MBX-8025, A Novel Peroxisome Proliferator Receptor-δ Agonist: Lipid and Other Metabolic Effects in Dyslipidemic Overweight Patients Treated with and without Atorvastatin

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Context: Preclinical and clinical studies suggest that peroxisome proliferator-activated receptor (PPAR)-δ agonists favorably affect multiple metabolic parameters that are otherwise proatherogenic, many that are not optimally managed with statins alone.

Objective: The aim of this study was to evaluate the effects of MBX-8025 (a novel PPAR-δ agonist) on lipid and other metabolic parameters associated with increased atherosclerotic risk, administered alone and in combination with atorvastatin.

Design and Setting: This was a randomized, double-blind, placebo-controlled, parallel group proof-of-concept study conducted at 30 U.S. research sites.

Participants: This study evaluated 181 overweight men and women with mixed dyslipidemia.

Intervention(s): Subjects were administered once daily placebo, atorvastatin 20 mg, or MBX-8025 at 50 or 100 mg alone or combined with atorvastatin for 8 wk.

Main Outcome Measures: The main efficacy measures included change from baseline in apolipoprotein B-100, lipid levels, high-sensitivity C-reactive protein, and additional metabolic parameters, as well as the effect on the metabolic syndrome and LDL particle size.

Results: Compared to placebo, MBX-8025 alone and in combination with atorvastatin significantly ($P < 0.05$) reduced apolipoprotein B-100 20–38%, LDL 18–43%, triglycerides 26–30%, non-high-density lipoprotein cholesterol 18–41%, free fatty acids 16–28%, and high-sensitivity C-reactive protein 43–72%; it raised high-density lipoprotein cholesterol 1–12% and also reduced the number of patients with the metabolic syndrome and a preponderance of small LDL particles. MBX-8025 was safe and generally well-tolerated. MBX-8025 also reduced liver enzyme levels.

Conclusion: MBX-8025, a novel PPAR-δ agonist, favorably affected multiple metabolic parameters with and without atorvastatin. A more complete understanding of MBX-8025 requires a larger future study. (*J Clin Endocrinol Metab* 96: 2889–2897, 2011)

Peroxisome proliferator-activated receptors (PPAR) are nuclear receptors that direct transcription of gene expression. Although primates are largely refractory to the proliferation of peroxisomes with PPAR agonists (1) (which is an effect pronounced in rodents), PPAR agonism has demonstrable metabolic and potentially therapeutic effects in humans, as evidenced by PPAR-α and -γ agonists approved for dyslipidemia and diabetes mellitus, respectively (2).

For years, the PPAR-δ receptor has represented a potential therapeutic target (3) because of its widespread expression in metabolically active tissues and its role in metabolic processes involved in diseases such as atherosclerosis and diabetes mellitus (4). Reported effects of PPAR-δ agonists have varied (5–12), and no PPAR-δ agonist is yet approved for treatment of diseases such as diabetes mellitus, dyslipidemia, or atherosclerosis. However, interest in exploring this mechanism persists, driven by the potential metabolic benefits of PPAR-δ agonists, such as a reduction in apolipoprotein B (Apo B-100) (13), reduction in low-density lipoprotein cholesterol (LDL-C) (13), reduction in triglycerides (TG) (13, 14), increase in high-density lipoprotein cholesterol (HDL-C) levels (4, 14), reduction in insulin (suggesting a decrease in insulin resistance) (13), reduction in hepatic glucose output (4), reduction of liver fat (13), and antagonism of multiple pathogenic inflammatory pathways (15). PPAR-δ agonism may also result in a net decrease in circulating free fatty acids (FFA), possibly due to an increase in adipocyte and skeletal muscle FFA oxidation (8, 16). In addition to reducing the lipotoxicity often associated with increased circulating FFA (17), these effects may contribute to improvements in parameters associated with the metabolic syndrome (4, 18), as well as the reduction in body weight sometimes reported with PPAR-δ agonists (19).

Many of the metabolic abnormalities listed above are especially prevalent in metabolic syndrome patients, such as hyperglycemia, hypertriglyceridemia, reduced HDL-C levels, hypertension, and increased concentrations of smaller, more dense LDL particles (20), the latter possibly associated with an increased atherogenic risk (21). PPAR-δ agonism may improve many of these parameters (13, 14), and although prior reports are limited, PPAR-δ agonism may also potentially increase peak LDL particle size (18).

MBX-8025 is an orally active, potent (2 nM), and specific (>750-fold and >2500-fold compared with PPAR-α or PPAR-γ receptors, respectively) PPAR-δ agonist being developed as a lipid-altering agent. This clinical "proof-of-concept" study evaluated lipid and other metabolic effects of MBX-8025, a novel PPAR-δ agonist, in patients with mixed dyslipidemia.

