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Elafibranor, an Agonist of the Peroxisome Proliferator-activated Receptor-α and -δ, Induces Resolution of Nonalcoholic Steatohepatitis Without Fibrosis Worsening

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Short title : Elafibranor RCT for NASH

Abbreviations: bNAS: baseline NAS; PP: per protocol; HOMA-IR: Homeostasis model assessment index; ITT: intention to treat; NAFLD: nonalcoholic fatty liver disease; NAS: NAFLD activity score; NASH: nonalcoholic steatohepatitis; PPAR : peroxisome proliferator activated receptor.

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Abstract

Background & Aims: Elafibranor is an agonist of the peroxisome proliferator activated receptor-α (PPARA) and peroxisome proliferator activated receptor-δ (PPARD). Elafibranor improves insulin sensitivity, glucose homeostasis, and lipid metabolism and reduces inflammation. We assessed the safety and efficacy of elafibranor in an international, randomized, double-blind placebo-controlled trial of patients with non-alcoholic steatohepatitis (NASH).

Methods: Patients with NASH without cirrhosis were randomly assigned to groups given elafibranor 80 mg (n=93), elafibranor 120 mg (n=91), or placebo (n=92) each day for 52 weeks at sites in Europe and the United States. Clinical and laboratory evaluations were performed every 2 months over this 1 year period. Liver biopsies were then collected and patients were assessed 3 months later. The primary outcome was resolution of NASH without fibrosis worsening, using protocol-defined and modified definitions. Data from the groups given the different doses of elafibranor were compared with those from the placebo group using step-down logistic regression, adjusting for baseline nonalcoholic fatty liver disease activity score (NAS).

Results: In intention-to-treat analysis, there was no significant difference between the elafibranor and placebo groups in the protocol-defined primary outcome. However, NASH resolved without fibrosis worsening in a higher proportion of patients in the 120 mg elafibranor group vs the placebo group (19% vs 12%; odds ratio [OR], 2.31; 95% confidence interval [CI], 1.02–5.24; *P*=.045), based on a post-hoc analysis for the modified definition. In post-hoc analyses of patients with NAS ≥4 (n=234), elafibranor 120 mg resolved NASH in

larger proportions of patients than placebo based on the protocol definition (20% vs 11%; OR=3.16; 95% CI, 1.22–8.13; *P*=.018) and the modified definitions (19% vs 9%; OR=3.52; 95% CI, 1.32–9.40; *P*=.013). Patients with NASH resolution after receiving elafibranor 120 mg had reduced liver fibrosis stages compared to those without NASH resolution (mean reduction of 0.65±0.61 in responders for the primary outcome vs an increase of 0.10±0.98 in non-responders; *P*<.001). Liver enzymes, lipids, glucose profiles, and markers of systemic inflammation were significantly reduced in the elafibranor 120 mg group vs the placebo group. Elafibranor was well tolerated and did not cause weight gain or cardiac events, but did produce a mild, reversible increase in serum creatinine (effect size vs placebo: increase of 4.31±1.19 µmol/L, *P*<.001).

Conclusions: A post-hoc analysis of data from trial of patients with NASH showed that elafibranor (120 mg/day for 1 year) resolved NASH without fibrosis worsening, based on a modified definition, in the intention-to-treat analysis and in patients with moderate or severe NASH. However, the predefined endpoint was not met in the intention to treat population. Elafibranor was well tolerated and improved patients' cardiometabolic risk profile. Clinicaltrials.gov number: NCT01694849

KEY WORDS: PPARA, PPARD, NAFLD, fatty liver

INTRODUCTION

Of all chronic liver diseases, non-alcoholic steatohepatitis (NASH) is of increasing concern, as it is highly prevalent, potentially severe and without approved therapy. NASH defines a subgroup of non-alcoholic fatty liver disease where liver steatosis co-exists with hepatic cell injury (apoptosis and hepatocyte ballooning), and inflammation [1]. It occurs in close association with overweight/obesity, type 2 diabetes and cardiometabolic conditions that define the metabolic syndrome [2]. Because of the prevalence of these comorbidities, NASH is emerging as the most common chronic liver disease.

NASH promotes liver fibrosis and some patients progress to severe hepatic diseases including cirrhosis, liver failure, HCC or require liver transplantation [3, 4]. Liver-related mortality is increased ten-fold in NASH patients compared to the general population [5]. However, NASH is also a multi-system disease that could worsen insulin resistance, the metabolic syndrome and the systemic inflammatory state [6]. Consequently, NASH patients also have an increased rate of cardiovascular events and neoplasia. These two latter conditions carry the heaviest toll in terms of mortality, the leading cause of death being from cardiovascular events [3, 7, 8].

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors playing key roles in cellular processes regulating metabolic homeostasis, immune-inflammation and differentiation. PPARγ agonists demonstrated efficacy in improving histology in NASH [9-11], but side effects such as congestive heart failure, peripheral edema, bone fractures and weight gain severely restrict their prescription and acceptance as long term therapies. PPARα is most prominently expressed in the liver and is activated by hypolipidemic fibrates. PPARα controls the lipid flux in the liver by modulating fatty acid transport and β-oxidation while improving plasma lipids by decreasing triglycerides and increasing HDL-cholesterol [12]. In addition, PPARα activation inhibits inflammatory genes induced by NF-kB and decreases the expression of acute phase response genes [12]. PPARδ (also called PPARβ) regulates metabolism in liver and peripheral tissues. PPARδ agonists enhance fatty acid transport and oxidation, increase HDL levels, and improve glucose homeostasis by enhancing insulin sensitivity and inhibiting hepatic glucose output [13]. Importantly, PPARδ exerts anti-inflammatory activities in macrophages and Kupffer cells [14]. In a pilot trial a selective PPARδ agonist reduced liver fat content while improving insulin sensitivity, plasma lipids and decreasing γGT [15].

Elafibranor (GFT505) is a dual PPARα/δ agonist which has demonstrated efficacy in disease models of NAFLD/NASH and liver fibrosis [16]. Elafibranor confers liver protection by acting on several pathways involved in NASH pathogenesis, reducing steatosis, inflammation, and fibrosis. In phase 2a trials in dyslipidemic, pre-diabetic and type 2 diabetic patients, elafibranor consistently improved plasma

lipids and glucose homeostasis, peripheral and hepatic insulin resistance, and reduced liver inflammatory markers [17, 18].

