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MEETING REPORT

AMERICAN DIABETES ASSOCIATION – 71ST SCIENTIFIC SESSIONS

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SUMMARY

The 71st American Diabetes Association (ADA) Scientific Sessions convened to bring together all the major players in research focusing on diabetes from a wide range of backgrounds to discuss a variety of topics, including basic, clinical and translational research, exercise and nutrition, and the array of comorbidities associated with the disease (e.g., retinal damage, cardiovascular disease and foot damage). These and many other subjects were discussed in symposia, debates, interest groups, state-of-the-art lectures, oral presentations and general poster sessions, as well as special lectures and addresses. With the continued increase in the cases of diabetes worldwide, with the U.S. alone having an estimated 26 million adult diabetics and predicted to potentially affect a third of all the U.S. population by 2050, this annual conference remains a valuable forum for sharing data to conquer this disease.

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TREATING DIABETIC NEPHROPATHY

As the leading cause of end-stage renal disease, diabetic nephropathy is a key area of research in diabetes. Bo Yeong Jong from Ewha Woman's University gave a presentation focused on targeting plasminogen activator inhibitor 1 (PAI-1), which favors extracellular matrix (ECM) accumulation in chronic kidney disease. Virtual screening led to the prototypic compound TM-5007, from which further structure–activity relationships led to TM-5275, which also showed antithrombotic benefits in rats and non-human primates, and TM-5441, which inhibited tissue plasminogen activator/PAI-1 complex formation. These compounds were studied in renal injury in streptozotocin (STZ)-induced diabetic mice. Oral TM-5275 (10 and 50 mg/kg/day) or TM-5441 (2 and 10 mg/kg/day) was administered for 16 weeks to diabetic and control mice. At 16 weeks after the injection of STZ, diabetic mice showed significantly increased plasma glucose levels of 575 and 588 mg/dL, respectively, for TM-5275 10 and 50 mg/kg/day, and 515 and 579 mg/dL, respectively, for doses of 2 and 10 mg/kg/day TM-5441; control mice receiving either 50 mg/kg of TM-5275 or 10 mg/kg of TM-5441 showed plasma glucose levels of 153 and 167 mg/dL, respectively. The treated mice also exhibited increased plasma creatinine levels, glomerular volume, fractional mesangial area and urinary albumin excretion compared with controls. The kidney-to-body weight ratio for mice treated with TM-5275 10 and 50 mg/kg/day was 9.7 and 9.3 g/kg, respectively, and 8.4 and 10.1 g/kg, respectively, for TM-5441 doses of 2 and 10 mg/kg/day; control mice receiving either 50 mg/kg of TM-5275 or 10 mg/kg of TM-5441 showed a kidney-to-body weight ratio of 5.9 and 5.6 g/kg, respectively. Furthermore, upregulation of renal PAI-1, fibronectin, collagen I, α-smooth muscle actin (α-SMA) and macrophage infiltration was also seen in diabetic mouse kidneys. TM-5275 or TM-5441 effectively inhibited albuminuria, renal and glomerular hypertrophy, and ECM accumulation in diabetic kidneys.

A notable feature of diabetic nephropathy is deposition of type IV collagen in the mesangial matrix. Mothers against decapentaplegic homolog 1 (SMAD family member 1, SMAD 1) transcriptionally regulates Col4 and α-SMA in vitro. Takashi Matsuba from Kyoto

University discussed the role of SMAD 1 signaling in diabetic nephropathy in vivo. Smad1-overexpressing (Smad1-Tg) mice did not show any glomerular lesions, but STZ-induced diabetic Smad1-Tg mice showed more prominent mesangial expansion and phosphorylation of Smad1 than diabetic wild-type mice; marked albuminuria was seen after induction of diabetes, and there was no difference in blood pressure or diabetic states between Smad1-Tg and wild-type mice. Bone morphogenetic protein 4 (BMP-4) was studied for the progression of diabetic nephropathy in vivo. Using RT-qPCR of RNA from isolated glomeruli, the expression of BMP-4 and its receptor was found to be increased along with phospho-Smad1 in STZ-induced diabetic mice at 36 weeks. It was confirmed by immunohistochemistry that increased BMP-4 occurred in podocytes and tubules, whereas its receptor bone morphogenetic protein receptor type-1A (activin receptor-like kinase 3, ALK-3) mainly increased in the mesangial area. Tamoxifen-inducible BMP-4 transgenic mice showed increased BMP-4 expression in glomeruli, resulting in marked mesangial matrix expansion even in the absence of diabetes. STZ mice treated with a neutralizing antibody against BMP-4 from 20 to 36 weeks showed a significant decrease in Smad1 phosphorylation, resulting in less mesangial expansion and Col4 accumulation than control animals. In mesangial cells, the treatment concentration-dependently inhibited the transcription of Col4 and α-SMA. BMP-4 increased the expression of α-SMA, which was blocked by an inhibitor of Smad1 phosphorylation. Overexpression of constitutive active Smad1 increased the transcriptional activity of α-SMA; an inactive form lacking phosphorylation sites eliminated this increase.

