objective** was to demonstrate the superiority of benfluorex combined with sulfonylurea compared to pioglitazone combined with sulfonylurea on LDL cholesterol level.
The **other secondary objectives** were to evaluate and compare over 1 year both combination therapies on the following: fasting Plasma Glucose evolution, Insulin Resistance assessed by homeostatic model assessment (HOMA-IR), cardiovascular risk profile, safety and acceptability, cost of the two treatments through an economic balance.
**Objectives of the lipid parameter substudy:** to demonstrate the superiority of the combination of benfluorex with a sulfonylurea compared to the combination of pioglitazone with a sulfonylurea on the decrease in total plasma apo B (primary objective) and to explore other lipid parameters and particularly LDL particle concentrations and size using Proton Nuclear Magnetic Resonance Spectroscopy (secondary objective).

**Methodology:**
Multicentre, international, randomised by IVRS, double-blind, double-dummy, parallel group, comparative phase III study (benfluorex *versus* pioglitazone as active comparator), stratified according to baseline HbA1c (≤ 8% or > 8%), and country.

**Number of patients:**
Sample size was estimated on the change from baseline to last value of HbA1c, to evidence a non-inferiority of benfluorex as compared to pioglitazone, using the one-sided Student t test at 2.5% type I error. It was initially planned in the study protocol that for a 1.5% standard deviation and a 0.40% for the clinical equivalence margin, 479 subjects per group to analyse in the Full Analysis Set were necessary to show a non-inferiority between groups if the true difference was equal to zero (± 0.05%), with at least a power of 95%.

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**Planned:** 1000 included patients (500 in each group), with at least 500 patients with baseline HbA1c > 8%, then reduced (Amendment No. 7) to 840 included patients, and 800 patients in the FAS, with at least 420 included patients with HbA1c > 8%. The number of patients was reduced as a re estimate of the variance of HbA1c (on blind data available) showed that the standard deviation was lower (1.1%) than expected (1.5%).
**Included**: 847 patients (423 patients in the benfluorex group and 424 in the pioglitazone group), 830 patients in the FAS (413 and 417 patients, respectively).

**Diagnosis and main criteria for inclusion:**
Outpatients with type 2 diabetes diagnosed according to WHO criteria, male or female aged ≥ 35 years and ≤ 80 years, with BMI between 25-40 kg/m$^2$ inclusive (except India: 23-40 kg/m$^2$) with a stable body weight, currently treated in monotherapy, with a sulfonylurea at stable dose, for at least 3 consecutive months prior to the selection visit and at 50% of the maximal recommended dose, with HbA1c > 7% and ≤ 10%, and without cardiac insufficiency (left ventricular ejection fraction < 40%).

**Study drug:**
Benfluorex (tablet), pioglitazone (capsule), and placebo (tablet or capsule) were administered three times daily according to the double-dummy design as: one capsule and one tablet during breakfast, one tablet during lunch and one tablet during dinner. In addition, all patients had their usual sulfonylurea maintained throughout the study except in case of severe or repeated hypoglycaemia (> 3 episodes in a month).

Benfluorex (Mediator®) was administered orally, according to the usual administration scheme described in the Summary of Product Characteristics (SPC), from 150 mg to 450 mg, as 1 to 3 tablets daily. The dose was 150 mg/day for 1 week, then increased at W2 to 300 mg/day. If fasting plasma glucose (FPG) level was ≥ 7.8 mmol/L at W8, the dose was increased to 450 mg/day, except in case of safety concerns. From W16 to W52, the dose could be adapted according to HbA1c (target level < 6.5%) and safety in order to obtain the maximal dose tolerated by the patient. If HbA1c was higher than 6.5% at dose 300 mg/day with a good tolerance, the dose was increased to 450 mg daily. At any time during the study and according to safety, the dose could be decreased.
Batch Nos.: L0009680; L0010106; L0012011; L0018310; L0021353; L0022269.

**Reference product:**
**Pioglitazone** (Actos®, Takeda) was administered orally from 30 mg to 45 mg, as 1 encapsulated tablet daily at breakfast. The dose was 30 mg/day that could be increased at W8 to 45 mg if FPG level was ≥ 7.8 mmol/L, except in case of safety concerns. From W16 to W52, the dose level could be adapted according to HbA1c (target level < 6.5%) and safety in order to obtain the maximal dose tolerated by the patient. If HbA1c was higher than 6.5% at dose 30 mg/day with a good tolerance, the dose was increased to 45 mg daily. At any time during the study and according to safety, the dose could be decreased.
**Benfluorex placebo** or **pioglitazone placebo** were administered orally, in order to maintain the blind.

**Duration of treatment:**
- A placebo 4-week run-in period (ASSE-W0): patients were to follow their usual sulfonylurea treatment.
- **A double-blind 52-week treatment period** (W0-W52) divided as followed:
  - An up-titration period (W0-W16) in order to reach the optimal dosage for both treatment groups according to the FPG level of the patient and the safety of the patient.
  - A dose adaptation period (W16-W52) in order to obtain the maximal dose tolerated by the patient according to the HbA1c and the safety of the patient.

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**Criteria for evaluation:**

**Efficacy measurements**

The main efficacy criterion was HbA1c, assessed at each visit (W0, W4, W8, W16, W28, W40 and W52), and analysed by standardised High Performance Liquid Chromatography (HPLC) method.

Secondary criteria were:

- LDL cholesterol measured at each visit by direct quantitative homogeneous enzymatic assay.
- Other fasting serum lipids:
  - Total cholesterol, HDL cholesterol, and triglycerides assessed at each visit.
  - Non-HDL cholesterol calculated as (total cholesterol – HDL cholesterol), Apo A1, Apo B, at W0, W28 and W52.
- FPG assessed at each visit.
- Fasting plasma insulin assessed at W0 and W52, in order to calculate HOMA-IR.
- High-sensitivity C-reactive protein (hs-CRP) at W0, W40, and W52.

All biological measurements were centrally assessed (BARC - Belgium).

- Waist circumference measured at W0, W28, and W52.