This phase II study was conducted to assess the efficacy of elafibranor for NASH in an international, randomized, placebo-controlled, multicenter, 1-year clinical trial.

METHODS

Study design

This international, multicenter, randomized placebo-controlled study tested elafibranor at the dose of 80mg and 120mg QD vs. placebo over 52 weeks and was conducted at 56 sites, 19 in the United States and 37 in 8 European countries. The study had a staggered design as requested by the regulatory agencies to test the safety of elafibranor over a 6 month period at the lower dose before exposing patients for one year the highest dose. During the first recruitment phase, 172 patients were screened between September 2012 and June 2013 for treatment with 80mg/d of elafibranor or placebo (allocation 2:1). The second recruitment period at the dose of 120 mg/d started in July 2013, when 179 patients were screened in 1 week. The randomization of this second cohort started in October 2013 (allocation of elafibranor 120mg or placebo in a 2:1 ratio), after unrestricted approval from the Independent Data and Safety Monitoring Board." The clinical study protocol was approved in all countries by National Authorities and Ethics Committees. All patients gave written informed consent. All authors had access to the study data and have approved and reviewed the final manuscript.

Patients

The inclusion criteria included: age 18-75 years and a histological diagnosis of non-cirrhotic NASH confirmed by a central pathologist. Patients were excluded if daily alcohol consumption was higher than 2 drink units/day (equivalent to 20 g.) in women and 3 drink units/day (30 g.) in men, if steatohepatitis was due to secondary causes, or if any other chronic liver disease was identified.

Randomization and masking

Randomization was obtained through a computer generated coding list, and treatment allocation was performed centrally for all sites through a web system, based on date of randomization, and stratified for diabetes. No stratification was made on investigation sites. Elafibranor and placebo were provided as identical capsules in wallets labeled with code numbers. Patients, investigators, clinical site staff and the pathologist were masked to treatment assignment. The allocation of treatment was done in a 1:1:1 ratio for the 3 treatment arms, placebo, elafibranor 80 and 120 mg.

Procedures

Patients were followed every 2 months with clinical and laboratory evaluations throughout the one year treatment period. An end-of-treatment biopsy and a 3-month post-treatment follow-up visit were performed. Screening and end-of-treatment biopsies were all read centrally by a single

pathologist in a blinded manner (PB). At end of study, all slides (baseline and end-of-study) were read in scrambled order. For inclusion, the liver biopsy needed to be collected within the past 9 months. Steatohepatitis was diagnosed based on the presence of steatosis (>5% of hepatocytes), hepatocyte ballooning and lobular inflammation. Fibrosis was evaluated using the NASH CRN fibrosis staging system. Included patients had a NAFLD activity score (NAS) ranging from 3 to 8, with at least 1 for steatosis, ballooning, and inflammation. All stages of fibrosis (0 to 3) were accepted, except for cirrhosis. Non-invasive panels for steatosis or fibrosis (Fatty Liver Index, SteatoTest, Fibrotest and the NAFLD Fibrosis score) were measured at baseline, 6 months and 12 months (end of treatment). Biological assessments were all centralized and performed at each visit for efficacy and safety purposes (cf. Supplementary data, study protocol).

Outcomes

The primary outcome was reversal of NASH without worsening of fibrosis. This was defined as per protocol, before study start, as the absence (score of 0) of at least one of the 3 components of NASH, i.e. steatosis, ballooning, and inflammation; worsening of fibrosis was defined as the progression to bridging fibrosis (i.e. stage 3) or cirrhosis in patients without bridging fibrosis at baseline or to cirrhosis in patients with bridging fibrosis at baseline.

After the study was completed a modified and more stringent definition was proposed by academic and regulatory experts and recommended by regulatory agencies for ongoing trials [19, 20]. It defines resolution of NASH as disappearance of ballooning (score=0) together with either disappearance of lobular inflammation or the persistence of mild lobular inflammation only (score=0 or 1) and resulting in an overall pathological diagnosis of either steatosis alone or steatosis with mild inflammation; any stage increase in fibrosis is considered fibrosis progression. Because this more stringent definition is now used for current and future trials, we will here report on both the protocol-defined and the post-hoc analysis of the modified definition.

Secondary outcomes included: changes in NAS between end-of-treatment and baseline biopsy (including the proportion of patients with a 2-point decrease); changes and improvements in individual histological scores of steatosis, ballooning, inflammation, and fibrosis; changes in liver enzymes, in non-invasive markers of steatosis and fibrosis, in lipid and glycemic parameters, in surrogate markers of insulin resistance (fasting insulin and HOMA scores); changes in systemic inflammatory markers; safety and tolerability of elafibranor at both doses.

Statistical methods

The main selection was the population of all randomized patients that received at least one dose of study drug (Intention to treat, ITT sample). To assess the robustness of findings sensitivity analyses were performed using the per protocol population (PP) defined as the ITT population with available liver biopsy at the end of the study. For sensitivity purposes, four post-hoc selections were considered: (1) Patients with bNAS>4 (moderate or high disease activity) which are similar to those included in previous NASH trials [11, 21]; (2) Patients with bNAS>4 and fibrosis of any stage at baseline; (3) patients with bNAS>4 and fibrosis stage 2 or higher at baseline (target patient population for current phase 3 trials) and (4) patients with bNAS>4 recruited in centers that randomized at least one patient in each treatment arm (justified by the strong treatment-center imbalance). The ITT population was the main selection and a significant effect observed in the ITT population was conditional to test the significance in the other subpopulations.

The main analysis was a mixed model featuring logistic regression on therapy response with treatment as fixed factor (placebo, 80mg, 120mg), adjusted for baseline NAS (bNAS). The multicenter context was accounted for by random factor. Based on the assumption of superiority of the 120mg dose, testing the 80mg dose was conditional to the significance of the effect of 120mg (step-down testing[22]). No multiplicity correction was needed due to step-down strategy[22]. For patients with liver biopsy unavailable at the end of treatment, a worst case imputation in assimilating missing value to therapy failure was considered.

Post-hoc analyses tested the main treatment effect and its interaction with baseline severity (bNAS).

For easier clinical discussion, Risk Ratio (RR) was reported with Odds Ratio (OR) derived from logistic regression. Geometric mean change over baseline and related t-tests were used to compare the treatment subgroups on biological parameters, composite biomarker scores for NAFLD and fibrosis.