SELENOPROTEIN AND CARDIOVASCULAR DISEASE

Amanda Cox (Wake Forest University) discussed the investigation of selenoprotein S (SelS; located on the endoplasmic reticulum and plasma membrane) for its association with a range of inflammatory markers. The role of SelS genetic variants was considered in terms of cardiovascular disease (CVD) risk in patients with type 2 diabetes. The association of 10 single nucleotide polymorphisms (SNPs) tagging the *SELS* gene was evaluated with subclinical CVD phenotypes, including coronary, carotid and aortic calcified plaque and intima–media thickness, C-reactive protein (CRP) concentrations and HbA1c; the study (Diabetes Heart Study) was carried out in 1,220 European Americans. Four of the SNPs considered (rs34713741, rs28665122, rs12917258 and rs4965373) showed a significant association with at least one of the vascular calcification phenotypes. The two most associated SNPs were rs34713741 and rs12917258, which were associated with coronary ($P = 1.25 \times 10^{-5}$, beta value = −0.547 and $P = 3.79 \times 10^{-6}$, beta value = −0.542, respectively), carotid ($P = 9.94 \times 10^{-6}$, beta value = −0.561 and $P = 1.75 \times 10^{-7}$, beta value = −0.626, respectively) and aortic calcified plaque ($P = 1.41 \times 10^{-4}$, beta value = −0.501 and $P = 5.68 \times 10^{-6}$, beta value = −0.547, respectively) under an additive model of inheritance, as well as with both CRP ($P = 0.0279$, beta value = −0.154 and $P = 0.0343$, beta value = −0.142, respectively) and HbA1c ($P = 0.0022$, beta value = −0.033 and $P = 6.45 \times 10^{-5}$, beta value = −0.041, respectively); these SNPs were also associated with all-cause mortality ($P = 0.0279$, beta value = −0.154 and $P = 0.0343$, beta value = −0.142, respectively) over a follow-up period of 7.3 years.

SK CHEMICALS' 11-β-HSD1 INHIBITOR

Inhibiting 11-β-hydroxysteroid dehydrogenase 1 (11-β-HSD1) as a potential therapeutic option for the treatment of type 2 diabetes and metabolic syndrome was described in a poster by Hye Young Han and colleagues from SK Chemicals. 11-β-HSD1 is a key enzyme that converts inactive cortisone to active cortisol (a key metabolic regulator that upregulates gluconeogenesis in the liver and downregulates glucose uptake in muscle and adipose tissue). 11-β-HSD1 is also highly expressed in liver and adipose tissues, and correlates positively with obesity, dyslipidemia, insulin tolerance and diabetes. In in vitro assays, IC_{50} values for the selected compound SKI-2852 (also referred to as NCE-402) for human 11-β-HSD1 and HEK-293 cells stably expressing human 11-β-HSD1 were 2.9 and 3.9 nM, respectively; in comparison, for AMG-221 (Amgen) the respective values were 9.2 and 18.4 nM. SKI-2852 showed over 1,000-fold selectivity against mineralocorticoid (MR) and glucocorticoid (GR) receptors. In a pharmacokinetic assay, SKI-2852 showed significantly reduced 11-β-HSD1 activity in liver at doses of 1, 3 and 10 mg/kg after 2 hours; after 6 hours, activity was only seen with the dose of 1 mg/kg. The compound was tested in *ob/ob* mice and showed reduced glucose levels (34% compared with vehicle), HbA1c levels (1.8%, vehicle-corrected) and cholesterol levels; total cholesterol for vehicle, sitagliptin, rosiglitazone and SKI-2852 was 340, 276, 279 and 283 mg/dL, respectively; body weight gain was 8.27, 9.35, 17.76 and 4.65 g, respectively. In a KK-Ay mouse model, reduced HbA1c levels (1.36%) were seen, as well as improved lipid profiles; total cholesterol for vehicle, sitagliptin and 3, 10 and 20 mg/kg of SKI-2852 was 162, 198, 145, 132 and 155 mg/dL, respectively. Following SKI-2852 administration in the DIO mouse model, there was significant inhibition of fat body mass gain and whole body weight increase, which was comparable to sitagliptin 20 mg/kg, although lean body mass gain was much improved over sitagliptin. In a hyperinsulinemic euglycemic clamp study, these mice showed significantly increased whole body and hepatic insulin sensitivity with SKI-2852 treatment.

