2. SYNOPSIS

Name of Sponsor/Company: Laboratoires GENFIT.	**Individual Study Table**	**(For National Authority Use only)**
Name of Finished Product: GFT505		
Name of Active Ingredient: 2-[2,6-dimethyl-4-[3-[4-(methylthio)phenyl]-3-oxo-1(E)-propenyl]phenoxy]-2-methylpropionic acid		

Title of Study:

A PILOT STUDY TO EVALUATE THE EFFICACY OF GFT505 (80 MG) ORALLY ADMINISTERED ONCE DAILY FOR 8 WEEKS ON INSULIN SENSITIVITY USING A GLUCOSE CLAMP TECHNIQUE AND SAFETY IN MALE PATIENTS WITH INSULIN RESISTANCE AND ABDOMINAL OBESITY.

A MULTICENTRE, RANDOMISED, SINGLE BLIND, PLACEBO-CONTROLLED, CROSS OVER STUDY.

Study Center/Investigator:

2 investigational centres were planned in France (Nantes & Lyon).

Both sites were active and enrolled at least one patient.

Publication (Reference):

NA.

Study Period:	**Phase of Development:**
18/01/2011 (First Patient First Visit) - 21/11/2011 (Last Patient Last Visit).	Phase IIa - Pilot study

Objectives:

⌦ **Primary objective:**

To evaluate in each patient the differences in Glucose Infusion Rate (GIR) measured at the end of 8 weeks treatment periods with GFT505 (80 mg/d per os) or placebo according to a cross-over design.

⌦ **Secondary objectives:**

To evaluate in each patient the differences in Hepatic Glucose Production (HGP) measured at the end of 8 weeks treatment periods with GFT505 (80 mg/d per os) or placebo according to a cross-over design.

To compare the changes from baseline to endpoint in GIR and HGP.

To compare the changes from baseline, achieved after 8-week treatment with GFT505 80 mg/d vs placebo in

- Glucose homeostasis (fasting glycaemia, HbA1c, insulinemia, C-peptide and HOMA-IR index, fructosamine levels),
- Lipid metabolism,
- Inflammatory markers and other parameters,
- Liver function (non-alcoholic fatty liver diseases markers).

To compare the changes from baseline in parameters associated with the glucose clamp procedures (GIR, HGP, ...) achieved at the end of the first 8-week treatment period in the two groups.

To compare gene expression (insulin signaling, lipid and glucose metabolism) in muscular tissue biopsy collected at the end of the first treatment period in the two groups.

To assess the safety of once-a-day administrations of oral doses of GFT505 80mg during 8 weeks.

Methodology:

This was a multicenter, randomised, single blind, placebo-controlled, cross over study. The randomisation was stratified by site.

The planned duration of the study was 26 weeks (+/- authorized margins) per patient:

- Selection visit prior to treatment period *(D-14 to D-1)*
- Randomisation visit *(D0)*
- Period T1: first period of treatment with GFT505 80mg or placebo for 8 weeks *(D1 to D56)*
- Wash-out period for 6 weeks *(D57 to D98)*

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- Period T2: second period of treatment with GFT505 80mg or placebo for 8 weeks *(D99 to D154)*
- Follow-up period for 2 weeks *(D155 to D169)*

Number of Patients (Planned, Entered, Randomized and Analysed):

Planned: 20 patients

Selected: 49 patients

Randomized: 22 patients

Treated: 22 patients (in this cross-over study, all of the 22 patients received GFT505 and placebo during one period treatment)

Safety analysis: 22 patients (in this cross-over study, all of the 22 patients received GFT505 and placebo during one period treatment)

Efficacy analysis: 22 patients (in this cross-over study, all of the 22 patients received GFT505 and placebo during one period treatment)

Diagnosis and Main Criteria for Inclusion:

Male patients, 18 to 75 years old, with waist circumference ≥ 94 cm, body mass index (BMI) ≤ 45 kg/m² and HOMA-IR > 3. Patients must present with diet and physical exercise stable within 3 months prior to screening ; they must be normotensive or must be taking antihypertensive medication at a stable dosage for at least 2 months prior to screening.