Subjects and Methods

Study design

This was a randomized, double-blind, placebo-controlled, parallel group study of 183 combined dyslipidemic patients, conducted at 30 U.S. sites from August 2007 through August 2008. After completing the informed consent process and qualifying for eligibility at screening, participants entered a 5-wk single-blind placebo run-in period, during which those previously treated with lipid-modifying drugs, such as a statin, ezetimibe, or their combination, underwent a washout of these agents. This was followed by an 8-wk randomized treatment period and a final safety evaluation visit 2 wk after the last dose was administered. Assessments of most efficacy and safety parameters were completed at baseline, at 2-wk intervals during the 8-wk treatment period including end of treatment, and at a 2-wk posttreatment follow-up visit. Study participants were centrally randomized at the study level in 1:1 fashion to one of six treatment groups for once-daily administration of: 1) placebo; 2) MBX-8025, 50 mg; 3) MBX-8025, 100 mg; 4) atorvastatin (ATV), 20 mg; 5) MBX-8025, 50 mg, + ATV, 20 mg; or 6) MBX-8025, 100 mg, + ATV, 20 mg.

Study participant inclusion and exclusion criteria

All eligible subjects had dyslipidemia, as described below. Inclusion criteria included men and women aged 18–75 yr with waist circumferences of at least 38 and 33 inches, respectively. Weight was required to be stable for at least 2 months before study entry, with no anticipated change in smoking pattern, nutritional intake, or activity level during the course of the trial, and consumption of no more than two alcoholic beverages per day.

Lipid eligibility was dependent upon lipid-altering therapy at screening. For those taking lipid-altering therapy, entry lipid criteria included LDL-C levels between 130 and 200 mg/dl, TG levels between 150 and 340 mg/dl, and HDL-C levels between 35 and 60 mg/dl. Potential study participants taking ezetimibe or a stable dose of statin therapy (or combination) must have met these lipid parameter criteria 4 wk after the protocol-permitted washout of these lipid-altering agents. For potential participants untreated with lipid-altering therapy before study entry, entry lipid criteria included LDL-C between 130 and 280 mg/dl, TG between 150 and 550 mg/dl, and HDL levels no greater than 60 mg/dl.

Exclusion criteria included an anticipated change, addition, or discontinuation of lipid-altering drugs, with the exception of washout of lipid-altering drugs, as previously discussed. Participants were also excluded if they had diabetes mellitus, cardiovascular disease, and known secondary causes of dyslipidemia. Laboratory exclusion criteria included liver enzyme abnormalities [alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase more than two times the upper limits of normal (ULN); bilirubin more than 1.5 times ULN; γ-glutamyltransferase (GGT) more than 2.5 times ULN]; creatine kinase (CK) more than three times ULN; or creatinine more than 1.5 mg/dl in men and 1.4 mg/dl in women.

This study was approved by an Institutional Review Board (IRB) and conducted under the guidelines of Good Clinical Practices, and study subjects underwent the informed consent process before any study-related procedures, as evidenced by their written signature on an IRB-approved informed consent document.

Efficacy endpoints

The primary efficacy endpoint of this proof-of-concept study was the absolute and percentage change of Apo B-100 from baseline to end of 8-wk treatment compared with placebo. Secondary efficacy endpoints included absolute and percentage change from baseline to end of 8-wk treatment compared with placebo in LDL-C, TG, HDL-C, total cholesterol, apolipoprotein A, non-HDL-C, FFA, body weight, and various lipid ratios. Tertiary endpoints included absolute and percentage change in body mass index (BMI), total body fat, and lean body mass by standardized and centrally read dual-energy x-ray absorptiometry (GE/Lunar, Madison, WI), anthropomorphic measurements (waist circumference, hip circumference, waist:hip circumference ratio), fasting glucose and post-oral glucose tolerance testing glucose and insulin, high molecular weight adiponectin, leptin, high-sensitivity C-reactive protein (hsCRP), homeostasis model assessment of insulin resistance (HOMA-IR), and the effects on the prevalence of the metabolic syndrome by adult treatment panel III (ATP III criteria) (22) and on the proportion of patients with a preponderance of small LDL particles. Laboratory samples were drawn in the morning after a minimum 10-h overnight fast.

LDL peak particle diameter was determined using ion mobility methodology (23), and a bimodal peak particle size distribution was used to define two LDL particle size groups: large (peak LDL diameter > 21.88 nm); and small (peak LDL diameter < 21.88 nm).

Safety endpoints

Safety assessments included adverse events (AE), clinical laboratory tests, 12-lead electrocardiograms, vital signs, and physical examination. An AE subcategory for muscle-related AE, based upon predefined criteria (see Table 3 footnote "b"), was also included. AE were assessed in accordance with International Conference on Harmonization guidelines and were deemed study-related if the investigator assessed causality as possibly or probably related to the study drug. Treatment-emergent laboratory abnormalities that were deemed clinically significant were captured as AE.

