Document title	**Clinical Study Synopsis**
Study title	**International FOLLOW-UP study, after the investigational drug exposure in diabetic patients previously included in the REGULATE trial (benfluorex *versus* pioglitazone).**
Study drug	**Not applicable**
Studied indication	**Not applicable**
Post development phase	**Interventional FOLLOW-UP study without further study treatment administration**
Protocol code	**CL3-00780-150**
Study initiation date	**28 July 2011**
Study completion date	**05 April 2013**
Main coordinator	[redacted] **France**
Company	**Institut de Recherches Internationales Servier (I.R.I.S.)** **50 rue Carnot** **92284 Suresnes Cedex - France**
Responsible medical officers	[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 3 February 2014**

~~CONFIDENTIAL~~

2. SYNOPSIS

Name of Company: **I.R.I.S** **50 rue Carnot** **92284 Suresnes Cedex - France**	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use only)***
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Title of study:
International FOLLOW-UP study, after the investigational drug exposure in diabetic patients previously included in the REGULATE trial (benfluorex *versus* pioglitazone).
Protocol No.: CL3-00780-150. EudraCT Number: 2011-001283-22.

Coordinator:
[redacted]
FRANCE

Study centres:
Multicentre study performed in patients still alive from the 845 type 2 diabetic patients exposed to one of the study drugs in the previous REGULATE trial (196 centres located in 8 countries). A total of 810 patients (as 6 patients died during the REGULATE trial and 29 patients in 11 centres could not be contacted mainly due to Health Authorities or investigator refusal) were expected to participate in the FOLLOW-UP study in 178 centres located in 8 countries, Argentina: 9 centres – 92 patients, Czech Republic: 8 centres – 53 patients, France: 113 centres – 242 patients, Germany: 17 centres – 134 patients, India: 9 centres – 130 patients, Romania: 4 centres – 35 patients, South Africa: 10 centres – 76 patients, Tunisia: 8 centres – 48 patients

Publication (reference): Derumeaux G *et al*. Echocardiographic evidence for valvular toxicity of benfluorex: a double-blind randomised trial in patients with type 2 diabetes - PloS One 2012; 7(6): e38273

Studied period:	**Phase of development of the study:**
Initiation date: 28 July 2011 (first FOLLOW-UP visit) Completion date: 05 April 2013 (last FOLLOW-UP contact last patient)	Post-development Phase

Objective:
The purpose of this study was to document the clinical condition of all patients who were included in the REGULATE trial and exposed to one of the study drugs (benfluorex or pioglitazone), in order to be able to describe the evolution of their cardiac condition (with a specific focus on valvular condition) and to assess the between-group global safety condition.
This FOLLOW-UP study was set-up further to a published request of the AFSSAPS (National Committee of Pharmacovigilance, November 2010) currently renamed ANSM (Agence Nationale de Sécurité des Médicaments et des produits de Santé).
Of note, the Scientific Committee suggested to conduct this FU study (09 July 2009).

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Methodology:
International, interventional FOLLOW-UP (FU) study of the REGULATE trial (CL3-00780-148 – Clinical report NP29244), without any study treatment administration, proposed to patients from the REGULATE trial who were exposed to one of the study drugs (benfluorex or pioglitazone).
In the FU study, performed about 4 years after the end of the REGULATE trial, the investigators were asked to make every effort to contact the patients who participated in the REGULATE trial to collect information on their health condition, especially their cardiac condition, to perform central echocardiographic assessement of the valvular heart status, and to record past drug exposures. One visit per patient was planned at the investigator's site called FOLLOW-UP visit (FU-VISIT). Additionally a single biological sampling was to be done within the following 7 days and a cardiac examination (including echocardiographic assessment) within the following 6 weeks. An optional visit according to the patient's wish could be planned for the optional pharmacogenetic investigation sampling, and/or with a shared discussion with the investigator on the results of the investigations performed in the FU study (echocardiography, ECG, biology).
Concerning patients for whom no direct contact could be obtained, an administrative survey was planned to be conducted, in order to collect additional information on vital status when possible, in compliance with local regulations (for patients lost-to follow-up and known to be alive after their REGULATE trial participation, as well as for those who died from unknown cause). In France an administrative survey was requested by the Comité de Protection des Personnes (CPP), the Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (CCTIRS) in the process of the Commission Nationale de l'Informatique et des Libertés (CNIL).

Number of patients:
Planned: all patients from the REGULATE trial exposed to one of the study drugs (845 patients: benfluorex = 422, pioglitazone = 423) and alive at the end of the REGULATE trial (839 patients: 420 patients in the benfluorex group and 419 in the pioglitazone group, as 6 patients died), of which 810 were expected to participate (as it was known that 29 patients could not be contacted mainly due to Health Authorities or investigator refusal or impossibility to participate (11 centres)).
Successful contact: 717/839 patients, 85.5% of the patients alive at the end of the REGULATE trial (360 in the former benfluorex group and 357 in the former pioglitazone group)
Participated (informed consent obtained for participation in the FU study): 620/717 patients, 86.5% of the patients successfully contacted (former benfluorex group = 309, former pioglitazone group = 311). No study treatment was given in this present study, and results are presented according to the treatment previously received by the patients in the REGULATE trial called "former benfluorex group" and "former pioglitazone group" in the present report, and also according to the global patient's exposure to benfluorex over and after the REGULATE trial (see post-hoc analysis hereafter).

Diagnosis and main criteria for inclusion:
All the patients from the REGULATE trial who had taken at least one dose of study treatment during the REGULATE trial and having given their written informed consent for the FOLLOW-UP study.

Study drug: Not applicable

Reference product: Not applicable

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Duration of treatment:
Previous REGULATE trial: patients received either benfluorex or pioglitazone treatments for a double-blind 52-week treatment period (W0-W52),
FU study: no study treatment was received by the patients. However, after the end of the REGULATE trial patients were followed by their personal doctor, and some of them could have been prescribed with benfluorex. To assess the safety of the patients, the cumulative exposure to benfluorex both during and after the REGULATE trial was taken into account in a post-hoc analysis. The former groups were analysed according to the cumulative exposure to benfluorex, and whatever the dose received (study treatment received during the REGULATE trial and/or in daily medical practice after the end of the REGULATE trial): ≥ 3 months or < 3 months (including those having only received pioglitazone, not exposed to benfluorex). In order to facilitate the reading of the present report, patients "exposed to benfluorex ≥ 3 months" were called "exposed" and the patients "exposed to benfluorex briefly < 3 months or not exposed to benfluorex" were called "not exposed".
In addition, a sensitivity analysis was performed taking into account the exposure of the patients to at least one dose of benfluorex *versus* those not exposed at all.

Criteria for evaluation:
Efficacy measurements: Not applicable
Safety measurements:
One FOLLOW-UP visit per patient was performed at the investigator's site during the study (on average 4 years after the end of the REGULATE trial), with laboratory test and cardiac examination (including echocardiography assessment) performed within 7 days and 6 weeks, respectively.