Test Product, Dose and Mode of Administration:

- Investigational medicinal product: **GFT505 80 mg**, 4 capsules of 20 mg each once daily before breakfast.
- Matching placebo: 4 capsules once daily before breakfast (capsules were identical to capsules of investigational product to keep double-blind conditions).

Duration of Treatment:

In this cross-over study, patients who satisfied all entry criteria were randomised into 2 parallel treatment sequences:

- Group 1: placebo first and then GFT505 80mg/d,
- Group 2: GFT505 80mg/d first and then placebo.

The total treatment duration was 16 weeks per patient divided into 2 treatment periods of 8 weeks each separated by a wash-out period of 6 weeks (total study duration for one patient: 26 weeks).

Criteria for Evaluation:

Primary endpoint:

To evaluate in each patient the differences in GIR measured at the end of 8-week treatment periods with GFT505 (80mg/d per os) or placebo according to a cross-over design.

Secondary endpoints:

- To evaluate in each patient the differences in HGP measured at the end of 8-week treatment periods with GFT505 (80mg/d per os) or placebo according to a cross-over design.
- To compare the changes from baseline to endpoint in GIR and HGP. The baseline was defined as the values of glucose clamp at V2. The same baseline was used for both periods. End-points were defined as glucose clamp values at V4 for the first period and as glucose clamp values at V7 for the second period.

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- To evaluate in each patient the differences in other parameters measured during the glucose clamp procedures performed at the end of 8-week treatment periods with GFT505 (80 mg/d per os) or placebo according to a cross-over design
  - O_2 consumption and CO_2 production (indirect calorimetry)
  - Percentage of lean mass and fat mass (impedancemetry)
  - Free fatty acid and triglycerides response following insulin infusion during clamps.
- To compare in each patient the changes from baseline, achieved after 8-week treatment with GFT505 80mg/d versus placebo in
  - Fasting glycaemia, HbA1c, insulinemia, C-peptide and HOMA-IR index, fructosamine levels,
  - Fasting TG, total cholesterol, HDL-C, LDL-C and non-HDL-C levels,
  - Inflammatory markers (fibrinogen, haptoglobin)
  - Liver functions: ALT, AST, GGT
- To compare the changes from baseline in parameters associated with the glucose clamp procedures (GIR, HGP, …) achieved at the end of the first 8-week treatment period in the two groups
  - GIR, HPG, FFA and TG response during clamps.
- To compare gene expression (insulin signalling, lipid and glucose metabolism) in muscular tissue biopsy collected at the end of the first treatment period in the two groups.
- To evaluate the safety of once-a-day administrations of oral doses of GFT505 80mg during 8 weeks, SAE, AE, physical examination, vital signs, medical history, ECG, haematology, biochemical markers.

Statistical Methods:

The statistical analysis was realized using the 9.2. SAS software (SAS Institute, Cary, NC, USA).

Definitions:

Baseline: For the GIR and HGP, baseline values were measured during glucose clamp at visit 2 before any drug intake. For other criteria, baseline values were defined as values measured at visit 2 for the first period and as values measured at visit 5 for the second period.

Endpoint: value measured at V4 for the first period and at V7 for the second period.

Descriptive statistics:

Continuous variables were described in each group by the number of documented patients, mean, standard deviation, range, median and amount of missing data.

Qualitative variables were described in each group by the frequency and percentage of each modality as well as amount of missing data.

Efficacy analysis:

The efficacy analysis was conducted on an intent-to-treat (ITT) basis.Tests were two-sided and the Type 1 error risk was set at 0.05.

For primary efficacy analysis, A mixed model was buit with treatment, period, centre, sequence and interaction treatment*centre as fixed factors and patient within sequence as random factor (carry over effect). Since the same baseline was used for both periods concerning GIR (primary endpoint) and HGP, no baseline term was added in the model. Treatment effect was adjusted on period and carry over effects. Lsmeans were derived from the model and the treatment effect was computed as the differences between Lsmeans

The same model was used for the main criterion and the secondary criteria. Slight changes were introduced for secondary criteria not measured during the glucose clamp: the baseline was added in the mixed model as fixed effect. Lsmeans were derived from the model and the treatment effect was computed as the differences between Lsmeans.

