Fasiglifam-Induced Liver Injury in Patients With Type 2 Diabetes: Results of a Randomized Controlled Cardiovascular Outcomes Safety Trial

Venu Menon,[1] A. Michael Lincoff,[1] Stephen J. Nicholls,[2] Susan Jasper,[1] Kathy Wolski,[1] Darren K. McGuire,[3] Cyrus R. Mehta,[4] Julio Rosenstock,[5] Claudia Lopez,[6] John Marcinak,[6] Charlie Cao,[6] and Steven E. Nissen,[1] for the GRAND 306 Investigators

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OBJECTIVE

To evaluate the cardiovascular (CV) safety of fasiglifam, a first-in-man G-protein–coupled receptor 40 (GPR40) agonist, in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

A phase 3 multicenter randomized double-blind placebo-controlled two-arm trial was intended to randomize 5,000 participants with type 2 diabetes at high CV risk to fasiglifam or placebo. The primary objective of the trial was to rule out an upper noninferiority bound >1.3 for a one-sided 97.5% confidence limit of the hazard ratio (HR) for CV composite events during treatment with fasiglifam compared with placebo. The primary outcome was the time to first occurrence of any component of the major adverse CV event composite of CV death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina.

RESULTS

The study enrolled 3,207 participants but was terminated because of liver safety concerns. Increased rates of liver enzyme elevation (AST/ALT ≥3–5 × upper limit of normal [ULN]) with fasiglifam were observed. The incidence of ALT or AST ≥3 × ULN with fasiglifam compared with placebo was 2.1% vs. 0.5%, $P < 0.001$, and the incidence for ≥10 × ULN was 0.31% vs. 0.06%, $P < 0.001$. A primary CV composite outcome occurred in 40 participants, 2.5% each in the fasiglifam and placebo arms at 12 months (HR 1.05; 95% CI 0.67, 1.63).

CONCLUSIONS

Development of fasiglifam was terminated due to concerns of drug-induced liver injury. Performance of a U.S. Food and Drug Administration–mandated CV outcomes trial supported the termination of the fasiglifam clinical program.

The G-protein–coupled receptor 40 (GPR40), a free fatty acid receptor 1, is a cell surface receptor expressed in the β-cells of human pancreatic islets (1,2). In the setting of an elevated glucose concentration, stimulation of this receptor by fatty acids as endogenous ligands or administration of synthetic ligands has been shown to enhance glucose-related insulin secretion (3,4). These findings led to the investigation of a new potential pharmacologic target in type 2 diabetes to effectively lower blood glucose with a low risk of hypoglycemia.

[1]Cleveland Clinic Coordinating Center for Clinical Research (C5Research), Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH
[2]South Australian Heart and Medical Research Institute, The University of Adelaide, Adelaide, Australia
[3]Division of Cardiology, Department of Internal Medicine, The University of Texas Southwestern Medical Center, Dallas, TX
[4]Cytel, Inc., Cambridge, MA
[5]Dallas Diabetes Research Center at Medical City, Dallas, TX
[6]Takeda Development Center Americas, Inc., Deerfield, IL

Corresponding author: Venu Menon, menonv@ccf.org.

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Fasiglifam (TAK-875), an investigational oral selective GPR40 agonist, was developed to be a first-in-class agent and demonstrated effectiveness in lowering blood glucose in patients with type 2 diabetes in a 12-week phase 2 randomized double-blind placebo- and active comparator (glimepiride)-controlled trial (5). In this trial, fasiglifam was well tolerated and demonstrated dose-response decreases in both HbA_{1c} and 2-h glucose area under the curve during oral glucose tolerance testing from 6.25 mg to 200 mg per day. Similar findings were also observed in a phase 2 trial in Japanese participants receiving 50 mg of fasiglifam, showing reductions in HbA_{1c} similar to that achieved with glimepiride (6). In another 24-week phase 3 double-blind placebo-controlled trial in Japanese patients, a significant improvement in glycemic control was also noted (7). These promising preliminary data resulted in the initiation of a large phase 3 program to evaluate the safety and efficacy of fasiglifam for the management of type 2 diabetes. In accordance with the U.S. Food and Drug Administration (FDA) guidance for the approval of new agents in type 2 diabetes, the development program included a cardiovascular (CV) safety trial of fasiglifam (8). Here we describe the design, conduct, and results of this CV outcomes trial obtained by the time the overall program was withdrawn.