- Transthoracic echocardiographic assessment performed according to the protocol used in the REGULATE (central reading and grading of echocardiographic valvular regurgitation by the Central Echo Reading Committee using the classification of the American Society of Echocardiography (Zoghbi, 2003), including 4 levels of regurgitation: trivial, mild, moderate or severe, the same as in the REGULATE trial).
- 12-lead electrocardiogram (ECG).
- Cardiac examination.
- Medical events since last visit in the REGULATE trial:
  - *Clinically relevant medical events* reported by the investigator as initially planned in the study protocol. No immediate notification was initially planned.
  - *Serious events (SAE).* The notion of SAE and the immediate notification of the SAE collected was introduced by Amendment Nos. 3 (France only) and 4 (all countries except France) with a different reporting whether or not the patient signed an informed consent for the FOLLOW-UP study:
    - Signed informed consent: all SAEs since the end of the REGULATE trial, and whether considered by the investigator as related or not to the REGULATE trial, and FOLLOW-UP procedure-related events.
    - No informed consent (whatever patients successfully contacted or not): only SAE related to the REGULATE trial according to the investigator.
- Biological parameters (local laboratory assessment): biochemistry (sodium, potassium, chloride, calcium, total proteins, albumin, creatinine and calculated creatinine clearance, total bilirubin, ALanine AminoTransferase (ALAT), ASpartate AminoTransferase (ASAT), Gamma-Glutamyl Transferase (GGT), alkaline phosphatase, N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) or Brain Natriuretic Peptide (BNP), if NT-proBNP was not available), haematology, and the following parameters considered as cardiac risk factors: total cholesterol, High-Density Lipoprotein (HDL) cholesterol, Low-Density Lipoprotein (LDL) cholesterol, glycated Haemoglobin (HbA1c).
- Physical examination: weight, height, sitting systolic/diastolic blood pressures, heart rate.
- Pharmacogenetic optional investigation proposed to patients from all involved countries except India. Results will be presented in a separate report.

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Criteria for evaluation (Cont'd):

Adjudication

An Adjudication Committee composed of 3 experts, 2 in cardiology: G. Durand de Gevigney M.D. and A. Serusclat M.D., cardiologists (Bron – France), and one in endocrinology: Prof. B. Bauduceau M.D., (Paris – France) adjudicated under a blinded procedure:

- Medical events reported by the investigator:
  - All the following events were adjudicated: fatal events (including death of unknown cause), hospitalisation for cardiovascular reason or for any other reason (including for diabetes management which last less than 24 hours), valvular abnormalities and pulmonary hypertension.
  - Other events were adjudicated only if they were considered relevant by the Adjudication Committee.
- Echocardiography abnormalities issued from the Echocardiography Central Reading as follows:
  - Valvular echocardiographic abnormalities: new or worsening (*i.e.* emergent) since last REGULATE echocardiography,
  - Peak TR velocity higher than 2.8 m/s.
- Other events not collected in the CRF and identified by the Adjudication Committee from the transmitted patient files (mainly hospital reports) as deemed to be relevant for adjudication.

Statistical methods

The followings Sets were defined (see Figure (2) 1): Safety Set (SS: at least one dose of study treatment received during the REGULATE trial), Safety Follow-up Set (SFUS: all patients who had taken at least one dose of REGULATE trial treatment and who allowed the investigator to collect medical information but did not participate in the REGULATE study follow-up OR who consented to participate in the FOLLOW-UP study OR with unsuccessful follow-up contact but with safety information reported in FU study), and echocardiography Sets corresponding to patients from the Safety Set, having an echocardiography (central reading) evaluable at FU study (*i.e.* ES1), at baseline in the REGULATE trial and at FU study (*i.e.* ES2), and at final REGULATE trial and at FU study (*i.e.* ES3).

Study outcome: descriptive statistics were provided

Safety analysis: mainly descriptive analyses and between group difference estimation (Odds Ratio and 95% confidence interval), for which safety data followed a central blinded review.

Valvular echocardiographic abnormalities

Emergent abnormalities were defined as new valvular echocardiographic abnormality detected or a worsening in the grade of a pre-existing abnormality, from baseline REGULATE to the FU echocardiography (ES2) or from final REGULATE to the FU echocardiography (ES3). These baseline and final REGULATE echocardiographies data used to define the emergence in ES2 and ES3 corresponded to the data obtained in the REGULATE trial (central reading).

- Description of the presence of the valvular echocardiographic abnormalities (functional or morphological, or each type of abnormality separately) according to the FOLLOW-UP echocardiography (central reading) in the ES1, and estimate of the between-group difference using an unadjusted logistic regression model (Odds Ratio and 95% confidence interval, and post-hoc p value). Same analysis was performed for valvular regurgitations abnormalities rated higher than trivial. The valvular aortic, mitral, or tricuspid regurgitations at the FU echocardiography were analysed taking into account all grades (absent, trivial, mild, moderate, severe) as an ordinal categorical variable using a proportional odds model.
- Of note, morphological abnormalities included abnormal thickness and calcifications; functional abnormalities included stenosis and regurgitations.

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Criteria for evaluation (Cont'd):

Valvular echocardiographic abnormalities (Cont'd)

- Emergence of valvular echocardiographic abnormalities (functional or morphological, or each type of abnormality separately) obtained by comparison of the echocardiography central reading results from the REGULATE trial and the FU study described according to two periods:
  - From the REGULATE trial baseline echocardiography to the FU echocardiography in the ES2.
  - From the last REGULATE trial echocardiography to the FU echocardiography in the ES3.

The proportion of patients with at least one emergent valvular echocardiographic abnormality in each treatment group was described and estimate of the between group difference was provided using an unadjusted logistic regression model (Odds Ratio, and 95% confidence interval, and post-hoc p value). These analyses were performed in the former benfluorex and pioglitazone groups. Same analyses (post-hoc) were performed taking into account the benfluorex cumulative exposure (exposed 3 months or more *versus* not exposed) during and after the REGULATE trial, of the patients of the former groups. Same analysis was performed for emergent valvular regurgitations abnormalities rated higher than trivial.

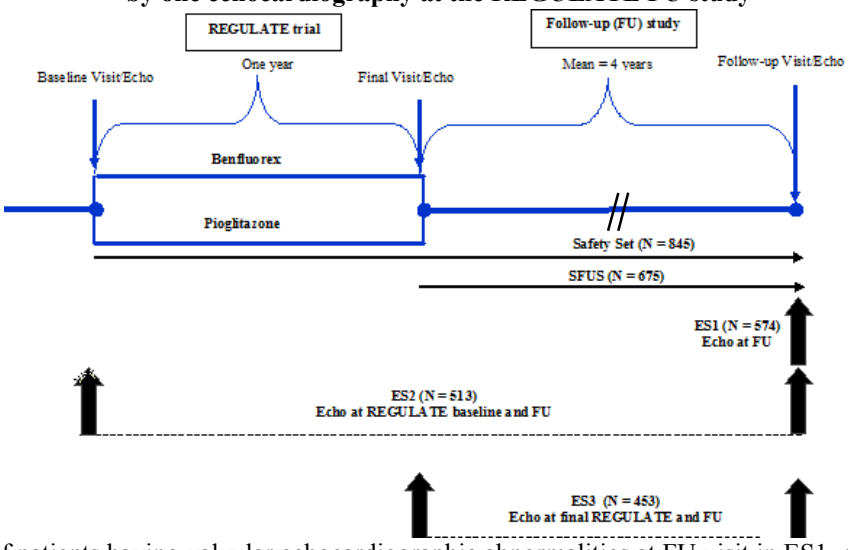
As sensitivity analysis, a multivariable analysis using a multiple logistic regression similar to the one used on the REGULATE trial analysis was performed to consider risk factors for emergent functional valvular abnormalities.

A sensitivity analysis was performed taking into account the exposure of the patients by at least one dose of benfluorex during the REGULATE trial and/or after the REGULATE trial. Same analyses as performed for the exposed or not exposed groups were conducted.