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Safety analysis:

The safety analysis was conducted in the safety population for the treatment period and in all screened patients for the screening period.

AEs were tabulated by system organ class and preferred term (according to the WHO Drug dictionnary). The descriptive analysis of AEs was broken down by 3 periods: the screening period, the efficacy treatment period and the follow-up period.

Evolutions from baseline to the end of each treatment period of haematology and biochemistry parameters and urinary analysis were analysed using a mixed model with period, treatment, centre and baseline as fixed factors and patient within sequence as random factor. The effect size was computed to test the difference between treatment periods.

Evolution during the follow-up period was described.

Summary - Conclusions:

In this cross-over study comparing glucose-clamp related values at the end of the two treatment periods, GFT505 was found to have significant effects on insulin sensitivity of the muscles and other peripheral tissues with a significant effect on the GIR (3.7±0.3 mg/kg/min after GFT505 vs 3.2±0.3 mg/kg/min after placebo, p=0.048).

Similarly, GFT505 was found to significantly increase the response of the liver to insulin action. Indeed, the relative decrease in HGP induced by the first level of insulin was -49±4% after GFT505 vs -34±4% after placebo (p=0.002).

Moreover, according to this analysis, GFT505 significantly lowers the free fatty acid (FFA) levels measured at the first insulin level (FFA 0.21mmol/L after GFT505 vs 0.27mmol/L after placebo, p=0.006).

	Placebo lsmeans±SE	**GFT505** lsmeans±SE	Effect size [IC 95%]	p
Glucose clamp test - Measurements at the end of 8 weeks of treatment periods				
GIR 1st level (mg/kg.min^{-1})	**0.24±0.08**	**0.52±0.08**	**0.29±0.08 [0.12 ; 0.45]**	**0.002**
GIR 2nd level (mg/kg.min^{-1})	**3.21±0.31**	**3.69±0.31**	**0.48±0.23 [0.01 ; 0.96]**	**0.048**
HGP 1st level (mg/kg.min^{-1})	**1.24±0.09**	**0.95±0.09**	**-0.29±0.09 [-0.49 ; -0.09]**	**0.006**
Absolute delta HGP 1st level-basal (mg/kg.min^{-1})	**-0.63±0.07**	**-0.86±0.07**	**-0.22±0.07 [-0.37 ; -0.07]**	**0.006**
Relative delta HGP 1st level-basal (%)	**-34.26±3.71**	**-49.23±3.71**	**-14.96±4.08 [-23.50 ; -6.42]**	**0.002**
Tissue glucose utilization 1st level (mg/kg.min^{-1})	1.48±0.05	1.48±0.05	0.00±0.07 [-0.14 ; 0.14]	0.95
FFA basal level (mmol/L)	**0.46±0.02**	**0.40±0.02**	**-0.06±0.02 [-0.11 ; -0.01]**	**0.02**
FFA 1st level (mmol/L)	**0.27±0.02**	**0.21±0.02**	**-0.06±0.02 [-0.10 ; -0.02]**	**0.006**
TG basal level (mmol/L)	**1.56±0.11**	**1.33±0.11**	**-0.23±0.08 [-0.40 ; -0.06]**	**0.01**
TG 1st level (mmol/L)	**1.48±0.11**	**1.24±0.11**	**-0.24±0.10 [-0.45 ; -0.04]**	**0.02**
TG 2nd level (mmol/L)	**1.41±0.11**	**1.12±0.11**	**-0.29±0.10 [-0.49 ; -0.08]**	**0.009**
O_2 consumption basal level (mL/min)	2.67±0.07	2.65±0.07	-0.02±0.04 [-0.10 ; 0.06]	0.56
O_2 consumption 1st level (mL/min)	2.62±0.07	2.66±0.07	0.04±0.04 [-0.06 ; 0.14]	0.41
O_2 consumption 2nd level (mL/min)	2.63±0.08	2.64±0.08	0.01±0.04 [-0.08 ; 0.09]	0.83
CO_2 production basal level (mL/min)	2.22±0.07	2.22±0.07	-0.01±0.05 [-0.11 ; 0.10]	0.90
CO_2 production 1st level (mL/min)	2.18±0.06	2.23±0.06	0.05±0.04 [-0.04 ; 0.14]	0.24
CO_2 production 2nd level (mL/min)	2.31±0.08	2.36±0.08	0.05±0.05 [-0.06 ; 0.17]	0.33
Body fat mass (% of total mass)	**26.89±1.33**	**29.81±1.33**	**2.92±1.32 [0.17 : 5.68]**	**0.04**

The primary analysis comparing values at the end of the two treatment periods is confirmed by a

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second analysis comparing evolutions vs baseline during each periods.

