

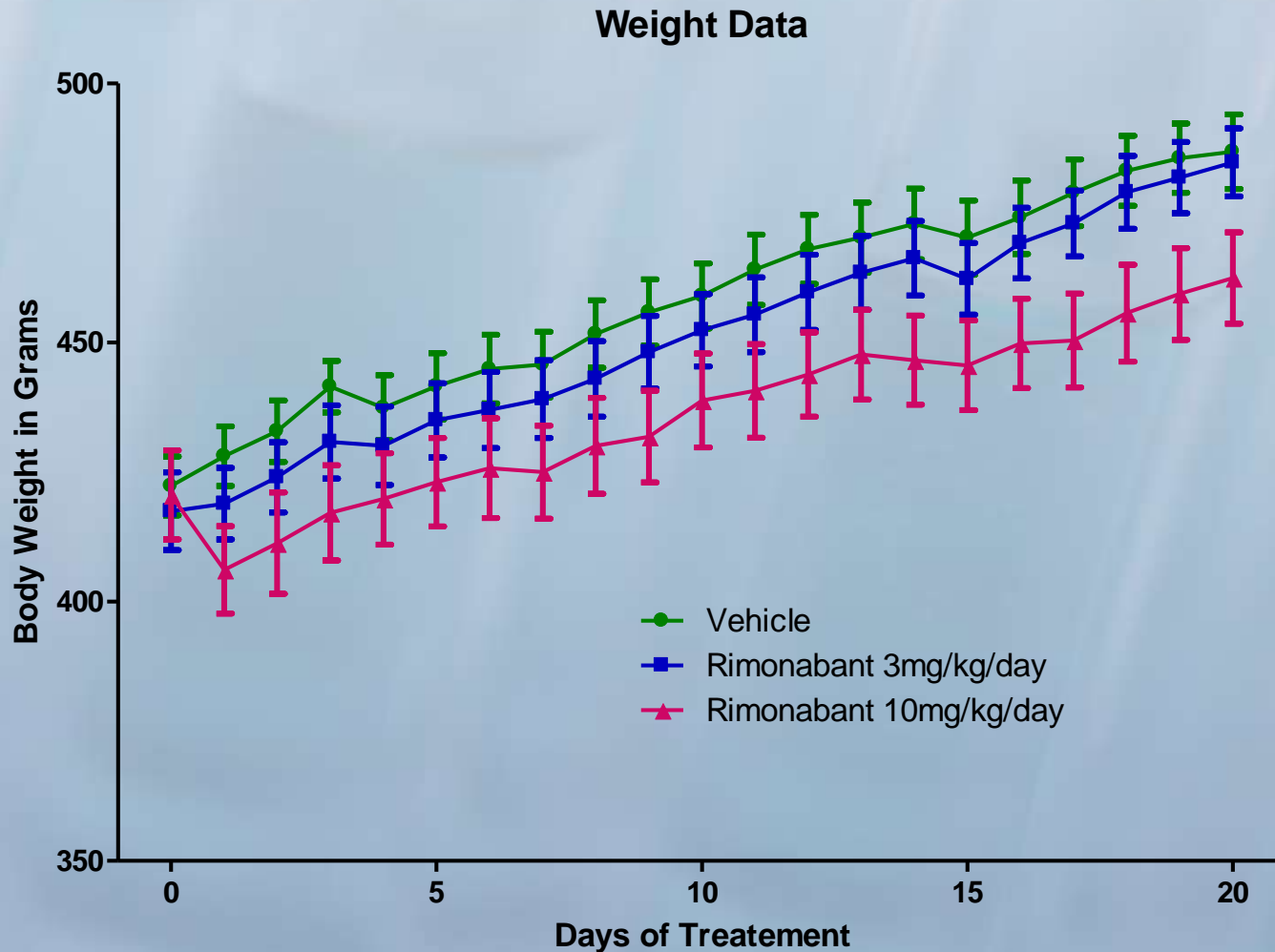
Outline of Presentation Contents

1. Introduction
2. Spontaneous or Synchronous Diabetes
3. Metabolic Syndrome Elements
 - A. Visceral Obesity
 - B. Insulin Resistance
 - C. Clamp Study
 - D. Dyslipidemia
 - E. Hypertension
4. Eating Behavior
5. Beta cell Failure
6. Renal Injury
 - A. Urinary biomarkers, Exp. 1, 2
 - B. RBM Biomarkers – Renal, Exp 3
 - C. Glomerular Pathology, EM, Exp 4
 - D. Synchronized Nephropathy, Exp 5
7. Osteoporosis
8. Wound Healing
9. RBM Biomarkers – Pro-Thrombotic
10. RBM Biomarkers - Inflammation
11. Therapeutic Efficacy
 - A. Common Anti-diabetic Compounds
 - B. Rimonabant
 - C. Niacin
12. Summary

