Effects of the New Dual PPARα/δ Agonist GFT505 on Lipid and Glucose Homeostasis in Abdominally Obese Patients With Combined Dyslipidemia or Impaired Glucose Metabolism

Bertrand Cariou, MD, PHD[1,2]
Yassine Zaïr, MD[1,2]
Bart Staels, PHD[3]
Eric Bruckert, MD[4]

OBJECTIVE—We evaluated the metabolic effects and tolerability of GFT505, a novel dual peroxisome proliferator–activated receptor α/δ agonist, in abdominally obese patients with either combined dyslipidemia or prediabetes.

RESEARCH DESIGN AND METHODS—The S1 study was conducted in 94 patients with combined dyslipidemia while the S2 study was conducted in 47 patients with prediabetes. Participants were randomly assigned in a double-blind manner to GFT505 at 80 mg/day or placebo for 28 (S1) or 35 (S2) days. Primary efficacy end points were changes from baseline at week 4 in both fasting plasma triglycerides and HDL cholesterol in the S1 group and 2-h glucose upon oral glucose tolerance test in the S2 group.

RESULTS—In comparison with placebo, GFT505 significantly reduced fasting plasma triglycerides (S1: least squares means −16.7% [95% one-sided CI −∞ to −5.3], $P = 0.005$; S2: −24.8% [−∞ to −10.5], $P = 0.0003$) and increased HDL cholesterol (S1: 7.8% [3.0 to ∞], $P = 0.004$; S2: 9.3% [1.7 to ∞], $P = 0.009$) in both studies, whereas LDL cholesterol only decreased in S2 (−11.0% [−∞ to −3.5], $P = 0.002$). In S2, GFT505 did not reduce 2-h glucose (−0.52 mmol/L [−∞ to 0.61], $P = 0.18$) but led to a significant decrease of homeostasis model assessment of insulin resistance (−31.4% [−∞ to 12.5], $P = 0.001$), fasting plasma glucose (−0.37 mmol/L [−∞ to −0.10], $P = 0.01$) and fructosamine (−3.6% [−∞ to −0.20], $P = 0.02$). GFT505 also reduced γ glutamyl transferase levels in both studies (S1: −19.9% [−∞ to −12.8], $P < 0.0001$; S2: −15.1% [−∞ to −1.1], $P = 0.004$). No specific adverse safety signals were reported during the studies.

CONCLUSIONS—GFT505 may be considered a new drug candidate for the treatment of lipid and glucose disorders associated with the metabolic syndrome.

Diabetes Care 34:2008–2014, 2011

Abdominal obesity is often associated with a clustering of cardiovascular risk factors including combined dyslipidemia (i.e., high plasma triglycerides and low HDL cholesterol concentrations), hypertension, and impaired glucose tolerance, a condition often referred to as the metabolic syndrome. Metabolic syndrome predisposes to type 2 diabetes and increases the risk of cardiovascular disease (1). Insulin resistance is the suspected underlying molecular mechanism sustaining these metabolic abnormalities. Thus, novel therapies improving insulin sensitivity should be considered, even though the regulatory agencies do not yet consider the metabolic syndrome an approved indication for drug therapy.

Peroxisome proliferator–activated receptors (PPARs) are fatty acid–activated nuclear receptors that regulate an array of physiological processes (2). The PPAR nuclear receptor subfamily is composed of three members: PPARα, PPARγ, and PPARδ (also known as PPARβ). Agonists of two of these receptors are currently used therapeutically, with the hypolipidemic fibrate drugs acting as PPARα agonists and the insulin-sensitizing thiazolidinediones acting as PPARγ agonists. Currently, there are no clinically used drugs that target PPARδ. PPARδ is widely expressed and plays a critical role in mitochondrial function, muscle development, fatty acid oxidation, and insulin sensitivity (3–7). Two-week clinical studies performed in healthy volunteers (8) and moderately overweight subjects (9) showed that the synthetic PPARδ agonist GW501516 reduces fasting plasma triglyceride and increases HDL cholesterol concentrations, indicating that the targeting of PPARδ may have beneficial effects in metabolic disorders.

GFT505 and its main active circulating metabolite, GFT1007, are PPAR modulators with preferential activity on PPARα (half-maximal effective concentration: 10–20 nmol/L) and additional activity on PPARδ (half-maximal effective concentration: 100–150 nmol/L). Both GFT505 and GFT1007 undergo extensive enterohepatic cycling and are liver targeted. Phase I studies in healthy volunteers showed that GFT505 at doses from 40 to 100 mg/day induces a dose-dependent reduction in plasma triglyceride and an increase in HDL cholesterol (10).

To further verify the potential metabolic benefits of GFT505, we conducted two phase IIa studies in patients with either combined dyslipidemia or prediabetes.

From the [1]Department of Endocrinology, L'institut du Thorax, Nantes University Hospital, Nantes, France; the [2]Clinical Investigations Center, Nantes University Hospital, Nantes, France; the [3]University Lille Nord de France, Inserm U1011, UDSL, Institut Pasteur de Lille, Lille, France; and the [4]Department of Endocrinology, Pitié-Salpêtrière University Hospital, Paris, France.
Corresponding author: Bertrand Cariou, bertrand.cariou@univ-nantes.fr.
Received 14 January 2011 and accepted 26 May 2011.
DOI: 10.2337/dc11-0093. Clinical trial reg. nos. NCT01271751 and NCT01275469, clinicaltrials.gov.
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc11-0093/-/DC1.