Statistical methods

The purpose of the planned statistical analyses for this phase 2 proof-of-concept study was to highlight the possible effects of MBX-8025 and identify areas of investigation for future clinical trials. Unless otherwise stated, all analyses were planned, specified, and approved in advance of database lock and unblinding. A sample size of 23 completers per group would provide 90% power to detect an 18% decrease in Apo B-100, assuming a common SD of 15.3, with a 0.05 two-sided significance level. A similar power existed to detect a comparable decrease in the most important secondary endpoint, LDL-C. Recruiting 180 subjects (30 subjects per group) would allow for a 25% dropout rate.

The change from baseline in all primary, secondary, and most tertiary efficacy endpoints was analyzed using a linear mixed effect model, estimated by restricted maximum likelihood with fixed effect factors for treatment and center, and baseline value as a covariate. For the primary endpoint (Apo B-100), a confirmatory mixed model analysis of covariance was completed, with fixed effect factors for treatment, center, week, the treatment-by-week interaction, and baseline Apo B-100 as terms. The variance-covariance structure over weeks was autoregressive. Unless otherwise stated, data are summarized and analyzed using the intent to treat (ITT) population at the 8-wk end of study visit. All analyses were two-sided with a significance level of 0.05. P values were reported at the nominal level for the pairwise treatment comparisons of MBX-8025 or ATV $vs.$ placebo, as well as the combination of MBX-8025 and ATV $vs.$ ATV or MBX-8025 alone. No adjustment was made for multiple comparisons. Analyses were completed using SAS v 8.2 (SAS Institute Inc., Cary, NC). Graphs were created using PRISM software (GraphPad v 5.01; GraphPad Software, Inc., San Diego, CA).

The subgroup analyses for the differential effects of baseline lipid levels (tertiles) on LDL-C and TG were analyzed by adding the baseline lipid-treatment interaction as an additional covariate in the linear model. These analyses were completed in the per-protocol population (n = 173), defined prospectively as those patients completing a minimum of 4 wk of double-blind therapy with 80% compliance and patients who did not use prohibited lipid-lowering medications that could confound results.

The effects on the prevalence of metabolic syndrome and the proportion of patients with a preponderance of small LDL particles were estimated from a repeated measures binary regression, with factors for treatment and baseline (metabolic syndrome) or treatment and visit (LDL particle size). The percentages of patients meeting these criteria were reported at both baseline and end of treatment. LDL particle size measurements were completed from archived samples after conclusion of the study and analyzed $post\ hoc$, without prespecification in the analysis plan.

The reporting of the safety data included all patients receiving at least one dose of study drug(s).

All AE were coded using the Medical Dictionary for Regulatory Activities and tabulated by System Organ Class and preferred term.

Results

Study subject disposition and baseline demographics

A total of 183 subjects were assigned to study treatment; 10 subjects withdrew from the study after administration of study drug, with two lost to follow-up before obtaining clinical and laboratory evaluation after the randomization visit. Therefore, 181 subjects comprised the ITT population. Table 1 describes the baseline demographics. In general, the patient population included overweight, mixed dyslipidemic, mostly Caucasian men and women with mean age in their 50s, with a high prevalence (63–71%) of meeting diagnostic criteria for the metabolic syndrome, and a high proportion (60–80%) with a preponderance of small LDL particles.

Primary, secondary, and tertiary efficacy parameters

Table 2 summarizes plasma lipid and lipoprotein changes after 8 wk of double-blind treatment. Most of