**Safety measurements**

- Adverse events.
- Specific adverse events: hypoglycaemia (defined as symptoms suggestive of hypoglycaemia according to the study protocol, such as confusion, sweating, and reported by the patient, not confirmed by blood glucose measurement). Hypoglycaemic episodes were considered as mild if they did not interfere with usual activities, moderate if they transiently interfered with usual activities, and severe if it required external assistance due to severe impairment in consciousness or behaviour. In case of severe or multiple (> 3 episodes per month) hypoglycaemic episodes, an adjustment in the antidiabetic treatment could be judged necessary by the investigator.). Other specific adverse events included oedema, heart failure, and anaemia.
- The Adjudication Committee reviewed: all serious events, adverse events that involved any cardiac or vascular disease (excluding pedal oedema with N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) ≤ 300 pg/mL), other cardiac events such as modification of cardiovascular concomitant treatments, any clinically significant adverse event whose diagnosis was uncertain.
- Central laboratory: biochemistry (total proteins, creatinine, albumin, sodium, potassium, chlorides, calcium, total bilirubin, alkaline phosphatase assessed at W0, W28 and W52, lactic acid and uric acid assessed at W0, W52, NT-proBNP assessed at W0, W28, W52, and in case of oedema, liver enzymes (ALAT, ASAT, γ-GT) assessed at each visit, and haematology (red blood cell count and indexes, white blood cell count and, differential, blood smears, and platelet count) assessed at each visit.
- Physical examination: body weight (and particularly in case of oedema and congestive heart failure), heart rate and blood pressure measured at each visit.
- Cardiac examination with electrocardiogram and echocardiography (M-mode, 2 D, colour Doppler) at inclusion and W52 (or in case of premature withdrawal, and in case of suspicion of heart failure):
  - ECG (12-lead) assessed locally.
  - Cardiac echography, first assessed locally, then by blinded central reading on an ongoing basis by one of three experts for complete assessment of cardiac function (ECHO1).
  - A complementary reading review, with side-by-side interpretation of paired echographic recordings (baseline, Week 52) was carried out in order to evaluate valvular status (ECHO2). Recordings were interpreted (semi-quantitative method) by agreement of 2 experts who were blinded to the treatment group but not to the echography sequence. Echography is a high sensitivity method for detection of grade 1 trivial, considered as non pathological valvular regurgitation. ECHO2 focused on morphological (including thickness, calcification) and functional valvular abnormalities (including regurgitation and stenosis). Regurgitation was rated as either grade 0 (absent), 1 (trivial), 2 (mild), 3 (moderate), or 4 (severe) (Singh, 1999).

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**Safety measurements (Cont'd)**
The economic balance analysis was not performed.

**Statistical methods:**
**Efficacy analysis:**
Efficacy analyses were performed in the FAS defined as all randomised patients who have taken at least one dose of study treatment and who have at least one baseline value and one post-baseline value of HbA1c, and in the Per Protocol Set (PPS) defined as all patients from the FAS with HbA1c > 7% and ≤ 10% at inclusion, a treatment compliance in the [80-120]% range, a long term measure of HbA1c under treatment (including patients treated at least for 46 weeks), and without any relevant other protocol deviations that could affect the evaluation of HbA1c.

- **Primary efficacy criterion: HbA1c (%)**

The main analytical approach was the change from baseline to last post-baseline value. The main analysis was the non-inferiority of benfluorex to pioglitazone on the change from baseline value to last post-baseline value, using a general linear model studying treatment effect, with baseline and country as covariates.

- **Secondary efficacy criteria**

The same model as for the main analysis of the main criterion was used to provide estimate of the treatment difference, its standard error and its 95% confidence interval on the secondary criteria (LDL cholesterol, fasting serum lipids, fasting plasma glucose, HOMA-IR and waist circumference). For LDL cholesterol, the superiority of benfluorex as compared to pioglitazone was tested and p-value provided. Within treatment group change over time between baseline and last post-baseline value was estimated on the secondary criteria using a two-sided paired Student's test and two-sided 95% confidence interval.

**Safety analysis**
Descriptive statistics were provided for safety criteria. In addition, for NT-proBNP, the last post-baseline value under treatment was compared between groups using a between group geometric mean ratio obtained from an analysis of covariance (general linear model) on log10 transformed value with log10 transformed baseline and country (fixed effects) as covariates. The within group evolution during the study was studied using a within group geometric mean ratio obtained from a two-sided paired Student's t test on log10 transformed values.
ECHO1: descriptive statistics on echocardiographic parameters (left ventricular function, filling pressure, pulmonary artery pressure) were provided.
ECHO2: descriptive statistics on the morphological and functional valvular abnormalities at baseline were provided. The rates of emergence of morphological and/or functional valvular abnormalities were compared between treatment groups, and the Odds Ratio and the corresponding 95% Confidence interval and p-value (Wald test) were provided.
For ECHO1 and ECHO2 analyses, complementary Sets were defined in order to include patients having assessable echocardiography according to the ECHO1 or ECHO2 criterion analysed.

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**SUMMARY - CONCLUSIONS**

STUDY POPULATION AND OUTCOME

**Disposition of patients**

| | | **Benfluorex** | **Pioglitazone** | **All** |
|---|---|---|---|---|
| **Included** | **n (%)** | **423 (100)** | **424 (100)** | **847 (100)** |
| In conformity with the protocol | n (%) | 304 (71.9) | 321 (75.7) | 625 (73.8) |
| With protocol deviation(s) before or at inclusion | n (%) | 119 (28.1) | 103 (24.3) | 222 (26.2) |
| **Randomised *** | **n (%)** | **423 (100)** | **423 (100) (1)** | **846 (100) (1)** |
| **Completed *** | **n (%)** | **326 (77.1)** | **337 (79.7)** | **663 (78.4)** |
| In conformity with the protocol | n (%) | 210 (49.6) | 223 (52.7) | 433 (51.2) |
| **Protocol deviations affecting efficacy *** | **n (%)** | **9 (2.1)** | **6 (1.4)** | **15 (1.8)** |
| **Withdrawn due to *** | **n (%)** | **97 (22.9)** | **86 (20.3)** | **183 (21.6)** |
| Adverse event | n (%) | 37 (8.7) | 34 (8.0) | 71 (8.4) |
| Non-medical reason | n (%) | 27 (6.4) | 31 (7.3) | 58 (6.9) |
| Lack of efficacy | n (%) | 27 (6.4) | 17 (4.0) | 44 (5.2) |
| Protocol deviation | n (%) | 6 (1.4) | 4 (0.9) | 10 (1.2) |
| Lost to follow-up | n (%) | - | - | - |
| **Full Analysis Set (FAS) *** | n (%) | 413 (97.6) | 417 (98.6) | 830 (98.1) |
| **Per Protocol Set (PPS) *** | n (%) | 322 (76.1) | 322 (76.1) | 644 (76.1) |
| **Safety Set *** | n (%) | 421 (99.5) | 423 (100) | 844 (99.8) |

*n number of patients; % calculated as percentage of included or* Randomised patients; (1) Patient No. 148 276 02110 1163 was not randomised by IVRS but completed the study; Of note, 2 randomised patients were excluded from the Safety Set in the benfluorex group as one had no post-baseline safety evaluation and the other did not take any study treatment.*

A total of 1487 patients were selected for the study. Of them, 847 patients were included and 846 patients were randomly assigned to the benfluorex group or the pioglitazone group (one patient received pioglitazone without any randomisation by IVRS). The randomisation was well balanced: 423 patients in each treatment group.