RESEARCH DESIGN AND METHODS

Eligibility and Study Design

This was a phase 3 global multicenter randomized double-blind placebo-controlled two-arm trial designed to evaluate the CV safety of fasiglifam compared with placebo when added to standard of care in patients with type 2 diabetes at high CV risk. The primary objective of the trial was to determine whether a one-sided upper 97.5% CI of the hazard ratio (HR) for a composite of CV events could rule out an HR of >1.3 for fasiglifam compared with placebo when given in combination with standard of care in subjects with type 2 diabetes and either clinically documented CV disease or multiple risk factors for CV events. An executive steering committee (ESC), consisting of academic members and two nonvoting representatives from the sponsoring company (Takeda Pharmaceuticals), designed the trial and was responsible for its conduct and for the presentation and publication of results. The trial was managed by an academic research organization, Cleveland Clinic Coordinating Center for Clinical Research (C5Research), in concert with the trial sponsor and a contract research organization, Quintiles. An independent data monitoring committee (DMC), consisting of physicians and statisticians, monitored the safety of the study and had access to unblinded data at prespecified intervals across the development program.

During preclinical development, hepatotoxicity was observed in dogs at doses of fasiglifam that did not indicate that these findings would be observed in humans at efficacious doses (unpublished data). Consequently, as part of the trial design, an independent liver safety evaluation committee (LSEC) was established, including experts in the field of drug-induced liver injury who were tasked with evaluating any potential liver safety events or suspected liver injury over the course of the trial. The LSEC applied a structured adjudication process as recommended by the U.S. Drug-Induced Liver Injury Network (DILIN) (9). Recommendations and findings of this committee were directly communicated to the DMC, without direct communication with the ESC.

Statistical analyses were performed by Takeda Pharmaceuticals, the trial sponsor, and independently replicated by a trial statistician at the academic research organization, C5Research at the Cleveland Clinic, who had independent access to the entire study database. The draft of the manuscript was written by the ESC, which takes responsibility for the accuracy and completeness of the reported data.

Study Patients

The trial (ClinicalTrials.gov identifier NCT01609582) was approved by the national and local ethical oversight committees for all participating sites, and all enrolled subjects provided written informed consent. Detailed inclusion criteria are presented in the Supplementary Data. In brief, participants 18 years of age or older with a diagnosis of type 2 diabetes and with an HbA_{1c} 7.0–10.5% were considered for participation. To be eligible for the trial, they were also required to have either prevalent atherosclerotic CV disease (prior myocardial infarction, symptomatic peripheral arterial disease, or cerebrovascular disease) or ≥ 1 CV risk factors (stable angina, multivessel coronary disease, history of percutaneous coronary intervention, or specific clinical criteria as outlined in the Supplementary Data).

Enrolled participants were advised to monitor glucose with a home monitor and consistently record blood glucose concentrations in diaries. Women of childbearing potential and sexually active with a nonsterilized male partner had to agree to use adequate contraception throughout the duration of the trial and for 30 days after last dose of study medication. Major exclusion criteria included prior exposure to any investigational medication within 30 days prior to screening or any exposure to investigational medication for diabetes or excluded medications within 3 months prior to potential study enrollment. Additional exclusion criteria were an ALT and/or AST level $>3.0 \times$ upper limit of normal (ULN), a total bilirubin level $>$ULN at screening, a known history of active infection with hepatitis B virus or hepatitis C virus requiring antiviral treatment, HIV disease, a history of drug or alcohol abuse within the 2 years prior to screening, or an estimated glomerular filtration rate ≤ 15 mL/min/1.73 m^2 based on MDRD calculation.