Deaths: the time to death (due to any cause) since the first REGULATE trial study drug intake was analysed for the Safety Set using an unadjusted Cox model. The hazard ratio (benfluorex *versus* pioglitazone) and the corresponding standard error and 95% CI were provided. An analysis of time to death related to each cause (cardiovascular/non cardiovascular/unclassified) was performed using competing risk method. These analyses were performed in the former groups, and according to benfluorex exposure as post-hoc analyses.

Other safety criteria: descriptive analyses were provided.

Figure (2) 1 - Sets used for the Safety Analysis of the patients randomised to either benfluorex or pioglitazone in the REGULATE trial, that could be followed after the end of the REGULATE trial by one echocardiography at the REGULATE FU study



The analyses of patients having valvular echocardiographic abnormalities at FU visit in ES1, emergent valvular echocardiographic abnormalities from the baseline REGULATE to the FU echocardiography in ES2, or from final REGULATE to the FU echocardiography in the Subset ES3 (patients having not taken benfluorex after the end of the REGULATE trial), and medical events in the SFUS are described in the Safety Results part hereafter.

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SUMMARY – CONCLUSIONS

STUDY OUTCOME

Table (2) 1 - Disposition of overall patients in the Safety Set and SFUS of the FU study

STATUS	**Safety Set (N = 845)**	**SFUS * (N = 675)**
	n (%)	n (%)
All [(1)]	**845 (100)**	**675 (100)**
Patients died during the REGULATE trial	6 ** (0.7)	
Patients alive at the end of the REGULATE trial	839	-
Patients not participating [(2)]	29 (3.4)	-
Patients expected to participate in FU study	**810**	
Successful contact	**717 (84.9)**	**636 (94.2)**
Patient consented to participate	620 (73.4)	620 (91.9)
Patient who died [(3)]	1 (0.1)	1 (0.1)
Patient refused to participate but allowed the collection of medical data	16 (1.9)	16 (2.4)
Patient refused to participate in the FU study	81 (9.6)	-
Unsuccessful contact	**93 (11.0)**	**39 (5.8)**
Patient alive [(4)]	30 (3.6)	6 (0.9)
Patient who died	33 (3.9)	33 (4.9)
Patient lost to follow-up	30 (3.6)	-

** Safety Set all patients who had taken at least one dose of REGULATE study treatment, SFUS all patients who had taken at least one dose of REGULATE trial treatment and who allowed the investigator to collect medical information but did not participate in the FU study, OR who consented to participate in the FU study, OR with unsuccessful follow-up contact but with safety information reported in FU study; N number of patients in the considered Set; n number of patients affected; % n/N*100; ** 2 patients in the former benfluorex group and 4 in the former pioglitazone group; (1) Patient No. 150 203 506 01644 randomised to benfluorex in the REGULATE trial was not in the Safety Set defined for REGULATE (as no post-baseline safety data was available) but proposed to participate in the FU study with vital status collected; (2) Due to investigator or Health Authority refusal, or impossibility for the centre to retrieve patient's information; (3) Patient No. 150 276 0214 00698 randomised to benfluorex in the REGULATE trial consented to participate and signed the informed consent for the FU study but died before the FOLLOW-UP visit due to pulmonary cancer; (4) Patients alive with unsuccessful contact (information obtained from other source information)*

Disposition of patients

Among the 845 patients having received at least one dose of one of the study drugs of the REGULATE trial (Safety Set of FU study: 422 patients in the benfluorex group and 423 patients in the pioglitazone group), 839 patients were alive at the end of the REGULATE trial (6 patients died during the REGULATE trial, 2 in the former benfluorex group and 4 in the former pioglitazone group), of which 810 were expected to participate in the FU study (29 patients from centres not participating). Most of these patients were successfully contacted: 717 patients, 84.9%, of which the majority consented to participate in the FU study: 620 patients, 73.4%. No relevant between group difference was observed regarding the disposition of patients in each former group (benfluorex or pioglitazone group) or in each group according to their cumulative exposure to benfluorex during and after the REGULATE trial (post-hoc analysis). Among the 14 patients for whom the administrative survey was performed in France, no new patient was identified as dead (2/14 were already known as dead).

The mean time from the last REGULATE visit to the FU visit was 47 months (median = 46 months), *i.e.* 3.9 years, with similar mean value in each group in the SFUS. In the SFUS, study treatments of the REGULATE trial were received for a mean (± SD) duration of 337.2 ± 92.7 days (ranging from 5 to 433 days) in the former benfluorex group, and 342.5 ± 82.0 days (ranging from 18 to 456 days) in the former pioglitazone group, with a median = 366 days in both groups.

Baseline demographic and other characteristics

In the SFUS, at selection in the REGULATE trial, patients were on average 59.0 ± 10.1 years old, most of them were aged 65 years or less (72.4% of the patients of the SFUS), and 6.1% older than 75 years. Most of the patients were male (57.2%). Patients were on average overweight, with a mean body mass index (BMI) of 29.6 ± 4.0 kg/m², ranging from 22.9 to 40.8 kg/m². Most of the patients had no smoking (86.7%) nor alcohol (80.4%) habit, and the majority had physical activity (65.5%). These baseline characteristics were similar in the two former treatment groups.

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SUMMARY – CONCLUSIONS (Cont'd)

At selection in the REGULATE trial, patients had type 2 diabetes diagnosed in average for about 6.9 ± 5.8 years, with no relevant between-group difference, in the SFUS. Other medical histories were mainly vascular disorders: 63.1%, mostly hypertension (60.0%), and metabolism and nutrition disorders: 50.8%, mostly hypercholesterolaemia (18.7%), hyperlipidaemia (12.4%), and dyslipidaemia (11.0%). No relevant between-group difference was observed, except for the following medical histories more frequently reported in the former benfluorex than in the former pioglitazone groups: myocardial ischaemia (3.6% *versus* 1.5%, respectively), coronary artery disease (2.4% *versus* 1.8%, respectively), and myocardial infarction (2.4% *versus* 1.2%, respectively). Before inclusion in the REGULATE trial, treatments having potential cardiac valve toxicity (as listed in the study protocol provided in Table (9.4.6) 1 were received by 4.9% of the patients from the SFUS (5.1% in the former benfluorex group and 4.7% in the former pioglitazone group). Before inclusion in the REGULATE trial, these treatments included mostly benfluorex (2.1% *versus* 2.4%, respectively), and analgesics, mainly ergot alkaloids (1.8% in each former treatment group). From the first study drug intake in the REGULATE trial, other treatments having potential cardiac valve toxicity were less frequently reported in the former benfluorex than in the pioglitazone groups (6.9% *versus* 10.3%, respectively). At FU visit, no relevant difference between the former groups was observed for the parameters assessed (age, physical examination, and smoking habit).

The demographic and other characteristics of patients from the Safety Set not included in the SFUS were in accordance with those described above for the SFUS.

Demographic and other baseline characteristics in these patients analysed according to their cumulative exposure to benfluorex (exposed or not) were similar to those described above (post-hoc analyses). In the ES1, ES2, and ES3, demographic and other baseline characteristics were globally similar to those described for the SFUS in former treatment groups or groups defined according to patients'cumulative exposure to benfluorex.

