2. SYNOPSIS

Name of Sponsor/Company: 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-methylpropanoic acid		

Title of Study:

A PILOT STUDY TO EVALUATE THE EFFICACY AND SAFETY OF GFT505 (30 MG) ORALLY ADMINISTERED FOR 28 DAYS IN PATIENTS WITH FREDERICKSON TYPE IIB DYSLIPIDEMIA (MIXED HYPERLIPIDEMIA). A DOUBLE BLIND, PLACEBO-CONTROLLED AND RANDOMIZED STUDY.

Study Center/Investigator:

25 investigation centres in France were planned.

The study was conducted in a total of 25 centres, among which only 22 were active and enrolled at least one patient. 17 of these 22 centres randomized at least one patient.

Publication (Reference):

NA.

Study Period:	**Phase of Development:**
September 10th, 2007 (First Subject First Visit) - January 15th, 2008 (Last Subject Last Visit).	Phase IIa

Objectives:

Primary objective:

To evaluate the efficacy of GFT505 30 mg in reducing serum triglyceride (TG) and increasing high density lipoprotein cholesterol (HDL-C) levels compared with placebo in patients with mixed hyperlipidemia.

To assess the tolerability and safety of once-a-day administrations of oral doses of GFT505 during 28 days.

Secondary objectives:

To evaluate the efficacy of GFT505 30 mg in reducing non HDL-C and low density lipoprotein cholesterol (LDL-C) levels compared with placebo.

To describe the evolution in serum TG, HDL-C, LDL-C and non HDL-C levels.

To describe the changes in other lipid parameters.

To describe the changes in inflammatory markers.

To evaluate the plasma exposure of GFT505 after repeated once daily administrations of GFT505.

Methodology:

This was a randomized, placebo-controlled, double-blind, 2 parallel groups study.

The planned duration of the study was 12 weeks maximum per patient:

- a screening period (4 to 6 weeks),
- a 4-week double-blind treatment period,
- a 2-week follow-up period.

During the screening period, patients were asked to start or continue adequate diet and exercise and to stop their lipid-lowering medication (for not treatment-naïve patients). For patient taking any lipid-regulating medication, the following was considered:

- a minimum of 6-week wash-out from fibrates
- a minimum of 4-week wash-out from all other classes of lipid-regulating therapies (including satins)

For patients not taking any lipid-regulating medication, they also entered a run-in period (6week minimum) after having received standard diet and exercise recommendations (except for patients who were already following adequate diet and exercise. In that case, visit V2 could be performed immediately).

A central pre-randomization by-phone system was used to randomise the patients into 2 double blind groups:

- 1 group with patients treated with GFT505 30 mg,
- 1 group with patients treated with a placebo.

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

Planned: 30 subjects (20 patients in the GFT505 group, 10 patients in the placebo group).
Selected: 81 subjects.
Randomized: 38 subjects (25 subjects in the GFT505 group, 13 subjects in the placebo group). One patient was pre-randomized in GFT505 group despite he actually was in screening failure. The treatment sending was cancelled the day of the randomization and patient was informed that he was in screening failure. He was excluded from analysis.
Analysed: 37 subjects were included both in the safety and efficacy analyses (24 in the GFT505 group, 13 in the placebo group).

Diagnosis and Main Criteria for Inclusion:

Patients:
Men or post-menopausal women (stable or continuous hormone replacement therapy if any), aged from 18 to 75 year-old, with mixed hyperlipidemia (type IIb Frederickson).

Clinical characteristics:
Non hypertensive or treated hypertensive patients (stable treatment and dose for at least 2 months, except non-permitted medications), with no history of cardiovascular heart disease, no diabetes mellitus (type I or II) and no cardiovascular risk higher than 20 % at 10 years using Framingham table. The body mass index (BMI) must be lower than 35 kg/m² and the blood pressure must be lower than 160/95 mmHg.

Laboratory values prior to randomization:
The TG level must be between 200 and 500 mg/dL (2.28 and 5.65 mmol/L) and the LDL-C level must be between 130 and 220 mg/dL (3.36 and 5.69 mmol/L). The creatinine clearance must be higher than 60 mL/mn (according to Cockroft-Gault formula) and creatinine must be lower than 180 µmol/L.