RESEARCH DESIGN AND METHODS

—Two prospective, randomized, parallel-group, double-blind, placebo-controlled studies were conducted with GFT505 (2-[2,6 dimethyl-4-[3-[4-(methylthio)phenyl]-3-oxo-1(E)-propenyl]phenoxyl]-2-methylpropanoic acid) in patients aged 18–75 years. In clinical study S1 (clinical trial reg. no. NCT01271751, clinicaltrials.gov), patients with combined dyslipidemia (1.69 ≤ triglyceride ≤ 6.78 mmol/L, HDL cholesterol ≤1.03 mmol/L for male subjects and HDL cholesterol ≤1.16 mmol/L for female subjects) and abdominal obesity (waist circumference ≥102 cm for male subjects and ≥88 cm for female subjects) were recruited from January 2009 to September 2009 at 36 centers in France, 6 in Romania, and 5 in Tunisia. Participants did not have previous cardiovascular disease and either were not hypertensive or were maintained at a stable dose of antihypertensive medication for at least 2 months prior to screening. Main exclusion criteria were BMI ≥40 kg/m^2, >5% weight change variation within 6 months prior to screening, blood pressure >160/95 mmHg, type 1 or type 2 diabetes, known familial hypercholesterolemia or type III hyperlipoproteinemia, creatinine clearance according to the Cockroft-Gault formula <60 mL/mn, and severe hepatic dysfunction (alanine aminotransferase [ALT], aspartate aminotransferase [AST], γ glutamyl transferase [gGT] >3 N, or alkaline phosphatase [ALP] >2 N). Lipid-lowering therapy was not permitted during the study. Patients were randomly assigned in a 2:1 design to once-daily 80 mg GFT505 (four capsules before breakfast) or placebo for 4 weeks. The primary end points were mean triglyceride and HDL cholesterol change from baseline for GFT505 versus placebo after 4 weeks. The study was considered positive if both primary end points were met. Secondary end points were comparisons of GFT505 versus placebo change from baseline for additional plasma lipid parameters, glucose homeostasis parameters, inflammatory markers, and safety parameters.

In clinical study S2 (clinical trial reg. no. NCT01275469, clinicaltrials.gov), subjects with prediabetes (fasting plasma glucose [FPG] between 6.1 and 7 mmol/L, 2-h glycemia upon 75-g oral glucose tolerance test [OGTT] ≥7.8 mmol/L within 7 days before randomization) and abdominal obesity (waist circumference ≥94 cm for male subjects and ≥80 cm for female subjects) were recruited from June 2009 to December 2009 at 20 centers in France. Main exclusion criteria were identical as for S1, except for lipid parameters: triglyceride >4.57 mmol/L and/or LDL cholesterol >5.68 mmol/L. Patients using oral antidiabetic drugs within the 3 months before randomization were excluded from the study. Patients were randomly assigned equally (1:1) to once-daily GFT505 80 mg or placebo for 5 weeks. The primary end point was mean 2-h plasma glucose upon OGTT change from baseline for GFT505 versus placebo after 4 weeks. Secondary end points were comparisons of GFT505 versus placebo change from baseline for FPG, fasting plasma insulin, homeostasis model assessment of insulin resistance (HOMA-IR), lipids, physical exercise test parameters, and inflammatory markers.

The studies were conducted in accordance with the ethical guidelines of the Declaration of Helsinki and were approved by institutional review boards/independent ethics committees at participating sites. Patients provided written informed consent before enrollment.

Measurements

Study visits with plasma sampling occurred at screening before the first administration, at days 0, 14, and 28 after the first administration, and 14 days after the end of the treatment period at days 42 (for S1) and 49 (for S2). In S2, a visit for exercise tests ($V_{O_{2max}}$, respiratory quotient, and heart rate and power at maximal exercise) was scheduled after 35 days of treatment. In S2, OGTTs were performed at days 0 and 28, with blood samples withdrawn at 0, 30, 60, 120, and 180 min after an oral glucose challenge (75 g). All plasma samples were centrally dosed

Table 1—*Baseline participant characteristics*

	Study 1		Study 2	
	Placebo	GFT505	Placebo	GFT505
n	31	63	24	23
Anthropometric parameters				
Age (years)	50 ± 12	49 ± 9	59 ± 11	58 ± 9
Sex (%)				
Male	71	84	63	65
Female	29	16	37	35
Weight (kg)	89 ± 14	92 ± 16	86 ± 13	82 ± 14
BMI (kg/m^2)	31.0 ± 3.7	31.2 ± 4.1	30.7 ± 3.7	29.8 ± 4.4
Waist circumference (cm)	107 ± 10	107 ± 8	104 ± 9	101 ± 9
SBP (mmHg)	133 ± 11	127 ± 12	133 ± 12	133 ± 13
DBP (mmHg)	81 ± 7	78 ± 8	81 ± 7	79 ± 7
Heart rate (bpm)	73 ± 7	71 ± 8	78 ± 12	75 ± 8
Current smoker (%)	32	30	13	17
Biochemical parameters				
Total cholesterol (mmol/L)	6.0 ± 1.6	5.7 ± 1.0	6.2 ± 1.6	6.3 ± 1.3
LDL cholesterol (mmol/L)	3.9 ± 1.5	3.5 ± 0.9	4.1 ± 1.4	4.1 ± 1.1
HDL cholesterol (mmol/L)	0.9 ± 0.1	0.9 ± 0.1	1.3 ± 0.4	1.2 ± 0.3
Triglyceride (mmol/L)	3.2 ± 1.0	3.2 ± 1.2	1.7 ± 0.7	2.2 ± 0.8
Free fatty acids (μmol/L)	425 ± 159	476 ± 224	623 ± 225	634 ± 211
FPG (mmol/L)	5.8 ± 0.7	5.7 ± 0.6	6.2 ± 0.6	6.1 ± 0.7
2-h glucose (mmol/L)	ND	ND	9.4 ± 2.6	8.6 ± 1.5
HbA_{1c} (%)	5.9 ± 0.6	5.8 ± 0.4	6.2 ± 0.4	6.1 ± 0.4
Fructosamine (μmol/L)	241 ± 19	237 ± 19	250 ± 24	250 ± 21
C-peptide (nmol/L)	ND	ND	1.0 ± 0.4	0.9 ± 0.3
Insulinemia (pmol/L)	93 ± 46	78 ± 65	78 ± 42	71 ± 34
HOMA-IR	3.4 ± 1.7	2.9 ± 2.9	3.1 ± 1.9	2.8 ± 1.5
ALT (IU/L)	33 ± 18	38 ± 22	32 ± 21	31 ± 15
AST (IU/L)	25 ± 12	24 ± 9	27 ± 14	23 ± 6
gGT (IU/L)	40 ± 21	41 ± 25	49 ± 35	33 ± 10
ALP (IU/L)	72 ± 19	72 ± 17	67 ± 16	71 ± 12
Creatinine (μmol/L)	84 ± 19	84 ± 17	80 ± 16	80 ± 11
Homocysteine (μmol/L)	14.7 ± 3.5	16.9 ± 12.3	18.5 ± 7.2	16.9 ± 3.1