Trial Drugs and Procedures

The trial intended to enroll ~5,000 participants with type 2 diabetes to be randomly assigned to study drug versus placebo across 700 sites globally. Randomization was stratified based on CV risk (prevalent disease vs. risk factors) and country of enrollment. On trial day 1, subjects were randomly assigned in a 1:1 ratio through an interactive telephone/web system to either fasiglifam 50 mg or matching placebo orally once daily in addition to standard of care. Subsequent clinic visits were scheduled monthly for the first 3 months, followed by additional visits at 4.5, 6, 7.5, 9, 10.5, and 12 months during the first year, then at months 16, 20, 24, and 30, with subsequent visits every 6 months thereafter during trial participation. The trial was intended to be an event-driven trial, and this would govern duration of study participation. As part of safety evaluation, routine centralized liver function testing was scheduled at 2, 4.5, 7.5, 10.5, 12, 16, 20,

24, and 30 months and every 6 months until end of trial.

Outcomes

The primary outcome of the trial was the time to first occurrence of any component of the primary major adverse CV event (MACE) composite of CV death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina (with or without revascularization). The secondary outcome included the time to first occurrence of the narrower composite outcome of any component of the triple end point of CV death, nonfatal myocardial infarction, and nonfatal stroke. An independent clinical events committee blinded to treatment adjudicated suspected trial outcomes using standard definitions proposed by the FDA (10).

Statistical Analysis

The primary analysis was by intention to treat to assess CV safety of fasiglifam versus placebo in terms of noninferiority. A two-step process in accordance with the FDA guidance was implemented. An initial interim analysis following the accrual of 60, 80, 100, 125, and 150 adjudicated primary MACE across multiple phase 2 studies in the development program was planned for an initial premarketing assessment. The goal of this process was to initially exclude a one-sided upper 97.5% CI of the HR of 1.8 for fasiglifam compared with placebo. As per the FDA guidance, achieving this goal would enable a New Drug Application submission for initial marketing approval while the concurrent CV outcomes trial was completed. If noninferiority of fasiglifam was confirmed during preliminary analyses, the CV trial would proceed to completion. Processes were in place to ensure that the unblinded interim results would only be available to a small team at the sponsor, who would not have subsequent involvement in the ongoing trial. This masked process would enable initiation of regulatory filing while continuing the FDA-mandated CV trial to assess whether the upper bound of 1.3 for a one-sided 97.5% CI for MACE could be excluded. Superiority would be assessed only if the noninferiority criteria were met. Two interim analyses and one final analysis were planned after accrual of ~325, 480, and 650 adjudicated primary MACE outcomes. The significance level at each analysis would be derived using O'Brien-Fleming boundaries with a one-sided overall type I error of 2.5% (using critical *P* values of 0.0015, 0.0086, and 0.0222, respectively).

We estimated a placebo event rate for the primary outcome of 3.0% annually and anticipated a yearly lost–to–follow-up rate of 1%. Using these assumptions, the trial intended to enroll a total of 5,000 participants (2,500 per treatment arm) over 24 months. A group sequential analysis after 650 adjudication-confirmed events would provide ~91% power to assess noninferiority of fasiglifam compared with placebo with a noninferiority margin of 1.3, a true HR of 1.0, and an overall one-sided 2.5% significance level. The cumulative power at the first (325 events) and second (480 events) interim analyses was expected to be about 28% and 70%, respectively, to declare noninferiority per the above assumptions and 99% power for an HR of 0.80 at study termination (650 events). The premarketing phase of the study also accounted for group sequential analyses after 60, 80, 100, 125, and 150 adjudication-confirmed events, which would provide ~94% power to declare noninferiority of fasiglifam to placebo with a noninferiority margin of 1.8, a true HR of 1.0, and an overall one-sided 2.5% significance level.

Due to premature study termination, all primary and secondary events were censored at 12 months. HRs and 95% CIs were calculated using the Cox proportional hazards model, with randomized treatment as a factor. Kaplan-Meier methodology was used to generate time-to-event plots. Categorical data were assessed using the Fisher exact test or χ^2 test, as appropriate. All statistical analyses were performed using SAS software (version 9.3; SAS Institute Inc., Cary, NC).

