fed serum triglyceride. CNX-013-B2 increases non-statistical significant fed insulin levels and improves muscle insulin sensitivity without increase in body weight. There was no change in the relative or absolute weight of liver, kidney, heart, and the different adipose depots. CNX-013-B2 shown non-significant decrease in heart triglyceride levels, increased phospho-AMPK levels, inhibited p70S6K pathway (reduces phospho-mTOR levels) and thus regulate protein synthesis. CNX-013-B2 reduces JNK signaling in heart significantly and enhances fat oxidation.

Conclusion: These findings indicate that CNX-013-B2, an orally bio available selective rexinoid has a potential to provide good glycemic control and reduce cardiac hypertrophy and can be good therapeutic agent for the treatment of type 2 diabetes.

OP7

EFFICACY, SAFETY, AND TOLERABILITY OF IPRAGLIFLOZIN IN ASIAN TYPE 2 DIABETIC PATIENTS WITH INADEQUATE GLYCEMIC CONTROL WITH METFORMIN. RESULTS OF A PHASE 3 RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, MULTICENTER TRIAL

L.-M. Chuang[1], K.W. Min[2], C.-H. Lu[3], S. Kokubo[4], S. Yoshida[4], B.S. Cha[5]. [1] *National Taiwan University Hospital, Taipei, Taiwan;* [2] *Eulji General Hospital, Seoul, Korea, Republic of;* [3] *Chiayi Christian Hospital, Chiayi City, Taiwan;* [4] *Astellas Pharma Inc., Tokyo, Japan;* [5] *Yonsei University College of Medicine, Seoul, Korea, Republic of*

Background: Ipragliflozin, a sodium-glucose cotransporter 2 (SGLT2) inhibitor, was recently approved in Japan for the treatment of type 2 diabetes. The objective of the present study was to examine the efficacy and safety of ipragliflozin in combination with metformin in Asian patients with type 2 diabetes in Taiwan and Korea.

Method: In this phase 3, multicenter, placebo-controlled, double-blind, parallel-group study, patients at 18 sites in Korea and 12 sites in Taiwan were randomized to either 50 mg ipragliflozin or placebo for 24 weeks while continuing metformin. All patients entered a 2-week run-in period before randomization. The main inclusion criteria were: age ⩾20 years, diagnosis of type 2 diabetes ⩾12 weeks before enrollment, stable diet and exercise regimen for ⩾8 weeks, hemoglobin A1c (HbA1c) of 7.0–10.0%, body mass index of 20.0–45.0 kg/m^2, and on a stable metformin dose of ⩾1500 mg/day (or ⩾1000 mg/day if safety concerns prohibited higher doses) for ⩾8 weeks. Patients using other oral agents entered an 8-week washout before the run-in period. Efficacy outcomes included the changes in HbA1c (primary efficacy outcome), fasting plasma glucose (FPG), fasting serum insulin, body weight (BW), waist circumference (WC) from baseline to the end of treatment (EOT) (with last observation carried forward [secondary efficacy outcomes]), and the proportion of patients with HbA1c <7.0% and <6.5% at EOT. Safety outcomes included treatment-emergent adverse events (TEAEs).