Baseline valvular echocardiographic abnormalities

Valvular echocardiographic abnormalities detected at the baseline REGULATE echocardiography (central reading) in patients of the FOLLOW-UP study (Safety Follow-Up Set)

Most of the patients of the SFUS (73.0%) had at least one functional abnormality on any valve, and nearly half of the patients (44.3%) had at least one morphological abnormality on any valve at the baseline REGULATE echocardiography. Results were similar in both former treatment groups.

- Morphological abnormalities affected mainly aortic (29.0% of the patients) and mitral (36.2%) valves, and were mainly thickness (27.0% and 33.3% and respectively, for aortic and mitral valves), with similar frequencies in both groups. Calcification affected aortic valve in 8.9% (10.5% *versus* 7.4%, respectively) and mitral valve in 6.8% of the patients, with similar results in both former treatment groups.
- Functional abnormalities affected mainly the mitral and tricuspid valves (53.2% and 60.6%, respectively). Functional abnormalities on aortic valve affected 14.2% of the patients (15.8% in the former benfluorex group *versus* 12.7% in the former pioglitazone group). The frequency of functional abnormalities on mitral valve was similar in both groups. For tricuspid valve, the frequency was 58.5% in the former benfluorex group *versus* 62.7% in the former pioglitazone group, respectively. Functional abnormalities for all valves were mainly trivial regurgitation (91.2%, 96.1%, 97.3%, respectively, of the patients having at least one regurgitation on aortic, mitral, or tricuspid valve). Aortic valve regurgitations were trivial in 96.0% of the patients (having at least one regurgitation on aortic valve) in the former benfluorex group *versus* 85.4% in the former pioglitazone group. Similar frequencies were observed for both groups for regurgitations on mitral and tricuspid valves. None of the regurgitation was rated severe.

Valvular echocardiographic abnormalities detected at the baseline REGULATE echocardiography in patients of the ES1, or ES2 were consistent with those described above in the SFUS. In ES2 (patients from the REGULATE Safety Set with both assessable echocardiographies at baseline REGULATE and FU), aortic regurgitations were reported at baseline in 16.9% in the former benfluorex group *versus* 12.0% in the former pioglitazone group. Of note, in patients of ES2, at baseline echocardiography, aortic regurgitations were reported in 17.3% *versus* 11.5%, in exposed *versus* not exposed group, respectively.

In ES2, functional abnormalities were detected in 83.6% of the patients, consistently with that observed in the REGULATE trial (Internal clinical report NP29244).

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

- **Valvular echocardiographic abnormalities results (Echocardiography, central reading)**

Table (2) 2 - Summary of valvular echocardiographic abnormalities in ES1, ES2

Set of analysis defined as Patients from the REGULATE SS with echo assessable at:		**ES1 (N = 574)** FU		**ES2 (N = 513)** Both REGULATE baseline and FU	
Patients having at least one valvular echocardiographic abnormality		**At FU**		**Emergent from baseline REGULATE to the FU**	
Analysis according to the randomised treatment in the REGULATE trial					
		Former B (N = 288)	Former P (N = 286)	Former B (N = 254)	Former P (N = 259)
Morphological	n (%)	155 (56.6)	144 (54.6)	100 (43.7)	97 (41.3)
	OR (SE) (1)	1.09 (0.19)		1 10 (0.21)	
	95% CI (2)/p(3)	[0.77 ; 1.53] 0.637		[0.76 ; 1.59] 0.602	
Functional	n (%)	256 (89.5)	235 (83.9)	135 (54.9)	122 (49.0)
	OR (SE) (1)	1.63 (0.41)		1 27 (0.23)	
	95% CI (2)/p(3)	[1.00 ; 2.68] 0.052		[0.89 ; 1.80] 0.191	
Valvular regurgitation	n (%)	254 (88.5)	235 (83.6)	133 (53.9)	118 (47.4)
	OR (SE) (1)	1.51 (0.37)		1 30 (0.23)	
	95% CI (2)/p(3)	[0.93 ; 2.44] 0.095		[0.91 ; 1.84] 0.151	
Aortic valve *	n (%)	77 (26.7)	55 (19.4)	48 (18.9)	38 (14.8)
	OR (SE) (1)	1.52 (0.30)		1 34 (0.32)	
	95% CI (2)/p(3)	[1.03 ; 2.25] 0.037		[0.84 ; 2.13] 0.223	
Mitral valve *	n (%)	189 (65.6)	186 (66.0)	64 (25.4)	66 (25.9)
	OR (SE) (1)	0.99 (0.17)		0.97 (0.20)	
	95% CI (2)/p(3)	[0.70 ; 1.39] 0.933		[0.65 ; 1.45] 0.900	
Tricuspid valve *	n (%)	206 (71.8)	201 (71.0)	68 (27.4)	61 (24.3)
	OR (SE) (1)	1.04 (0.19)		1.18 (0.24)	
	95% CI (2)/p(3)	[0.72 ; 1.49] 0.843		[0.79 ; 1.76] 0.427	
		ES1 (N = 574)		**ES2 (N = 513)**	
Post-hoc analysis according to patient exposure to benfluorex (< or ≥ 3 months) during and after the REGULATE trial					
		Exposed (N = 296)	Not exposed (N = 278)	Exposed (N = 260)	Not exposed (N = 253)
Morphological	n (%)	161 (57.3)	138 (53.7)	104 (44.6)	93 (40.3)
	OR (SE) (1)	1.16 (0.20)		1 20 (0.22)	
	95% CI (2)/p(3)	[0.82 ; 1.63] 0.402		[0.83 ; 1.73] 0.341	
Functional	n (%)	263 (89.5)	228 (83.8)	139 (55.4)	118 (48.4)
	OR (SE) (1)	1.64 (0.41)		1 33 (0.24)	
	95% CI (2)/p(3)	[1.00 ; 2.68] 0.050		[0.93 ; 1.89] 0.119	
Valvular regurgitation	n (%)	261 (88.5)	228 (83.5)	136 (54.0)	115 (47.1)
	OR (SE) (1)	1.52 (0.37)		1 32 (0.24)	
	95% CI (2)/p(3)	[0.94 ; 2.45] 0.090		[0.92 ; 1.87] 0.128	
Aortic valve	n (%)	82 (27.7)	50 (18.1)	54 (20.8)	32 (12.8)
	OR (SE) (1)	1.73 (0.35)		1.79 (0.43)	
	95% CI (2)/p(3)	[1.16 ; 2.58] 0.007		[1.11 ; 2.88] 0.017	
Mitral valve	n (%)	192 (65.1)	183 (66.6)	64 (24.9)	66 (26.4)
	OR (SE) (1)	0.94 (0.17)		0 92 (0.19)	
	95% CI (2)/p(3)	[0.66 ; 1.33] 0.714		[0.62 ; 1.38] 0.700	
Tricuspid valve	n (%)	213 (72.2)	194 (70.6)	69 (27.3)	60 (24.4)
	OR (SE) (1)	1.08 (0.20)		1 16 (0.24)	
	95% CI (2)/p(3))	[0.75 ; 1.56] 0.662		[0.78 ; 1.74] 0.462	

*SS: Safety Set; FU: FOLLOW-UP; Echo: echocardiography; ES1, ES2, Echocardiography Set 1, 2; B: benfluorex; P: pioglitazone; Valvular echocardiographic abnormalities assessed according to American Society of Echocardiography (Zoghbi, 2003); N: total number of patients in each considered group; n: number of patients affected; %: (n/number of patients with assessable value)*100; * Post-hoc analysis ; Emergent abnormality was defined as a new or worsening echocardiographic abnormality, to note, the occurrence of a regurgitation rated trivial was considered as emergent; (1): OR: Odds ratio (Standard Error) between the two groups based on an unadjusted logistic regression model; (2): 95% Confidence Interval of the odds ratio provided by unadjusted logistic regression model; (3): Wald test p-value*

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

To note some patients randomised either to benfluorex (n = 422) or pioglitazone (n = 423) during the REGULATE trial, have received benfluorex after the end of this trial in medical daily practice. In order to better assess the valvular condition of the patients (having an echocardiography at FU) the post-hoc analysis according to the overall cumulative exposure of the patients to benfluorex (*i.e.* during and/or after the REGULATE trial) is presented hereafter, in ES1 and ES2.