When compared to baseline value, GIR 1st level increased of 0.12±0.33 mg/kg/m^{-1} from baseline to the end of the period under GFT505 (p=0.09), that is a significant difference against evolution during placebo period (p=0.002). In the meantime, HGP 1st level significantly decreased under GFT505 (p=0.007), a significant difference against placebo period (p=0.006), signing a decrease in hepatic neoglucogenesis. Blood FFA significantly decreased from baseline to the end of the period under GFT505 both at basal level (p=0.02) and at 1st level (p=0.006). The decrease in TG measured during hyperinsulinemic-euglycemic clamp unless failing to reach within-group significance (p=0.11 and p=0.08 respectively for basal level and 1st level) significantly decreased against placebo (p=0.01 and p=0.02 respectively). There was no variation of the body fat mass under GFT505.

	Placebo m±SD p within group	**GFT505** m±SD p within group	Effect size [IC 95%]	p
Glucose clamp test - Absolute change from baseline to endpoint				
GIR 1st level (mg/kg.min^{-1})	**-0.17±0.33 0.02**	**0.12±0.33 0.09**	**0.29±0.08 [0.12 ; 0.45]**	**0.002**
GIR 2nd level (mg/kg.min^{-1})	-1.15±1.41 0.02	-0.54±1.58 0.24	0.65±0.41 [-0.27 ; 1.56]	0.15
HGP 1st level (mg/kg.min^{-1})	**0.10±0.40 0.44**	**-0.19±0.35 0.007**	**-0.29±0.09 [-0.49 ; -0.09]**	**0.006**
Absolute delta HGP 1st level-basal (mg/kg.min^{-1})	**0.33±0.44 0.002**	**0.10±0.41 0.35**	**-0.22±0.07 [-0.37 ; -0.07]**	**0.006**
Tissue glucose utilization 1st level (mg/kg.min^{-1})	-0.07±0.29 0.15	-0.08±0.28 0.10	0.00±0.07 [-0.14 ; 0.14]	0.95
FFA basal level (mmol/L)	**-0.07±0.14 0.045**	**-0.13±0.14 0.0008**	**-0.06±0.02 [-0.11 ; -0.01]**	**0.02**
FFA 1st level (mmol/L)	**0.00±0.12 0.81**	**-0.07±0.09 0.0005**	**-0.06±0.02 [-0.10 ; -0.02]**	**0.006**
TG basal level (mmol/L)	**-0.01±0.60 0.44**	**-0.24±0.71 0.11**	**-0.23±0.08 [-0.40 ; -0.06]**	**0.01**
TG 1st level (mmol/L)	**-0.03±0.65 0.60**	**-0.27±0.77 0.08**	**-0.24±0.10 [-0.45 ; -0.04]**	**0.02**
TG 2nd level (mmol/L)	0.14±0.39 0.27	-0.15±0.54 0.27	-0.24±0.17 [-0.63 ; 0.14]	0.19
O_2 consumption basal level (mL/min)	0.02±0.18 0.72	0.00±0.10 1.00	-0.02±0.04 [-0.10 ; 0.06]	0.56
O_2 consumption 1st level (mL/min)	0.05±0.18 0.48	0.09±0.17 0.16	0.04±0.04 [-0.06 ; 0.14]	0.41
O_2 consumption 2nd level (mL/min)	-0.03±0.22 0.81	-0.02±0.17 0.92	0.01±0.04 [-0.08 ; 0.09]	0.83
CO_2 production basal level (mL/min)	0.08±0.19 0.20	0.07±0.15 0.18	-0.01±0.05 [-0.11 ; 0.10]	0.90
CO_2 production 1st level (mL/min)	0.06±0.17 0.29	0.11±0.16 0.05	0.05±0.04 [-0.04 ; 0.14]	0.24
CO_2 production 2nd level (mL/min)	0.00±0.24 0.95	0.04±0.13 0.33	0.05±0.05 [-0.06 ; 0.17]	0.33
Body fat mass (% of total mass)	**-2.93±7.09 0.055**	**0.00±7.35 0.39**	**2.92±1.32 [0.17 ; 5.68]**	**0.04**