Early Termination

Recruitment into the trial began on 1 June 2012. As part of ongoing trial surveillance, the DMC observed increased rates of biochemical liver injury with exposure to fasiglifam compared with placebo. Based on the observations of the DMC, and with additional insight provided by the LSEC, the sponsor and executive committee mutually decided to terminate the fasiglifam clinical development program including this trial on 21 December 2013. Although the DMC found insufficient efficacy data to make any reliable inference, the committee found no reason to believe that there were unique attributes of fasiglifam to justify a profile of clear liver toxicity risk. At study termination, a total of 3,207 of the planned 5,000 participants had been enrolled and randomized to receive fasiglifam (n = 1,604) or placebo (n = 1,603). The study flow is illustrated in the Supplementary Data. At study termination, <1% of participants were lost to follow up and similar numbers of subjects withdrew from the treatment and placebo arms of the trial.

RESULTS

Baseline characteristics of study participants are presented in Table 1. The median duration of exposure to fasiglifam and placebo were 248 and 249 days, respectively. The median HbA_{1c} at study entry was similar in the fasiglifam and placebo groups (8.2% vs. 8.1%, P = 0.08), as were median fasting plasma glucose levels (168 vs. 164 mg/dL, P = 0.23). At 3 months, the median HbA_{1c} (n = 1,254) in the placebo arm was 7.8%, representing a median change from baseline of −0.3%; in contrast, among patients randomized to fasiglifam, the median HbA_{1c} was 7.4%, representing a median decrease from baseline of −0.8% ($P < 0.001$ for difference compared with placebo). Temporal changes in HbA_{1c} levels over the study duration are illustrated in the Supplementary Data.

At trial termination, a primary CV event had occurred in 40 participants (2.5%) each in the fasiglifam and placebo arms (HR 1.05; 95% CI 0.67, 1.63). The Kaplan-Meier curve of the time to initial primary CV event is illustrated in Fig. 1 (upper panel) and is similar for the fasiglifam and placebo groups. Of note, the secondary CV outcome of death, myocardial infarction, and stroke occurred in 27 participants (1.7%) exposed to fasiglifam compared with 35 (2.2%) receiving placebo (Fig. 1, lower panel).

Table 2 illustrates the timing and rates of liver function test abnormalities (AST and ALT ≥3 × ULN) during the course of the trial. While numerically small, rates of enzyme elevation were higher with fasiglifam compared with placebo with absolute differences noted as early as 1 month following randomization. No cases were observed of elevation in

Table 1—Demographics and baseline characteristics of study population

	Fasiglifam, *n* = 1,604	Placebo, *n* = 1,603
Age, years	63.4 ± 9.2	63.9 ± 9.0
Aged ≥65 years	753 (47)	809 (51)
Men	1,041 (65)	1,060 (66)
Duration of diabetes, years	12.3 (7.0–17.8)	12.5 (7.5–17.8)
HbA_{1c}, %	8.2 (7.5–9.0)	8.1 (7.5–8.9)
BMI, kg	32.4 ± 7.5	32.1 ± 6.1
White race	1,246 (78)	1,265 (79)
Enrollment in U.S.	559 (35)	559 (35)
Current smoker	328 (20)	330 (21)
Prior hypertension	1,146 (71)	1,140 (71)
Prior myocardial infarction	408 (25)	431 (27)
Prior percutaneous intervention	213 (13)	207 (13)
Prior coronary-artery bypass grafting	57 (4)	77 (5)
Prior heart failure	173 (11)	193 (12)
Prior stroke	129 (8)	134 (8)
Prior peripheral artery disease	108 (7)	102 (6)
Medications administered at baseline		
Insulin	778 (49)	777 (48)
Biguanides	1,056 (66)	1,075 (67)
Sulfonylureas	640 (40)	659 (41)
Thiazolidinediones	57 (4)	48 (3)
DPP-4 inhibitors	180 (11)	179 (11)
Aspirin	721 (45)	710 (44)
Clopidogrel	525 (33)	540 (34)
Diuretics	591 (37)	636 (40)
β-Blockers	932 (58)	961 (60)
Calcium-channel blockers	481 (30)	530 (33)
ACE inhibitors	866 (54)	844 (53)
Angiotensin II agonists	443 (28)	493 (31)
Statins	1,218 (76)	1,225 (76)

Data are mean ± SD, median (interquartile range), or *n* (%). DPP-4, dipeptidyl peptidase 4.