TABLE 1. Baseline demographics and biochemical characteristics of ITT population

Variables	Placebo	8025-50	8025-100	ATV	8025-50/ATV	8025-100/ATV
n (ITT)	31	28	32	31	30	29
Age (yr)	54.9 ± 1.5	54.3 ± 2.2	54.6 ± 1.9	54.3 ± 1.9	54.6 ± 1.7	52.6 ± 1.7
Females, n (%)	15 (48)	11 (39)	17 (53)	18 (58)	18 (60)	16 (55)
Caucasians, n (%)	30 (97)	24 (86)	32 (100)	30 (97)	25 (83)	27 (93)
Metabolic syndrome, n (%)[a]	22 (71)	19 (68)	20 (63)	21 (68)	20 (68)	21 (72)
Impaired fasting glucose, n (%)[b]	14 (45)	14 (50)	18 (56)	11 (35)	14 (47)	8 (28)
HOMA-IR[c]	3.0 ± 0.3	2.5 ± 0.3	2.7 ± 0.4	3.0 ± 0.3	2.8 ± 0.3	2.8 ± 0.6
BMI (kg/m^2)	33.4 ± 0.8	33.5 ± 1.3	31.8 ± 0.6	34.0 ± 1.2	33.8 ± 1.1	35.2 ± 1.1
Total cholesterol (mg/dl)	251.7 ± 5.8	254.6 ± 6.1	250.6 ± 6.4	245.4 ± 5.5	258.4 ± 6.6	239.8 ± 4.8
Non-HDL cholesterol (mg/dl)	207.6 ± 5.5	210.1 ± 5.9	206.3 ± 5.7	202.6 ± 4.9	213.8 ± 6.0	197.6 ± 4.5
LDL-C (mg/dl)	160.7 ± 4.3	169.3 ± 5.0	163.6 ± 6.3	165.1 ± 5.0	175.0 ± 5.3	157.6 ± 3.1
HDL-C (mg/dl)	43.6 ± 1.3	44.6 ± 1.2	44.3 ± 1.7	42.7 ± 1.5	44.8 ± 1.5	42.6 ± 1.2
TG (mg/dl)	254.6 ± 22.5	214.8 ± 14.0	236.3 ± 16.3	199.8 ± 11.6	196.2 ± 13.5	211.6 ± 13.9
FFA (mmol/liter)	0.6 ± 0.0	0.6 ± 0.0	0.6 ± 0.1	0.6 ± 0.0	0.5 ± 0.0	0.6 ± 0.1
Apo B-100 (mg/dl)	119.0 ± 3.2	122.6 ± 3.7	120.3 ± 3.5	119.6 ± 3.1	126.2 ± 3.5	114.8 ± 1.9
Apo A-1 (mg/dl)	135.1 ± 3.7	133.4 ± 2.9	134.3 ± 4.0	128.2 ± 3.6	134.0 ± 3.3	129.6 ± 2.6
Alkaline phosphatase (U/liter)	81.9 ± 3.4	73.7 ± 3.4	78.7 ± 3.2	84.5 ± 3.3	71.7 ± 3.4	75.6 ± 3.5
GGT (U/liter)	32.6 ± 3.1	33.2 ± 3.2	32.7 ± 3.0	27.2 ± 3.1	27.7 ± 3.2	33.8 ± 3.3

Data are shown as mean ± SE, unless otherwise indicated.

[a] Patients were diagnosed with metabolic syndrome according to NCEP ATP III criteria (22).

[b] World Health Organization criteria.

[c] Data are shown as median ± SE.

the lipid changes were observed within 2 wk of initiating therapy. Compared with placebo, MBX-8025 significantly reduced Apo B-100 in all treatment groups ($P < 0.0001$). Specifically, MBX-8025 (both doses) reduced Apo B-100 by 20% (−23 mg/dl), whereas ATV reduced Apo B-100 by 34% (−41 mg/dl). Both doses of MBX-8025 combined with ATV reduced Apo B-100 by 32 to 38% (−37 to −48 mg/dl), which was significantly greater than with MBX-8025 alone but not significantly different than with ATV alone.

All treatment groups significantly decreased LDL-C levels ($P < 0.0001$). Compared with placebo, MBX-8025 at 50 and 100 mg monotherapy reduced LDL-C by 18 and 22%, respectively, whereas ATV reduced LDL-C by 41%. MBX-8025 + ATV combination therapy reduced LDL-C 40–43%, which was significantly more than MBX-8025 monotherapy. Although neither MBX-8025 + ATV combination treatment reduced LDL-C more than ATV alone in the ITT population, within a per-protocol subpopulation representing the highest baseline LDL-C (by tertile), the addition of MBX-8025 to

TABLE 2. Percentage change from baseline to 8-wk treatment in plasma lipids, lipoproteins, and metabolic parameters in ITT population