Data are means ± SD unless otherwise indicated. DBP, diastolic blood pressure; ND, not determined; SBP, systolic blood pressure.

for efficacy and safety markers (Eurofins Medinet, Plaisir, France). Vital signs, physical examination, and adverse event assessment were performed at each visit. Electrocardiograms were performed at randomization and final visits.

Statistical analyses

For both S1 and S2, statistical analyses were conducted on an intent-to-treat basis, including all selected patients who had taken at least one unit of the study drug (GFT505 or placebo) with at least one baseline and postbaseline evaluation. For S1, a total sample size of 90 individuals (60 GFT505 and 30 placebo) was required to provide 80% power to detect mean 20 and 12% differences for triglyceride and HDL cholesterol, respectively, between GFT505 and placebo, assuming an SD of 35% for triglyceride and 20% for HDL cholesterol. For S2, a sample size of 26 individuals in each group was required to provide 80% power to detect a mean 20 mg/dL difference in 2-h glucose upon OGTT, assuming an SD of 25 mg/dL. To test the superiority of GFT505 over the placebo, tests were one sided. The α risk was set to 0.05. Because the S1 study was considered positive only if both primary end points were met, the α risk was not adjusted for multiplicity. Comparisons between GFT505 and placebo were computed using relative change of efficacy parameters as the explained variable, group as the explaining variable, and baseline values as the covariate. Least squares means were computed. Effect size was computed as difference between least squares means for the comparison of GFT505 versus placebo and expressed as least squares means ± SE along with 95% one-tailed CI. To overcome the nonnormal distribution of some efficacy parameters, we confirmed results of the global generalized linear model with Wilcoxon test. Analyses were performed using the SAS software (version 9.1; SAS Institute, Cary, NC).

RESULTS—In the S1 and S2 studies, 94 and 47 subjects, respectively, were randomly assigned to receive 80 mg/day GFT505 or placebo (Supplementary Fig. 1). All patients were analyzed on an intention-to-treat basis; 81 of 94 patients in S1 and all randomized patients in S2 completed the study without any major deviation. For each study, baseline demographics and biochemical characteristics were similar among the GFT505 and placebo groups (Table 1).

Lipid homeostasis

After 28-days' treatment with GFT505, several lipid parameters improved significantly from baseline. Compared with placebo (Fig. 1*A* and *B* and Tables 2 and 3), GFT505 reduced fasting plasma triglyceride levels, with a relative effect size versus placebo of −16.7% (95% one-sided CI −∞ to −5.3 [S1; $P = 0.005$]) and −24.8% (−∞ to −10.5 [S2; $P = 0.0006$]). GFT505 also increased HDL cholesterol, with a relative effect size versus placebo of 7.8% (3–∞ [S1; $P = 0.004$]) and 9.3% (1.7–∞ [S2; $P = 0.009$]). In S2 only, significant reductions in total cholesterol (effect size −8.7% [−∞ to −3.7]; $P = 0.0005$), non-HDL cholesterol (−13.3% [−∞ to −6.9]; $P = 0.0001$), and LDL cholesterol (−11% [−∞ to −3.5]; $P = 0.002$) were obtained in response to GFT505 treatment. In both studies, the increase in HDL cholesterol in the GFT505 group was paralleled by an increase in apolipoproteins AI (S1 effect size 5.6% [2.4–∞], $P = 0.002$; S2 3.3% [−1.9 to ∞], nonsignificant) and AII (S1 15.5% [12.8–∞]; S2 17.6% [10.9–∞], all $P < 0.0001$). Apolipoprotein B (apoB) was significantly reduced following GFT505 treatment in both studies (S1 −6.6% [−∞ to −1.4], $P = 0.03$; S2 −14.0% [−∞ to −8.3], $P < 0.0001$). Consistent with the hypotriglyceridemic effect of GFT505, apoCIII, an inhibitor of lipoprotein lipase activity (11), decreased