For sample size calculations we assumed a 20% and 45% responder rate in the placebo and 120mg dose groups, respectively, and a drop-out rate of 25%. 90 patients per group were required to reach this difference with a power of 80% at a two–sided 0.05 significance test level. The analyses were conducted with the Statistical Package R (release 3.1.1), all tests were conducted at 0.05 two-sided level.

Role of the funding source

The GOLDEN505 study was sponsored by Genfit SA. The protocol was written by a panel of academic experts and sponsor representatives and amended in accordance to input from regulatory bodies.

The corresponding author had full access to all the data in the study and had final responsibility for manuscript submission.

RESULTS

A total of 276 patients were randomized, 92 in the placebo group, 93 in the elafibranor 80mg group and 91 in the elafibranor 120mg group **(Figure 1)**. Two patients did not receive the study medication and the remaining 274 patients constitute the ITT population. 33 patients (12%) dropped-out during the study **(Supplementary Table 1)**. Final liver biopsies were available in 237 patients (77, 82, and 78 patients in the placebo, elafibranor 80 mg, and elafibranor 120 mg groups respectively). Of these only five patients were no longer diagnosed as having NASH on the baseline biopsy upon scrambled re-reading at end of study. This did not modify the overall results.

Table 1 shows the baseline characteristics across treatment groups. The elafibranor arms contained less Caucasians, less men, more diabetics, and overall higher HOMA-IR and insulin levels than the placebo group.

Table 2 shows the response rates and corresponding RRs in the ITT population for the primary outcome. There was no difference between the elafibranor arms and placebo according to the protocol-defined definition. A post-hoc analysis using the modified definition of response shows that the response rate was significantly higher for the 120 mg arm than for placebo, 19% vs. 12%, (OR=2.31, 95%CI [1.02,5.24], p=0.045. The 80 mg arm did not perform better than placebo for both definitions of response, the protocol-based and the modified definition (OR=1.48, 95%CI [0.7-3.14], p=0.30 and 1.11, CI95%[0.48-2.57], p=0.80, respectively) or for any other histological analysis.

Results of the secondary histological outcomes (**Supplementary Table 3)** show no significant difference between elafibranor and placebo. Nonetheless, the efficacy of the 120mg dose to reduce the NAS by 2-points and to improve steatosis, ballooning, and lobular inflammation was more pronounced with increasing baseline severity, in contrast to the absence of a clear pattern in the placebo or 80mg groups.

A number of post-hoc, secondary analyses were performed. Importantly, there was a strong interaction effect between baseline severity and elafibranor dose which was significant for 120 mg for both the protocol-defined (OR:2.63, 95%CI[1.25-5.52], p=0.012) and modified definition (OR:2.76, 95%CI[1.33-5.76], p=0.007) (supplementary Table 2). The significant interaction effect with baseline severity indicated that the efficacy of elafibranor 120 mg vs. placebo increased with baseline severity. Hence the exclusion of patients with mild disease activity (bNAS=3, N=40) revealed a significant direct effect of elafibranor 120 mg vs. placebo (OR=3.16, 95%CI [1.22-8.13] and 3.52, CI95%[1.32-9.40], for the protocol-defined and modified definitions, respectively) in the remaining population of 234 pts with bNAS>4 (85% of the ITT population); there was no significant difference for the 80 mg arm.

Overall, the 120 mg elafibranor dose doubled the proportion of responders vs. placebo in patients with bNAS>4.

As patient recruitment was based on a wide spectrum of baseline severity (NAS 3-8 and fibrosis stage 0-3), we performed post-hoc analyses in NAS≥4 populations with increasing fibrosis stages (**Table 3**). The response rates of 120 mg elafibranor for the protocol-defined definition were significantly higher than that of placebo, while there was no significant difference for the 80 mg arm. The 120 mg dose was also more effective in the subpopulation of patients with any fibrosis (F1-F3), as well as in those with moderate or advanced fibrosis (F2-F3) **(Table 3)**. The results were qualitatively similar when using the modified definition (data not shown).

Because of a heterogeneous center effect and the unbalanced treatment-center distribution (due to the staggered design and an unexpected high rate of recruitment), we performed an analysis in the subset of bNAS>4 patients recruited in centers that randomized at least one patient in each treatment arm (N=120, **Supplementary Table 4**). The response rates were 29% and 26% (protocol-defined and modified definitions) vs. 5% placebo (p=0.01 and 0.02, respectively). 48% of patients improved the NAS by >2 points (vs. 21% in the placebo arm, p=0.013). Hepatocyte ballooning and lobular inflammation were also significantly improved, with a trend towards improvement in steatosis but not fibrosis.

Finally, we tested whether patients that achieved resolution of NASH without worsening of fibrosis in the 120 mg elafibranor arm also experienced improvement in fibrosis. **Supplementary Figure 1** shows strong reductions in fibrosis, hepatocyte ballooning and the NAS (all p<0.001) as well as in lobular inflammation and steatosis (both p<0.05), when compared to non-responders to the same regimen. These findings were similar with both definitions of response.

Patients treated with both elafibranor doses (80mg and 120mg) improved liver function tests (ALT, GGT and alkaline phosphatase, **Figure 2a,b,c**) and lipid parameters (triglycerides, LDL-cholesterol, HDL-cholesterol, **Figure 2d,e,f**). In diabetic patients (40% of the EES population) elafibranor improved fasting serum glucose (-0.98±0.56mmol/L for 120mg vs. placebo, p=0.08) and HbA1c (-0.46% for 120mg vs. placebo, p=0.038,) as well as markers of insulin resistance (fasting insulin, HOMA-IR and circulating free fatty acids, **Figure 3**). There was a clear reduction in systemic inflammatory markers such as hsCRP (-42% for 120mg vs. placebo, p=0.161), fibrinogen and haptoglobin at both doses (**Supplementary Figure 2a**). In line with the histological changes, serum panel biomarkers of steatosis and fibrosis such as SteatoTest®, FLI, Fibrotest®/FibroSure® and the NAFLD Fibrosis score, showed significant reductions in patients treated with elafibranor 120mg compared to placebo (**Supplementary Figure 2b**).