FREE FATTY ACID RECEPTOR FFA1 AGONIST CNX-011-67

Activation of free fatty acid receptor FFA1 (GPR40) has been shown to enhance insulin sensitivity. Jagannath Madanahalli and colleagues from Connexios Life Sciences described a highly selective, potent and safe FFA1 receptor agonist, CNX-011-67, which enhanced glucose responsiveness and insulin secretion in isolated rat and human islets. At a glucose concentration of 17 mM, insulin was > 0.3 ng/islet in untreated animals and approximately 0.2 ng/islet in treated animals. The drug enhanced first-phase insulin secretion in 12-week-old male Wistar rats receiving an oral dose of 5 mg/kg CNX-011-67. Glucose metabolism, insulin secretion and islet insulin content were enhanced even under conditions of stress (e.g., chronic glucolipotoxicity). The drug also reduced beta cell apoptosis almost to control levels. Delayed onset of hyperglycemia was seen in male ZDF rats, with HbA1c of 5.18% compared to 5.50% for untreated mice. Plasma fructosamine was reduced from 236.66 to 111.25 μM with treatment in these rats. In adult n2-STZ rats treated with CNX-011-67 15 mg/kg b.i.d., there was enhanced glucose responsiveness and insulin content. At the time of presentation, CNX-011-67 was in IND-enabling studies under GLP conditions.

CBX-229801: PRECLINICAL DATA

James Callaway and colleagues from Cebix detailed their attempts to develop a compound that would replace circulating levels of C-peptide with an extended half-life for the potential treatment of complications resulting from diabetes. The compound discussed was a PEGylated C-peptide termed CBX-129801 (Ersatta™), which can be delivered subcutaneously. In monkeys, the compound showed a half-life of 70 hours. In vitro, biological activity was confirmed by its ability to elicit extracellular signal-regulated kinase ERK1/2 phosphorylation in human kidney cells. In vivo in a rat STZ-induced model of diabetes, 4-5 m/s reversal of sensory nerve conduction velocity impairment was seen. At this time phase Ib studies were under way.

LX-4211 IN TYPE 2 DIABETES

A dual inhibitor of the sodium/glucose cotransporters 1 and 2 (SGLT1 and SGLT2), LX-4211, was discussed by David Powell (Lexicon Pharmaceuticals). Data were presented from a phase I clinical trial (NCT01188863) that studied single 300-mg oral doses of LX-4211 (as 2 x 150-mg tablets, 6 x 50-mg tablets or a 300-mg solution) in a randomized, open-label, Latin square crossover design in 12 patients. The absorption rate for the liquid formulation was threefold faster than for the tablets, and mean C_{max} was significantly greater for this formulation. AUC values for both tablet options were similar, but about 25% less than for the liquid formulation. Mean half-lives were similar. All doses showed a clinically significant increase in 24-hour urinary glucose excretion, ranging from 73.1 to 84.8 g compared with 17.3 g at baseline. All formulations significantly decreased plasma glucose and insulin levels between 0 and 13 hours after dosing; in this time period they all also significantly decreased plasma insulin levels (indicating glycemic control), increased circulating levels of total glucagon-like peptide 1 (GLP-1), circulating levels of active GLP-1 and circulating levels of peptide YY (PYY). There were no severe adverse events. All reported events were mild, except one case of moderately severe headache in the 6 x 50-mg treatment group. Most events were gastrointestinal and more were seen in patients receiving the liquid formulation.