Test Product, Dose and Mode of Administration:

- GFT505: 2-[2,6-dimethyl-4-[3-[4-(methylthio)phenyl]-3-oxo-1(E)-propenyl]phenoxy]-2-methylpropanoic acid supplied as hard gelatin capsules dosed at 10 mg (size 2). The daily dose was 30 mg. Oral route. 3 capsules once daily before breakfast.
- Placebo: Hard gelatin capsules matching GFT505 capsules. Oral route. Once daily before breakfast.

Duration of Treatment:

4 weeks.

Criteria for Evaluation:

Primary efficacy assessment:
- Decrease in serum TG level from baseline to D28 (V5)
- Increase in serum HDL-C level from baseline to D28 (V5)

Secondary efficacy assessment:
- Decrease in serum non HDL-C and LDL-C levels from baseline to D28 (V5)
- Changes from baseline to all study visits in other lipids (TG, HDL-C, total cholesterol, free fatty acids (FFA)) and special lipids (small dense LDL, remnants, Apolipoprotein (Apo) AI, Apo AII, Apo B, Apo CIII, Apo CIII/B, Apo CIII-nonB)
- Changes from baseline to D28 (V5) in inflammatory markers: hsCRP, TNF-α, IL-6, fibrinogen

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Safety parameters:

- ❑ Serious adverse event (SAEs)
- ❑ Adverse events (AEs)
- ❑ Physical examination
- ❑ Vital signs
- ❑ Medical history
- ❑ Electrocardiogram
- ❑ Hematology (WBC and differential count, RBC, hemoglobin, hematocrit and platelets, haptoglobin, prothrombin, reticulocytes count)
- ❑ Biochemical markers (plasma glucose, HbA1c, insulin, CPK, AST, ALT, GGT, TSH, alkaline phosphatases, creatinine, troponin, total and conjugated bilirubin, urea, uric acid, albumin, homocystein, fibrinogen, total proteins, electrolytes)
- ❑ Urinalysis

Statistical Methods:

Handling of missing data:
Missing data were not replaced.

Definitions:
Baseline: (value V2 +value V3)/2 or ((valueV2+value V2b)/2 + value v3)/2 (if value V2b available). Use of retest value if available.
End point: value V5 or value at premature termination visit if the patient prematurely dropped out.

Descriptive statistics:
Continuous variables were described for each group by the number of documented patients, mean, standard deviation, 95 % two-sided confidence interval (when relevant) and number of missing data.

Binary and categorical variables were described for each group by the frequency and percentage of each modality as well as the number of missing data.

Efficacy analysis:

The main analysis was conducted on an intent-to-treat basis (ITT), using the 9.1. SAS software (SAS Institute, Cary, NC, USA).

The primary endpoints were TG and HDL-C percent change from baseline to endpoint comparing GFT505 to placebo. Change in lipids between baseline and endpoint were computed as follows: endpoint value – baseline value. So a decrease in lipids gave a negative value.

The statistical analyses compared the group receiving GFT505 to placebo. In order to test the superiority of the GFT505 over the placebo, tests were one-sided. The α risk was set at 0.05. Changes in TG and HDL-C were described in the two groups. Differences between GFT505 and placebo were described along with the 95% confidence interval.

For all statistical tests, a generalised linear model was built with group as explaining variable and baseline as covariate (ANCOVA). Effect size was computed as difference between Lsmeans for the comparison of GFT505 versus placebo and one sided 95% CI were estimated.

Safety analysis:

The frequency of subjects experiencing a specific adverse event was tabulated by group, system organ class, and high-level term.

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Summary - Conclusions:

From 81 selected patients with Frederickson Type IIb dyslipidemia, 37 patients were randomly allocated to 2 treatment groups: GFT505 30 mg/d (N=24) or placebo (N=13).