During the study, the withdrawals (21.6% of the included patients) were comparable in each group: 22.9% in the benfluorex group and 20.3% in the pioglitazone group, mainly due to adverse events (8.4%) and non-medical reasons (6.9%). No patient was lost to follow-up during the study.

A total of 663 patients (78.4%) completed the study (326 patients in the benfluorex group and 337 patients in the pioglitazone group).

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**SUMMARY - CONCLUSIONS(Cont'd)**

STUDY POPULATION AND OUTCOME (Cont'd)

**Main demographic and other baseline characteristics in the Randomised Set**

| | | | **Benfluorex (N = 423)** | **Pioglitazone (N = 423)** | **All (N = 846)** |
|---|---|---|---|---|---|
| **Age** (years) | | Mean ± SD | 59.6 ± 10.3 | 58.6 ± 10.6 | 59.1 ± 10.5 |
| | | Min - Max | 35 - 80 | 34 - 80 | 34 - 80 |
| | ≤ 65 | n (%) | 294 (69.5) | 306 (72.3) | 600 (70.9) |
| | > 75 | n (%) | 26 (6.1) | 26 (6.1) | 52 (6.1) |
| **Sex** | Men | n (%) | 225 (53.2) | 239 (56.5) | 464 (54.8) |
| **Ethnic origin** | Caucasian | n (%) | 319 (75.4) | 327 (77.3) | 646 (76.4) |
| | Asian | n (%) | 83 (19.6) | 74 (17.5) | 157 (18.6) |
| | Other | n (%) | 21 (5.0) | 22 (5.2) | 43 (5.1) |
| **Weight** (kg) | | Mean ± SD | 79.7 ± 14.0 | 81.4 ± 14.8 | 80.5 ± 14.4 |
| | | Min - Max | 50 - 133 | 49 - 146 | 49 - 146 |
| **BMI** (kg/m$^2$) | | Mean ± SD | 29.4 ± 4.0 | 29.7 ± 4.1 | 29.5 ± 4.0 |
| | | Min - Max | 22.9 - 40.6 | 22.9 - 40.8 | 22.9 - 40.8 |
| **Waist circumference** (cm) | | Mean ± SD | 100.6 ± 11.9 | 102.1 ± 12.3 | 101.3 ± 12.1 |
| | | Min - Max | 68.5 - 140.0 | 52.0 - 168.0 | 52.0 - 168.0 |
| **Duration of diabetes** (years) | | Mean ± SD | 7.4 ± 6.0 | 6.7 ± 5.9 | 7.1 ± 6.0 |
| | | Min - Max | 0.3 - 36.3 | 0.3 - 39.8 | 0.3 - 39.8 |
| **HbA1c** (%) | | Mean ± SD | 8.3 ± 0.8 | 8.3 ± 0.8 | 8.3 ± 0.8 |
| | | Min - Max | 7.1 - 10.0 | 7.1 - 10.0 | 7.1 - 10.0 |
| | ]7 ; 8]% | n (%) | 182 (43.0) | 185 (43.7) | 367 (43.4) |
| | > 8% | n (%) | 241 (57.0) | 237 (56.0) | 478 (56.5) |
| **Fasting plasma glucose** (mmol/L) | | Mean ± SD | 9.9 ± 2.7 | 9.8 ± 2.5 | 9.9 ± 2.6 |
| | | Min - Max | 4.0 - 29.3 | 4.2 - 20.5 | 4.0 - 29.3 |

Regarding main demographic and other baseline characteristics, no relevant between-group differences were observed. At inclusion, in the Randomised Set, patients were on average 59.1 ± 10.5 years old, most of them (70.9%) aged 65 years old or less, and 6.1% older than 75 years. About half of the patients were male (54.8%), and most were Caucasian (76.4%). Mean BMI was 29.5 ± 4.0 kg/m².

Patients had type 2 diabetes for about 7 years, and for slightly longer in the benfluorex group than in the pioglitazone group (about 6 months). At entry in the study, all were receiving a sulfonylurea treatment (except one in the benfluorex group who received repaglinide), mainly glimepiride (37.0%), gliclazide (31.6%) and glibenclamide (26.7%). For most of the patients (96.0%), the dose received was ≥ 50% of the maximum dose recommended.

82.3% of the patients were receiving concomitant treatments at inclusion, mainly agents acting on the renin-angiotensin system (44.7%), serum lipid reducing agents (33.5%), antithrombotic agents (23.2%), and beta blocking agents (19.6%). No relevant between-group difference was observed.

At entry in the study, a majority of patients reported comorbidities such as hypertension (59.8%), and dyslipidaemia (42.2%). In addition, 10.2% had history of macrovascular complications including coronary heart disease, stroke, peripheral arterial disease (slightly more in the benfluorex group than in the pioglitazone group: 11.8% *versus* 8.5%, respectively), 4.0% had microvascular complications including nephropathy (8 patients, 1.9% in each group) and retinopathy slightly more frequently reported in the benfluorex group than in the pioglitazone group (2.8% *versus* 1.7%, respectively). Neuropathy was more frequently reported in the benfluorex group than in the pioglitazone group: 8.0% *versus* 5.7%, respectively. Creatinine clearance was ≤ 60 mL/min in 36 patients (8.5%) in the benfluorex group and 24 patients (5.7%) in the pioglitazone group.