PRECLINICAL DATA FOR JD-5037

Joseph Tam of the National Institutes of Health (NIH) discussed JD-5037 (Jenrin Discovery), a peripherally restricted cannabinoid CB_1 receptor inverse agonist that is 10-fold more potent (K_i = 0.35 nM) than its parent compound ibipinabant (BMS-646256, SLV-319; K_i = 7.8 nM). Compared with ibipinabant, JD-5037 displayed reduced brain penetration and negligible brain occupancy (similar to vehicle). The compound did not lead to CB_1 receptor occupancy in the brain, as tested by ex vivo CB_1 radioligand binding. No anxiety-like behavior was seen, and it did not block CB_1-mediated catalepsy nor elicit central CB_1-mediated hyperlocomotion. JD-5037 improved glycemic control independently of body weight and food intake. When administered for 7 days, JD-5037 (3 mg/kg) reduced body weight and food intake in high-fat diet-induced obese but not genetically obese (*ob/ob*) mice; however, it corrected hyperglycemia, attenuated hyperinsulinemia and glucose intolerance, and increased insulin sensitivity in both models. The drug has a low-nanomolar K_d value and therapeutically relevant efficacy was seen in the management of obesity-related insulin resistance in type 2 diabetes models. Therefore, JD-5037 may be a promising treatment for type 2 diabetes without centrally mediated side effects.

ZEALAND'S GLP-1 DUAL PEPTIDE AGONIST

ZP-3022 (Zealand Pharma) is a novel and potent GLP-1/gastrin dual peptide agonist, for which data were presented by Zealand's Keld Fosgerau. Using female *db/db* mice, treatment was given as the following modalities: 1) prevention (daily treatment for 93 days with vehicle or 100 nmol/kg exenatide [exendin-4; Byetta®], liraglutide [Victoza®] or ZP-3022); 2) treatment (vehicle for the first 50 days before entering peptide treatment as with the prevention regimen for 43 days); or 3) drug holiday (treatment with peptides for 50 days on the same regimen and then continued on vehicle for 43 days). In oral glucose tolerance tests (OGTTs) a significant ($P < 0.001$) improvement in glucose clearance was seen on treatment with ZP-3022 compared with vehicle control, regardless of the treatment modality. This effect was maintained for weeks after the treatment was stopped. EC_{50} values for exenatide, liraglutide, [Leu15]-hGastrin-17 and ZP-3022 for the GLP receptor were 0.03, 0.18, > 1,000 and 0.03 nM, respectively; values for the cholecystokinin CCK_2 (CCK-B/gastrin) receptor were > 1,000, > 1,000, 3.0 and 11.5 nM, respectively.

Dr. Fosgerau also discussed preclinical data on another GLP-1 dual agonist, ZP-2929 (Zealand Pharma/Boehringer Ingelheim), which has been shown to improve glycemic control while also decreasing body weight. In the first study described, female *db/db* mice were treated every other day for 21 days with s.c. vehicle, insulin glargine (Lantus®; 6 U/day), insulin detemir (Levemir®; 12 U/day), ZP-2929 (20 nmol/kg/day), insulin glargine plus ZP-2929 or insulin detemir plus ZP-2929, and fasting blood glucose was studied. The change in blood glucose for ZP-2929 was similar to that for insulin detemir; however, there was an increased reduction with the combination regimens, most notably in combination with insulin glargine, although both dual therapies showed significance ($P < 0.001$ vs. vehicle). In terms of body weight, the most significant reduction was seen with ZP-2929 alone ($P < 0.001$; a loss of approximately 3 g). The combination treatments showed similar results to vehicle by the end of the study (approximately 0-1 g increase), whereas there was increased body weight with insulin glargine and insulin detemir alone (approximately 5 g).

In a second study of ZP-2929 referred to in this presentation, male C57BL/6J mice kept on a high-fat diet for 40 weeks until study start were treated for 10 days with either vehicle, liraglutide (40 nmol/kg/day) or ZP-2929 (10, 20 or 40 nmol/kg/day); two further groups were pair-fed with either liraglutide or high-dose ZP-2929. Body weight was seen to be most reduced with high-dose ZP-2929 alone (30% reduction), with the pair-fed to high-dose treatment being the next best, with a reduction of approximately 20%; all other doses (except vehicle) resulted in a reduction of approximately 10%. Body fat was most reduced with high-dose ZP-2929 alone, although all study regimens showed a significant reduction. In terms of body lean composition and reduction in food and water intake, high-dose ZP-2929 had the most significant effect; more severe losses in body and fat mass were seen compared with liraglutide, which could be linked to the decrease in food intake.

PRECLINICAL STUDIES OF UGP-281

UGP-281 (Unigene) is a potent anorexigenic peptide that is an amylin receptor agonist. Nozer Mehta and colleagues from Unigene discussed male Sprague-Dawley rat and beagle dog studies of the compound. Rats administered UGP-281 (5 and 20 μg/kg i.m.) for 20 days showed a significant reduction in food intake of approximately 55% and 84%, respectively, which then increased over the study period but remained approximately 25% lower than at the start of the study. Body weight was reduced over time on both doses, reaching approximately 5.7% and 8.8%, respectively, at the end of the study period. In beagle dogs receiving enteric-coated capsules of the compound there was a significant and sustained weight reduction of approximately 8% over 5 weeks. At the most effective doses, no nausea or malaise was seen in either rats or dogs.