Valvular echocardiographic abnormalities at FU in ES1 *(patients from the REGULATE SS, with an assessable echocardiography at FU, N = 574)* – ***Post-hoc analysis in the exposed versus not exposed patients***

At echocardiography FU visit, whatever the baseline valvular status in the REGULATE trial, more than half of the patients had at least one morphological abnormality in ES1 (57.3% *versus* 53.7%, respectively, in the exposed *versus* not exposed patients). More than 80% of the patients had functional abnormalities in both groups (89.5% in the patients exposed *versus* 83.8% in not exposed, OR = 1.64, 95% CI = [1.00 ; 2.68], p = 0.050), mainly driven by valvular regurgitation (88.5% *versus* 83.5%, respectively, OR = 1.52, 95% CI = [0.94 ; 2.45], p = 0.090).

Regurgitations affected aortic valve in about one quarter of the patients. Regurgitations affected mostly the mitral and tricuspid valves (more than 65% of the patients) with similar frequency in both groups. Aortic regurgitations were more frequent in exposed than not exposed patients (27.7% *versus* 18.1%, respectively). A statistically significant between-group difference was evidenced: OR = 1.73, 95% CI = [1.16 ; 2.58], p = 0.007. Aortic regurgitations were mainly rated trivial (15.2% *versus* 11.6% of the patients, respectively). An analysis considering aortic regurgitation as an ordinal categorical variable was performed to take into account all levels of grade of regurgitation. This led to an OR = 1.76, 95% CI = [1.19 ; 2.62], p = 0.005. Aortic regurgitations rated mild were detected in 11.2% *versus* 5.8%, respectively, and moderate in 4 patients, 1.4% *versus* 2 patients, 0.7%, respectively. While no aortic regurgitation rated moderate was observed in the REGULATE trial, 6 were observed in the FU study (4 patients (1.4%) in the exposed *versus* 2 (0.7%) in the not exposed patients). Aortic regurgitations rated mild or moderate were observed at FU in 37 patients, 12.5% of the exposed patients *versus* 18 patients, 6.5% in the not exposed patients, OR = 2.05, 95% CI = [1.14 ; 3.69], p = 0.017.

Mitral regurgitation were mainly rated trivial (53.2% *versus* 57.1%, respectively). Mitral regurgitations rated mild were reported in 11.2% *versus* 8.7%, respectively, and moderate in 2 patients in each group. Mitral regurgitations rated mild or moderate were reported in 35 patients, 11.9% *versus* 26 patients, 9.5%, OR = 1.29, 95% CI = [0.75 ; 2.20], p = 0.4.

Tricuspid regurgitations were mainly rated trivial, with similar frequency in both groups (61.7% *versus* 62.2%, respectively). Tricuspid regurgitations rated mild were reported in 9.5% *versus* 6.6%, respectively, and moderate in 1.0% (3 patients) *versus* 1.8% (5 patients), respectively.

None of the valvular echocardiographic regurgitation was rated severe. Valvular regurgitation that affected at least 2 valves was reported with similar frequency in both groups (58.3% *versus* 59.7%, respectively).

These results were consistent with those obtained in the former groups (see Table (2) 2).

The post-hoc sensitivity analysis performed in the patients exposed to at least one dose of benfluorex (N = 315) *versus* not exposed at all (N = 259) during the REGULATE trial and/or after the REGULATE trial showed similar trends: aortic regurgitations were detected in 27.3% of the patients exposed by at least one dose of benfluorex *versus* 17.9% not exposed, OR = 1.72, 95% CI = [1.15 ; 2.58], p = 0.008, mitral regurgitations in 66.2% *versus* 65.2%, respectively, OR = 1.05, 95% CI = [0.74 ; 1.48], p = 0.8, tricuspid regurgitations in 72.9% *versus* 69.5%, respectively, OR = 1.18, 95% CI = [0.82 ; 1.70], p = 0.4.

Emergent valvular echocardiographic abnormalities (new or worsening) from baseline REGULATE to the FU echocardiography in ES2 *(patients from the REGULATE SS, having both baseline REGULATE and FU assessable echocardiographies, N = 513)* – ***Post-hoc analysis in the exposed versus not exposed patients***

Emergent morphological, functional abnormalities or regurgitations were detected in about half of the patients from baseline REGULATE to the FU echocardiography in ES2. Emergent regurgitation on aortic valve affected less than 20% of the patients, and mitral or tricuspid valve about 25% of the patients (see Table (2) 2).

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Emergent aortic regurgitations were more frequently reported in the exposed than not exposed patients (20.8% *versus* 12.8%, respectively), with a between-group difference statistically significant (OR = 1.79, 95% CI = [1.11 ; 2.88], p = 0.017). The results of the analysis performed in the former groups were consistent, but with a between-group difference numerically less pronounced (18.9% *versus* 14.8%, OR = 1.34, 95% CI = [0.84 ; 2.13], p = 0.2). For most of the patients, the grade of the aortic regurgitation was unchanged (72.7% in the exposed group *versus* 82.2% in the not exposed group), decreased by at least one grade in 3.9% *versus* 3.6%, respectively. Emergent aortic regurgitations were mainly rated trivial (7.7% *versus* 7.9%, respectively) and mild (11.5% *versus* 4.0%, respectively). Moderate aortic regurgitation was detected in 1.5% *versus* 0.8%, respectively. Emergent aortic regurgitations rated mild or moderate were reported in 34 patients, 13.1% *versus* 12 patients, 4.8%, OR = 2.98, 95% CI = [1.51 ; 5.91], p = 0.002.

Emergent mitral regurgitations were reported with similar frequency in both groups (24.9% *versus* 26.4%, respectively). The grade was unchanged for most of the patients (60.4% *versus* 58.5%, respectively), and decreased by at least one grade in 13.1% *versus* 13.8%, respectively. Emergent mitral regurgitations were mainly rated trivial (12.3% *versus* 17.8%, respectively), and mild (11.5% *versus* 7.5%, respectively). Moderate was reported in 2 patients in both groups. Mitral regurgitations rated mild or moderate were reported in 32 patients, 12.5% *versus* 21 patients, 8.4%, OR = 1.55, 95% CI = [0.87 ; 2.77], p = 0.1.

Emergent tricuspid regurgitations were reported in 27.3% in the exposed group *versus* 24.4% in the not exposed group. The grade was unchanged for about half of the patients, with a similar frequency in both groups (53.9% *versus* 54.2%, respectively), and decreased by at least one grade in 15.8% *versus* 18.6%, respectively. Emergent tricuspid regurgitations were mainly rated trivial (15.4% *versus* 17.8%, respectively). They were mild in 10.4% *versus* 5.1%, respectively, and moderate in 2 patients in each group.

None of the emergent valvular echocardiographic regurgitation was rated severe. Valvular regurgitation that affected at least 2 valves was reported with similar frequency in both groups (15.0% *versus* 15.4%, respectively).