Result: Between November 2011 and January 2013, 171 patients were randomized to and administered ipragliflozin (N = 87) or placebo (N = 83). The mean changes (± standard deviation) in HbA1c were significantly greater [–0.94±0.75% (baseline: 7.74±0.78%)] in the ipragliflozin group than in the placebo group [–0.47±0.81% (baseline: 7.75±0.72%)] with placebo-adjusted mean difference of –0.47% (P < 0.001). The proportions of patients with HbA1c <6.5% in the ipragliflozin and placebo groups increased from 1.1% (1/87) and 0% (0/83), respectively, at baseline to 25.9%, (22/85) and 9.6% (8/83), respectively, at EOT. The proportions of patients with HbA1c <7.0% in the ipragliflozin and placebo groups increased from 11.5% (10/87) and 3.6% (3/83), respectively, at baseline to 69.4% (59/85) and 44.6% (37/83), respectively, at EOT. The changes in FPG, BW and WC were also significantly greater in the ipragliflozin group than in the placebo group, with placebo-adjusted mean differences of –14.1 mg/dL, –1.24 kg, and –0.91 cm, respectively (P < 0.001 for FPG and BW, P = 0.032 for WC). The reductions in systolic blood pressure (–6.8±14.1 vs. –1.3±12.9 mmHg), diastolic blood pressure (–3.7±9.4 vs. –1.0±8.0 mmHg) and triglycerides (–24.6±91.9 vs. +10.7±79.6 mg/dL) were greater in the ipragliflozin group than in the placebo group. The most common TEAEs (ipragliflozin vs. placebo) were upper respiratory tract infections (9.2% [8/87] vs. 12.0% [10/83]) and urinary tract infections (6.9% [6/87] vs. 2.4% [2/83]). There were no episodes of hypoglycemia or genital infection in either group. Polyuria occurred in 1.1% (1/87) in the ipragliflozin group and pollakiuria occurred in 4.8% (4/83) in the placebo group.

Conclusion: Ipragliflozin improved HbA1c and FPG, reduced BW, WC, blood pressure and triglycerides, and was well tolerated when used in combination with metformin in Asian patients with type 2 diabetes.

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OP8

THE 2-WEEK FASTING GLUCOSE AS A PREDICTOR OF GLYCEMIC RESPONSE TO ONCE-WEEKLY DULAGLUTIDE 1.5 MG

S. Gough[1], G. Grunberger[2], T. Forst[3], V. Pechtner[4], R. Shaginian[5], H. Wang[6], L. Fernandez[7]. [1] *University of Oxford and Oxford University Hospitals NHS Trust, Oxford Centre for Diabetes Endocrinology and Metabolism, Oxford, United Kingdom;* [2] *Grunberger Diabetes Institute, Bloomfield Hills, MI, United States;* [3] *Profil Mainz, Mainz, Germany;* [4] *Lilly Diabetes, Eli Lilly and Company, Neuilly-Sur-Seine, France;* [5] *Lilly Diabetes, Eli Lilly and Company, Houten, Netherlands;* [6] *Eli Lilly and Company, Indianapolis, IN, United States;* [7] *Lilly Diabetes, Eli Lilly and Company, Indianapolis, IN, United States*

Background: To assess whether laboratory fasting blood glucose (FBG) in patients with type 2 diabetes mellitus (T2DM) measured early in treatment with the once-weekly glucagon-like peptide-1 (GLP-1) receptor agonist dulaglutide (DU) 1.5 mg predicts glycemic response.

Method: *Post-hoc* analyses were conducted separately for 2 double-blind, randomized Phase 3 studies (AWARD-5, in combination with metformin, and AWARD-1, in combination with metformin and pioglitazone) in patients with T2DM assigned to once-weekly DU 1.5 mg. In AWARD-5, FBG values were categorized at baseline and week 2 as follows (using tertiles): Low (L, <142 mg/dL); Intermediate (I, ⩾142 to <185 mg/dL); and High (H, ⩾185 mg/dL). Treatment response was assessed at week 12 (AWARD-5) or 13 (AWARD-1) and 26 (AWARD-5, AWARD-1) by the following composite efficacy endpoint (CEE): A1c <7.0% or A1c reduction from baseline >0.8% (if baseline A1c <8.0%); >1.1% (if baseline A1c ⩾8.0% and <9.0%); or >1.6% (if baseline A1c ⩾9.0%). Association between FBG categories and the CEE was analyzed using chi-square tests.