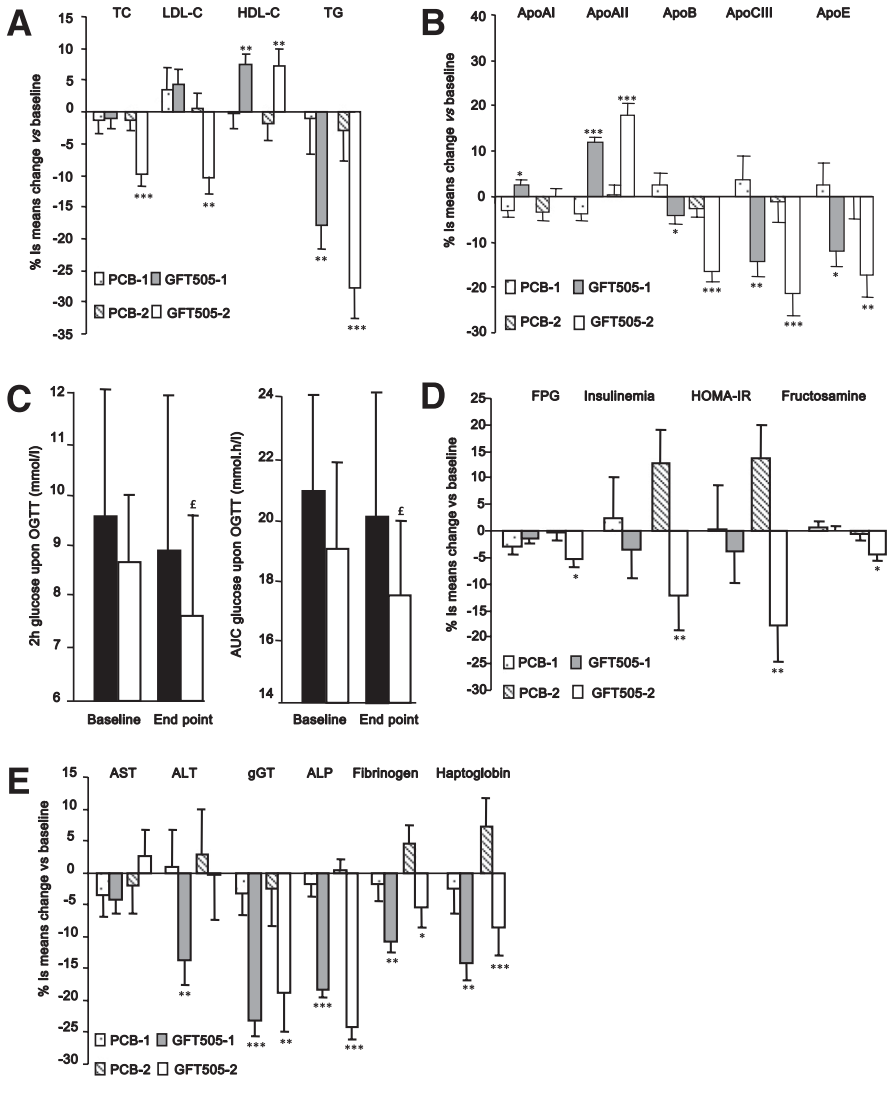

Figure 1—*Changes in metabolic parameters. Least squares (ls) means changes in lipid parameters* (A *and* B)*, glucose homeostasis parameters* (C *and* D)*, and liver function and inflammatory markers* (E) *from baseline at end point (week 4).* C: ■*, Placebo;* □*, GFT505-2. Data are least squares means ± SD.* P *value vs. placebo:* *< *0.05,* **< *0.001,* ***< *0.0001.* £P *value vs. baseline* < *0.05. AUC, area under the curve; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; PCB, placebo; TC, total cholesterol, TG, triglyceride.*

Table 2—*Changes in metabolic and safety parameters in S1*

	Placebo: change vs. baseline		80 mg/day GFT505: change vs. baseline		Effect size vs. placebo	
	Day 14	Day 28	Day 14	Day 28	Day 28	*P*
Triglyceride (mmol/L)	−0.04 ± 0.96	−0.05 ± 1.05	−0.70 ± 0.99***	−0.58 ± 1.13***	−16.7 (−∞ to −5.3)	**0.005†**
HDL cholesterol (mmol/L)	−0.02 ± 0.11	−0.01 ± 0.13	0.07 ± 0.10***	0.07 ± 0.13***	7.8 (3.0–∞)	**0.004**
Non-HDL cholesterol (mmol/L)	0.01 ± 0.49	−0.09 ± 0.59	−0.23 ± 0.68*	−0.14 ± 0.79	−1.4 (−∞ to 4.3)	NS
Total cholesterol (mmol/L)	−0.02 ± 0.51	−0.10 ± 0.59	−0.16 ± 0.68	−0.08 ± 0.75	0.06 (−∞ to 4.6)	NS
LDL cholesterol (mmol/L)	0.04 ± 0.43	0.02 ± 0.62	0.10 ± 0.66	0.12 ± 0.64	0.8 (−∞ to 7.9)	NS
VLDL cholesterol (mmol/L)	−0.04 ± 0.44	−0.11 ± 0.57	−0.33 ± 0.40***	−0.26 ± 0.46***	−10.8 (−∞ to 3.8)	NS†
Free fatty acids (μmol/L)	ND	−8.5 ± 210.5	ND	−15.2 ± 146.6	−7.6 (−∞ to 4.9)	NS†
ApoCIII (mg/dL)	ND	0.03 ± 2.51	ND	−1.49 ± 3.07***	−17.9 (−∞ to −7.5)	**0.003**
ApoAI (g/L)	ND	−0.04 ± 0.10*	ND	0.02 ± 0.11	5.6 (2.4–∞)	**0.002**
ApoAII (g/L)	ND	−0.02 ± 0.04**	ND	0.04 ± 0.04***	15.5 (12.8–∞)	**<0.0001**
ApoE (mg/dL)	ND	0.00 ± 2.29	ND	−1.27 ± 2.70***	−14.3 (−∞ to −4.1)	**0.03†**
ApoB (g/L)	ND	0.02 ± 0.12	ND	−0.05 ± 0.18*	−6.6 (−∞ to −1.4)	**0.03†**
FPG (mmol/L)	−0.05 ± 0.39	−0.18 ± 0.41*	−0.01 ± 0.44	−0.09 ± 0.50	1.5 (−1.4 to ∞)	NS
Insulin (pmol/L)	−4.9 ± 45.1	−10.5 ± 56.2	−8.6 ± 55.7	−11.2 ± 56.6	−6.0 (−∞ to 9.6)	NS†
HOMA-IR	−0.14 ± 1.92	−0.35 ± 2.37	−0.35 ± 2.65	−0.49 ± 2.72	−4.1 (−∞ to 13.1)	NS†
HbA_{1c} (%)	ND	−0.09 ± 0.23	ND	0.02 ± 0.21	1.3 (−0.1 to ∞)	NS
Fructosamine (μmol/L)	ND	0.2 ± 15.0	ND	0.1 ± 18.1	−0.4 (−∞ to 2.2)	NS
ALT (UI/L)	−1.4 ± 0.1	−0.9 ± 9.6	−6.5 ± 13.7***	−7.1 ± 13.6***	−14.7 (−∞ to −3.25)	**0.001†**
AST (UI/L)	−0.9 ± 7.8	−2.2 ± 6.4	−0.9 ± 6.9	−1.4 ± 5.3*	−0.7 (−∞ to 6.38)	NS
gGT (UI/L)	−0.4 ± 7.1	−1.1 ± 9.0	−8.7 ± 11.4***	−11.0 ± 14.0***	−19.9 (−∞ to −12.8)	**<0.0001**
ALP (UI/L)	−0.9 ± 13.7	−1.7 ± 5.8	−11.0 ± 7.2***	−13.1 ± 9.3***	−16.4 (−∞ to −12.4)	**<0.0001**
Fibrinogen (g/L)	−0.26 ± 0.55*	−0.12 ± 0.49	−0.25 ± 0.59**	−0.39 ± 0.50***	−8.8 (−∞ to −3.6)	**0.003**
Haptoglobin (g/L)	ND	−0.09 ± 0.50	ND	−0.23 ± 0.29***	−11.7 (−∞ to −3.7)	**0.002**
hsCRP (g/L)	ND	−1.9 ± 13.2	ND	−1.1 ± 5.5	−0.8 (NA)	NS
Interleukin-6 (pg/mL)	ND	−0.6 ± 5.1	ND	0.5 ± 2.4	6.3 (−∞ to 33.1)	NS†
Creatinine (μmol/L)	−2.6 ± 6.8*	−1.6 ± 6.5	2.4 ± 10.1	3.4 ± 9.2	5.0 (−1.7 to ∞)	**0.007**
Homocysteine	ND	0.55 ± 2.17	ND	1.71 ± 4.65	6.0 (−∞ to 14.4)	NS†