These results were consistent with those obtained in the former groups (see Table (2) 2).

The result of the **multivariable analysis** conducted on functional valvular abnormalities in ES2 was consistent with that obtained with the unadjusted statistical analysis.

The **post-hoc sensitivity analysis** performed in the patients exposed to at least one dose of benfluorex (N = 274) *versus* not exposed at all (N = 239) during the REGULATE trial and/or after the REGULATE trial showed similar trends: aortic regurgitations were detected in 20.1% of the patients exposed to at least one dose of benfluorex *versus* 13.1% not exposed, OR = 1.66, 95% CI = [1.03 ; 2.68], p = 0.038, mitral regurgitations in 25.8% *versus* 25.4%, respectively, OR = 1.02, 95% CI = [0.68 ; 1.52], p = 0.9, tricuspid regurgitations in 28.1% *versus* 23.3%, respectively, OR = 1.29, 95% CI = [0.86 ; 1.93], p = 0.2.

Evolution of the valvular echocardiographic abnormalities in the Subset ES3 (*patients from the REGULATE SS, having both REGULATE final and FU assessable echocardiographies, and having not taken benfluorex after the end of the REGULATE trial (N = 427))* - ***Post-hoc analysis in the former groups***

A total of 427 patients (Subset ES3) out of the 453 patients (ES3) did not receive any benfluorex treatment after the end of the REGULATE trial. In order to assess the cardiac valve evolution of the patients after benfluorex discontinuation, the analysis was performed in the former randomised groups on the Subset of patients having not taken benfluorex after the end of REGULATE trial (N = 427), see Table (2) 3 hereafter. No between-group difference was observed regarding the overall evolution of the morphological abnormalities (all valves together), or regurgitation for mitral or tricuspid valves.

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Table (2) 3 - Valvular emergent echocardiographic abnormalities from REGULATE final to the FU echocardiography in patients from the ES3, for whom benfluorex (in daily medical practice) was not received after the end of REGULATE trial - Post-hoc analysis - Subset ES3 (N = 427)

At least one echocardiographic valvular abnormality		**Former benfluorex (N = 216)**	**Former pioglitazone (N = 211)**
Morphological	n (%)	75 (38.3)	76 (39.0)
	OR (SE) [(1)]	0.97 (0.20)	
	95% CI [(2)]/p[(3)]	[0.65 ; 1.46] 0.886	
Functional	n (%)	100 (47.2)	96 (46.8)
	OR (SE) [(1)]	1.01 (0.20)	
	95% CI [(2)]/p[(3)]	[0.69 ; 1.49] 0.945	
Valvular regurgitation	n (%)	96 (45.1)	93 (45.4)
	OR (SE) [(1)]	0.99 (0.19)	
	95% CI [(2)]/p[(3)]	[0.67 ; 1.45] 0.952	
Aortic valve	n (%)	32 (14.8)	30 (14.5)
	OR (SE) [(1)]	1.03 (0.28)	
	95% CI [(2)]/p[(3)]	[0.60 ; 1.76] 0.925	
Mitral valve	n (%)	47 (21.9)	51 (24.4)
	OR (SE) [(1)]	0.87 (0.20)	
	95% CI [(2)]/p[(3)]	[0.55 ; 1.36] 0.535	
Tricuspid valve	n (%)	49 (23.0)	44 (21.1)
	OR (SE) [(1)]	1.12 (0.26)	
	95% CI [(2)]/p[(3)]	[0.71 ; 1.78] 0.629	

*FU: FOLLOW-UP; Subset ES3: Echocardiography SubSet 3; B: benfluorex; P: pioglitazone; Valvular echocardiographic abnormalities assessed according to American Society of Echocardiography (Zoghbi, 2003); N: total number of patients in each considered group; n: number of patients affected; %: (n/number of patients with assessable echocardiography)*100;; Emergent abnormality was defined as a new or worsening valvular abnormality, to note, the occurrence of a regurgitation rated trivial was considered as emergent; (1): OR: Odds ratio (Standard Error) between the two groups based on an unadjusted logistic regression model; (2): 95% Confidence Interval of the odds ratio provided by unadjusted logistic regression model; (3) Wald test p value*

In patients who did not receive benfluorex after the end of the REGULATE trial, emergent morphological abnormalities were reported in about 40% of the patients, and functional abnormalities in about half of the patients (including mainly regurgitation) with similar frequency in both groups (see Table (2) 3 above).

Emergent aortic regurgitation was reported with similar frequency in both groups (14.8% in the former benfluorex group *versus* 14.5% in the former pioglitazone group). For most of the patients, the grade of the aortic regurgitation did not change from final to the FU echocardiography (75.0% *versus* 78.7%, respectively). A decrease by at least one grade was reported in 9.7% *versus* 4.7%, respectively. Considering all grades together, emergent aortic regurgitations were reported with similar frequency in both groups: 14.8% *versus* 14.5%, OR = 1.03, 95% CI = [0.60 ; 1.76], p = 0.9. Emergent aortic regurgitations were mainly rated trivial (3.7% *versus* 9.5%, respectively) and mild (10.6% *versus* 3.8%, respectively). Moderate was detected in 1 *versus* 2 patients, respectively. Aortic regurgitations rated mild or moderate on echocardiographies were reported in 2 patients at final REGULATE and in 25 patients at FU in the former benfluorex group *versus* 2 patients at final REGULATE and 12 patients at FU in the former pioglitazone group. Among these aortic regurgitations rated mild or moderate, those emergent at FU were reported in 24 patients, 11.1% in the former benfluorex group *versus* 10 patients, 4.8% in the former pioglitazone group, OR = 2.46, 95% CI = [1.15 ; 5.29], p = 0.021. The results of this FU study with controlled groups suggest a progression of the aortic regurgitation after a 4-year period, following a 1-year previous treatments, more pronounced in patients treated with benfluorex.

In patients for whom no aortic regurgitation was observed at the final REGULATE trial (149 patients in the former benfluorex group and 181 patients in the former pioglitazone group), and who did not receive benfluorex after the end of the REGULATE trial, emergent aortic regurgitation was detected at FU in 9 patients, 6.0% (trivial: 8, mild: 1) *versus* 23 patients, 12.9% (trivial: 20, mild: 3), OR = 0.44, 95% CI = [0.20 ; 0.97], p = 0.043.

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SUMMARY – CONCLUSIONS (Cont'd)

SAFETY RESULTS (Cont'd)

Emergent mitral regurgitation was reported in 21.9% *versus* 24.4%, respectively. For most of the patients, the grade of the mitral regurgitation did not change from final to the FU echocardiography (62.5% *versus* 60.7%, respectively). A decrease by at least one grade was reported in 15.3% *versus* 13.7%, respectively. Emergent mitral regurgitation were mainly rated trivial (11.1% *versus* 16.6%, respectively). In patients for whom no mitral regurgitation was observed at the final REGULATE trial emergent regurgitation was detected at FU on mitral valve in 35.2% (trivial: 24, mild: 1) *versus* 45.5% (all trivial: 35), respectively.

Emergent tricuspid regurgitation was reported in 23.0% *versus* 21.1%, respectively. For most of the patients, the grade of the tricuspid regurgitation did not change from final to the FU echocardiography (58.3% in both groups). A decrease by at least one grade was reported in 17.1% *versus* 19.9%, respectively. Emergent tricuspid regurgitation was mainly rated trivial (13.4% *versus* 15.2%, respectively). In patients for whom no tricuspid regurgitation was observed at the final REGULATE trial emergent regurgitation was detected at FU on tricuspid valve in 53.3% (trivial: 29, mild: 3) *versus* 62.3% (trivial: 32, mild: 1), respectively.