serum total bilirubin ≥2 × ULN in association with elevation of liver transaminases. There was one case of a patient with an ALT >20 × ULN and total bilirubin of 1.9 mg/dL (1.6 × ULN). This case was adjudicated by the LSEC as a near Hy's law case. The incidence of ALT or AST ≥3 × ULN with fasiglifam compared with placebo was 2.1% vs. 0.5%, $P < 0.001$, and the incidence for ≥10 × ULN was 0.31% vs. 0.06%, $P < 0.001$. At the final study visit, the mean change in AST levels in the placebo group from baseline was −1.0 units/L (*n* = 1,511) compared with +2.4 units/L with fasiglifam (*n* = 1,509; $P < 0.001$). Similarly, mean ALT levels at the final trial visit were −1.3 units/L for placebo compared with +4.2 units/L for fasiglifam, $P < 0.001$. To highlight individual patient liver function test responses to fasiglifam and placebo, Fig. 2 highlights the most extreme observations for bilirubin versus AST/ALT for each trial participant during the course of the trial. The horizontal dotted line corresponds to a bilirubin levels of 2 × ULN and the vertical dotted line corresponds to transaminase level of 3 × ULN. This results in four quadrants with the top left representing participants exhibiting isolated hyperbilrubinemia and the top right participants who fulfill criteria for Hy's law (11). The bottom left quadrant represents individual participants within the normal range, and the bottom right shows study participants who met criteria for liver injury during the course of the trial (Temple's Corollary range). A clear hazard for increased risk with fasiglifam exposure is noted. No significant biochemical elevations of alkaline phosphatase were noted during study conduct. No cases fulfilling Hy's law (ALT or AST >3 × ULN simultaneous with total bilirubin >2 × ULN) were noted, although there was one case of near Hy's law identified (11). The overall rates of other adverse and serious adverse events encountered during study participation were comparable between the randomized groups as detailed in the Supplementary Data.

CONCLUSIONS

The fasiglifam drug development program was terminated due to evidence of increased liver injury in subjects with type 2 diabetes exposed to this agent. Although GPR40 agonism with fasiglifam resulted in a modest decrease in HbA_{1c} without increased risk for hypoglycemia, the signal for liver injury with exposure to fasiglifam was thought to far outweigh any potential benefits of glycemic control and low risk of hypoglycemia with this agent. No excess CV events were noted with exposure to fasiglifam when the study was terminated.

Drug-induced liver failure is the most common etiology of acute hepatic failure in the developed world (12,13). Occurrence of drug-induced liver injury (DILI) is a recognized hurdle in drug development and is the most frequent reason for regulatory intervention by the FDA (14,15). Although dose-dependent mechanisms of DILI can be identified during early drug development in preclinical and early clinical studies confined to animals and healthy volunteers, identification and characterization of low frequency idiosyncratic drug-induced liver injury at this stage is both challenging and unlikely. Infrequent DILI events may also be difficult to distinguish from background events in the placebo arm and can also go unrecognized during the entire phase 2/3 developmental program and approval process. As a result, these low frequency events may only be recognized during postmarketing surveillance when large numbers of patients are exposed, as was the case with troglitazone and bromfenac (16,17). During the clinical development of troglitazone, a first-in-class peroxisome proliferator–activated receptor γ agonist for use in type 2 diabetes, 1.9% (48/2,510) of patients had an ALT elevation to >3 × ULN, 0.8% had an ALT >8 × ULN, and 0.2% had ALT >30 × ULN. Following drug approval, over 2 million patients were exposed, resulting in 94 cases of liver failure before it was withdrawn from the market.