Elafibranor was safe and well tolerated. Clinical adverse events were mostly mild and similar in the placebo and elafibranor arms (**Table 4**). There were no cardiovascular events or deaths in the elafibranor arms. Six patients (6.5%) were discontinued for AE in the placebo, 7 (7.9%) in the 80mg and 5 (5.4%) in the 120mg groups. There was a mild, reversible but statistically significant increase in serum creatinine (effect size vs. placebo: +4.31±1.19 µmol/L, $p<0.001$). Other renal markers such as cystatin C and microalbuminuria remained normal. The increase in creatinine led to a reported renal impairment/failure in seven patients treated with elafibranor (**Supplementary Table 5**). All of them had increased creatinine at baseline; one of them had significant pre-existing increases in creatinine, cystatin C, urinary NGAL, urinary creatinine, serum albumin and urinary albumin, and decreased creatinine clearance, and was therefore discontinued. Weight did not change and there was no significant reduction in hematocrit or hemoglobin vs. placebo. Serious adverse events (SAE) occurred in 11 patients in the placebo (12%), 15 in the 80 (16.1%) and 14 in the 120mg (15.8%) arms. Treatment-related SAE occurred in 2 patients in the 80 mg elafibranor arm (spontaneous abortion; ataxia, fasciculation and tremor), in 2 patients in the elafibranor 120 mg arm (acute pancreatitis; Parkinson disease) and in 4 patients from the placebo arm (renal cancer; breast cancer; bladder cancer; pancreatic cancer).

Neoplastic SAEs were reported in 6 patients during the study and the 3-month follow-up periods: one bladder cancer in the elafibranor 80mg arm (unlikely related to study drug), in a patient with previous doubtful cytological lesions, and 5 cancers in the placebo arm (the four described above and one esophageal cancer considered unlikely related to study drug).

DISCUSSION

This randomized controlled trial provides evidence of efficacy of the dual PPARα/δ activator elafibranor on both histological reversal of NASH and metabolic improvement in patients with NASH. Both are important objectives on the path of controlling NASH. Steatohepatitis is indirectly associated with reduced hepatic survival in NAFLD [5, 23]. It drives fibrogenesis, a slow process of hepatic scar formation that can result in cirrhosis and its deadly complications such as liver failure, portal hypertension and hepatocellular carcinoma. Consequently clearance of steatohepatitis [24], i.e. reversal to a normal liver or to steatosis without steatohepatitis -a condition not associated with increased hepatic morbidity or mortality-, is expected to improve hepatic prognosis and is now accepted as the best, short-term surrogate for histological improvement in NASH trials [25, 26].

When analyzed according to the a priori, protocol-defined primary outcome there were no significant differences in treatment response between the two elafibranor groups and placebo. However, when using an updated, modified definition of reversal of NASH without worsening of fibrosis[19, 20], the 120 mg elafibranor arm performed significantly better than placebo in the ITT population. The latter definition is more stringent than the one used in the protocol. First, it places emphasis on hepatocyte ballooning, a sign of liver-cell injury and cardinal feature of steatohepatitis that is associated with disease progression and enhanced fibrogenesis. In contrast, the protocol-based definition required the disappearance of either steatosis, inflammation or hepatocyte ballooning. Second, based on older data showing that bridging fibrosis but not earlier stages is associated with liver-related mortality[23, 27-29], only progression to bridging fibrosis (or to cirrhosis) was considered "worsening of fibrosis" in the protocol-based definition. Instead, the modified definition defines worsening of fibrosis as any one stage increase based on recent data showing that even early fibrosis is associated with global and liver-related mortality[7]. Importantly, this more stringent definition led to a lower placebo effect. Earlier studies have not explicitly defined reversal of NASH and subtle differences in the criteria used might explain the variable rates of response in the placebo group (from 13%[21] to 21%[11]). Therapeutics in NASH is an evolving field and previous trials have used an aggregate histological score, the NAS, as a primary endpoint [11, 21]. However the prognostic value of the NAS is not established [7, 23, 30]. We expect that future, large phase 3 trials will be using this more stringent definition of response, and therefore we here report on both definitions of primary response in an attempt to facilitate comparisons of the magnitude of the effect both across trials and across classes of pharmacological agents. Interestingly, for both definitions there was a significant interaction effect with baseline activity suggesting that the latter is an important determinant of the efficacy of elafibranor.

Regardless of the definition of response, elafibranor at 120 mg was significantly superior to placebo in the post-hoc analysis after excluding the 15% of patients with mild steatohepatitis (i.e. bNAS of 3). The 80 mg dose was not significantly better than placebo in any primary or secondary histological analyses. Patients with mild but well-defined NASH were allowed to participate because of early concerns about recruitment feasibility, and because it was assumed that resolution of NASH was dependent on the presence of NASH and not on a particular level of severity. In these patients with mild steatohepatitis there was an unexpectedly high placebo response rate that may have led to a lack of treatment effect in the planned primary outcome assessment. As well, the observation that elafibranor is more efficient in more severe disease is consistent with recent data showing that hepatic PPARα expression is reduced in advanced inflammatory and fibrotic NASH and that resolution of NASH is associated with a recovery of PPARα expression [31]. Whatever the explanation for the failure of elafibranor to significantly outperform placebo in patients with mild disease, it is important to note that these patients are usually not considered eligible for pharmacological therapy but rather should be managed through dietary and lifestyle changes. The two previous large trials in NASH that had NAS reduction as a primary outcome, only included patients with a NAS of 4 or higher [11, 21] and current practice for drug development is to include only patients with moderate or severe disease defined by a NAS≥4. Similarly, it has been shown that fibrosis is a strong predictor of liver-related deaths[7] and patients with fibrosis are at highest need for pharmacotherapy. In secondary analyses of patients with moderate or severe NASH, 120 mg elafibranor was better than placebo regardless of the presence or severity of fibrosis. The histological benefit of the 120mg dose was mirrored by a significant improvement in liver function tests in particular ALT, gamma GT and alkaline phosphatase, and in non-invasive serum panels of steatosis (Steatotest®, FLI) and fibrosis (NAFLD Fibrosis score and Fibrotest®), which are likely more sensitive and earlier response indicators than histology.

In order to randomize 270 patients, 56 sites were selected, with competitive recruitment and centralized randomization. Due to the unexpectedly high recruitment rates and the staggered design, treatment distribution across the sites was imbalanced. Patient recruitment ranged from 1 to 24 randomized patients per site, and only 15 sites had patients randomized in all 3 treatment arms. In an exploratory, post-hoc analysis designed to control for both center effect and baseline severity, the efficacy of 120 mg elafibranor was explored in the subset of patients with bNAS≥4 from centers that randomized at least one patient per treatment arm. Both NASH resolution and a reduction by >2 points in the NAS were achieved more often than placebo. Interestingly, the 21% response rate of the placebo arm for a 2-point NAS reduction is comparable to previous studies [11, 21], thus suggesting that this subgroup of the population is representative of patients included in previous trials.