Patients were treated for 28 days with the study drugs. The ITT analysis involved 37 patients. Patients were 54±9 year-old with a sex ratio largely in favour of men (84 %). Almost all patients were white. They weighted 80±12 kg with a BMI of 28±3 kg/m². The two randomized groups were well balanced at entry regarding demographics, biometrics, medical history, alcohol consumption, lipids, inflammatory markers, homocystein and creatinine. Compliance was very good in both groups.

Efficacy results:

TG and HDL-C varied as follows (relative change from baseline). Difference between GFT505 and placebo did not reach significance.

	GFT505	Placebo	Effect size	p
	lsmeans±SE	lsmeans±SE		
TG	-11.96±6.80	-3.24±9.24	-8.72 [-∞ - 10.69]	0.45
HDL-C	-0.67±2.20	-6.01±2.99	5.35 [-0.94 - +∞]	0.16

No significant difference was found between GFT505 and placebo regarding other lipid parameters or inflammatory markers, homocystein and creatinine, as described below:

	GFT505	Placebo	Effect size	p
	lsmeans±SE	lsmeans±SE		
Non HDL-C	-5.68±2.75	-1.03±3.73	-4.65 [-∞ - 3.19]	0.32
LDL-C	-3.53±2.74	0.75±3.73	-4.28 [-∞ -3.56]	0.36
TC	-4.74±2.28	-1.88±3.10	-2.87 [-∞ - 3.65]	0.46
FFA	12.46±7.71	6.11±10.67	6.35 [-16.06 - +∞]	0.63
Apo AI	0.51±2.22	-2.01±3.01	2.53 [-3.80 - +∞]	0.50
Apo AII	8.29±2.39	1.43±3.25	6.86 [0.03 - +∞]	0.10
Apo B	-2.90±3.14	3.82±4.27	-6.73 [-∞ - 2.24]	0.21
Apo CIII	-11.33±8.77	1.41±11.91	-12.74 [-∞ - 12.27]	0.39
Apo E	-18.80±6.82	-7.69±9.27	-11.11 [-∞ - 8.37]	0.34
Apo CIII/LpB	-8.58±12.53	4.85±16.67	-13.43 [-∞ - 21.86]	0.52
Apo CIII/Lp non B	-7.35±3.66	-3.00±4.87	-4.35[-∞ - 5.96]	0.48
Apo E/LpB	-23.71±8.42	-8.59±11.25	-15.12 [-∞ - 8.85]	0.29
Apo E/Lp non B	-1.08±6.15	7.97±8.21	-9.05 [-∞ - 8.42]	0.39
Remnant Lp	-22.13±7.67	-5.16±10.43	-16.97 [-∞ - 4.93]	0.20
Fibrinogen	-0.30±4.15	4.14±5.68	-4.44 [-∞ - 7.58]	0.54
Hs-CRP	84.15±58.07	54.36±78.96	29.79 [-136.16 - +∞]	0.76
TNF-α	4.97±3.72	2.46±5.16	2.51 [-8.30 - +∞]	0.70
IL-6	40.61±91.36	229.94±124.35	-189.33 [-∞ - 72.28]	0.23
Homocystein	10.85±3.72	-1.27±5.05	12.12 [1.51 - +∞]	0.06
Creatinine	0.46±2.38	4.29±3.24	-3.83 [-∞ - 3.00]	0.35

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Safety results:

GFT505 appeared to be well tolerated. No abnormal evolution of laboratory values (ionogram, liver enzymes, bilirubin, CPK, renal function tests, glycaemic balance, and blood cell count), vital signs or ECGs was pointed out during the trial.

Twenty adverse events (AEs) occurred within the treatment period or the next 30 days and were therefore considered as emergent. They were reported by 12 patients, 6 from each treatment group (25.00 % in the GFT505 group, 46.15 % in the placebo group). None of the reported AE was judged related to study drug in the GFT505 group and none led to study drug discontinuation. No SAE was reported during the trial.

Conclusion:

In a double-blind, placebo-controlled and randomized study involving 37 patients, no effect of GFT505 against placebo has been demonstrated. Administered orally for 28 days at the daily dosage of 30mg, GFT505 was found to be well tolerated.