Characteristics of Metabolic Syndrome Seen in the ZDSD Rat

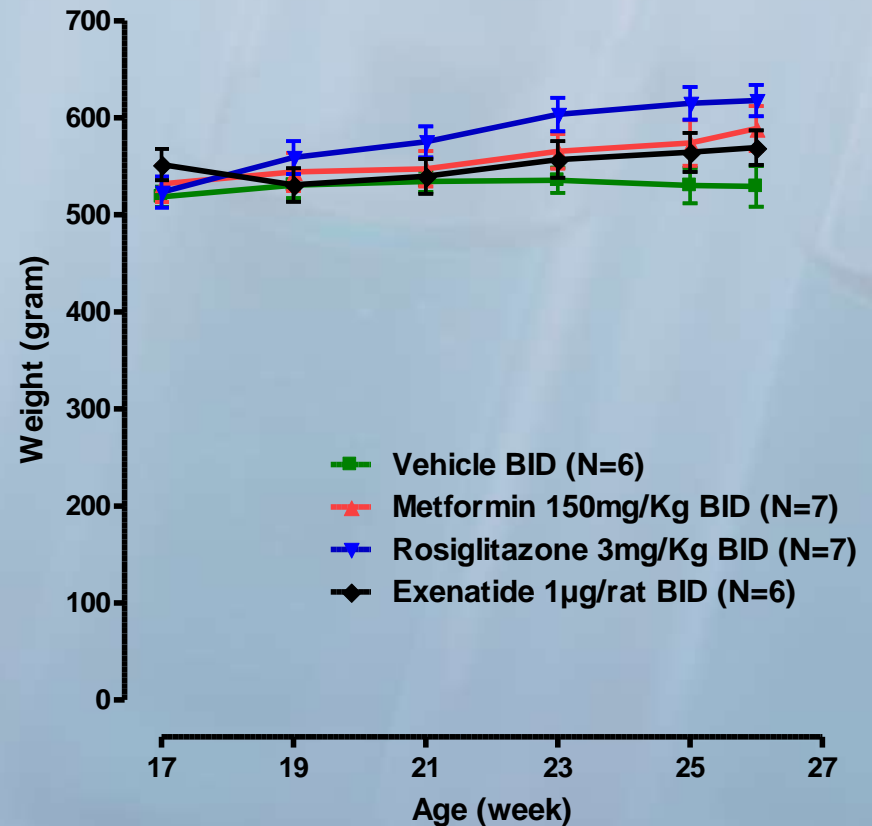
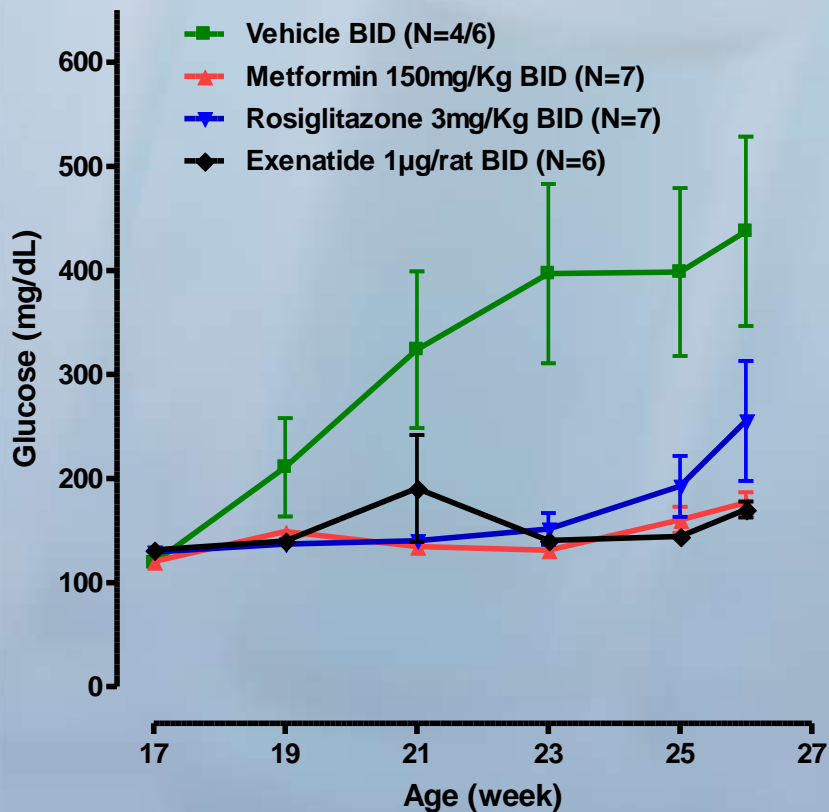
- Increased body weight with increased abdominal fat
- Insulin resistance / Glucose intolerance
- Hyper-lipidemia
- Increased blood pressure / Hypertension
- Increased Serum BioMarkers of Coagulation inflammation and Vascular Disease
- Increased fed and fasting glucose and HbA1c levels

Rimonabant in ZDSD (11-14 weeks old)



Slower weight gain with high dose Rimonabant (5008 chow).