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**SUMMARY - CONCLUSIONS (Cont'd)**

STUDY POPULATION AND OUTCOME (Cont'd)

**Efficacy parameters at baseline in the Randomised Set**

Mean HbA1c was 8.3 ± 0.8%, and the majority of the patients (56.5%) had HbA1c > 8%. All patients had HbA1c > 7% or ≤ 10%. FPG was on average 9.9 ± 2.6 mmol/L and triglycerides: 1.9 ± 0.9 mmol/L. Lipid profile was within normal range: total cholesterol was 5.0 ± 1.0 mmol/L, LDL cholesterol: 3.1 ± 0.8 mmol/L, HDL cholesterol: 1.2 ± 0.3 mmol/L. Regarding the efficacy parameters at baseline, no relevant between-group difference was detected, except that HOMA-IR, as surrogate of insulin resistance, was slightly lower in the benfluorex group than in the pioglitazone group (HOMA-IR: 6.4 ± 5.2 *versus* 6.6 ± 7.0, respectively), and waist circumference was smaller in the benfluorex group than in the pioglitazone group: 100.6 ± 11.9 cm *versus* 102.1 ± 12.3 cm, respectively. Mean BMI was 29.5 ± 4.0 kg/m², and was similar in each group.

Over the W0-W52 period, **treatment duration** was on average 331 ± 97 days for tablets or capsules, in the FAS. The global compliance was on average 94.8 ± 11.9% for tablets and 95.7 ± 11.6% for capsules, in the FAS, with 94% of the patients within the [80 ; 120]% range for tablets or capsules. No relevant between-group difference was detected. From W16, most of the patients were treated with the maximal dose: 81.7% of the patients received benfluorex 450 mg daily and 73.4% received pioglitazone 45 mg daily. At last evaluation, these rates were slightly increased: 83.3% and 79.9%, respectively.

In the FAS and the PPS demographic and other baseline characteristics were similar to those previously described in the Randomised Set, and no relevant between-group difference was detected.

EFFICACY RESULTS

- **Primary efficacy criterion: HbA1c (%)**

**Main statistical analysis: change from baseline to last post-baseline value in the FAS**

In the FAS, the mean HbA1c (%) decreased from baseline to last value in both groups. At last value, HbA1c was 7.8 ± 1.3% in the benfluorex group and 7.5 ± 1.3% in the pioglitazone group. Mean changes from baseline to last value were: -0.54 ± 1.12% in the benfluorex group and -0.88 ± 1.24% in the pioglitazone group. Non-inferiority of benfluorex *versus* pioglitazone was not verified (E (SE) = 0.33 (0.08)%, 95% CI = [0.17; 0.49], p = 0.19).

In the PPS, mean changes in HbA1c from baseline to last value under treatment were slightly larger than in the FAS: -0.70 ± 1.05% in the benfluorex group and -1.04 ± 1.11% in the pioglitazone group, but the non-inferiority analysis yielded similar results (E (SE) = 0.32 (0.08), 95% CI = [0.16 ; 0.47], p = 0.14).

**Change in HbA1c (%) from baseline to last post-baseline value in the FAS (N = 830)**

| **HbA1c (%)** | | **Benfluorex (N = 413)** | **Pioglitazone (N = 417)** |
|---|---|---|---|
| Baseline | Mean ± SD | 8.31 ± 0.82 | 8.33 ± 0.83 |
| END | Mean ± SD | 7.77 ± 1.31 | 7.45 ± 1.30 |
| **Change (END-baseline)** | Mean ± SD | -0.54 ± 1.12 | -0.88 ± 1.24 |
| Statistical analysis | | | |
| | E (SE) (1) | 0.33 (0.08) | |
| | 95% CI (2) | [0.17 ; 0.49] | |
| | p-value (3) | 0.19 | |

*END = last value; (1) Estimate (Standard Error) of the difference (benfluorex minus pioglitazone) between adjusted group means; (2) 95% Confidence Interval of the estimate; (3) For a non-inferiority one-sided test (alpha = 2.5%) obtained from an analysis of covariance with baseline and country (fixed effects) as covariates and a 0.4% margin of clinical relevance*

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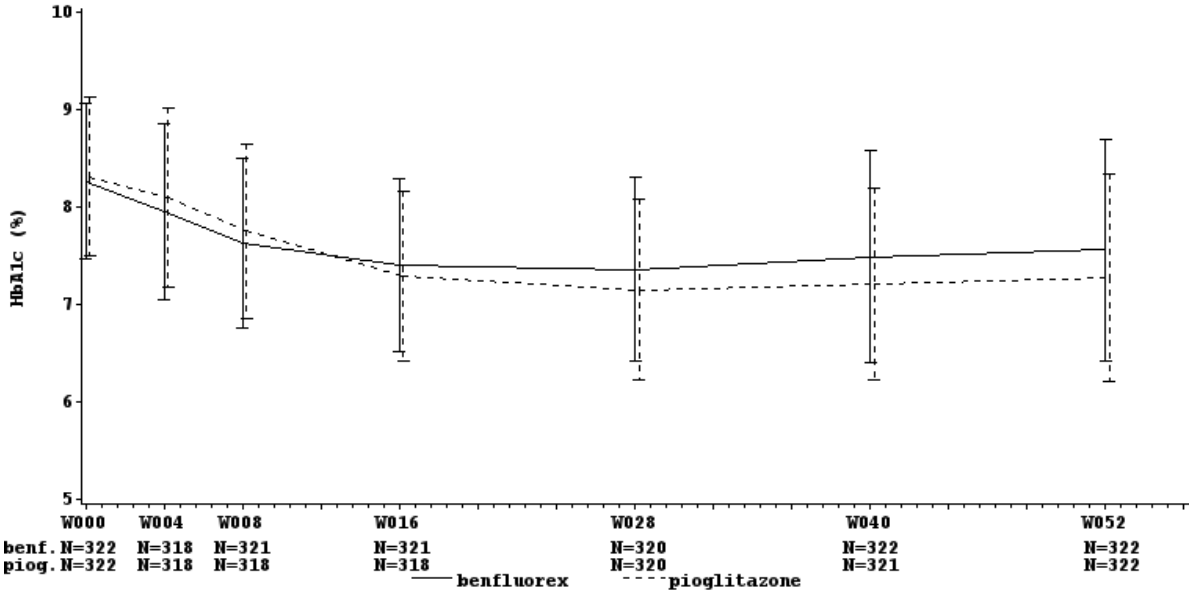
**SUMMARY - CONCLUSIONS (Cont'd)**
EFFICACY RESULTS (Cont'd)

**HbA1c (%) mean +/- SD at each visit in the PPS**




**Within group change in HbA1c**
The decrease in HbA1c (%) from baseline to last value in the FAS was statistically significant in both treatment groups ($p < 0.0001$). Similar results were obtained in the PPS ($p < 0.0001$).