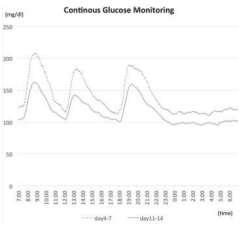
Result: In AWARD-5, mean baseline A1c for DU 1.5 mg (N = 304) was 8.1%. At baseline, mean FBG was 176 mg/dL, and 33% (n = 99), 32% (n = 97), and 36% (n = 108) of patients had FBG in L, I, and H categories, respectively. After 2 weeks of treatment, mean FBG was 129 mg/dL, and 68% (n = 208), 21% (n = 64), and 11% (n = 32) of patients had FBG in L, I, and H categories, respectively. At week 26, mean A1c was 6.9%. There was a strong association between FBG at week 2 and achieving the CEE at week 26 (p < 0.001). A significantly higher percentage of patients in FBG category L (83% [172/208]) at week 2 met the CEE at week 26 compared to patients in FBG categories I (61% [39/64]), p < 0.001, and H (34% [11/32]), p < 0.001. CEE results

at week 12 were consistent with those at week 26. Similar findings were seen using AWARD-1 data.
Conclusion: The identification of patients most likely to respond to a specific treatment is important when attempting to individualize patient care. Predictors of treatment success for other weekly GLP-1 receptor agonists have, to date, not been reported. In patients treated with once-weekly DU 1.5 mg in AWARD-5 and AWARD-1, FBG values at week 2 were strongly associated with glycemic response at week 26 as measured by a CEE. The probability of achieving glycemic response at week 26 was greatest for patients in the lower FBG categories at week 2.
FBG values at week 2 may be an early and useful measurement for predicting glycemic response to once-weekly DU 1.5 mg treatment in patients with T2DM.

OP9
IMPROVEMENT OF DAILY GLYCEMIC PROFILE AND REDUCTION OF BODY WEIGHT WITH SGLT2 INHIBITOR IPRAGLIFLOZIN IN JAPANESE OBESE ADULTS WITH TYPE 2 DIABETES MELLITUS

M. Kusama[1], R. Imamine[1], Y. Kouchi[1], M. Kawai[1], M. Minatoguchi[1], A. Mizoguchi[1], A. Watarai[2], A. Kanai[2], T. Kawamura[2], N. Hotta[1], E. Nakashima[1]. [1] *Department of Diabetes and Endocrinology,* [2] *Center for Preventive Medicine, Japan Labour Health and Welfare Organization, Chubu Rosai Hospital, Nagoya, Japan*

Background: Ipragliflozin (IPR), a highly selective SGLT2 inhibitor, improves glycemic control and promotes body weight (BW) loss in patients with type 2 diabetes mellitus (T2DM). But no reports have been published about the effect of IPR on daily glucose profile in drug naïve T2DM patients by using continuous blood glucose monitoring (CGM).
Method: Six T2DM patients treated with diet and exercise therapy (Age 57.3±12.5 years, HbA1c 7.3±0.9 %, BW 76.8±8.1 kg, BMI 29.9±3.7 kg/m^2 (Data are expressed by mean ± SD)) were enrolled under hospitalization in this study. Drug naïve T2DM patients were treated with diet and exercise therapy for 7 days after admission and starting IPR (50 mg/day) from day 8. Patients' daily glucose profiles were assessed by CGM at the day 4–7 (control period) and day 11–14 (IPR period). We also evaluated the change of BW, body mass index (BMI), and body fat ratio through the study period. Blood chemistry (fasting plasma glucose, homeostasis model assessment ratio (HOMA-R), blood ketone body, free fatty acid, adiponectin, lipid profiles, liver and renal function) and other metabolic markers such as amino acids, lactic acid, pyruvic acid were evaluated in both day 8 (control period) and day 14 (after IPR treated for 1 week). Moreover, we measured the 24-hour urine glucose amount and electrolytes (include Na+, Ca++) excretion in urine at the baseline and during trial period.