The mechanism of liver injury with fasiglifam in the CV outcomes trial remains uncertain. A similar pattern of hepatic injury was also observed with fasiglifam across other ongoing studies

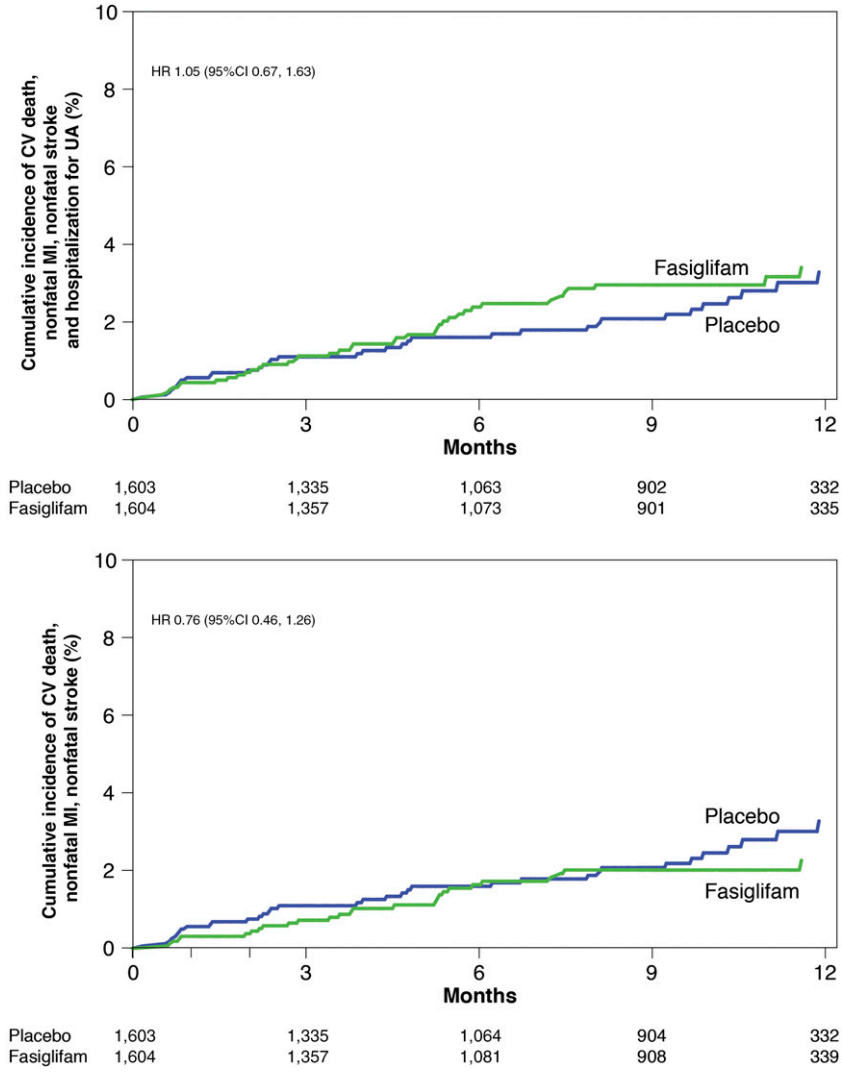

Figure 1—Kaplan-Meier survival curves for the primary composite outcome of death, nonfatal myocardial infarction, and nonfatal stroke and hospitalization for unstable angina (UA) (upper panel) and for the secondary composite outcome of death, nonfatal myocardial infarction (MI), and nonfatal stroke (lower panel).

in the phase 3 program by the shared DMC. In an open-label phase 3 Japanese study, higher rates of elevated transaminases were noted with fasiglifam 50 mg daily as compared with a 25-mg dose (18). Numerically greater rates were also noted in small phase 3 placebo-controlled trials evaluating fasiglifam that enrolled worldwide or were restricted to Japan (7,19). In addition, there was one near Hy's law case identified in the CV outcomes trial that was important in the decision to terminate the fasiglifam clinical program.

The timing of the elevation of liver transaminases appears heterogeneous, suggesting a variable latency and an idiosyncratic mechanism. In a recent animal study by Li et al. (20) using intravenous fasiglifam dosages of 100 mg/kg, the investigators evaluated the effects of fasiglifam on hepatobiliary transporters in a rat model. They reported that fasiglifam inhibited the efflux transporter multidrug-resistance associated proteins (MRP2/Mrp2) and uptake transporters Na^+ taurocholate cotransporting peptide (Ntcp) and organic anion transporting polypeptide (OATP/Oatp) with potential detrimental effects on bile acid and bilirubin homeostasis. Fasiglam was also noted to alter bile acid homeostasis in both dogs and rats in another study (21). It is uncertain whether the observed liver injury represents a specific drug effect or a class effect intrinsic to this novel target. Given the number of alternate agents currently available for type 2 diabetes, the future development of fasiglifam could not be justified given the observed liver injury signal. Other more potent GPR40 agonists such as AMG 837 and AM-4668 remain in development (22,23).