GLUCOSE-LOWERING EFFECT OF LY-2409021 IN MICE

The glucagon receptor antagonist LY-2409021 (Eli Lilly) is currently in phase II studies in patients with type 2 diabetes. Thomas Farb and colleagues from the company presented preclinical data from mouse studies. The compound's K_i values for the human glucagon receptor, mouse glucagon receptor, human GLP-1 receptor and human GIP receptor were 6.66, 75.3, 1350 and 355 nM, respectively; the K_b value for cAMP antagonism was 25.7 nM. In 10-week-old male *ob/ob* mice orally administered LY-2409021 at doses of 1, 3, 10, 30 and 50 mg/kg, there was acute glucose lowering, with *P* values of < 0.05 compared to vehicle dose and predose with doses of 10 mg/kg upwards. Plasma glucagon levels were also increased most effectively at the 30 and 50 mg/kg doses (> 150 pg/mL compared with < 100 pg/mL for vehicle). Plasma fructosamine levels were significantly decreased in the 50 mg/kg group –from 335 μmol/L predose to 270.7 μmol/L at day 14. In C57BL/6 mice treated with STZ to induce diabetes prior to dosing, blood glucose values showed a dose-dependent reduction, with an ED_{50} of 1.39 mg/kg 6 hours after administration. Plasma insulin levels showed no change following administration of LY-2409021. In the liver of glucagon receptor knockout mice, [^{125}I]-glucagon binding was < 4% compared with control. LY-2409021-treated mice showed significant receptor occupancy at the doses of 1, 3 and 30 mg/kg.

DURATION-3: 84-WEEK DATA

Michaela Diamant from the VU Medical Centre presented data from an open-label, comparator-controlled extension of the DURATION-3 study in which it was previously shown that weekly exenatide (Byetta®) resulted in a greater HbA1c reduction, a reduced risk of hypoglycemia and progressive weight loss at 26 weeks in patients with type 2 diabetes on metformin alone or in combination with a sulfonylurea compared with insulin glargine (Lantus®; Sanofi). In the extension study, therapy was continued for a total of 84 weeks; 173 patients in each group completed the study. HbA1c reduction from baseline to 84 weeks was significantly greater for weekly exenatide (–1.2%) compared with insulin glargine (–1.0%; *P* = 0.029), consistent with a lower endpoint HbA1c for weekly exenatide (7.1%) than for insulin glargine (7.3%; *P* = 0.029). From week 26 to week 84 HbA1c increases were observed in both treatment groups (exenatide 0.4%; insulin glargine 0.3%). A similar proportion of patients on exenatide and insulin glargine achieved endpoint HbA1c of < 7.0% (45% versus 37%, respectively; *P* = 0.084), yet a higher proportion of patients on exenatide achieved HbA1c –6.5% (31% versus 20%; *P* = 0.009). Weekly exenatide patients lost weight (–2.1 kg), while those on insulin glargine gained weight (+2.4 kg) by the end of the study. Within the subgroup on metformin plus sulfonylurea, the overall incidence of minor hypoglycemia was 24% for the exenatide group compared with 54% for insulin glargine (*P* < 0.001). For the metformin alone group, 8% of patients on exenatide versus 32% on insulin glargine reported minor hypoglycemia (*P* < 0.001). There were less treatment-emergent adverse events (TEAEs) in the 26- to 84-week group (9) compared with the baseline- to 26-week study (69.5). These events were mostly mild and consistent in both studies. When asked about quality of life, Dr. Diamant noted that questionnaires relating to this had not been carried out.