Since prevention of the occurrence of cirrhosis is the ultimate goal, both from a clinical and a regulatory standpoint [26], drug therapies for NASH should ideally impede fibrogenesis, either directly or indirectly, as a consequence of clearing steatohepatitis. Fibrosis reduction has been an elusive goal so far [11, 32], but recently, a randomized trial of obeticholic acid reported a reduction in fibrosis stage over 18 months of therapy in NASH patients [21]. The GOLDEN505 trial was shorter and not designed for anti-fibrotic end-points. It provided nonetheless the proof-of-principle that resolution of steatohepatitis can result in improvement of fibrosis, an indirect anti-fibrotic effect. Responders for the primary endpoint, at the 120mg elafibranor dose, experienced a significant reduction in fibrosis, which was not seen in the overall group of treated patients. Whether a direct anti-fibrotic potency of elafibranor, reported in experimental murine models of fibrosis [16], can be reproduced in humans deserves specific testing in longer trials. Future phase 3 trials will evaluate the effect of elafibranor on the rate of progression to cirrhosis as a result of the resolution of NASH or also through a direct anti-fibrotic effect.

An equally important aspect when treating patients with NASH is the requirement for absence of deterioration (or at best improvement) of the cardiometabolic comorbidities that contribute to overall mortality [25, 26]. Moreover, insulin resistance, an almost constant feature of NASH, could be causally related to the hepatic build-up of fat, induction of lipotoxic compounds within the liver and systemic and adipose tissue inflammation. All these pathways contribute to liver injury and fibrosis and therefore improving insulin sensitivity could also have beneficial effects on hepatic damage, as trials of pioglitazone have shown [9-11]. As expected from earlier phase 2 studies [17, 18], including a hyperinsulinemic-euglycemic clamp study in insulin-resistant patients, elafibranor improved markers of insulin resistance such as the HOMA-IR index, hyperinsulinemia, and free fatty acids and also significantly reduced HbA1c in diabetics which reflects improved glycemic control. The pro-atherogenic lipid profile of NASH patients was also improved with significant reductions of total and LDL-C, and increases in HDL-C at both elafibranor doses. Remarkably, the improvements in glycemic and lipid parameters were achieved in patients already treated with conventional glucose and lipid-lowering therapies which suggests an additional, direct effect of PPARα/δ agonism. It is interesting to note that contrary to placebo-induced resolution of NASH, patients that met the primary endpoint on elafibranor also exhibited a greater degree of improvement of metabolic and inflammatory parameters than non-responders. The temporal interaction and dose-dependency between the metabolic effects and the histological response of elafibranor remains to be elucidated in larger trials.

Elafibranor showed a very good tolerability and safety profile throughout the one year exposure in this trial. This is of paramount importance as NASH therapies are expected to be taken

on a long term basis. Moreover, these patients often have asymptomatic liver disease and therefore are less willing to tolerate drug-induced side-effects in the long-term. There was a mild, isolated and reversible increase in creatinine levels in some patients and longer post-treatment follow-up is necessary to confirm the reversibility of this biological effect. PPARα agonists such as fenofibrate are known to induce reversible increases in serum creatinine without promoting renal failure, as a result of a pharmacodynamic effect [33-35]. The mechanisms are not entirely known but might involve increased skeletal muscle production. An improvement in renal function upon fibrate treatment has been reported in a meta-analysis [36] that described a reduction in albuminuria progression. Here, the increase in creatinine was lower than that observed with fenofibrate (7.1% with 120 mg elafibranor vs. 17.2% with fenofibrate; a >20% increase in half of the treated population from the ACCORD trial [34]). Nonetheless the absence of an adverse effect of elafibranor on renal function in patients with NASH should be confirmed in larger trials.

This trial has several other strengths and some limitations. The rigorous centralized pathological reading for both inclusion and end-of-treatment biopsies avoided inclusion of patients without clearly defined NASH [24] and provided uniformity and lack of inter-observer variability for the assessment of histological endpoints. The proportion of screen failures for histology was low, thus ensuring that included patients were representative of most real-life NASH patients seen in tertiary centers. Likewise, the low proportion of missing end-of treatment biopsies minimized potential biases due to patient retention. Another strength is that this was the first large, international, multicenter trial in NASH. However, there were also methodological limitations. The staggered design of the trial could have resulted in unequal access to the three treatment arms as the randomization sequence was not set upfront for the three arms. The competitive recruitment resulted in a variable number of included patients in each center and in an uneven distribution between treatment arms that contributed to a significant center effect. Finally, the inclusion of patients with mild steatohepatitis (bNAS3) might have blunted the effect of elafibranor in the overall ITT population, as it resulted in a high placebo response rate. Nonetheless, the size of the trial allowed exploratory subgroup analyses that strengthened the demonstration of efficacy. While secondary analyses are to be considered with caution, this was not a registration, phase 3 trial, but a proof-of-concept, phase 2b exploratory trial designed to inform the design of subsequent, larger, pivotal studies.

The results of this trial compare favorably with results of other investigational agents tested in comparable trials. For instance in the FLINT trial, obeticholic acid induced resolution of NASH in 22% of patients vs. 13% in the placebo group. The difference became significant in a post-hoc analysis of the subset of patients with well-defined steatohepatitis at baseline: 19% vs. 8%, respectively, $p<0.05$. These rates of response are very close to those obtained in the current trial in the ITT

population and in the subset with NAS≥4 (all FLINT participants had a NAS≥4). In post-hoc analyses from the subgroup of patients with well-defined NASH in the PIVENS trial, pioglitazone induced resolution of steatohepatitis in 47% of patients (21% for placebo, p=0.001) and vitamin E in 36% (p=0.05). Direct comparisons between molecules are misleading in the absence of head-to-head trials, and because of differences in inclusion criteria and in definitions of histological response. Importantly, a detailed definition of "resolution of steatohepatitis" is not available from FLINT or PIVENS. In addition, there was no requirement for the absence of “worsening of fibrosis” when defining resolution of NASH as an endpoint for either PIVENS or FLINT, which further limits comparisons between rates of response with the GOLDEN trial. Only large, phase 3 trials will provide reliable estimates of treatment response for obeticholic acid and elafibranor, but what is clear so far is that a majority of patients are non-responders and that additional pharmacological strategies will be necessary to optimize the response rate.