**Responders for HbA1c**
In the FAS, the rate of responders (defined as HbA1c ≤ 7%) was lower in the benfluorex group than in the pioglitazone group: 31.7% *versus* 47.7%, respectively (Odds Ratio = 0.45, 95% CI = [0.33 ; 0.61]).
Similar results were obtained in the PPS.

- **Secondary efficacy criteria**

**LDL cholesterol and other fasting serum lipids** are presented in Table hereafter.
Benfluorex and pioglitazone decreased the mean **LDL cholesterol** from baseline to last value, and the decrease was two fold larger within the benfluorex group (-0.24 ± 0.66 mmol/L) than within the pioglitazone group (-0.12 ± 0.74 mmol/L). The between-group difference was statistically significant and the superiority of benfluorex *versus* pioglitazone was demonstrated ($p = 0.005$).
**Total cholesterol** decreased in the benfluorex (-0.16 ± 0.82 mmol/L, $p < 0.0001$), but not in the pioglitazone group (0.08 ± 0.90 mmol/L, $p= 0.07$), and the between-group difference was statistically significant (E (SE) = -0.25 (0.06) ; 95% CI = [-0.36 ; -0.13]).
For lipid parameters results obtained in the PPS were similar.
The decrease in the mean **ratio total cholesterol/HDL cholesterol** from baseline to last value in both groups (-0.17 ± 0.92 and -0.10 ± 1.00, respectively) was statistically significant ($p < 0.001$ and $p = 0.047$, respectively, complementary analysis). No statistically significant between-group difference was observed (E (SE) = -0.09 (0.06), 95% CI = [-0.22 ; 0.03]).

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**SUMMARY - CONCLUSIONS (Cont'd)**

EFFICACY RESULTS (Cont'd)

**Fasting serum lipids in the FAS (N = 830)**

| **Parameters** (unit) | | **Benfluorex (N = 413)** | **Pioglitazone (N = 417)** | **Between-group statistical analysis** |
|---|---|---|---|---|
| **LDL cholesterol** (mmol/L) | | | | E (SE) [(1)]; 95% CI [(2)] ; p [(3)] |
| Baseline | Mean ± SD | 3.11 ± 0.83 | 3.15 ± 0.81 | |
| END-baseline | Mean ± SD | -0.24 ± 0.66 | -0.12 ± 0.74 | -0.13 (0.05) ; [-0.22 ; -0.04]; **0.005** |
| Within-group analysis [(4)] | | **p < 0.0001** | **p = 0.001** | |
| **Total cholesterol** (mmol/L) | | | | E (SE) [(1)]; 95% CI [(2)] |
| Baseline | Mean ± SD | 5.01 ± 0.99 | 5.02 ± 0.92 | |
| END - baseline | Mean ± SD | -0.16 ± 0.82 | 0.08 ± 0.90 | -0.25 (0.06) ; **[-0.36 ; -0.13]** |
| Within-group analysis [(4)] | | **p < 0.0001** | p = 0.07 | |
| **HDL cholesterol** (mmol/L) | | | | |
| Baseline | Mean ± SD | 1.25 ± 0.32 | 1.22 ± 0.31 | |
| END - baseline | Mean ± SD | 0.01 ± 0.23 | 0.06 ± 0.20 | -0.05 (0.02) ; **[-0.08 ; -0.02]** |
| Within-group analysis [(4)] | | p = 0.68 | **p < 0.0001** | |
| **Triglycerides** (mmol/L) | | | | |
| Baseline | Mean ± SD | 1.92 ± 0.97 | 1.96 ± 0.90 | |
| END - baseline | Mean ± SD | -0.14 ± 0.98 | -0.21 ± 0.95 | 0.06 (0.06) ; [-0.07 ; 0.18] |
| Within-group analysis [(4)] | | **p = 0.006** | **p < 0.0001** | |

*END = last value; (1) Estimate (Standard Error) of the difference (benfluorex minus pioglitazone) between adjusted group means; (2) 95% Confidence Interval of the estimate; (3) for a superiority two-sided test (alpha=5%) obtained from an analysis of covariance with baseline and country (fixed effects) as covariates; (4) Student's t test*

**Fasting plasma glucose**

The decrease in mean FPG from baseline to last value in the FAS was smaller in the benfluorex group than in the pioglitazone group: -1.2 ± 2.9 mmol/L *versus* -1.7 ± 2.9 mmol/L, respectively ($p < 0.0001$ in each treatment group). The between-group difference was statistically significant (E (SE) = 0.56 (0.18) mmol/L, 95% CI = [0.21 ; 0.90]). Results were similar in the PPS.

**Insulin resistance (HOMA-IR)**

Mean HOMA-IR decreased from baseline to last value in the FAS, and the mean change was smaller in the benfluorex group than in the pioglitazone group: -1.2 ± 6.9 ($p = 0.001$) *versus* -2.5 ± 6.2 ($p < 0.0001$), respectively. The between-group difference was statistically significant (E (SE) = 1.04 (0.41), 95% CI = [0.23 ; 1.85]).

**Waist circumference**

The decrease in mean waist circumference from baseline to last value was -1.9 ± 4.8 cm ($p < 0.0001$) in the benfluorex group, and the increase in the pioglitazone group was 2.0 ± 5.5 cm ($p < 0.0001$). The between-group difference was statistically significant in favour of the benfluorex group (E (SE) = -4.12 (0.37) cm, 95% CI = [-4.84 ; -3.39]). Similar results were obtained in the PPS.

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**SUMMARY - CONCLUSIONS (Cont'd)**

EFFICACY RESULTS (Cont'd)

**Weight**

The mean weight increased steadily in the pioglitazone group (3.3 ± 4.2 kg, $p < 0.0001$) from baseline to last value, but not in the benfluorex group (-1.6 ± 3.5 kg, $p < 0.0001$), with a statistically between-group difference ($p < 0.0001$, unplanned analysis). Substantial weight increase from baseline to last value (corresponding to a relative change in weight ≥ 5%) affected 40% of the patients in the pioglitazone group while it affected few patients in the benfluorex group (1.7%). Mean BMI increased in the pioglitazone group (1.2 ± 1.6 kg/m²) but not in the benfluorex group (-0.6 ± 1.3 kg/m²).