COMBINATION OF LINAGLIPTIN AND METFORMIN IN TYPE 2 DIABETES

Thomas Haak from Diabetes Center Mergentheim discussed data on the dipeptidyl peptidase 4 (DPP IV) inhibitor linagliptin (Ondero®, Tradjenta™) in combination with metformin. The study enrolled both type 2 patients with reasonable control (HbA1c around 8.7%) and those with poor control (11.7%). The 24-week, double-blind, placebo-controlled, randomized study enrolled 791 patients with type 2 diabetes, who received 2.5 mg linagliptin 2.5 mg b.i.d. with either low- or high-dose (500 or 1000 mg) metformin b.i.d., or linagliptin 5 mg/day, metformin either at 500 or 1000 mg b.i.d. alone, or placebo. Patients with a baseline HbA1c of ≥ 11% received open-label combination therapy with linagliptin 2.5 mg b.i.d. plus 1000 mg metformin b.i.d. (n = 66). Mean baseline HbA1c was between 8.5 and 8.7%, and 11.8% in the open-label arm. For the combination of linagliptin 2.5 mg + metformin 500 or 1000 mg, the placebo-corrected reduction in HbA1c was –1.3% and –1.7%, respectively. Both combination regimens were superior to the monotherapy arms (–0.6%, –0.8% and +1.2%, respectively, for linagliptin, low- and high-dose metformin). In patients with poor glycemic control, mean change in HbA1c from baseline was –3.7%. Adverse event rates were similar across treatment arms. The total number of hypoglycemic events during combination treatment was low, with five patients (18%) receiving linagliptin in combination with metformin. The difference in body weight after treatment with linagliptin 2.5 mg + metformin 1000 mg compared with metformin 1000 mg alone was –0.23 kg. These studies were not carried out in obese patients, so figures were expected to differ if such data were taken into account. Combination of linagliptin with metformin significantly improved glycemic control towards treatment targets without weight gain and with a low risk of hypoglycemia. Dr. Haak noted that ultimately metformin performs well enough alone, although linagliptin will be useful as an added therapy in patients where metformin does not provide good control. It was thought that linagliptin should be added as soon as a patient was found not to have good control; however, future studies and regulatory guidelines will dictate application.

FFA1 RECEPTOR AGONIST TUG-469

Susanne Ullrich (University of Tubingen) and colleagues investigated the effects of FFA1 activation by small receptor agonists on glucose-dependent insulin secretion and apoptotic cell death. They

also analyzed the underlying molecular mechanism. One compound, TUG-469, contained a *para*-subsitituted dihydrocinnamic acid moiety and specifically bound to FFA1. In INS-1E cells, mouse and human islets, TUG-469 (10 μM) stimulated insulin secretion of human islet and INS-1E cells without inducing apoptotic cell death. This was accompanied by increased cystosolic Ca^{2+}. Inhibitors of ryanodine-sensitive and inositol triphosphate (IP_3)-sensitive Ca^{2+} release did not affect this stimulation. This study showed FFA1 to be a suitable therapeutic target for insulin secretion increase, without adverse effects on beta cell survival.

PHASE I DATA FOR LY-2409021

Following on from poster-presented murine data for Eli Lilly's glucagon receptor antagonist LY-2409021, Ronan Kelly presented phase I data for the compound from a randomized, double-blind, placebo-controlled study examining the safety, tolerability, pharmacokinetics and short-term (28-day) efficacy of once-daily doses of 5, 30, 60 or 90 mg in patients with type 2 diabetes treated with diet and exercise or metformin (N = 47; mean fasting blood glucose [FBG] = 148 mg/dL; HbA1c = 8.0%). By day 28, mean changes in HbA1c were statistically significant over baseline in all treatment groups (–0.49%, –0.69%, –0.89% and –1.02%, respectively, for placebo, metformin and doses of LY-2409021 of 30 and 60 mg), such that significant reductions versus placebo were seen only at doses of 60 and 90 mg LY-2409021. The ED_{50} value for glucose lowering was 5 mg. Fasting glucagon significantly increased by 0.6-, 1.5-, 2.5- and 4.2-fold, respectively, over baseline, and fasting active GLP-1 was increased by 59% at 90 mg LY-2409021. Onset of effect was lower at the low doses, but by the end of the study the effect was similar at all doses of LY-2409021. The range of exposure exceeded that needed for glucose lowering, but did not move into the hypoglycemia range. There were no adverse events related to treatment; one serious adverse event of exacerbation of spinal osteoporosis was seen at 5 mg LY-2409021 3 weeks after the final dose was administered, which was thought not to be drug-related. There were four incidents of mild to moderate hypoglycemia (two at the 90-mg dose), but there was no effect on body weight, blood pressure or heart rate. However, five of nine patients at the 90-mg dose had increased alanine aminotransferase (ALT; threefold normal levels) and aspartate aminotransferase (AST) results were similar. Circulating glucagon showed a fourfold increase at 90 mg. There was no significant change in cholesterol levels, although HDL cholesterol was increased at the doses of 30 and 90 mg. The 5- and 30-mg doses were deemed suitable for further development.