Data are absolute means ± SE change from baseline at end points (days 14 and 18) or percent least squares means (95% one-sided CI). Statistical analyses were conducted on an intent-to-treat basis with Student *t* test for within-group comparison between baseline and end points (*$P < 0.05$; **$P < 0.01$; ***$P > 0.001$). Effect size vs. placebo is expressed as pecent least squares means (95% one-sided CI), with *P* value from ANOVA. Boldface values indicate statistically significant data. NA, not available; ND, not determined; NS, nonsignificant. †Nonnormal distribution with effect size vs. placebo expressed as % of means, with *P* value from nonparametric Wilcoxon test.

(S1 −17.9% [−∞ to −7.5], $P = 0.003$; S2 −20.2% [−∞ to −6.7], $P = 0.0004$) following GFT505 administration. The hypolipidemic effects of GFT505 were also observed after 14 days of treatment (Tables 2 and 3). In both studies, all lipid parameters returned to baseline values 2 weeks after treatment cessation (data not shown).

Glucose homeostasis

To specifically assess the effect of GFT505 on glucose homeostasis, the S2 study was conducted in patients with prediabetes (Fig. 1*C* and *D* and Table 3). Whereas GFT505 did not significantly reduce 2-h plasma glucose levels after the OGTT (effect size 0.52 mmol/L [95% one-sided CI −∞ to 0.61], $P = 0.18$), small but significant reductions in FPG (−0.37 mmol/L [−∞ to −0.10], $P = 0.01$) and fructosamine (−9.46 μmol/L [−∞ to −0.60], $P = 0.02$) were observed in the GFT505 group. GFT505 seemed to exert an insulin-sensitizing effect, with a significant decrease in fasting insulinemia (effect size vs. placebo from baseline to end point −24.8% [−∞ to −6.5], $P = 0.005$) and HOMA-IR index (effect size −31.4% [−∞ to −12.5], $P = 0.001$). The concentration of circulating adiponectin, a PPARγ target gene (12), was not altered following GFT505 treatment. In S1, glucose homeostasis parameters were not modified by GFT505 treatment (Table 2). There were no effects of GFT505 on exercise test parameters in S2 (data not shown).

Liver function and inflammatory markers

Levels of gGT, a marker of liver dysfunction, were significantly reduced in GFT505 versus placebo patients (S1 effect size −19.9% [95% one-sided CI −∞ to −12.8], $P < 0.0001$; S2 −15.1% [−∞ to −1.1], $P = 0.004$). In addition, GFT505 significantly decreased ALT levels in S1 (−14.7% [−∞ to −3.2], $P = 0.02$), with no effect on AST concentrations. A consistent and highly significant reduction of ALP levels was observed following GFT505 treatment in both studies (S1 −16.4% [−∞ to −12.4]; S2 −24.5% [−∞ to −19.1], all $P < 0.0001$) (Tables 2 and 3 and Fig. 1*D*). GFT505 reduced both haptoglobin (S1 −11.7% [−∞ to −3.7], $P = 0.008$; S2 −15.8% [−∞ to −3.1], $P = 0.008$) and fibrinogen (S1 −8.8% [−∞ to −3.6], $P = 0.003$; S2 −10.0% [−∞ to −1.1], $P = 0.01$) levels, with no effect on high-sensitivity C-reactive protein concentrations.

Safety

GFT505 showed a good tolerance profile. For S1, 28 adverse events were reported by 23 patients: 13 of 63 in the GFT505