Consistent with previous trials, activation of GPR40 with fasiglifam was associated with an improvement in glycemic control compared with placebo, each added to standard of care. While the absolute degree of glucose reduction associated with fasiglifam cannot be determined in the context of this study design, the degree of HbA_{1c} lowering in the treatment arm was similar to that noted in recent CV trials evaluating the safety of dipeptidyl peptidase 4 or sodium–glucose cotransporter 2 inhibitors (24–27). If the observed liver injury in the present trial is not due to a class effect with this mechanism, GPR40 agonism may yet prove to be a novel target for the treatment of type 2 diabetes that may provide additional value in combinations with other agents with different mechanisms of action.

No conclusions regarding the CV safety of fasiglifam are possible given the early termination of the trial with only 80 primary end point events accrued; up to 150 events had been expected to be required to establish the upper limit of the CI for the HR of <1.8 in the premarketing phase and up to 650 events to establish the upper limit of CI <1.3 for the postmarketing phase. However, at study termination, the secondary outcome (currently preferred CV outcome recommended by the FDA) showed an HR of 0.76 (95% CI 0.46, 1.26), while the primary composite end point had an HR of 1.05 (95% CI 0.67, 1.63), both of which were within the safety parameters that would enable potential marketing approval.

The findings of our study also highlight the role of the FDA guidance in requiring CV outcomes trials for newer agents for type 2 diabetes. Prior to the guidance, approval of agents for type 2 diabetes was focused on proving safety and glycemic efficacy in trials that were of relatively short duration, 6–12 months, including participants at low risk for complications. As a result, the effect of these agents on modifying CV risk, the major cause of morbidity in patients with diabetes, was poorly defined. Following the mandate of the guidance, large outcomes trials have helped define the safety and efficacy of novel agents in type 2 diabetes, in patients both with and

Table 2—Timing and number of participants with abnormal liver transaminases (ALT/AST ≥3 × ULN)

	Elevated AST ≥3 × ULN		Elevated ALT ≥3 × ULN	
	Placebo	Fasiglifam	Placebo	Fasiglifam
Baseline	2/1,603	2/1,601	3/1,603	4/1,601
During treatment	4/1,511 (0.3%)	21/1,509 (1.4%)	6/1,511 (0.40%)	32/1,510 (2.1%)
Month 1	0/1,485	3/1,487	1/1,488	4/1,490
Month 2	1/1,341	4/1,327	1/1,342	5/1,328
Month 3	1/1,223	4/1,211	1/1,225	5/1,212
Month 4.5	1/1,069	4/1,079	0/1,070	7/1,080
Month 6	1/961	2/959	2/963	8/962
Month 8	0/925	1/917	0/926	4/917
Month 9	0/672	2/677	2/672	3/678
Month 10	0/377	1/381	1/379	2/381
Month 12	0/260	1/251	0/261	1/251
Month 16	0/67	0/68	0/67	0/68
Month 20	0/2	0/5	0/2	0/5
Final visit	2/1,511	12/1,509*	1/1,511	22/1,510#

*P = 0.007 by Fisher exact test. #P = 0.0005 by Fisher exact test.