PSN-821 IN TYPE 2 DIABETES

Matthew Goodman of Prosidion discussed a study of his company's *GPR119* receptor agonist PSN-821 in patients with type 2 diabetes that considered the compound's effect on energy intake after 14 days. This compound potently stimulates insulin and GLP-1 release and has been shown to reduce glucose levels and induce weight loss in preclinical studies. Patients in this study were treated with 250 mg b.i.d. PSN-821 as monotherapy, after a washout period for other oral antidiabetics, or metformin in combination with either 250 or 500 mg PSN-821. The twice-daily monotherapy dose was well absorbed and showed linear and dose-proportional plasma concentrations. After 14 days of treatment, the median t_{max} of PSN-821 in plasma ranged from 2 to 5 hours, and the half-life ranged from approximately 5.5 to 7 hours post-dose; co-administration with metformin did not affect pharmacokinetic parameters for either dose. Mean FPG change for placebo, 250 mg PSN-821, 250 and 500 mg PSN-821 plus metformin was –0.7, –2.0, –2.3 and –2.1 mmol/L, respectively. Plasma glucose showed a marked change after 14 days and reactive $AUC_{glucose\ 0\text{-}5\ h}$ versus placebo was statistically significant. Energy intake change was –2%, –5%, –10% and –40%, respectively. Body weight loss was –1, –2.2, –2 and –2.1 g, respectively, which was not considered statistically significant. There was a no to modest change in lipids, adiponectin and leptin, and vital signs. There were no serious adverse events and TEAEs were comparable to placebo. Most were gastrointestinal-related (e.g., abdominal pain, breath odor and flatulence), with one incidence each of dry skin and decreased appetite. Dose–response may be due to two different mechanisms of action: glucose lowering at low doses and energy intake reduction at higher doses.

TWi'S DIACERIN PHASE IIB STUDY

Calvin Chen of TWi Biotechnology discussed his company's phase II studies with the IL-1β inhibitor diacerein. The compound was studied for safety and efficacy in patients with type 2 diabetes as an add-on therapy. Primary endpoints were change from HbA1c baseline at 24 weeks. Patients (N = 76) received either diacerein (50 mg/day) or placebo, and final data were received from 26 treated and 30 placebo patients. Diacerein was administered as a 4-week run in due to transient diarrhea seen with initial dosing. A statistically significant mean reduction of –0.63% HbA1c was seen with the drug ($P < 0.05$), which began at week 16 (0.6%); FPG was also reduced versus placebo ($P = 0.0372$). There were no significant changes in high-sensitivity C-reactive protein (hsCRP) and IL-6, lipid profile, body weight or blood pressure. Adverse event data showed a slight increase in upper respiratory tract infections following treatment with diacerein (five versus two for placebo). Overall, reported adverse events were similar to placebo (20 and 18). Phase IIb dose-finding trials are ongoing in the U.S. and Taiwan (NCT01276106) to look for optimal dosing.

CLINICAL DATA ON MERCK'S MK-0893

Merck's MK-0893, a glucagon receptor antagonist, was discussed in two separate presentations. Samuel Engel from Merck Sharp & Dohme (MSD) considered the efficacy and tolerability of the compound in patients with type 2 diabetes. MK-0893 has a t_{max} and a half-life in man of 5-6 hours and 60-100 hours, respectively; it reaches steady state in about 2 weeks. The phase IIb study tested a range of doses (20, 40, 60 and 80 mg/day) and compared them with metformin (1000 mg b.i.d.) and placebo in 342 patients, with the endpoints of glycemic control and change in FPG and fasting GLP-1 levels from baseline. Mean FPG reduction levels for placebo, metformin and 20, 40, 60 and 80 mg MK-0893 were –1.8, –37.3, –32.4, –48.4, –53 and –63 mg/dL, respectively. This reached its peak at 2 weeks and then remained stable for the duration of the study. HbA1c reduction was 0.54%, –0.78%, –0.60%, –0.99%, –1.14% and –1.52%, respectively, and this may not have reached a plateau at 12 weeks for MK-0893 doses. Fasting glucagon showed no change for placebo and metformin, but a threefold increase with

the high dose of MK-0893. Changes in insulin levels were most significant in the 60- and 80-mg groups. GLP-1 showed a dose-dependent and moderate increase (threefold increase in total GLP-1 with the high dose); no increase was seen in active GLP-1. Adverse events were approximately the same for all groups, and only one case of hypoglycemia was seen in the MK-0893 80-mg group. An LDL cholesterol increase of 16% was seen at the highest dose, and HDL cholesterol showed signs of increase at the doses of 60 and 80 mg. No significant change was seen in triglycerides in all groups. Body weight dropped in metformin and placebo groups, but at 80 mg MK-0893 there was an increase of approximately 2 kg in body weight. ALT levels increased by around 35-40% in the 60- and 80-mg groups, with one patient in the 60-mg group reaching threefold the upper limit; this patient discontinued the study. The issues with increased cholesterol and liver enzymes may limit the therapeutic index of this compound; these increases may be mechanism-based.