The evolution of the grade of the regurgitation in patients having at least one regurgitation rated trivial or above on aortic valve at the final REGULATE echocardiography was: unchanged at FU in 33.3% *versus* 37.0%, respectively, in the former benfluorex *versus* former pioglitazone group, decreased by at least one grade in 31.8% *versus* 37.0%, respectively, and increased by at least one grade in 34.8% *versus* 25.9%, respectively. The evolution of the grade of the regurgitation in patients having at least one regurgitation rated trivial or above on mitral, or tricuspid valves was similar in the two former groups in the Subset ES3.

The frequency of patients affected by regurgitation on at least 2 valves was similar in the two former groups (12.7% *versus* 14.1%, respectively).

- **Medical events**

Table (2) 4 - Summary of Medical events

Events including blinded Adjudication Committee conclusion		**Former benfluorex**	**Former pioglitazone**
		n (%)	n (%)
Patients in the SFUS [1]	**N**	**335**	**340**
At least one medical event	n (%)	305 (91.0)	298 (87.6)
Cardiac disorders (SOC)	n (%)	233 (69.6)	220 (64.7)
At least one serious medical event [2]	n (%)	113 (33.7)	120 (35.3)
At least one medical event leading to hospitalisation	n (%)	99 (29.6)	110 (32.4)
Patients in the Safety Set [3]	**N**	**422**	**423**
Deaths (from the first study drug intake in the REGULATE trial)	n (%)	21 (5.0)	19 (4.5)
Cardiovascular death [4]	n (%)	5 (1.2)	3 (0.7)
Non-cardiovascular death [4]	n (%)	10 (2.4)	11 (2.6)
Death of cause not classified [4]	n (%)	6 (1.4)	5 (1.2)

N number of patients in each former group and Set considered; SOC System Organ Class; (1) From the day following the last REGULATE visit to the FU visit; (2) Seriousness was assessed by the investigator, not by the Adjudication Committee; (3) Deaths until the last available information were taken into account – To note 6 patients died during the REGULATE trial (2 in the former benfluorex group and 4 in the former pioglitazone group); (4) Cause of death assessed by the Adjudication Committee

The following events (including adjudication's diagnosis) were reported from the end of the REGULATE trial to the FOLLOW-UP visit, in the SFUS:

Medical events

Most of the patients reported medical events (305 patients, 91% of the SFUS in the former benfluorex group, and 298 patients, 87.6% in the former pioglitazone group), mainly affecting the System Organ Class (SOC) Cardiac disorders: 69.6% in the benfluorex group and 64.7% in the former pioglitazone group.

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When regarding cardiac disorders reported by the investigators, excluding all preferred terms related to valvular events, cardiac disorders were reported with similar frequency in both groups (16.1% *versus* 14.1%, respectively).

Regarding the possible effect of the study drugs on pulmonary arterial pressure, two echocardiographic parameters were used to assess, Peak TR velocity (pTrV) and pulmonary acceleration time (AcT). These parameters could be measured by the central readers in a large proportion of patients: in 224 and 492 patients respectively and in a well-balanced number of patients according to their exposure. The mean pTrV was 2.3 ± 0.3 m/s in exposed and not exposed patients. One patient (not exposed one) had a pTrV higher than 3.4 m/s, the cut-off value for diagnosis of likely pulmonary hypertension (Guidelines ESC/ERS, 2009). The mean AcT was 124 ± 20 ms in exposed patients *versus* 125 ± 22 ms in not exposed ones. A post-hoc analysis of AcT per classes: > 130 ms (normal), [100-130 ms] (borderline) and < 100 ms, using published cut-off values for the evaluation of the pulmonary pressure (Sven-Olof Granstam, 2013) showed that 6% of exposed patients were in the class [< 100 ms] *versus* 9 % of not exposed ones. From these large sets of patients, no between group difference was observed regarding echocardiographic parameters used to assess pulmonary pressure. Among the 16 cases which were presented for adjudication with a possible diagnosis of pulmonary hypertension, two cases (one exposed patient and one not exposed) had a clinically relevant increase of pulmonary pressure.

Serious medical events

The seriousness criteria was assessed by the investigators (not by the Adjudication Committee). Serious medical events (including adjudication's conclusion) were reported in 33.7% in the former benfluorex group and 35.3% in the former pioglitazone groups, mainly affecting the SOC Cardiac disorders: 7.5% and 4.7%, respectively, in each group.

Medical events leading to hospitalisation (main reason for hospitalisation adjudicated)

Medical events leading to hospitalisation affected 29.6% patients *versus* 32.4%, respectively, mainly affecting the SOC Cardiac disorders: 21 patients, 6.3% *versus* 13 patients, 3.8%, respectively. No relevant difference in term of the nature and frequency of preferred terms affected was observed, except for angina unstable and myocardial infarction more frequently reported in the former benfluorex than in the former pioglitazone groups (3 patients *versus* 1 patient, respectively, for each preferred term).

Deaths (diagnosis and cause adjudicated)

A total of 40 deaths (21 patients, 5.0% in the former benfluorex group and 19 patients, 4.5% in the former pioglitazone group) were identified since the beginning of the REGULATE trial to the FU visit: 6 occurred during the REGULATE trial and 34 after the end of REGULATE trial. The cause of the death (cardiovascular, non-cardiovascular, cause not classified) was determined by the Adjudication Committee.

- **8 due to cardiovascular cause**:
  - 5 patients in the former benfluorex group: mesenteric infarction due to endocarditis (that occurred about 5 years after the last benfluorex study drug intake, that had been received for 30 days) in a patient with a pre-existing aortic valve incompetence, cor pulmonale (due to chronic obstructive pulmonary disease according to the investigator), myocardial infarction (due to medical history according to the investigator), and cardiac failure for 2 patients (due to intercurrent disease for one patient and medical history for the other according to the investigator).
  - 3 patients in the former pioglitazone group: aortic aneurysm rupture (due to intercurrent illness), sudden death (in one patient having received about one year of pioglitazone treatment during the REGULATE trial, and no benfluorex after the end of the REGULATE trial), and myocardial infarction in a patient who died during the REGULATE trial.
- **21 due to non-cardiovascular cause**: 10 patients in the former benfluorex group and 11 patients in the pioglitazone group, with no specific preferred term identified.

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SUMMARY – CONCLUSIONS (Cont'd)
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- **11 not classified as cardiovascular or not cardiovascular cause**: 6 patients in the former benfluorex group and 5 patients in the pioglitazone group.

None of the deaths was related to a cardiac valvular abnormality.

Analysis in the patients exposed to benfluorex or not exposed: medical events and deaths
The distribution of medical events by SOC and preferred term were very close to those described above in terms of frequency. Deaths occurred in 16 patients, 3.9% in the patients exposed to benfluorex and 24 patients, 5.5% in those not exposed.

- **Pharmacovigilance reporting**

In accordance with the clinical protocol amended (Amendments 3 and 4 to the protocol), for REGULATE follow-up participants, pharmacovigilance immediate and periodic reporting followed European Directive 2001/20/EC and national legal provisions for clinical trials. Adverse events of patients treated by benfluorex after REGULATE trial and who did not consent to participate to FOLLOW UP REGULATE were managed and reported according to spontaneous reporting rules (volume 9A).