Variables	Placebo	8025-50	8025-100	ATV	8025-50/ATV	8025-100/ATV
Total cholesterol	−1.4 ± 1.9	−14.8 ± 1.9[a]	−16.9 ± 2.4[a]	−31.2 ± 1.6[a]	−33.1 ± 2.0[a,b]	−31.5 ± 2.2[a,b]
Non-HDL	−1.8 ± 2.1	−20.1 ± 2.2[a]	−23.6 ± 3.04[a]	−38.3 ± 1.7[a]	−42.8 ± 2.3[a,b]	−38.7 ± 2.9[a,b]
LDL-C	−0.2 ± 2.3	−18.4 ± 2.3[a]	−21.8 ± 3.4[a]	−41.1 ± 2.0[a]	−43.4 ± 2.4[a,b]	−40.3 ± 3.2[a,b]
HDL-C	1.3 ± 2.0	9.9 ± 2.8	13.2 ± 3.3[a]	2.3 ± 2.2	13.0 ± 3.5[a,c]	2.5 ± 4.0[b]
TG	−4.5 ± 4.6	−32.4 ± 4.9[a]	−32.7 ± 4.9[a]	−18.2 ± 5.6[a]	−34.7 ± 8.0[a]	−30.9 ± 5.6[a]
FFA	8.1 ± 9.6	−15.8 ± 6.7[a]	−14.2 ± 5.6[a]	3.0 ± 7.4	−19.5 ± 7.1[a]	−7.6 ± 9.6
Apo B-100	−0.1 ± 3.0	−20.0 ± 2.8[a]	−20.2 ± 3.1[a]	−34.3 ± 1.6[a]	−38.2 ± 2.0[a,b]	−32.2 ± 2.5[a,b]
Apo A-1	−1.2 ± 2.9	0.5 ± 2.4[a]	4.1 ± 1.7[a]	−0.7 ± 2.1[a]	2.7 ± 1.9[a,b]	−2.7 ± 3.0[b]
LDL-C/HDL-C	−1.2 ± 1.7	−24.5 ± 2.8[a]	−29.0 ± 3.8[a]	−42.4 ± 1.6[a]	−48.8 ± 2.7[a,b]	−38.0 ± 5.2[a,b]
Apo B-100/Apo A-1	1.6 ± 2.2	−19.9 ± 2.6[a]	−22.2 ± 3.8[a]	−33.4 ± 1.6[a]	−39.6 ± 2.0[a,b]	−27.7 ± 4.3[a]
HOMA-IR[d]	−6.6 ± 117.3	−8.0 ± 7.9	−27.3 ± 7.5[a]	−10.8 ± 7.8	−18.4 ± 20.6	−1.6 ± 16.8
Alkaline phosphatase	−4.2 ± 2.1	−31.9 ± 2.1[a]	−42.8 ± 2.0[a]	6.4 ± 2.0[a]	−27.6 ± 2.1[a,c]	−38.3 ± 2.2[a,c]
GGT	−3.2 ± 4.2	−23.6 ± 4.3[a]	−28.2 ± 4.1[a]	2.4 ± 4.2	−24.5 ± 4.3[a,c]	−31.6 ± 4.5[a,c]

Data are shown as mean ± SE, unless otherwise indicated.

[a] Significant difference between placebo and treatment group at $P < 0.05$.

[b] Significant difference between monotherapy and respective combination therapy at $P < 0.05$.

[c] Significant difference between ATV and combination therapy at $P < 0.05$.
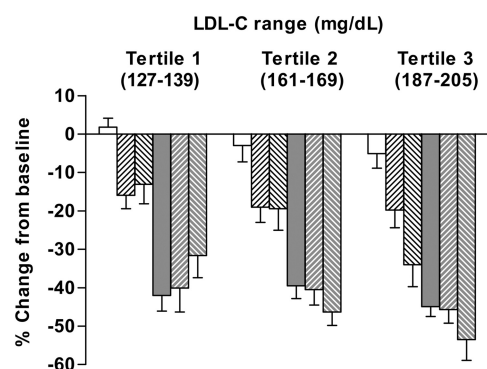
[d] Data are shown as median ± SE.

FIG. 1. Effects of MBX-8025 on LDL-C by baseline lipid level (tertile) compared with placebo, with or without ATV 20 mg/d. *Leftmost bar*, Placebo; *second bar from left*, MBX-8025–50; *third bar from left*, MBX-8025–100; *fourth bar from left*, ATV; *fifth bar from left*, MBX-8025–50/ATV; *sixth bar from left*, MBX-8025–100/ATV.

ATV appeared to provide some additional nonstatistically significant LDL-C lowering, as depicted in Fig. 1.

All treatment groups significantly decreased TG levels compared with placebo. MBX-8025 monotherapy at both doses reduced TG levels 26–30% ($P < 0.0001$). ATV monotherapy reduced TG levels by 14% ($P < 0.01$). Neither dose of MBX-8025 combined with ATV reduced TG significantly more than MBX-8025 alone. As was the case for LDL-C, the results suggested a trend toward greater TG reductions with MBX-8025 in those with the highest baseline TG values by tertile (Fig. 2), although this did not reach statistical significance.

MBX-8025 100 mg and MBX-8025 50 mg + ATV significantly increased HDL-C more than placebo. ATV monotherapy did not significantly increase HDL-C levels. In concordance with the pattern of change in HDL-C, Apo A-1 mean values generally increased from baseline for the MBX-8025 active treatment groups, except in the group treated with MBX-8025 100 mg + ATV.