Table 3—*Changes in metabolic and safety parameters in S2*

	Placebo: change vs. baseline		80 mg/day GFT505: change vs. baseline		Effect size vs. placebo	
	Day 14	Day 28	Day 14	Day 28	Day 28	*P*
Triglyceride (mmol/L)	0.02 ± 0.51	−0.06 ± 0.52	−0.77 ± 0.58***	−0.71 ± 0.59***	−24.8 (−∞ to −10.5)	**0.0003†**
HDL cholesterol (mmol/L)	0.01 ± 0.16	−0.04 ± 0.15	0.12 ± 0.12***	0.08 ± 0.18*	9.3 (1.7–∞)	**0.009**
Non-HDL cholesterol (mmol/L)	−0.28 ± 0.45**	−0.07 ± 0.45	−0.84 ± 0.58***	−0.76 ± 0.61***	−13.3 (−∞ to −6.9)	**0.0001**
Total cholesterol (mmol/L)	−0.26 ± 0.45**	−0.11 ± 0.48	−0.73 ± 0.58***	−0.68 ± 0.62***	−8.7 (−∞ to −3.7)	**0.0005**
LDL cholesterol (mmol/L)	−0.14 ± 0.40	0.02 ± 0.45	−0.53 ± 0.44***	−0.46 ± 0.57***	−11.0 (−∞ to −3.5)	**0.002**
VLDL cholesterol (mmol/L)	−0.14 ± 0.42	−0.09 ± 0.37	−0.31 ± 0.32***	−0.31 ± 0.40**	−25.1 (−∞ to −3.7)	**0.04†**
Free fatty acids (μmol/L)	ND	−120 ± 275*	ND	−95 ± 319	7.3 (−∞ to 27.2)	NS†
ApoCIII (mg/dL)	ND	0.00 ± 1.41	ND	−2.11 ± 2.58***	−20.2 (−∞ to −6.7)	**0.0004†**
ApoAI (g/L)	ND	−0.05 ± 0.11*	ND	−0.01 ± 0.16	3.3 (−1.9 to ∞)	NS
ApoAII (g/L)	ND	0.00 ± 0.03	ND	0.07 ± 0.06***	17.6 (10.9–∞)	**<0.0001**
ApoE (mg/dL)	ND	0.01 ± 1.52	ND	−1.87 ± 2.63**	−17.3 (−∞ to −3.3)	**0.008**
ApoB (g/L)	ND	−0.03 ± 0.10	ND	−0.21 ± 0.14***	−14.0 (−∞ to −8.3)	**<0.0001†**
FPG (mmol/L)	−0.10 ± 0.46	−0.05 ± 0.48	−0.31 ± 0.59*	−0.33 ± 0.56*	−5.2 (−∞ to −0.6)	**0.01**
Insulin (pmol/L)	0.7 ± 25.6	5.0 ± 30.5	−7.1 ± 24.1	−10.0 ± 18.9*	−24.8 (−∞ to −6.5)	**0.005†**
HOMA-IR	0.00 ± 1.20	0.16 ± 1.42	−0.39 ± 1.07	−0.59 ± 0.90	−31.4 (−∞ to −12.5)	**0.001**
2-h glucose (mmol/L)	ND	−0.53 ± 1.98	ND	−0.93 ± 1.81*	−5.9 (−∞ to 7.1)	NS
HbA_{1c} (%)	ND	0.01 ± 0.18	ND	0.10 ± 0.19*	1.4 (0.35–∞)	NS
Fructosamine (μmol/L)	ND	−1.8 ± 15.9	ND	−11.3 ± 15.1*	−3.6 (−∞ to −0.2)	**0.02**
ALT (UI/L)	−3.3 ± 7.5*	−1.2 ± 9.8	−3.7 ± 8.0*	−2.1 ± 8.9	−3.2 (−∞ to 16.7)	NS
AST (UI/L)	−3.0 ± 7.8	−2.4 ± 8.6	−0.3 ± 4.6	0.3 ± 4.8	8.3 (−1.24 to ∞)	NS†
gGT (UI/L)	−4.9 ± 13.0	−2.7 ± 19.2	−5.5 ± 6.8***	−6.0 ± 12.0**	−15.1 (−∞ to −1.1)	**0.004†**
ALP (UI/L)	−0.2 ± 5.5	−0.0 ± 6.2	−14.0 ± 7.7***	−18.0 ± 8.5***	−24.5 (−∞ to −19.1)	**<0.0001**
Fibrinogen (g/L)	−0.17 ± 0.71	0.12 ± 0.54	−0.02 ± 0.70	−0.25 ± 0.61	−10.0 (−∞ to −1.1)	**0.01†**
Haptoglobin (g/L)	0.00 ± 0.24	0.08 ± 0.29	−0.03 ± 0.50	−0.15 ± 0.27*	−15.8 (−∞ to −3.1)	**0.008**
hsCRP (mg/L)	ND	−0.2 ± 2.9	ND	−0.0 ± 1.2	−11.5 (−∞ to 26.9)	NS†
Interleukin-6 (pg/mL)	ND	−0.7 ± 3.1	ND	−0.9 ± 2.6	−37.8 (−∞ to −11.9)	**0.05†**
Creatinine (μmol/L)	−1.2 ± 10.2	−1.1 ± 8.0	4.9 ± 8.3*	5.0 ± 9.5*	6.0 (0.87–∞)	**0.01**
Homocysteine (μmol/L)	ND	−1.8 ± 3.9	ND	−0.8 ± 3.7	0.56 (−12.5 to 14.9)	NS

Data are expressed as absolute means ± SE change from baseline at end points (days 14 and 28) and percent least squares means (97.5% one-sided CI). Statistical analyses were conducted on an intent-to-treat basis with Student *t* test for within-group comparison between baseline and end points (*$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$). Effect size vs. placebo is expressed as percent least squares means (95% one-sided CI) with *P* values from ANOVA. Boldface values indicate statistically significant data. ND, not determined; NS, nonsignificant. †Nonnormal distribution with effect size vs. placebo expressed as % of means, with *P* value from nonparametric Wilcoxon test.

group and 10 of 31 in the placebo group. Among these adverse events, two were judged as possibly related to GFT505: one case of mild gastroenteritis and one case of moderate headache. No adverse events led to the discontinuation of GFT505, and no serious adverse events related to GFT505 were reported. For S2, 20 adverse events were reported by 11 patients: 7 of 23 in the GFT505 group and 4 of 24 in the placebo group. Six of these adverse events were considered to possibly be related to GFT505: atrial fibrillation, which was diagnosed at the week 4 visit in a 75-year-old male patient with a long history of hypertension (*n* = 1), back pain (*n* = 1), diarrhea (*n* = 1), gastritis (*n* = 1), flatulence (*n* = 1), and gastrointestinal hypermotility (*n* = 1). No abnormal evolutions of laboratory values were observed from baseline to end point. All safety parameters including ionogram, hematological parameters, creatine phosphokinase, and homocysteine (Tables 2 and 3) concentrations remained steady throughout the study without difference between treatment groups. However, a slight and reversible increase of plasma creatinine was observed in the S2 GFT505 group (5 ± 9.5 μmol/L vs. baseline; $P = 0.02$, *t* test) (Tables 2 and 3).