GFT505 treatment showed a favorable trend to reduce fasting glycemia and fasting insulin and consequently improved HOMA-IR but none of these effects reached statistical significance. The same evolution is noted for the other glycemic parameters. A slight not clinically relevant increase in HbA1C was depicted..

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	Placebo m±SD p within group	**GFT505** m±SD p within group	Effect size [IC 95%]	p
Glycemic parameters - Absolute change from baseline to endpoint				
HOMA-IR	0.12±2.25 0.57	-0.31±2.38 0.76	-0.43±0.50 [-1.48 ; 0.61]	0.39
Fasting glycemia (mmol/L)	-0.01±0.51 0.50	-0.21±0.70 0.31	-0.23±0.13 [-0.51 ; 0.05]	0.11
Insulinemia (mUI/L)	0.32±8.22 0.72	-0.60±7.21 0.96	-0.87±1.6 [-4.40 ; 2.67]	0.61
C-peptide (nmol/L)	0.05±0.17 0.26	0.03±0.19 0.55	-0.03±0.04 [-0.10 ; 0.05]	0.48
Fructosamine (µmol/L)	1.27±17.60 0.73	-4.14±12.62 0.14	-4.88±2.70 [-10.55 ; 0.79]	0.09
Leptin (pg/mL)	723±3261 0.38	-324±2428 0.86	-1084±858 [-2885 ; 718]	0.22
HbA1c (%)	**-0.03±0.22 0.78**	**0.12±0.22 0.02**	**0.14±0.06 [0.01 ; 0.26]**	**0.03**

The evolution of lipid parameters from baseline to the end of period was favourable under GFT505 with significant differences against placebo for TG, total cholesterol, LDL-Cholesterol, non-HDL-Cholesterol, apoB and Apo A2. HDL-Cholesterol, VLDL Cholesterol and Apo A1 did not vary.

	Placebo m±SD p within group	**GFT505** m±SD p within group	Effect size [IC 95%]	p
Lipid parameters - Absolute change from baseline to endpoint				
TG (mmol/L)	**0.06±0.69 0.32**	**-0.24±0.48 0.06**	**-0.27±0.09 [-0.45 ; -0.08]**	**0.007**
Total cholesterol (mmol/L)	**0.01±0.53 0.94**	**-0.52±0.65 0.0003**	**-0.50±0.15 [-0.82 ; -0.18]**	**0.004**
LDL cholesterol (mmol/L)	**-0.05±0.37 0.56**	**-0.53±0.49 <0.0001**	**-0.45±0.12 [-0.69 ; -0.21]**	**0.001**
Non HDL cholesterol (mmol/L)	**0.02±0.46 0.77**	**-0.56±0.61 <0.0001**	**-0.53±0.15 [-0.83 ; -0.22]**	**0.002**
HDL cholesterol (mmol/L)	0.00±0.15 0.64	0.03±0.14 0.37	0.03±0.04 [-0.05 ; 0.12]	0.40
VLDL cholesterol (mmol/L)	0.07±0.25 0.27	-0.02±0.22 0.89	-0.07±0.05 [-0.17 ; 0.04]	0.21
Apo A1 (g/L)	0.01±0.16 0.98	0.00±0.15 0.97	-0.01±0.04 [-0.09 ; 0.08]	0.82
Apo B (g/L)	**-0.01±0.11 0.39**	**-0.15±0.11 <0.0001**	**-0.13±0.03 [-0.18 ; -0.07]**	**0.0002**
Apo A2 (mg/dL)	**-0.97±3.34 0.13**	**2.04±3.67 0.002**	**3.00±0.95 [1.00 ; 5.00]**	**0.006**

Pro-inflammatory states are one the mechanisms leading to the progressive deterioration of beta cell function and decrease in the functional beta cell mass. Inflammatory markers significantly decreased from baseline to endpoint of the period under GFT505, thus leading to a significant difference against placebo (p=0.045 for fibrinogen; p=0.01 for haptoglobin).