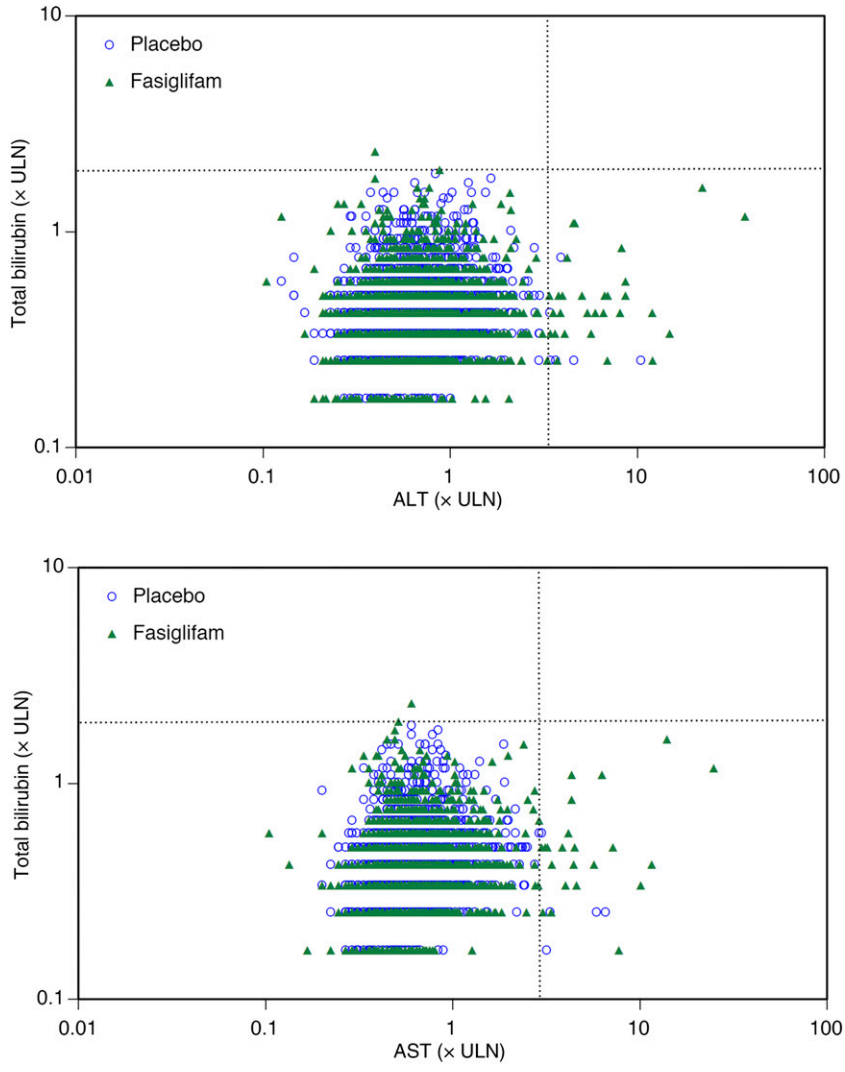

Figure 2—Evaluation of drug-induced serious hepatotoxicity plot for total bilirubin (× ULN) vs. ALT (× ULN) for fasiglifam and placebo (*A*) and for total bilirubin (× ULN) vs. AST (× ULN) for fasiglifam and placebo (*B*).

at risk for developing CV complications. The CV safety of saxagliptin, alogliptin, and sitagliptin on the end points of CV death, myocardial infarction, and stroke has now been established (24–26). The FDA has reported an increased risk of heart failure with saxagliptin and alogliptin and recommends caution when utilizing other agents in the class like sitagliptin and linagliptin. For the first time, agents have been identified that reduce CV morbidity and mortality in subjects with type 2 diabetes at high risk for CV events: empagliflozin, canagliflozin, liraglutide, and semaglutide (27–30). The FDA requirement to conduct the fasiglifam CV outcomes trial with a large number of patients and a longer duration of treatment provided important information about liver safety that supported the termination of the fasiglifam clinical program. Thus, although the FDA guidance was intended primarily to elucidate the effects of diabetes agents on CV risk, the resultant trial designs have also improved our ability to detect off-target low frequency non-CV safety signals prior to marketing, preventing unnecessary risk exposures.

Author Contributions. V.M. was responsible for trial design and conduct and interpretation of trial results and is the primary author of the manuscript. A.M.L., S.J.N., D.K.M., C.R.M., J.R., C.L., J.M., and S.E.N. were responsible for trial design and conduct, interpretation of trial results, and review and editing of the manuscript. S.J. was responsible for conduct of the trial and review of the manuscript. K.W. was responsible for statistical analysis, interpretation of results, and review and editing of the manuscript. C.C. was responsible for trial design and conduct, statistical analysis, interpretation of trial results, and review and editing of the manuscript. V.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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