In the **lipid parameter substudy** (N = 160, benfluorex group: N = 75, pioglitazone group: N = 85), the mean total plasma apo B (g/L) slightly decreased from baseline to last value in both groups: -0.07 ± 0.19 g/L in the benfluorex group and -0.08 ± 0.20 g/L in the pioglitazone group. The superiority of benfluorex over pioglitazone was not demonstrated (E (SE) = 0.01 (0.03) g/L, 95% CI = [-0.05 ; 0.07], p = 0.64). The analysis of the lipid particle profiles using NMR spectroscopy, including LDL particle concentrations, yielded no other meaningful findings.

SAFETY RESULTS

**Adverse events**

**Summary of results**

| | | **Benfluorex (N = 421)** | **Pioglitazone (N = 423)** |
|---|---|---|---|
| Patients having reported | | | |
| At least one emergent adverse event | n (%) | 268 (63.7) | 266 (62.9) |
| At least one treatment-related emergent adverse event | n (%) | 82 (19.5) | 110 (26.0) |
| At least one emergent hypoglycaemia | n (%) | 38 (9.0) | 56 (13.2) |
| At least one emergent severe hypoglycaemia | n (%) | - | - |
| Patients having experienced | | | |
| At least one serious adverse event (including death) | n (%) | 38 (9.0) | 31 (7.3) |
| At least one treatment-related serious adverse event | n (%) | 4 (1.0) | 3 (0.7) |
| Patients withdrawn | | | |
| Due to an adverse event | n (%) | 37 (8.8) | 34 (8.0) |
| Due to a serious adverse event | n (%) | 18 (4.3) | 16 (3.8) |
| Due a treatment-related adverse event | n (%) | 22 (5.2) | 18 (4.3) |
| Due a treatment-related serious adverse event | n (%) | 4 (1.0) | 4 (0.9) |
| Patients who died | n (%) | 2 (0.5) | 4 (0.9) |

**Emergent adverse events** (EAE)

Emergent adverse events affected each group with a similar frequency: 63.7% in the benfluorex group *versus* 62.9% in the pioglitazone group. The most frequently reported system organ classes were infections and infestations (24.9% *versus* 28.6%, respectively), gastrointestinal disorders (14.7% *versus* 11.8%, respectively), and musculoskeletal and connective tissue disorders (13.1% *versus* 15.6%, respectively).

The most frequently reported EAE were hypoglycaemia with a lower frequency in the benfluorex group than in the pioglitazone group (9.0% *versus* 13.2%, respectively; p = 0.05, complementary analysis), and diarrhoea with a higher frequency in the benfluorex group than in the pioglitazone group (4.3% *versus* 1.9%, respectively, p = 0.05, complementary analysis).

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**SUMMARY - CONCLUSIONS (Cont'd)**

SAFETY RESULTS (Cont'd)

Other events of interest mentioned in the Summary of Product Characterisics **(SPC)** for benfluorex were reported during the study with a low frequency: vertigo (1.4% *versus* 0.7%, respectively), headache (1.0% *versus* 0.9%, respectively), depression (1.4% *versus* 0.2%, respectively), sleep disorder (0.7% *versus* none, respectively), insomnia (0.5% in each group), agitation (none), asthenia (0.7% *versus* 0.9%, respectively), and fatigue (0.7% *versus* none, respectively). Events mentioned in SPC for pioglitazone and more frequently reported with pioglitazone were: weight increased (3.1% *versus* none in the benfluorex group), anaemia (1.9% *versus* 0.7% in the benfluorex group), all oedema (grouping oedema, oedema peripheral, pitting oedema and gravitational oedema; 7.3% *versus* 2.1% with benfluorex), erectile dysfunction (none *versus* 0.9%, respectively), arthralgia (1.2% *versus* 0.9%, respectively), fractures (grouping rib and upper limb fractures, stress fracture and osteoporotic fracture; 0.8% *versus* 0.2% with benfluorex), dizziness (1.4% *versus* 0.2% with benfluorex).

Cardiac valvular events (reported on the basis of local echocardiographic interpretation) were more frequently reported in the benfluorex group than in the pioglitazone group (18 *versus* 5 patients, respectively). Cardiac valvular assessments based on central reading of Doppler echography are presented in the echography section (page 13). Most frequently reported abnormalities as adverse events were aortic valve incompetence (5 patients in the benfluorex group *versus* none in the pioglitazone group), mitral valve incompetence (4 patients *versus* 1, respectively), cardiac valve disease (3 patients *versus* 1, respectively), and heart valve insufficiency (3 patients *versus* none, respectively).

Most of the patients had EAE rated as mild (45.4% and 47.0%, respectively). Most of the emergent adverse events recovered (81.2%).

**Treatment-related EAE** according to investigator's opinion were less frequently reported in the benfluorex group than in the pioglitazone group: 82 patients (19.5%) *versus* 110 patients (26.0%), respectively. They affected mainly metabolism and nutrition disorders (9.5% *versus* 13.7%, respectively), mostly hypoglycaemia (9.0% and 13.2%, respectively), with a lower frequency reported in the benfluorex group than in the pioglitazone group, except for gastrointestinal disorders (4.8% *versus* 2.1%, respectively) with a higher frequency in the benfluorex group than in the pioglitazone group, mainly due to diarrhoea (2.1% *versus* 0.7%, respectively).

**Emergent adverse events leading to treatment discontinuation** affected 9.5% of the patients in the benfluorex group and 8.3% in the pioglitazone group. They were mainly cardiac disorders (1.7% in each group), and gastrointestinal disorders with a slightly higher frequency in the benfluorex group than in the pioglitazone group (2.1% *versus* 0.5%, respectively).

**Emergent suspected hypoglycaemia** affected patients of the benfluorex group less frequently than the pioglitazone group: 38 patients (9.0%) *versus* 56 patients (13.2%), respectively. The majority of the patients had hypoglycaemia of mild intensity (7.1% in the benfluorex group and 10.4% in the pioglitazone group). None of the patients experienced severe hypoglycaemia.

In all**, 6 patients died**, 2 patients in the benfluorex group and 4 in the pioglitazone group, none considered as treatment-related according to the investigator's opinion:

- In the benfluorex group: 1 metastatic neoplasm, and 1 renal failure (after surgery of a metastatic ovarian cancer).
- In the pioglitazone group: 1 road traffic accident, 1 plasmocytoma, 1 aspergillosis (in a patient with pre-existing asthma treated with corticosteroids), and 1 myocardial infarction.