Regarding other efficacy parameters, all treatment groups significantly reduced non-HDL-C levels more than
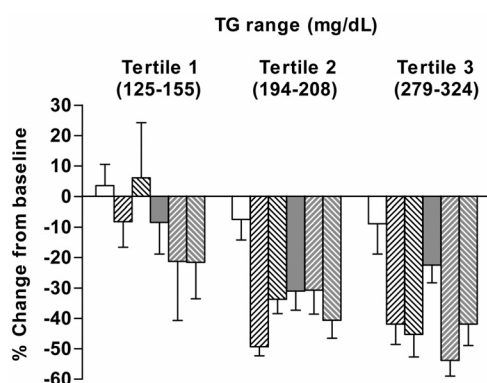
placebo ($P < 0.0001$). In contrast to ATV monotherapy, all MBX-8025 treatment groups significantly reduced FFA more than placebo ($P < 0.05$). All treatments also trended toward producing decreases in hsCRP, although generally these changes were not significant. Among a subpopulation of study subjects with baseline hsCRP of at least 2 mg/liter, MBX-8025 50 mg monotherapy, ATV monotherapy, and both doses of MBX-8025 combined with ATV all significantly reduced hsCRP more than placebo, ranging from −43% in monotherapy to −72% in combination ($P < 0.05$). Although MBX-8025 generally demonstrated favorable trends in a number of tertiary endpoints from baseline to end of treatment (*e.g.* fasting glucose, fasting insulin, HOMA-IR, percentage body fat, body lean mass, and waist circumference), only a reduction in median HOMA-IR of 27% in the MBX-8025 100 mg monotherapy group reached statistical significance. However, Fig. 3A shows that, with the exception of the
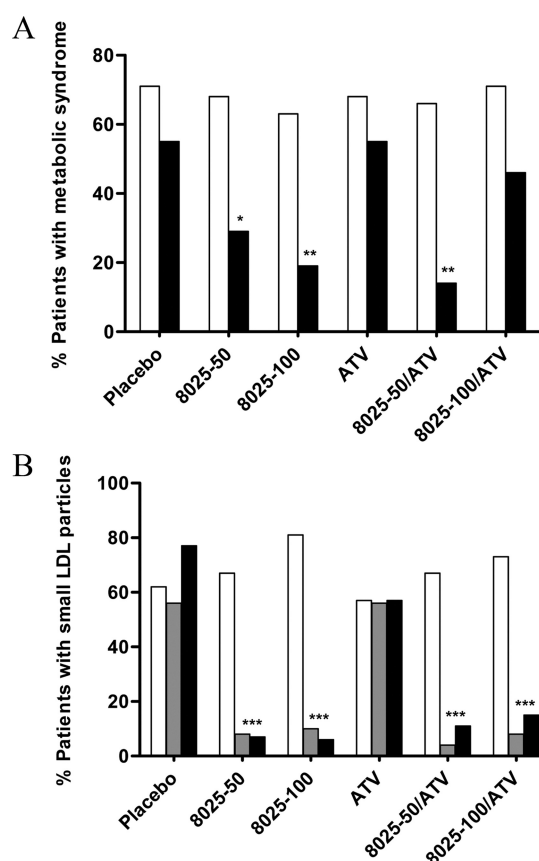
FIG. 3. A, Effects of MBX-8025 with or without ATV 20 mg on the percentage of subjects with metabolic syndrome compared with placebo and ATV alone. *, $P < 0.05$ vs. placebo and vs. ATV; **, $P < 0.01$ vs. placebo and vs. ATV. P values for pairwise treatment comparisons were estimated from logistic regression. *White bars*, baseline; *black bars*, 8-wk treatment. B, Effects of MBX-8025 with or without ATV 20 mg on the percentage of subjects with a preponderance of small LDL particles compared with placebo and ATV alone. ***, $P \leq 0.001$ vs. placebo and vs. ATV. P values for pairwise treatment comparisons were estimated from logistic regression. *White bars*, baseline; *gray bars*, 4-wk treatment; *black bars*, 8-wk treatment.

FIG. 2. Effects of MBX-8025 on TG levels by baseline TG (tertile) compared with placebo, with or without ATV 20 mg/d. *Leftmost bar*, Placebo; *second bar from left*, MBX-8025–50; *third bar from left*, MBX-8025–100; *fourth bar from left*, ATV; *fifth bar from left*, MBX-8025–50/ATV; *sixth bar from left*, MBX-8025–100/ATV.

combination of MBX-8025 100 mg + ATV, the metabolic effects of MBX-8025 monotherapy and combination therapy resulted in a significantly lower prevalence (14–29%) of the metabolic syndrome by ATP III criteria (22), compared with placebo and ATV alone ($P < 0.05$ or < 0.01).

Neither MBX-8025 monotherapy, ATV monotherapy, nor MBX-8025 + ATV combination therapy significantly altered blood pressure, body weight, BMI, glucose or insulin levels with glucose tolerance testing, leptin, or high molecular weight adiponectin.

LDL particle size groups

As shown in Fig. 3B, MBX-8025, with and without ATV, resulted in a significantly lower proportion of patients (10–20%) with a preponderance of small LDL particles compared with placebo and ATV alone ($P \leq 0.001$ for both).