- **HbA1c at FU**

Regarding HbA1c (assessed by local laboratories) in ES1, the mean value at FU was 7.94 ± 1.65% in the exposed to benfluorex group *versus* 8.05 ± 1.68% in the not exposed group. The percentage of patients having taken at least one treatment containing insulin from the last REGULATE trial visit to the FU was 26.4% in the exposed to benfluorex group *versus* 28.1% in the not exposed group, in ES1.

CONCLUSION

The FOLLOW-UP (FU) study, that took place about 4 years after the REGULATE trial, aimed to assess the clinical condition of the patients included in the REGULATE trial, randomised either to benfluorex or pioglitazone for about one year. Of the 839 patients alive after the REGULATE trial, vital status was obtained in 780 patients, 93.0%, safety information was collected in 675 patients, 80.5%, and echocardiographic data was available in 574 patients, 68.4%, and a low rate of patients was lost to follow-up (3.6%). Of note, 29 patients, 3.5% could not participate due to centre or Health Authority refusal. As some patients from the REGULATE trial could have received benfluorex after the end of REGULATE, the cumulative exposure to benfluorex during and after the REGULATE trial was taken into account in a post-hoc analysis. Patients were considered exposed to benfluorex if they received at least 3 months during and after the REGULATE trial. A sensitivity analysis was conducted taking into account the exposure of at least one dose of benfluorex from the REGULATE trial to the FU. Demographic and other baseline characteristics were in accordance with those observed in the REGULATE trial, and no relevant between-group difference was observed. At baseline echocardiography (central reading) in the REGULATE trial (before any study treatment of the Regulate trial intake), a large majority of patients (84% of the patients having both REGULATE trial baseline and FU echocardiographies interpretable) had functional valvular abnormalities, and half of patients had morphological abnormalities detected on any valve.
There was no obvious bias in the selection of the patients in the FU study.

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CONCLUSION (Cont'd)

At the echocardiography performed during the FU study (574 patients, ES1), whatever the valvular status of the patients at baseline in the REGULATE trial, no relevant between-group difference (exposed *versus* not exposed) was observed in the frequency of patients having at least one morphological abnormality, or regurgitation on mitral or tricuspid valves.
Aortic regurgitation was more frequently reported in the patients exposed to benfluorex *versus* not exposed patients: 27.7% *versus* 18.1%, respectively, with a statistically significant between-group difference (OR = 1.73, 95% CI = [1.16 ; 2.58], p = 0.007). Aortic regurgitations (according to Zoghbi classification) were mainly rated trivial (15.2% *versus* 11.6% of the patients assessable for the grade, respectively, in the exposed *versus* not exposed patients), and mild (11.2% *versus* 5.8%, respectively), and moderate regurgitation was detected in few patients (4 *versus* 2 patients, respectively). Aortic regurgitations rated mild or moderate were observed at FU in 12.5% of the exposed patients *versus* 6.5% in the not exposed patients, OR = 2.05, 95% CI = [1.14 ; 3.69], p = 0.017. No regurgitation with grade severe was reported at FU echocardiography.

Emergent valvular abnormalities (new or worsening), detected over a 5-year period, between the REGULATE baseline and the FU echocardiography (513 patients, ES2), did not show between-group difference in the frequency of patients having at least one morphological abnormality, and regurgitation on mitral or tricuspid valves. Emergent aortic regurgitations were more frequently reported in the exposed *versus* not exposed patients: 20.8% *versus* 12.8%, respectively, with a statistically significant between-group difference (OR = 1.79, 95% CI = [1.11 ; 2.88], p = 0.017). Emergent aortic regurgitations were mainly rated trivial (7.7% *versus* 7.9%, respectively in exposed *versus* not exposed group), and mild (11.5% *versus* 4.0%, respectively). Moderate regurgitation was detected in 1.5% *versus* 0.8%, respectively. Emergent aortic regurgitations rated mild or moderate were reported in 13.1% *versus* 4.8%, OR = 2.98, 95% CI = [1.51 ; 5.91], p = 0.002.

As a reminder, the results of the REGULATE trial (Internal clinical report NP29244) showed that emergent regurgitations from baseline to final echocardiography were statistically significantly higher in benfluorex *versus* pioglitazone group: 27.2% *versus* 11.2%, OR = 2.97; 95% CI = [1.91 ; 4.63], p < 0.0001, and those detected on the aortic valve were statistically significantly higher in the benfluorex than in the pioglitazone group (13.6% *versus* 1.0%, respectively, OR = 15.52, 95% CI = [4.76 ; 50.66], p < 0.0001.

From the end of the REGULATE trial to the FU echocardiography, over a 4-year period, in patients who did not receive benfluorex after the end of the REGULATE trial (427 patients, Subset ES3), no between-group difference was observed regarding the overall evolution of the morphological abnormalities (all valves together), or regurgitation for mitral or tricuspid valves.
However, aortic regurgitations rated mild or moderate on echocardiographies were reported in 2 patients at final REGULATE and in 25 patients at FU in the former benfluorex group *versus* 2 patients at final REGULATE and 12 patients at FU in the former pioglitazone group. Among these aortic regurgitations rated mild or moderate, those emergent at FU were reported in 24 patients, 11.1% in the former benfluorex group *versus* 10 patients, 4.8% in the former pioglitazone group, OR = 2.46, 95% CI = [1.15 ; 5.29], p = 0.021. A progression of the aortic regurgitations after a 4-year period, following a 1-year previous treatments, was more pronounced in patients treated with benfluorex.
However, among these Subsets of patients, those who did not receive benfluorex after the end of the REGULATE trial (N = 427), and did not have echocardiographic aortic regurgitation at the end of the REGULATE trial, had no increased risk of a valvular regurgitation (aortic, mitral, or tricuspid) (aortic regurgitation: 6.0% *versus* 12.9%, respectively, OR = 0.44, 95% CI = [0.20 ; 0.97], p = 0.043).

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CONCLUSION (Cont'd)

Regurgitations that affected at least two valves were reported with similar frequencies in both groups.

The sensitivity analysis performed in patients exposed by at least one dose of benfluorex *versus* not exposed at all showed similar trends than those observed in the exposed *versus* not exposed groups.

Among the 16 cases presented to the Adjudication Committee identified as a possible pulmonary hypertension, two cases (one exposed patient and one not exposed patient) presented with clinically relevant increase of pulmonary pressure.

No relevant between-group difference was observed in the rate of the global mortality or cardiovascular mortality, medical events, serious medical events including those leading to hospitalisation, whatever the analysis performed (randomised groups, *i.e.* former groups, or according to benfluorex exposure). None of the hospitalisation was due to a cardiac valve disease. No clinical symptom related to valvular disease was reported.

The REGULATE trial and the FOLLOW-UP study allowed to provide information about the evolution of the valvular alterations induced by benfluorex during a 5-year period (one year exposure+4 year follow-up).

Overall, in this FOLLOW-UP study with controlled groups, conducted 4 years after the end of the REGULATE trial, a difference remained in the frequency of aortic valvular regurgitations with a higher frequency in patients exposed to benfluorex.

A progression of the aortic regurgitations after a 4-year period, following a 1-year previous treatments, was more pronounced in patients treated with benfluorex.

The FOLLOW-UP study does not show any evidence of delayed valvular alteration in patients free of valvular alteration at the end of the one year exposure to benfluorex.

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