Among them, 2 patients died after the treatment study period (renal failure in the benfluorex group and aspergillosis in the pioglitazone group).

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**SUMMARY - CONCLUSIONS (Cont'd)**
SAFETY RESULTS (Cont'd)

**Serious emergent adverse events** affected 9.0% of the patients in the benfluorex group and 7.3% in the pioglitazone group. They were mainly cardiac disorders (6 *versus* 7 patients, respectively), musculoskeletal and connective tissue disorders (6 *versus* 1 patient, respectively), nervous system disorders (4 patients in each group), including ischaemic stroke (2 patients *versus* 1 patient, respectively). No particular preferred term was affected by serious emergent adverse events. Serious emergent cardiac disorders (assessed by the adjudication committee) were reported with similar frequency in each group (1.4% versus 1.7%): myocardial infarction (2 patients versus 3, respectively), angina unstable (none versus 1 patient, respectively), cardiac failure (1 patient versus none, respectively), cardiac failure acute (1 patient versus none, respectively), cardiac failure congestive (none versus 1 patient, respectively), myocardial ischaemia (none versus 1 patient, respectively), sick sinus syndrome (1 patient versus none, respectively), acute coronary syndrome (none versus 1 patient, respectively), and congestive cardiomyopathy (1 patient versus none, respectively).

Serious emergent adverse events were considered related to the study treatment by the investigator in 4 patients in the benfluorex group (cardiac failure, cardiac failure acute, congestive cardiomyopathy, global amnesia) and 3 patients in the pioglitazone (myocardial ischaemia, pulmonary oedema, and 1 patient had pharyngeal oedema and hepatitis). All but one in the pioglitazone group (pharyngeal oedema) led to treatment discontinuation. All recovered, except myocardial ischaemia in the pioglitazone group.

**Biochemical and haematological parameters**
Neither clinically relevant changes nor differences between groups over time were detected in mean biochemistry values (excluding lipids). Emergent potentially clinically significant abnormal (PCSA) laboratory values were sparse in all groups (< 4%) and similar in both groups except GGT, more frequently reported in the benfluorex group than in the pioglitazone group (3.7% *versus* 2.2%, respectively).
For haematological parameters, neither clinically relevant changes nor differences between groups over time were detected, except a mild decrease in mean haemoglobin in the pioglitazone group, consistent with haemodilution mentioned in the SPC (-5.1 ± 9.3 g/L in the pioglitazone group versus -1.3 ± 8.3 g/L in the benfluorex group). Emergent low PCSA values were detected for haemoglobin in 4.0% of the patients in the benfluorex group and 6.7% in the pioglitazone group. PCSA were sparse for the other parameters.
**NT-proBNP** slightly increased from baseline to last value under treatment in both groups (geometric means): from 50.2 pg/mL to 69.8 pg/mL in the benfluorex group ($p < 0.0001$) and from 49.8 pg/mL to 64.5 pg/mL in the pioglitazone group ($p < 0.0001$). The between-group difference was not statistically significant ($p = 0.21$). During the study, the number of patients with at least one emergent NT-proBNP alert values (> 300 pg/mL in patients less than 75 years and > 450 pg/mL in patients older than 75 years) was 19 (4.5%) in the benfluorex group and 32 (7.6%) in the pioglitazone group, with no statistically significant between-group difference ($p = 0.07$). The number of patients with at least one emergent NT-proBNP values > 200 pg/mL was 32 (7.6%) in the benfluorex group and 43 (10.2%) in the pioglitazone group, with no statistically significant between-group difference ($p = 0.21$).

**Physical examination and vital signs**

No clinically relevant change over time or between-group difference was observed for sitting blood pressures and heart rate.

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**SUMMARY - CONCLUSIONS (Cont'd)**

SAFETY RESULTS (Cont'd)

**Echocardiography (central reading)**

A total of 683/844 patients *i.e.* 80.9% (348 patients in the benfluorex group and 335 patients in the pioglitazone group) had an evaluable baseline echocardiography and at least one post-baseline echocardiography.

- **Cardiac function (ECHO1)**

At baseline LVEF was 69.0 ± 7.2% in the benfluorex group and 69.1 ± 7.1% in the pioglitazone group, and mean change was 0.4 ± 7.5% and 0.2 ± 8.2%, respectively.

Mean baseline values of left ventricular function and filling pressure parameters were normal and similar in both groups, and mean changes over time were small, with no clinical significance.

The change in pulmonary arterial pressure was evaluable in 68 patients, and no clinically relevant change was detected from baseline to last post-baseline evaluation. The mean change over time was 1.1 ± 6.7 mmHg in the benfluorex group and 2.4 ± 6.9 mmHg in the pioglitazone group. Pulmonary arterial pressure above 40 mmHg after baseline was detected in 4 patients in the benfluorex group and 9 patients in the pioglitazone group.

- **Valvular status (ECHO2)**

The demographic and other baseline characteristics of the patients from the ECHO2 Set (N = 683) were similar in both treatment groups and were comparable to those described in the Randomised Set for the overall population (N = 846).

For the 615/683 patients (90.0%) assessable for valvular morphological or functional abnormalities, mean treatment duration was 345.9 ± 79.5 days (from 15 to 457 days), with no relevant difference between groups, and the mean time between the baseline and the last echography assessed was 352.4 ± 73.6 days (from 2 to 513 days).

At **baseline**, a total of 314 patients (51.1%) had at least one morphological valvular abnormality (aortic 33.1%, mitral 41.5%, tricuspid 3.5%), with similar numbers in both treatment groups. Morphologic abnormalities were mainly abnormal thickness (aortic 31.1%, mitral 38.6%, tricuspid 3.5%), fewer baseline echographies showed calcification (aortic 9.5%, mitral 7.6%, tricuspid none), with similar frequencies reported in each treatment group.

Baseline functional abnormalities were very frequent. A total of 515 patients (84.2%) had at least one functional abnormality in any valve. 15.5% of patients had aortic regurgitation (AR), mostly trivial (14.9%). Mild AR was found in 4 pioglitazone patients; no moderate or severe grade AR was observed.

Aortic valve stenosis was found in 7 benfluorex and 4 pioglitazone patients. Mitral regurgitation (MR) was frequent (60.8%) at baseline, mainly trivial MR (59.3%). No severe MR was observed. Mitral stenosis was observed in 3 patients. Tricuspid regurgitation was very frequent at baseline (72.3%), mainly trivial tricuspid regurgitation (71.8%). Neither moderate or severe tricuspid regurgitation nor stenosis were detected.