Safety

Table 3 reports the safety summary of this study. In total, 250 AE (regardless of causality) were reported in 115 subjects during the course of this study and were generally balanced across the treatment groups. The three most frequent AE, and the only ones occurring in greater than 5% of study participants receiving study drug, were: upper respiratory tract infection (7.1%), nasopharyngitis (6.6%), and a predefined category of AE with potential attribution to muscle (defined in Table 3 footnote "b") (8.7%). Of the 250 AE found in this study, 32 in 24 subjects were considered "drug-related" as previously defined.

Three subjects experienced a total of six serious adverse experiences (SAE) during this study, all determined by the investigators to be unrelated to the study drug. One subject experienced atrial fibrillation and was diagnosed with esophageal carcinoma, one subject experienced moderate chest pain, and one subject experienced SAE of acute renal failure, pancreatitis, and rhabdomyolysis (after being found unconscious and severely dehydrated, attributed to angiotensin-converting enzyme-inhibitor and excessive nonsteroidal antiinflammatory drug use). All of the SAE resolved before conclusion of the study, with the exception of the esophageal carcinoma.

Five subjects withdrew due to AE. Two subjects on MBX-8025 100 mg + ATV combination were withdrawn due to asymptomatic elevations in CK (>10 times the ULN), judged to be study drug related. One of these had concomitant abnormal aspartate aminotransferase/alanine aminotransferase (although less than three times ULN with normal GGT and alkaline phosphatase). The second was the MBX-8025 100 mg + ATV combination subject with the previously described unrelated SAE of renal failure, pancreatitis, and rhabdomyolysis. Two patients on ATV monotherapy withdrew due to myalgia without increases in CK, thought to be study-drug related. No subjects treated with MBX-8025 monotherapy were withdrawn due to muscle AE or elevated CK.

Seven subjects had an AE of increased CK, including three of the subjects summarized above who were withdrawn. All were administered MBX-8025 with or without ATV, and all but one case were assessed by the respective investigators as being study-drug related; however, four of the cases were clinically mild, with CK values less than two or three times the ULN.

Subjects administered MBX-8025, regardless of combinational therapy, had mild but statistically significant decreases in mean red blood cell count, hemoglobin, and hematocrit from baseline compared with groups that did not receive MBX-8025 (mean decreases of 0.7 to 1.4% *vs.*

TABLE 3. MBX-8025 safety and tolerability, with and without ATV

AE	Placebo	8025-50	8025-100	ATV	8025-50/ATV	8025-100/ATV	Total
Safety population	31 (16.9)	29 (15.8)	32 (17.5)	31 (16.9)	30 (16.4)	30 (16.4)	183
Total AE	33 (13.2)	40 (16.0)[a]	49 (19.6)	55 (22.0)[a]	35 (14.0)[a]	38 (15.2)	250
Subjects with AE	20 (64.5)	17 (58.6)	20 (62.5)	23 (74.2)	18 (60.0)	17 (56.7)	115
Subjects with treatment-related AE	0 (0)	2 (6.9)	4 (12.5)	6 (19.4)	7 (23.3)	5 (16.7)	24 (13.1)
Subjects with SAE	0 (0)	0 (0)	0 (0)	1 (3.2)	0 (0)	2 (6.7)	3
Subjects with severe AE	1 (3.2)	1 (3.4)	0 (0)	2 (6.5)	1 (3.3)	1 (3.3)	6
Subjects who discontinued due to AE	0 (0)	0 (0)	0 (0)	2 (6.5)	0 (0)	3 (10.0)	5
AE occurring in ≥5% of subjects (no. of subjects with AE)							
Muscle tox AE[b]	2 (6.5)	3 (10)	2 (6.3)	4 (13)	2 (6.7)	3 (10)	16 (8.7)
Upper respiratory tract infection	3 (9.7)	1 (3.4)	3 (9.4)	3 (9.7)	2 (6.7)	1 (3.3)	13 (7.1)
Nasopharyngitis	3 (9.7)	3 (10.0)	2 (6.3)	1 (3.2)	3 (10.0)	0 (0.0)	12 (6.6)

All data are shown as number (%).

[a] One subject had two occurrences of the same preferred term AE in this regimen. For the purpose of this table, this AE is counted as two AE.

[b] An *a priori* predefined "super-category" of AE terms likely to indicate muscle pathology, including "myalgias," "muscle pain," "muscle cramps," "myopathy," "myositis," "muscle aches," "muscle weakness," "fibromyalgia," and "CPK increased" (>5 × ULN).

placebo, without dose-response). Platelet mean values were modestly but significantly increased from baseline in groups receiving MBX-8025. The highest mean value for any treatment group in platelet count was $342,000 \times 10^9$/liter (within the normal range). The highest platelet count in a subject treated with MBX-8025 was $609,000 \times 10^9$/liter, reflecting a 17% increase from an elevated baseline of $519,000 \times 10^9$/liter, whereas the highest platelet count in the study was a patient treated with placebo who had a value of $817,000 \times 10^9$/liter. White blood cell counts did not significantly change with any treatment group.