In conclusion, this randomized controlled trial provides evidence that pharmacological modulation of the PPARα/δ nuclear receptors results in substantial histological improvement in NASH, including resolution of steatohepatitis, and improvement of the cardiometabolic risk profile, with a favorable safety profile. Larger phase 3 trials of elafibranor in the target population of patients with moderate to severe NASH are warranted.

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LEGENDS TO THE FIGURES

Figure 1. Trial profile.

Figure 2. Changes from baseline in liver enzymes (2A,2B,2C) and plasma lipids (2D,2E,2F) in treatment groups of the efficacy evaluable set (N=237).

Results are expressed in mean values of changes from baseline during treatment with placebo (N=77), elafibranor-80mg (N=82) and elafibranor-120mg (N=78). Error bars represent 95% CIs. ALT: Alanine aminotransferase (2A); Gamma-GT: gamma glutamyltranspeptidase (2B).

Figure 3. Elafibranor-induced changes in glucose homeostasis markers in type 2 diabetic patients.

Type 2 diabetic patients account for 40% of the ITT population (N=94). Mean changes vs. baseline in Elafibranor-80mg (N=31) and Elafibranor 120 mg (N=35) groups were compared with the changes in placebo group using a mixed model with group as fixed factor and baseline value as a covariate. The effect size compared to placebo was calculated and expressed as LSMean. Error bars represent 95% CIs. #p<0.05 vs. placebo; ##p<0.01 vs. placebo.

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Table 1. Baseline characteristics of the study population (FAS). Values are expressed as mean

	Placebo (N=92)	GFT505 80mg (N=93)	GFT505 120mg (N=89)
Demographics			
Age, years; mean (SD)	52·4 (11·9)	52·7 (11·0)	52·4 (11·6)
Male, %	60%	53%	53%
Race, Caucasian, %	92·4%	94·6%	79·8%
BMI, kg/m², mean (SD)	30.9 (4·2)	31·8 (5·2)	31·0 (4·4)
Weight, kg; mean (SD)	88·7 (16)	89·6 (17·8)	90·2 (15·6)
Waist circumference, cm, mean (SD)	104·7 (10·5)	106·4 (13·1)	106·3 (10·3)
Comorbidities, n (%)			
Type 2 diabetes	33 (36%)	37 (40%)	37 (42%)
Arterial hypertension	43 (47%)	47 (50%)	55 (62%)
Hyperlipidemia	50 (54%)	46 (49%)	58 (65%)
Cardiovascular disease	5 (5%)	5 (5%)	6 (7%)
Concomitant medications, n (%)			
Metformin	30 (32·6%)	30 (32·3%)	34 (38·2%)
Insulin	9 (9·8%)	15 (16·1%)	7 (7·9%)
Statins	31 (33·7%)	28 (30·1%)	33 (37·1%)
Vitamin E ≤400UI/d	0 (0%)	2 (2·2%)	3 (3·4%)
PUFA ≤2g/d	5 (5·4%)	5 (5·4%)	10 (11·2%)
Biology (mean (SD))			
ALT (U/L)	63·8 (39·9)	60·7 (40·2)	63.8 (43·7)
AST (U/L)	44·5 (28·6)	40·9 (27·0)	41·7 (23·8)
GGT (U/L)	80·1 (102·8)	75·1 (69·0)	66·7 (65·4)
Alkaline phosphatase, (U/L)	76·8 (22·7)	73·8 (23·4)	77·5 (21·0)
Total bilirubin, mg/dL	10·0 (5·9)	9·6 (5·4)	10·5 (8·5)
Triglycerides, mmol/L	1·8 (1·1)	1·8 (0·9)	2·0 (1·1)
Total cholesterol, mmol/L	4·8 (1·1)	5·1 (1·2)	4·8 (1·1)
HDL-cholesterol, mmol/L	1·3 (0·3)	1·3 (0·4)	1·2 (0·3)
LDL- cholesterol, mmol/L	2·8 (0·9)	3·0 (1·0)	2·7 (0·9)

Fasting glucose, mmol/L	5·8 (1·5)	6·1 (2·1)	6·2 (2·1)
Fasting insulin, pmol/L	154·2 (80)	193·9 (205)	180·3 (144)
HOMA-IR	5·9 (3·9)	8·4 (10·9)	7·6 (8·1)
HbA1c, %	6·0 (0·8)	6·0 (0·9)	6·2 (1·1)
Fibrinogen, g/L	3·3 (0·6)	3·2 (0·7)	3·4 (0·8)
Haptoglobin, g/L	1·24 (0·6)	1·30 (0·5)	1·30 (0·6)
Alpha 2 macroglobulin, g/l	2·26 (0·97)	2·28 (0·82)	2·39 (0·84)
Histology (mean (SD))	**N=92**	**N=93**	**N=89**
	N=45	N=54	N=26
Median time interval historical biopsy-inclusion, (days)	79·4 (67·7)	110·7 (86·1))	58·2 (50·9)
NAS	5·0 (1·3)	5·0 (1·2)	4·9 (1·3)
NAS = 3, n (%)	16 (17·4%)	10 (10·8%)	14 (15·7%)
NAS score 4-5, n (%)	45 (48·9%)	54 (58·0%)	45 (50·6%)
NAS 6-8, n (%)	31 (33·7%)	29 (31·2%)	30 (33·7%)
Hepatocyte ballooning	1·4 (0·5)	1·4 (0·5)	1·4 (0·5)
Lobular inflammation grade	1·4 (0·6)	1·4 (0·6)	1·4 (0·5)
Steatosis grade	2·2 (0·7)	2·3 (0·8)	2·2 (0·8)
Fibrosis stage	1·5 (1·0)	1·5 (1·1)	1·7 (0·9)
Stage 0, n (%)	15 (16·3%)	20 (21·5%)	5 (5·6%)
Stage 1, n (%)	32 (34·8%)	28 (30·1%)	39 (43·8%)
Stage 2, n (%)	25 (27·2%)	22 (23·7%)	25 (28·1%)
Stage 3 (bridging fibrosis), n (%)	20 (21·7%)	23 (24·7%)	20 (22·5%)

Table 2. Response rates and main analyses according to protocol-defined and the modified definitions of response.