In another study presented by Marcella Ruddy (MSD), it was noted that phase I studies had shown an IC_{50} value for the glucagon receptor of 60 nM, and that the drug was well tolerated up to 1000 mg as a single dose or up to 180 mg as a daily dose. The compound improved hyperglycemia in hGCGR DIO mice with approximately 50% blockade of acute glucagon challenge response, demonstrating near-maximal glucose response in a chronic model. In part 1 of an initial study described, healthy patients were studied for glucagon-induced blockade using MK-0893 doses of 10, 40 or 200 mg for 24 hours. In part 2, subjects were randomized to receive a sequence of three possible treatments: placebo, 200 and 1000 mg MK-0893. Healthy patients showed a pronounced decrease in glycemic conversion (59%) at the 200-mg dose and near-maximal blockade of glucagon-induced glucose excursions at the 1000-mg dose. Doses chosen for the proof-of-concept study were 40 and 120 mg. In the phase IIa study, patients with type 2 diabetes receiving 40 or 120 mg MK-0893, metformin or placebo showed a change from baseline of –37, –60.8, –36.3 and –11.7 mg/dL, respectively. In a 24-hour glucose profile, mean plasma glucose was dose-dependently reduced (40 mg MK-0893 was similar to metformin and 120 mg significantly lowered fasting and postprandial glucose). There were no serious adverse events or hypoglycemia reported. The 120-mg dose of MK-0893 showed increases in AST, ALT and bilirubin, and lipid profiles, as reported above. Near-maximal blockade of glucagon-induced glycemic response was seen, as was significant glucose lowering without hypoglycemia. The liver enzyme effect was noted to have not been seen in animal studies. Studies were planned to assess the hypoglycemic potential with combination therapy using MK-0893.

CCX-140 DATA

Markolf Hanefeld from Gesellschaft fur Wissens- und Technologietransfer der TU Dresden discussed data on the chemokine CCR2 receptor antagonist CCX-140 (CCX-140-B; ChemoCentryx) from a phase II study in patients with type 2 diabetes. In phase I studies the compound was well tolerated, with linear pharmacokinetics; t_{max} was 1.4-3.2 days and half-life was 40-58 hours. In the 4-week, randomized, double-blind, placebo-controlled phase II study (with 4-week follow-up) carried out in Australia, the Czech Republic, Germany, Hungary and New Zealand, doses of CCX-140 of 5 and 10 mg/day were tested in patients (N = 157) on background metformin treatment and compared with pioglitazone (Actos). Patients had a body mass index of between 25 and 45 and baseline HbA1c was 7.40-7.58%; 96% of patients completed the study. There were no serious adverse events, although five withdrawals occurred, including one patient due to gouty arthritis (the patient had a history of gout) in the 10-mg group and a case of dyspepsia in the 5-mg group. There were no clinically relevant changes in monocyte counts. There were no safety concerns regarding laboratory hematology, chemistry or urinalysis. A dose-dependent decrease was seen in FPG at 2 weeks, which was equal to pioglitazone for 10 mg CCX-140; for the placebo, 5-mg CCX-140, 10-mg CCX-140 and pioglitazone groups results were –0.09%, –0.09%, –0.23% and –0.13%, respectively. Fructosamine was lowered by CCX-140, but not as strongly as pioglitazone. Plasma C-C motif chemokine 2 (monocyte chemotactic protein 1, MCP-1) showed little change. No significant effect was seen on fasting plasma insulin. Minor improvements were seen in the oral glucose tolerance test. C-reactive protein data were variable but not significant across all groups. No effect was seen on cholesterol, FFA, body weight or hematocrit. Mean trough plasma levels of CCX-140 were 1269 and 2355 ng/mL for doses of 5 and 10 mg, respectively.

DISCLOSURES

The author states no conflicts of interest.

The website for this meeting can be found at http://professional.diabetes.org/Congress_Display.aspx?TYP=9&CID=82452.