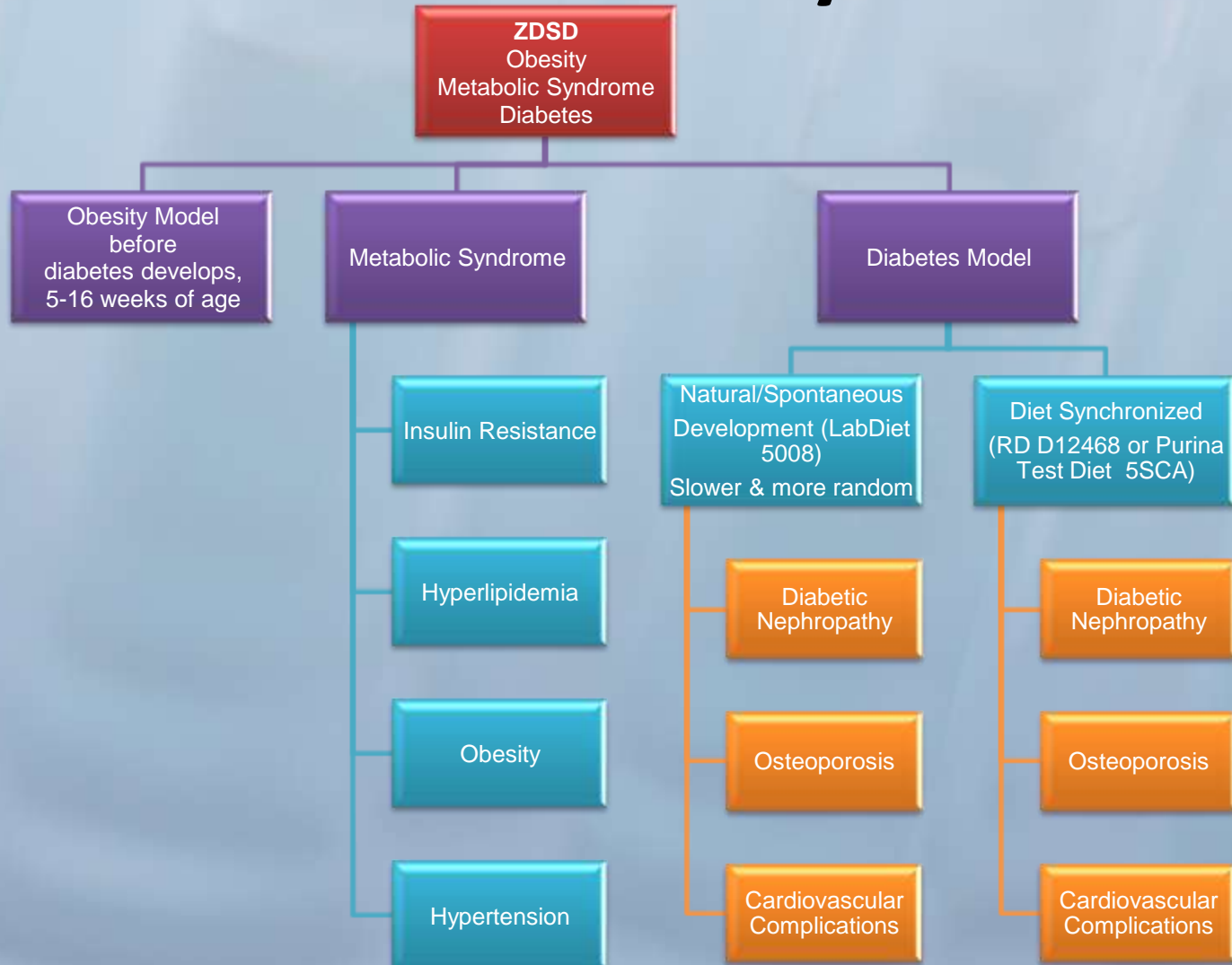
Anti-diabetic Drug Treatment Prevents Diabetes and Weight Loss in ZDSD Rats (5008 Chow)



Diabetic Nephropathy in the ZDSD Rat

- Increased kidney weight
- Increased urinary markers for kidney disease
- Increased serum markers for kidney disease
- Glomerular sclerosis
- Nodular sclerosis, KW nodules
- Thickening basement membrane of glomerular capillaries
- Podocyte effacement on glomerular capillaries⁵

The ZDSD Rat: One rodent – Many Models



Summary of ZDSD Characteristics

- **Conforms to the FDA's guidelines for development of therapeutics for obesity, metabolic syndrome, and type II diabetes.**
- **Intact leptin pathway.**
- **Insulin resistance, elevated glucose levels and glucose intolerance develop early.**
- **Mirrors the progression of type II diabetes in humans.**
- **Progresses through Insulin resistance, hypertension, dyslipidemia, obesity & diabetes.**
- **Diet sensitive.**
- **Responsive to: TZDs, Metformin, Exenatide, Sitagliptin, Niacin, Rimonabant & Glyburide.**
- **Exhibits diabetic complications: nephropathy, osteoporosis and cardiovascular.**
- **Complications of diabetes develop over reasonable timeframes.**