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	Placebo m±SD p within group	**GFT505** m±SD p within group	Effect size [IC 95%]	p
Inflammatory markers - Absolute change from baseline to endpoint				
Fibrinogen (g/L)	**0.09±0.80 0.68**	**-0.29±0.25 <0.0001**	**-0.39±0.18 [-0.76 ; -0.01]**	**0.045**
Haptoglobin (g/L)	**-0.10±0.22 0.08**	**-0.23±0.15 <0.0001**	**-0.13±0.05 [-0.23 ; -0.03]**	**0.01**
hsCRP (mg/L)	0.54±6.23 0.58	-0.11±1.12 0.28	-0.82±1.23 [-3.40 ; 1.76]	0.51

ALT significantly decreased during GFT505 period. Effect size versus placebo period was -7.17±2.28 U/L for absolute change (p=0.006) and -20.47±6.14 % for relative change (p=0.004). Similarly, GGT decreased with effect size of -9.90±7.09 U/L (p=0.18) for absolute change and -30.45±8.94 % (p=0.003) for relative change. Finally, Alkaline phosphatase significantly decreased with an effect size -11.57±1.73 U/L for absolute change (p<0.0001) and -19.28±2.90 % for relative change (p<0.0001).

Finally, quantitative RT-PCR gene expression analysis of selected genes (PPAR target genes and genes implicated in lipid and glucose metabolism) on skeletal muscle biopsy samples revealed no significant differences in expression between patients treated for 8 weeks with either placebo or GFT505 80 mg/day. Expression levels were highly variable, especially for the PPARδ target gene PDK4 and for the key lipogenic transcription factor SREBP-1c.

In patients with insulin resistance, the impaired insulin response is at least partly due to accumulation of TG into skeletal muscles and in the liver resulting in FFA increase and reduction of mitochondrial faty acid beta-oxydation. Increase in HGP is associated with impaired glucose tolerance and type 2 diabetes. GFT505 is a dual PPARα and PPARδ modulator. PPARα is mainly expressed in the liver, reducing VLDL production and plasma TG and enhancing ApoA1 and Apo A2, two anti-atherogenic HDL apoliproteins. PPARδ activation promotes fatty acid β-oxydation. In this study GFT505 significantly decreased plasma TG, increased ApoA2 and decreased FFA during hyperinsulinemic-euglycemic clamp. GFT505 also demonstrated an action on glucose utilization by peripheral tissues (as assessed by the increase of GIR during hyperinsulinemic-euglycemic clamp) and a reduction of hepatic glucose production. Thus, GFT505 by improving altered lipid profile, improving glucose homeostasis and decreasing inflammatory markers demonstrated interesting properties in male patients with insulin resistance. Finally, in parallel with improvements of insulin resistance, plasma lipid and inflammation markers, clincallly relevant reductions in markers of liver dysfunction were observed which could of interest because non-alcoholic fatty liver deseases are often encountered in patients with insulin resistance and/or type 2 diabetes.

GFT505 showed a good tolerance profile. A total of thirty seven (37) emergent AEs were reported during the 2 treatment periods: 16 AEs were reported by 10 patients (45.5%) when treated with GFT505 80 mg/d and 21 AEs were reported by 15 patients (68.2%) when treated with placebo. Among these AEs, 4 were judged related to GFT505: one case of gastrointestinal pain upper, one case of fatigue, one case of eczema and one case of sweat gland disorder, all of mild intensity. During the trial, no AE led to the discontinuation of GFT505 and no SAE related to GFT505 was reported. Six additional AEs were reported during the 6-week wash-out period and 8 were reported during the 2-week follow-up period; none of them was judged related to GFT505. No abnormal evolution of laboratory values, vital signs or ECGs was pointed out from baseline to end of study. All parameters remained steady throughout the study without difference between treatment groups. So GFT505 at 80mg/d appeared to be well tolerated in this trial over 56 days.

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