CONCLUSIONS—These two phase IIa studies provide the first clinical evidence that the use of the dual PPARα/δ agonist GFT505 improves multiple metabolic parameters in abdominally obese patients with either combined dyslipidemia or prediabetes.

After 1 month of oral treatment at a dose of 80 mg/day, GFT505 significantly improved lipid homeostasis. In both studies, GFT505 reduced plasma triglyceride concentrations (by 16.7% in S1 and 24.8% in S2) and increased HDL cholesterol (by 7.8% in S1 and 9.3% in S2). These studies confirmed the results from a previous phase I study demonstrating that GFT505 (80 mg/day) leads to a 30% reduction of plasma triglyceride and a 12% increase of HDL cholesterol in healthy volunteers (10). From a mechanistic point of view, these effects correlated with a parallel decrease of plasma ApoCIII, an inhibitor of lipoprotein lipase activity (11), and apoB, whereas GFT505 increased plasma concentrations of apolipoproteins associated with HDL cholesterol particles, apoAI and apoAII. All of these effects are similar to those of fibrates, suggesting PPARα-mediated effects (13–15). An additional role for PPARδ activation in the lipid effects of GFT505 cannot be excluded given that a 2-week treatment of moderately obese patients with a pure PPARδ synthetic

agonist, GW501516, led to similar effects on plasma triglyceride and HDL cholesterol (9). Furthermore, GW501516 increases HDL cholesterol plasma concentrations and stimulates reverse cholesterol transport in obese monkeys (16).

GFT505 treatment also improved insulin sensitivity in patients with both impaired fasting glucose and impaired glucose tolerance, with a 30% decrease of HOMA-IR. In addition, slight but significant reductions of FPG and fructosamine were observed in the GFT505 group. In a comparable population of patients with impaired glucose tolerance, 10-week treatment with metformin or pioglitazone led to a quantitatively similar decrease in fasting glucose levels (~6 mg/dL), as observed in S2 with GFT505 (17). In addition, metformin improves insulin sensitivity without significantly improving 2-h glucose levels during OGTT (17). This insulin-sensitizing effect of GFT505 was probably linked to PPARδ activation for the following reasons: *1*) PPARα activation by fenofibrate does not improve hepatic and peripheral insulin sensitivity in glucose clamp studies (18,19); *2*) similar to GFT505, the pure PPARδ agonist GW501516 improves insulin resistance and glucose tolerance in mouse models of diabetes (4); *3*) 2-week treatment with GW501516 decreases fasting plasma insulin and HOMA-IR in moderately obese men (9); and *4*) there is not an increase in plasma adiponectin levels, a well-known marker of PPARγ activity. A phase II clinical trial is currently recruiting to confirm the hypoglycemic potential of GFT505 in drug-naïve patients with type 2 diabetes (clinical trial reg. no. NCT01261494, clinicaltrials.gov). In addition, the insulin-sensitizing action of GFT505 is being assessed using the hyperinsulinemic-euglycemic clamp method in patients with the metabolic syndrome (clinical trial reg. no. NCT01271777, clinicaltrials.gov).

The cardiovascular benefit of fibrate therapy remains intensively debated. Whereas the combination of fenofibrate with simvastatin failed to reduce major cardiovascular events in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (20), results from a large meta-analysis suggested that fibrates may reduce the risk of coronary events in individuals exhibiting high cardiovascular risk and combined dyslipidemia (21). Thus, the cardiovascular consequences of the GFT505-mediated changes in lipid and glucose metabolism should be assessed in a dedicated cardiovascular outcome study.

Significant improvement in markers of liver dysfunction was observed in GFT505-treated patients, including decreases in gGT, ALT, and ALP levels. One hypothesis is that PPARδ activation may exert a beneficial effect against the development of nonalcoholic fatty liver disease (NAFLD), as suggested by studies in mice (22). Accordingly, GW501516 has been shown to simultaneously reduce gGT and liver fat content by 20% in overweight subjects (9). In contrast, the PPARα agonist clofibrate does not exert clinical benefit in patients with NAFLD (23).

Though no serious adverse events were reported, the short-term treatment period of both studies (maximum 35 days) is a limitation in assessment of the long-term safety of GFT505. Notably, GFT505 did not increase plasma homocysteine concentrations. As previously reported with fenofibrate therapy, a reversible and moderate increase in plasma creatinine levels was observed in the GFT505 group. However, recent prespecified analyses from the Fenofibrate Intervention and Event Lowering (FIELD) study indicate that this effect is rapidly reversible and suggest that fenofibrate may delay albuminuria and glomerular filtration rate impairment in patients with type 2 diabetes (24).

In conclusion, the current results position the dual PPARα/δ agonist GFT505 as a new drug candidate to improve multiple features of the metabolic syndrome, including combined dyslipidemia, type 2 diabetes, and NAFLD. The short treatment period and the use of a single dose of GFT505 are the major limitations of the present proof-of-concept studies. The efficacy and safety of GFT505 remain to be confirmed over a longer period in a dose range–finding study.

Acknowledgments—This study was funded by Genfit, Loos, France. B.C. has acted as an investigator for Boehringer Ingelheim, Eli Lilly & Co, Genfit, Johnson & Johnson, Novo Nordisk, and Roche and has received fees for consultancy, speaking, travel, or accommodation from AstraZeneca, Eli Lilly & Co., Pierre Fabre, Genfit, GlaxoSmithKline, Novartis, Novo Nordisk, Merck, sanofi-aventis, Servier, and Takeda. Y.Z. has received fees for speaking, travel, or accommodation and has acted as an investigator for AstraZeneca, Boehringer Ingelheim, Genfit, GlaxoSmithKline, Merck, Novo Nordisk, and sanofi-aventis. B.S. has received consultancy fees from Genfit and Merck. E.B. has received fees for presentations and participation to boards and has acted as an investigator for Abbott, AstraZeneca, Genfit, Merck, Novo Nordisk, Pfizer, sanofi-aventis, and Schering-Plough. No other potential conflicts of interest relevant to this article were reported.