No relevant between group differences in functional valvular status were observed.

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**SUMMARY - CONCLUSIONS (Cont'd)**

SAFETY RESULTS (Cont'd)

**Emergent valvular abnormalities (ECHO2)**

- **Morphological valvular abnormalities**

Emergent morphological valvular abnormalities were those that appeared after baseline. A total of 12 patients (2.0%) had emergent morphological abnormalities: 8 patients (2.6%) in the benfluorex group *versus* 4 patients (1.3%) in the pioglitazone group. The between-group difference was not statistically significant (Odds ratio = 1.99; 95% CI = [0.59 ; 6.69], p = 0.26, Wald test).

Among these 12 patients, 9 patients (7 in the benfluorex group and 2 in the pioglitazone group) had pre-existing valvular abnormalities (morphologic and/or functional), including 6 patients (5 and 1, respectively) with other valvular morphologic abnormalities.

The emergent abnormalities were:

- Abnormal aortic thickness: 6 patients in the benfluorex group versus none in the pioglitazone group.
- Abnormal mitral thickness: 1 patient *versus* 4 patients, respectively.
- Aortic calcification: 1 patient *versus* none, respectively. Of note, this patient (No. 00319) had pre-existing abnormalities on the 3 valves (aortic valve abnormal thickness with stenosis and trivial regurgitation, mitral valve abnormal thickness and calcification, and trivial tricuspid regurgitation) and medical history of diabetes for 30 years, arterial hypertension, coronary artery disease, dyslipidaemia, and obesity.

No abnormality of chordae tendinae was reported on echocardiography.

- **Functional valvular status**

No emergent stenosis was detected in any valve, whatever the treatment group. Regurgitation was considered as emergent when it appeared or involved a worsening of the grade (*i.e.* an increase) on treatment. A total of 115 patients (19.3%) had emergent regurgitation: 82 patients (27.2%) in the benfluorex group *versus* 33 patients (11.2%) in the pioglitazone group. The between-group difference was statistically significant (Odds ratio = 2.97; 95% CI = [1.91 ; 4.63], p < 0.0001, Wald test). A multivariate analysis using a logistic regression, showed that the adjusted OR obtained was similar (OR = 3.20, 95% CI = [2.03 ; 5.05], p < 0.001, Wald test). Emergent regurgitations were:

- Aortic regurgitation: 42 patients (13.6%) in the benfluorex group (including 40 patients with trivial AR) versus 3 patients (1.0%) in the pioglitazone group, with a statistically significant between-group difference (OR = 15.52; 95% CI = [4.76 ; 50.66], p < 0.0001).
- Mitral regurgitation: 22 patients (7.1%) versus 14 patients (4.7%), respectively, mostly trivial, with no statistically significant between-group difference (OR = 1.58; 95% CI = [0.79 ; 3.16], p = 0.19).
- Tricuspid regurgitation: 33 patients (10.9%) versus 17 patients (5.7%), respectively, mostly trivial, with a statistically significant between-group difference (OR = 2.01; 95% CI = [1.10 ; 3.70], p = 0.024).

Among the patients with emergent regurgitation, most of them *i.e.* 98/115 (72/82 in the benfluorex group and 26/33 in the pioglitazone group) had other valvular abnormalities at baseline (morphologic and/or functional).

The emergent regurgitations were mainly rated as trivial (grade = 1) more frequently in the benfluorex group than in the pioglitazone group: 81 patients (26.9%) *versus* 30 patients (10.2%), with a statistically significant between-group difference (Odds ratio = 3.25; 95% CI = [2.06 ; 5.13]; p < 0.0001, Wald test). Emergent regurgitation considered as overt (grade > 1) was detected in 2 patients (0.7%) in the benfluorex group and 3 patients (1.0%) in the pioglitazone group (p = 0.64).

No regurgitation rated as moderate or severe was emergent during the study.

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**SUMMARY - CONCLUSIONS (Cont'd)**

SAFETY RESULTS (Cont'd)

**Emergent valvular functional abnormality according to grade (ECHO2)**

| Emergent valvular abnormality | Grade Baseline to last | | Benfluorex | Pioglitazone |
|---|---|---|---|---|
| **Aortic regurgitation** | | N | 309 | 302 |
| | Grade 0 to 1 | n (%) | 40 (12.9) | 3 (1.0) |
| | Grade 0 to 2 | n (%) | 1 (0.3) | - |
| | Grade 1 to 2 | n (%) | 1 (0.3) | - |
| **Mitral regurgitation** | | N | 309 | 300 |
| | Grade 0 to 1 | n (%) | 21 (6.8) | 13 (4.3) |
| | Grade 1 to 2 | n (%) | 1 (0.3) | 1 (0.3) |
| **Tricuspid regurgitation** | | N | 304 | 299 |
| | Grade 0 to 1 | n (%) | 33 (10.9) | 15 (5.0) |
| | Grade 1 to 2 | n (%) | - | 2 (0.7) |

*N number of patients in the valvular Set; n number of patients affected; Grade 0 absent; grade 1 trivial; grade 2 mild; % calculated as number of patients affected x 100/total number of patients in the group.*
*Note one patient could have several valvular abnormalities*

**CONCLUSION**

**In conclusion, patients with type 2 diabetes not controlled under sulfonylurea monotherapy treatment treated over 1 year with benfluorex, had a clinically and statistically significant decrease in HbA1c. The antidiabetic effect of benfluorex was confirmed in this study (-0,54%), although the non-inferiority of benfluorex *versus* pioglitazone treatment was not demonstrated. Superiority of benfluorex *versus* pioglitazone to decrease LDL cholesterol was shown. Both treatments significantly decreased triglycerides, fasting plasma glucose, and improved insulin resistance although with a lower magnitude in the benfluorex group. Over 1 year, body weight and waist circumference increased with pioglitazone but not with benfluorex. Safety profiles were in accordance with SPCs. A mild increase in plasma NT-proBNP was observed in both groups, however no change in cardiac function assessed by echocardiography was detected in any group. Valvular structure and function assessment was performed using a method of blinded central reading with a high sentitivity for the detection of trivial grade regurgitation. Emergent trivial regurgitations occurred more frequently with benfluorex than with pioglitazone, and were observed mostly in the aortic valve. Between-group differences in morphological abnormalities and regurgitations above grade 1 were non-significant.**

**Date of the Report: 17 December 2010**