	Protocol-defined primary outcome								
	·	**Placebo**		**Elafibranor 80mg**		**Elafibranor 120mg**		**OR (CI 95%)***	**p-value***
N	**NAS**	Percent	Count	Percent	Count	Percent	Count		
274	Total	17%	(92)	23%	(93)	21%	(89)	1·53 [0·70, 3·34]	0·280
234	NAS≥4 (Moderate & severe)	11%	(76)	20%	(83)	20%	(75)	3·16 [1·22, 8·13]	0·018
40	NAS 3 (Mild)	50%	(16)	40%	(10)	29%	(14)		
	Modified definition of response								
	·	**Placebo**		**Elafibranor 80mg**		**Elafibranor 120mg**		**OR (CI 95%)***	**p-value***
N	**NAS**	Percent	Count	Percent	Count	Percent	Count		
274	Total	12%	(92)	13%	(93)	19%	(89)	2·31 [1·02, 5·24]	0·045
234	NAS≥4 (Moderate & severe)	9%	(76)	13%	(83)	19%	(75)	3·52 [1·32, 9·40]	0·013
40	NAS 3 (Mild)	25%	(16)	10%	(10)	21%	(14)		

*Elafibranor 120mg versus placebo, direct treatment effect

Table 3· Response rate and main analyses for the modified definition of response in patients with bNAS≥4 and various stages of fibrosis at baseline.

POPULATION (N)	SELECTION	TREATMENT ARM, N			OR [CI 95%]*	p-value*
		Placebo, %	Elafibranor 80mg, %	Elafibranor 120mg, %		
All NAS≥4	**N=234¶**	N=76	N=83	N=75		
		9%	**13%**	**19%**	**3·52 [1·32,9·40]**	**0·013**
	N=202§	N=63	N=72	N=67		
		11%	**15%**	**21%**	**3·26 [1·17, 9·02]**	**0·024**
NAS≥4 with fibrosis (any stage)	**N=204¶**	N=66	N=67	N=71		
		11%	**15%**	**20%**	**3·75 [1·39,10·12]**	**0·009**
	N=176§	N=55	N=58	N=63		
		13%	**17%**	**22%**	**3·22 [1·15, 8·99]**	**0·026**
NAS≥4 with moderate/advanced fibrosis (F2, F3)	**N=118¶**	N=41	N=39	N=38		
		7%	**10%**	**13%**	**18·46 [4·80,70·96]**	**0·0001**
	N=99§	N=32	N=33	N=34		
		9%	**12%**	**15%**	**10·59 [2·52,44·50]**	**0·002**

¶: all patients; **§**: patients with end of trial liver biopsy; * 120 mg elafibranor vs· placebo, direct treatment effect

Table 4. Most frequent reported treatment related AEs.

Adverse event	Elafibranor 80mg N=93	Elafibranor 120mg N=89	Placebo N=92	Total N=274
Nausea	13 (13·98%)	9 (10·11%)	9 (9·78%)	31 (11·31%)
Headache	6 (6·45%)	7 (7·87%)	8 (8·7%)	21 (7·66%)
Diarrhoea	6 (6·45%)	5 (5·62%)	4 (4·35%)	15 (5·47%)
Fatigue	5 (5·38%)	5 (5·62%)	4 (4·35%)	14 (5·11%)
Asthenia	4 (4·3%)	0 (0%)	2 (2·17%)	6 (2·19%)
Renal failure*	1 (1·08%)	4 (4·49%)	0 (0%)	5 (1·82%)
Renal impairment*	0 (0%)	2 (2·25%)	0 (0%)	2 (0·73%)
Abdominal pain	0 (0%)	5 (5·62%)	6 (6·52%)	11 (4·01%)
Abdominal pain, upper	1 (1·08%)	3 (3·37%)	3 (3·26%)	7 (2·55%)
Vomiting	5 (5·38%)	3 (3·37%)	2 (2·17%)	10 (3·65%)
Myalgia	5 (5·38%)	2 (2·25%)	2 (2·17%)	9 (3·28%)
Decreased appetite	3 (3·23%)	5 (5·62%)	0 (0%)	8 (2·92%)
Rash	3 (3·23%)	4 (4·49%)	1 (1·09%)	8 (2·92%)
Pruritus	1 (1·08%)	1 (1·12%)	2 (2·17%)	4 (1·46%)

* Term of adverse event as reported by the investigator, not based on any specific definition.