No subject in any treatment group experienced a liver transaminase elevation three times ULN or greater. In contrast, Table 2 describes how mean alkaline phosphatase and GGT levels decreased from baseline in subjects receiving MBX-8025, whereas mean GGT levels increased from baseline in subjects receiving ATV alone.

Discussion

Statins effectively lower cholesterol levels but may not correct all atherogenic metabolic parameters in patients with mixed dyslipidemia, including increased TG, increased non-HDL-C, decreased HDL-C, and increased proportion of small, dense LDL. Furthermore, statins do not improve metabolic parameters such as insulin resistance, hepatic steatosis, and body fat composition, and may even increase the risk of type 2 diabetes mellitus (24). Although statins are efficacious in reducing atherosclerotic coronary heart disease (CHD) risk by about 30%, statin-treated patients at high risk for CHD have substantial residual risk of CHD, supporting the potential benefits of therapies with complementary effects upon other proatherogenic factors. This study was performed to evaluate the metabolic effects of MBX-8025, a novel PPAR-δ agonist, with or without ATV.

This trial was a randomized, double-blind, placebo-controlled, parallel group study of 181 evaluable overweight men and women with mixed dyslipidemia, who were mostly Caucasian with mean age in their 50s, and with a high prevalence of the metabolic syndrome and small LDL particles. With few exceptions among individual groups, MBX-8025 50 mg and 100 mg significantly reduced Apo B-100, LDL-C, TG, non-HDL-C, FFA, and hsCRP (among those with elevated hsCRP at baseline); raised HDL-C; and resulted in a lower percentage of study participants meeting diagnostic criteria for the metabolic syndrome. MBX-8025 also resulted in a markedly lower proportion of participants with a preponderance of small LDL particles, a characteristic feature of the atherogenic dyslipidemia of the metabolic syndrome (20).

Combining MBX-8025 with ATV maintained the significant LDL-C and Apo B-100 lowering observed with ATV and produced added efficacy effects in reducing TG and non-HDL-C, small, dense LDL particles, and hsCRP. The combination of MBX-8025 with ATV 20 mg also reduced the number of patients meeting the diagnostic criteria for metabolic syndrome.

In a subpopulation with the highest baseline tertile of LDL-C levels, MBX-8025 added to ATV seemed to provide additive LDL-C lowering in this pilot study, with the same metabolic effect applying to TG levels. An appropriate add-on trial would be required to further explore this potential and optimize the combined use of MBX-8025 and statins.

In general, MBX-8025 did not significantly alter high molecular weight adiponectin, leptin, blood pressure, body weight, BMI, anthropomorphic measurements, body composition, glucose, insulin, or HOMA-IR. However, trends in improvements in insulin resistance and waist circumference, combined with the significant effects on TG and HDL-C levels, helped account for the lower number of participants meeting the diagnostic criteria of metabolic syndrome.

From a safety perspective, overall adverse experiences were generally similar among all treatment groups, and no drug-related SAE or deaths occurred in any treatment group. No study subjects withdrew from the study due to adverse experiences in the MBX-8025 monotherapy groups. However, three subjects receiving MBX-8025 100 mg in combination with ATV withdrew, at least in part, due to elevated CK. MBX-8025 was also associated with mild, but significant decreases in red blood cell count, hemoglobin, and hematocrit and moderate increases in platelet counts. A more complete understanding of the MBX-8025 safety profile requires a larger study. Otherwise, MBX-8025 reduced liver enzymes (*e.g.* GGT and alkaline phosphatase), conceivably due to a reduction in hepatic fat, which has been demonstrated with other PPAR-δ agonists in humans (13).

The findings of this study are generally consistent with the known metabolic effects of PPAR-δ receptor agonism. Although more needs to be learned, PPAR-δ nuclear receptors are ubiquitous proteins, being located in tissues such as skeletal muscle, heart, liver, and adipose tissue. The best described nonpharmacological ligands are fatty acids. Once activated, PPAR-δ nuclear receptors regulate the transcription of target genes related to lipid and glucose metabolism, energy storage, and other processes, which are effects largely dependent on the affiliated body tissue, and mechanistic effects consistent with the results of this study.

The constellation of effects observed with PPAR-δ agonists in preclinical and clinical studies to date suggest that these agents may be well-suited to address the multiple proatherogenic defects associated with mixed dyslipidemia. The mechanisms underlying these effects, their clinical significance, and the relative safety and efficacy of MBX-8025 compared with existing metabolic drug treatments merit further study in larger clinical trials.

Acknowledgments

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