B.C. participated in the study as an investigator, contributed to discussion, wrote the first draft, and reviewed and edited the manuscript. Y.Z. participated in the study as an investigator and reviewed and edited the manuscript. B.S. designed the study, contributed to discussion, and reviewed and edited the manuscript. E.B. participated in the study as the principal investigator, contributed to discussion, and reviewed and edited the manuscript.

Parts of this study were presented in poster form at both the 70th Scientific Sessions of the American Diabetes Association, Orlando, Florida, 25–29 June 2010 (abstract no. 677 and late-breaking abstract no. 12), and the 46th Annual Meeting of the European Association for the Study of Diabetes, Stockholm, Sweden, 20–24 September 2010 (abstract no. 880).

The authors acknowledge Pierre Clerson (Orgamétrie) for his advice on statistical analysis and Lesley Millat (Genfit) for her careful rereading of the manuscript. The authors also thank Rémy Hanf (Genfit) for his support in conducting the trials. The authors thank the investigators and contributors from each of the study sites.

References

1. Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001;24:683–689
2. Staels B, Fruchart JC. Therapeutic roles of peroxisome proliferator-activated receptor agonists. Diabetes 2005;54:2460–2470
3. Reilly SM, Lee CH. PPAR delta as a therapeutic target in metabolic disease. FEBS Lett 2008;582:26–31
4. Tanaka T, Yamamoto J, Iwasaki S, et al. Activation of peroxisome proliferator-activated receptor delta induces fatty acid beta-oxidation in skeletal muscle and attenuates metabolic syndrome. Proc Natl Acad Sci USA 2003;100:15924–15929
5. Wang YX, Lee CH, Tiep S, et al. Peroxisome-proliferator-activated receptor delta activates fat metabolism to prevent obesity. Cell 2003;113:159–170
6. Luquet S, Lopez-Soriano J, Holst D, et al. Peroxisome proliferator-activated receptor delta controls muscle development and oxidative capability. FASEB J 2003;17:2299–2301
7. Lee CH, Olson P, Hevener A, et al. PPARdelta regulates glucose metabolism and insulin sensitivity. Proc Natl Acad Sci USA 2006;103:3444–3449

8. Sprecher DL, Massien C, Pearce G, et al. Triglyceride:high-density lipoprotein cholesterol effects in healthy subjects administered a peroxisome proliferator activated receptor δ agonist. Arterioscler Thromb Vasc Biol 2007;27:359–365
9. Risérus U, Sprecher D, Johnson T, et al. Activation of peroxisome proliferator-activated receptor (PPAR)δ promotes reversal of multiple metabolic abnormalities, reduces oxidative stress, and increases fatty acid oxidation in moderately obese men. Diabetes 2008;57:332–339
10. Hanf R, Darteil R, Hum DW, Staels B. GFT505 efficacy and safety in healthy volunteers and patients suffering from atherogenic dyslipidemia. Diabetes 2010; 59(Suppl. 1):A185
11. Caron S, Staels B. Apolipoprotein CIII: a link between hypertriglyceridemia and vascular dysfunction? Circ Res 2008;103: 1348–1350
12. Maeda N, Takahashi M, Funahashi T, et al. PPARgamma ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. Diabetes 2001;50:2094–2099
13. Staels B, Vu-Dac N, Kosykh VA, et al. Fibrates downregulate apolipoprotein C-III expression independent of induction of peroxisomal acyl coenzyme A oxidase. A potential mechanism for the hypolipidemic action of fibrates. J Clin Invest 1995;95: 705–712
14. Hennuyer N, Poulain P, Madsen L, et al. Beneficial effects of fibrates on apolipoprotein A-I metabolism occur independently of any peroxisome proliferative response. Circulation 1999;99:2445–2451
15. Vu-Dac N, Schoonjans K, Kosykh V, et al. Fibrates increase human apolipoprotein A-II expression through activation of the peroxisome proliferator-activated receptor. J Clin Invest 1995;96:741–750
16. Oliver WR Jr, Shenk JL, Snaith MR, et al. A selective peroxisome proliferator-activated receptor δ agonist promotes reverse cholesterol transport. Proc Natl Acad Sci USA 2001;98:5306–5311
17. Rasouli N, Kern PA, Reece EA, Elbein SC. Effects of pioglitazone and metformin on β-cell function in nondiabetic subjects at high risk for type 2 diabetes. Am J Physiol Endocrinol Metab 2007;292: E359–E365
18. Belfort R, Berria R, Cornell J, Cusi K. Fenofibrate reduces systemic inflammation markers independent of its effects on lipid and glucose metabolism in patients with the metabolic syndrome. J Clin Endocrinol Metab 2010;95:829–836
19. Fabbrini E, Mohammed BS, Korenblat KM, et al. Effect of fenofibrate and niacin on intrahepatic triglyceride content, very low-density lipoprotein kinetics, and insulin action in obese subjects with nonalcoholic fatty liver disease. J Clin Endocrinol Metab 2010;95:2727–2735
20. Ginsberg HN, Elam MB, Lovato LC, et al.; ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010;362:1563–1574
21. Jun M, Foote C, Lv J, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. Lancet 2010;375:1875–1884
22. Nagasawa T, Inada Y, Nakano S, et al. Effects of bezafibrate, PPAR pan-agonist, and GW501516, PPARdelta agonist, on development of steatohepatitis in mice fed a methionine- and choline-deficient diet. Eur J Pharmacol 2006;536:182–191
23. Laurin J, Lindor KD, Crippin JS, et al. Ursodeoxycholic acid or clofibrate in the treatment of non-alcohol-induced steatohepatitis: a pilot study. Hepatology 1996; 23:1464–1467
24. Davis TM, Ting R, Best JD, et al.; Fenofibrate Intervention and Event Lowering in Diabetes Study investigators. Effects of fenofibrate on renal function in patients with type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study. Diabetologia 2011; 54:280–290