Figure 1

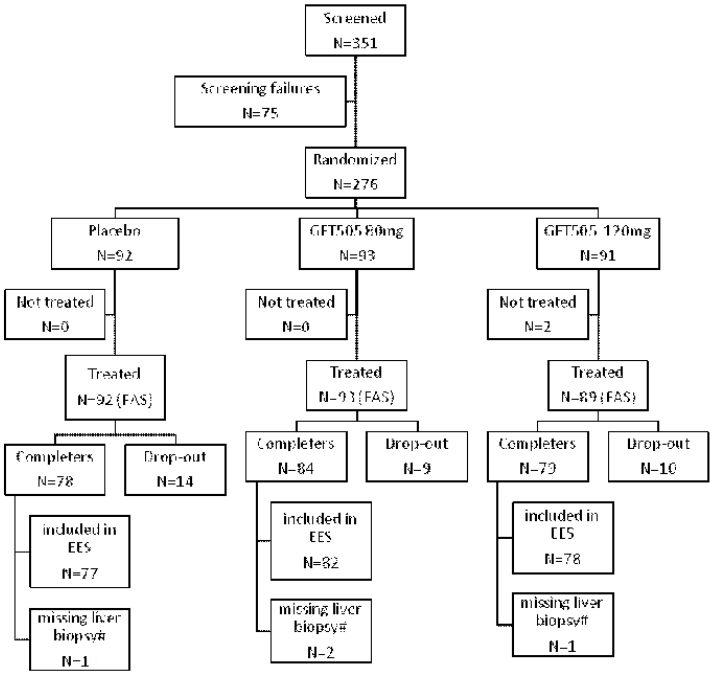
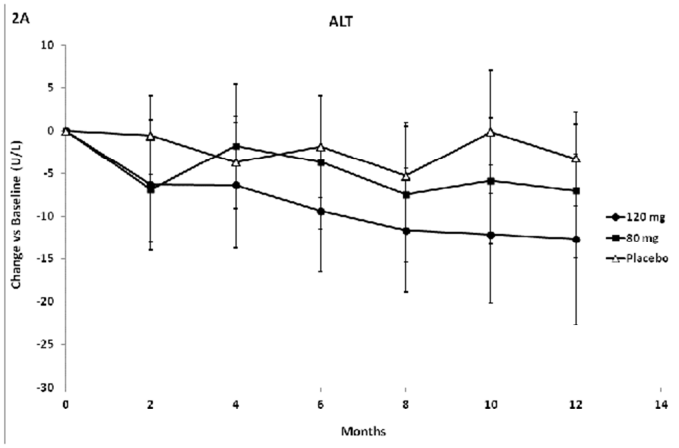
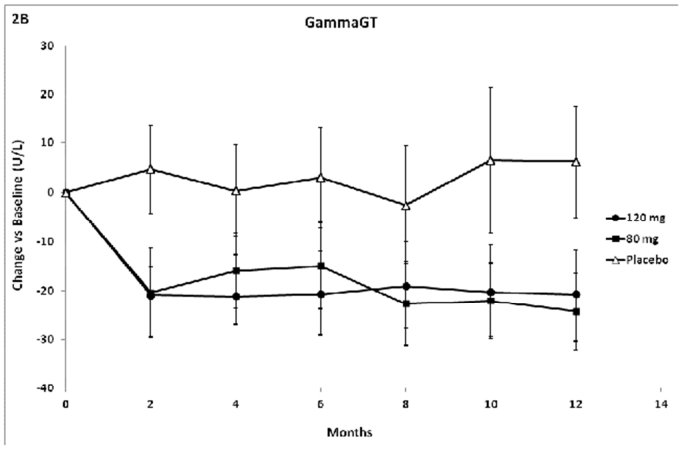
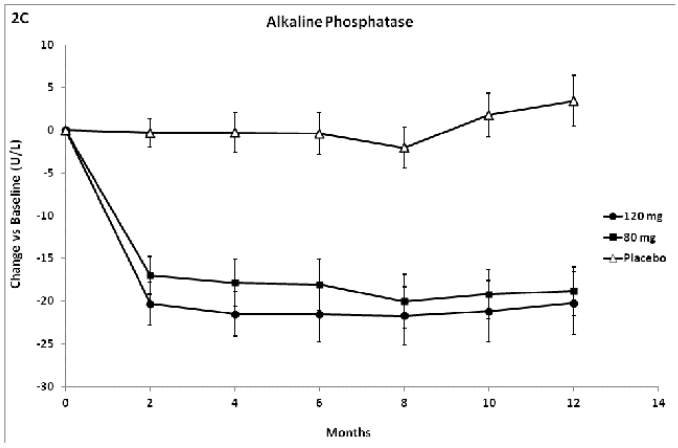
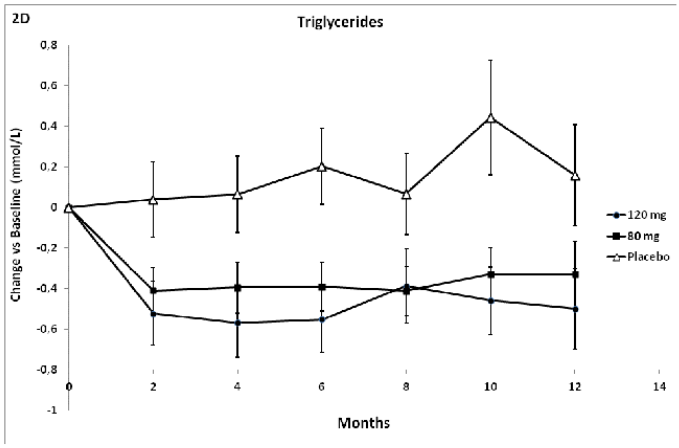


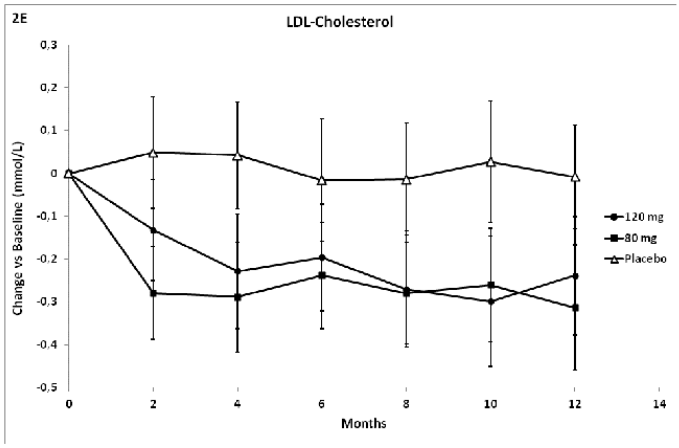
Figure 2.

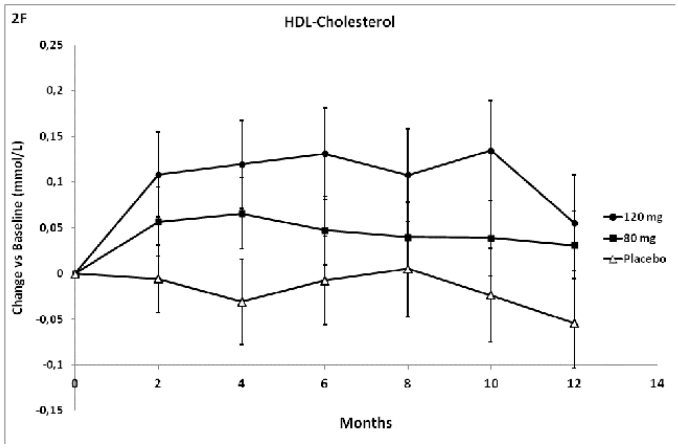





2C
Alkaline Phosphatase
Change vs Baseline (U/L)
10
5
0
-5
-10
-15
-20
-25
-30
0
2
4
6
8
10
12
14
Months
120 mg
80 mg
Placebo


2D
Triglycerides
Change vs Baseline (mmol/L)
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
0
2
4
6
8
10
12
14
Months
120 mg
80 mg
Placebo


2E
LDL-Cholesterol
Change vs Baseline (mmol/L)
0,3
0,2
0,1
0
-0,1
-0,2
-0,3
-0,4
-0,5
0
2
4
6
8
10
12
14
Months
120 mg
80 mg
Placebo


2F
HDL-Cholesterol
Change vs Baseline (mmol/L)
0,25
0,2
0,15
0,1
0,05
0
-0,05
-0,1
-0,15
0
2
4
6
8
10
12
14
Months
120 mg
80 mg
Placebo