Result: The greater improvement of average blood glucose (ABG) was significantly observed with IPR treatment (ABG 116.5±24.0 mg/dl;day 11–14) than with control (diet and exercise therapy) (ABG 140.2±38.3 mg/dl;day 4–7) ($p < 0.05$) on CGM. Mean standard deviation (SD) of glucose variability was also reduced with IPR than with control (21.3±5.2 vs. 31.5±11.3 mg/dl, respectively), but the difference of SD was not significant. HOMA-R was significantly improved with IPR (–0.45; $p = 0.05$). LDL-cholesterol and triglyceride levels significantly decreased in day 14 (–17.7 mg/dl and –14.8 mg/dl, $p = 0.05$). On the other hand, although adiponectin level decreased (–0.05 μg/ml) and free fatty acid level increased (+138.5 mEq/l) in day 14, the changes were not significant. Moreover, the reduction of mean BW was significantly achieved with IPR in day 14 (BW 74.1±7.1 kg) compared with diet and exercise period in day 1 (BW 76.8±8.1 kg) and in day 8 (BW 75.2±6.8 kg) ($p < 0.05$). After starting IPR, the maximum average 24-hour urine glucose amount excreted in urine was 51.1±14.0 g/day. No adverse events were observed through the study period.
Conclusion: In spite of only short term investigation, monotherapy of IPR 50 mg/day for Japanese patients with T2DM under hospitalization significantly improved glycemic profile observed by CGM. IPR also provided the significant reduction of BW, and it was well tolerated in short terms. Moreover, these data indicate the possibility that IPR improves lipid profiles. Furthermore, increasing number of participants with T2DM will be needed to clarify these findings.

OP10
EFFICACY AND SAFETY OF LIRAGLUTIDE IN JAPANESE TYPE 2 DIABETIC PATIENTS TREATED OVER 2 YEARS

H. Shimizu[1], H. Akiyama[2]. [1] *Department of Diabetes and Endocrinology, Internationa University of Health and Welfare Hospital, Nasusiobara,* [2] *Department of Endocrinology, Toho Hospital, Midori, Japan*

Background: Glucagon-like peptide-1 (GLP-1) is involved in the regulation of appetite, in addition to the stimulation of insulin secretion and inhibition of glucagon secretion in a glucose-dependent manner. GLP-1 receptor (GLP-1R) agonist, liraglutide, improves glycemic control with a significant reduction of body weight in type 2 diabetic (T2DM) patients. However, there is a possibility that GLP-1R may exist in thyroid C-cell, and that exogenously repeated administration of GLP-1 agonist may affect thyroid C-cell function, and may cause thyroid C-cell proliferation in T2DM patients treated with GLP-1R agonist for a long period. It is still unknown that the risk of occurrence of thyroid C-cell tumor in Japanese T2DM patients treated with liraglutide for a few years. In the present study, we evaluated efficacy of liraglutide and its safety on the thyroid glands in Japanese type 2 diabetic (T2DM) patients over 2 years.
Method: Twelve T2DM out-patients (8 males, 4 females, age; 57.3±9.7 year-old, BMI; 30.76±5.61 kg/m^2) without renal failure and/or overt osteoporosis were followed up over 2 years (32.3±6.8 months) with liraglutide treatment. In addition to the evaluation of glycemic control state and body weight change, thyroid function was estimated by measuring thyroid hormone concentrations, and their thyroid glands were also morphologically screened.
Result: The final average dose of liraglutide was 0.83±0.16 mg, once a day. Mean change in body weight and BMI from baseline was –3.91±4.34 kg (from 82.73±20.33 kg to 78.82±20.49 kg), –1.53±1.65 kg/m^2 (from 30.76±5.61 kg/m^2 to 29.23±5.63 kg/m^2). And mean change in casual postprandial glucose levels and HbA1c from baseline were –24.3±60.3 mg/dl (from 171.8±48.0 mg/dl to 147.5±48.9 mg/dl), –0.48±1.11 % (from 7.39±0.59 % to 6.92±0.62 %) respectively. Serum TSH, free thyroxine, free thyronine levels were within normal range in all patients, but only one case showed a slight increase of serum thyroglobulin level. Serum Ca, IP, and calcitonin levels were also within normal range in all patients. Ultrasonography in the thyroid gland demonstrated small cysts in 5 patients, and small hypoechoic masses in 5 patients, but no obvious tumor region indicating thyroid C-cell tumor was found at all in all patients.
Conclusion: In conclusion, the treatment by GLP-1R agonist, liraglutide, in Japanese T2DM patients was well tolerated for 30 months, and no thyroid C-cell tumor was found at all in those patients after the treatment over 30 months.