in vivo 2) to further test established models of cholesterol metabolic regulation on LDLr and PCSK9 turnover after feeding mice a cholesterol enriched diet. We hypothesize that a cholesterol enriched diet will decrease both LDLr and PCSK9 synthesis rates. In order to test this, mice were fed a cholesterol enrich diet for 1 week and metabolically labeled with heavy water (^2H_2O) up to 36 hours. LDLr and PCSK9 were immunoprecipitated from liver and deuterium incorporation into LDLr and PCSK9 were measured via mass spectrometry. Our results revealed high cholesterol feeding down-regulated cholesterol synthesis and LDLr fractional synthesis rate decreased from 10.0% to 6% per hour. PCSK9 concentration also decreased from 1 to 0.2 (ng/ml / total mg protein), but the synthesis rate increased from 9.0%/day in control mice to 19.5%/day in high cholesterol diet. These results suggest high cholesterol feeding increases PCSK9 synthesis that potentially depletes the intracellular pool to target LDLr to the lysosome thus decreasing LDLr turnover. This research provides a flux-based approach to measure the kinetics of LDLr and PCSK9 for a molecular based kinetic insight of their functions in physiology, disease and therapy.

Diabetes Mellitus and Glucose Metabolism

IMPACTS OF METABOLISM ON CLINICAL CHALLENGES

Efficacy and Safety of Higher Dulaglutide Doses (3.0 MG and 4.5 MG) When Added to Metformin in Patients With Type 2 Diabetes: A Phase 3, Randomized, Double-Blind, Parallel ARM Study (Award-11)

Juan Pablo Frias, MD, PhD[1], Luis Nevárez Ruiz, MD[2], Ying Grace Li, PhD[3], Zhuoxin Yu, PhD[4], Zvonko Milicevic, MD[5], Brad Woodward, MD[4], David A. Cox, PhD[6].

[1]National Research Institute, San Diego, CA, USA, [2]Hospital Angeles Chihuahua, Chihuahua, Mexico, [3]Lilly USA, Indianapolis, IN, USA, [4]Eli Lilly and Company, Indianapolis, IN, USA, [5]ELI LILLY REGIONAL OPS, Wien, Austria, [6]Lilly Rsrch Labs, Indianapolis, IN, USA.

OR26-08

Dulaglutide (DU) approved at doses of 0.75 and 1.5 mg once-weekly is an effective glucose lowering agent for treatment of type 2 diabetes (T2D). We hypothesized that higher investigational DU doses may provide further improvements in glucose control and body weight (BW) with an acceptable safety profile. The primary objective was to demonstrate superiority of once-weekly DU 3 mg and/or 4.5 mg to DU 1.5 mg for A1C change from baseline (BL) at 36 weeks (wks) in patients (pts) with inadequately controlled T2D on metformin therapy. Secondary objectives (controlled for multiplicity) included change in BW and % of pts achieving A1C <7% at 36 wks. Patients were randomized (1:1:1) to once-weekly DU 1.5 mg (n=612), DU 3 mg (n=616), and DU 4.5 mg (n=614). All pts initiated once-weekly DU 0.75 mg for 4 wks, followed by step-wise dose escalation every 4 wks to the randomized dose of 1.5 mg, 3 mg, or 4.5 mg. Two estimands were defined for efficacy analyses: an efficacy estimand (data on-treatment without rescue medication) and a treatment-regimen estimand (all data regardless of adherence or initiation of rescue). At BL, patients had a mean of: age 57.1 yrs, T2D duration 7.6 yrs, and A1C 8.6%, BW 95.7 kg, and BMI 34.2 kg/m^2. Using the efficacy estimand, the DU 3 mg and 4.5 mg doses were superior to the DU 1.5 mg dose for A1C change from BL (1.5 mg, 1.53%; 3 mg, 1.71% [p=0.003]; 4.5 mg, 1.87% [p<0.001]), % of patients achieving HbA1c <7% (1.5 mg, 57%; 3.0 mg, 65% [p=0.006]; 4.5 mg, 71% [p<0.001]) and BW change from BL (1.5 mg, 3.1 kg; 3 mg, 4.0 kg [p=0.001]; 4.5 mg, 4.7 kg [p<0.001]). Using the treatment-regimen estimand, DU 4.5 mg was superior to DU 1.5 mg for A1C change, while the DU 3 mg dose did not achieve statistical significance (1.5 mg, 1.54%; 3.0 mg, 1.64% [p=0.096]; 4.5 mg, 1.77% [p<0.001]). Using the treatment-regimen estimand, more patients achieved A1C <7% with higher DU doses (1.5 mg, 50%; 3 mg, 56%; 4.5 mg, 62%) and results for BW change were similar to the efficacy estimand (1.5 mg, 3.0 kg; 3 mg, 3.8 kg; 4.5 mg, 4.6 kg), but the approach for type I error control did not permit formal statistical comparisons of these secondary objectives using this estimand. The safety profile for the higher DU doses was consistent with that known for 1.5 mg. The most commonly reported adverse events were nausea (DU 1.5 mg, 13.4%; DU 3 mg, 15.6%; DU 4.5 mg, 16.4%), vomiting (DU 1.5 mg, 5.6%; DU 3 mg, 8.3%; DU 4.5 mg, 9.3%), and diarrhea (DU 1.5 mg, 7.0%; DU 3 mg, 11.4%; DU 4.5 mg, 10.7%). Treatment discontinuation due to adverse events through 36 wks was low and similar across dose groups (DU 1.5 mg, 4.2%; DU 3 mg, 5.5%; DU 4.5 mg, 5.0%). In pts with T2D and inadequate glycemic control on metformin, escalation from DU 1.5 mg to DU 3 mg or DU 4.5 mg once-weekly provided clinically relevant, dose-related improvements in glycemic control and BW with an acceptable safety profile.

Adipose Tissue, Appetite, and Obesity

ADIPOSE TISSUE BIOLOGY AND OBESITY II

Development of a Conceptual Model to Present the Impacts of Obesity on Physical Functioning

Jiat Ling Poon, PhD[1], Chris Marshall, MSc[2], Chloe Johnson, MSc[2], Hannah Pegram, BSc[2], Maile Hunter, MBA[3], Hongjun Kan, PhD[4], Nadia Ahmad, MD, MPH[5].

[1]ELI LILLY & COMPANY, Indianapolis, IN, USA, [2]DRG Abacus, Manchester, United Kingdom, [3]DRG Abacus, Nashville, TN, USA, [4]Eli Lilly and Company, Indianapolis, IN, USA, [5]Eli Lilly and Company, New Canaan, CT, USA.

SUN-LB102

Title: Development of a conceptual model to present the impacts of obesity on physical functioning **Background.** Obesity is a chronic disease with a significant negative impact on health-related quality of life (HRQoL) and specifically, physical functioning, including the ability to complete activities of daily living (ADLs). Weight loss based on lifestyle management (e.g. diet, exercise), surgery, and pharmacotherapy can improve physical functioning; however, there is a need for further qualitative research to support the content validity of patient-reported outcome (PRO) measures for use in clinical studies of obesity and thus