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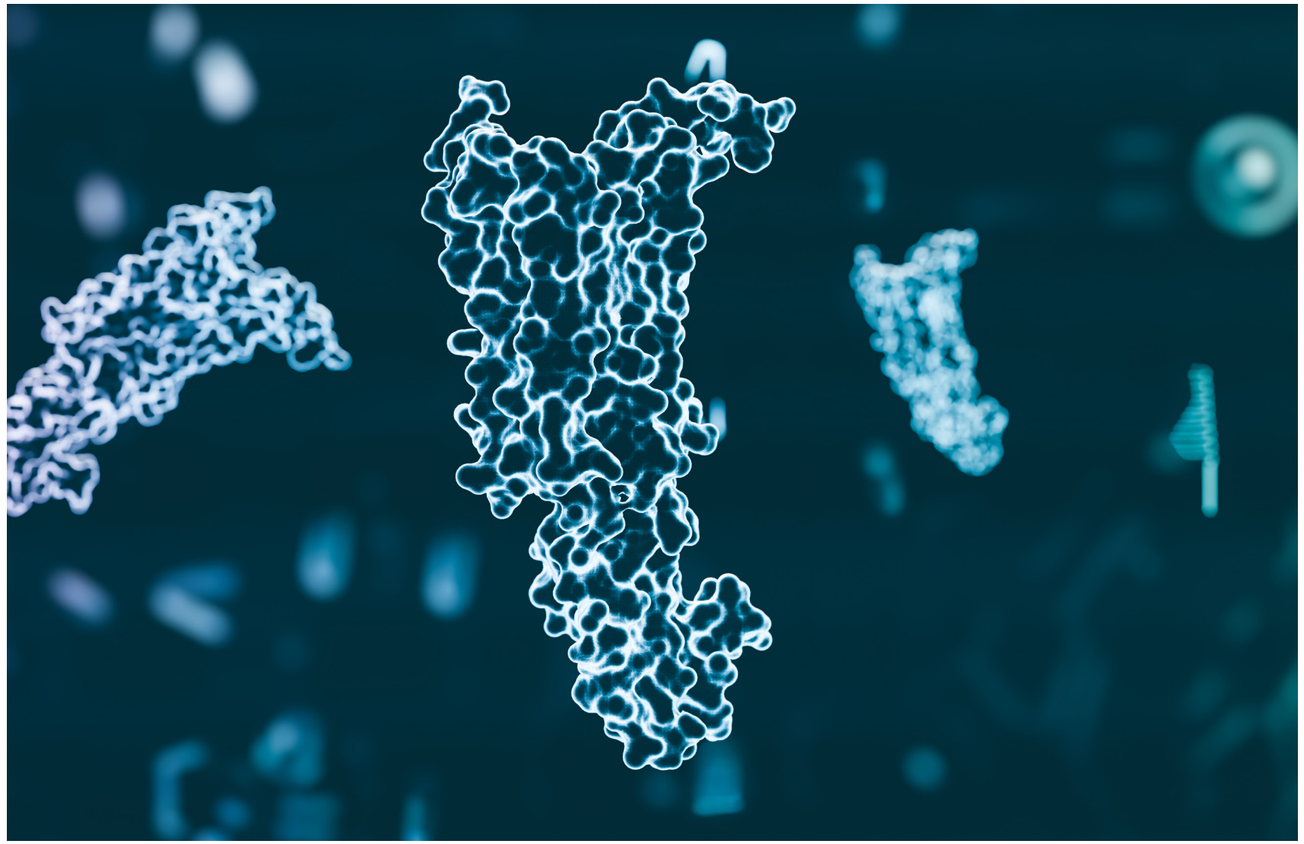

Analysis of Toxicity Characteristics of GLP-1 Receptor Agonists in Non-clinical Safety Evaluation

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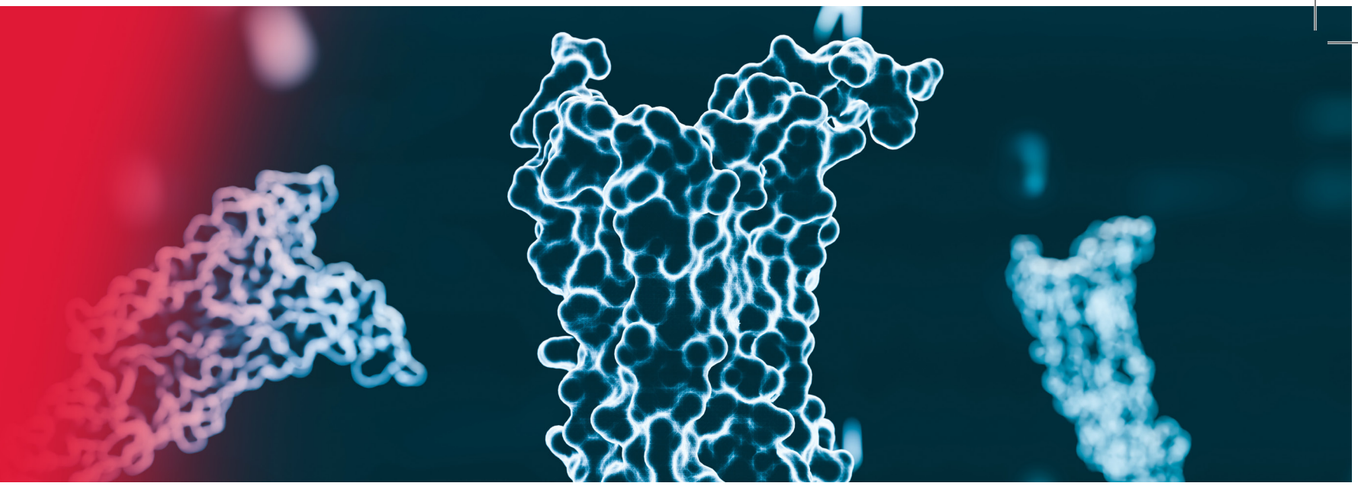

INTRODUCTION

Glucagon-like peptide-1 receptor agonist (GLP-1 RA) is a new hypoglycemic drug class that can reduce blood glucose and help with weight loss by activating the GLP-1 receptor. GLP-1 RA also has multiple clinical benefits, including controlling body weight and improving non-alcoholic fatty liver disease, and is gradually becoming the primary prescription drug for the treatment of diabetes. This abstract summarizes the results of the toxicity studies of GLP-1 RA conducted in our facility, combined with the toxicity characteristics of similar marketed products, to provide a reference basis for non-clinical safety evaluation and toxicity analysis of such products.

METHODS

SD (Sprague-Dawley) rats and cynomolgus monkeys were selected for the general toxicity studies. SD rats and New Zealand (NZ) rabbits were selected for the reproductive toxicity study. Every study was divided into 4 groups: control, low, middle and high dose groups, and the GLP-1 RA was administered by subcutaneous injections. Indicators in general toxicity study included clinical observation, body weight, food consumption, body temperature, electrocardiogram, blood pressure, clinical pathological parameters (hematology, coagulation, and clinical chemistry), organ weight, gross anatomy and histopathological examination. Indicators in the reproductive toxicity study included: clinical observation, body weight, food consumption, gross anatomy and cesarean section examination of F0, reproductive capacity (pregnancy, delivery and lactation), fertility, embryo-fetal development, and development of F1 generation.

RESULTS

General Toxicity Characteristics: Generally, rats and cynomolgus monkeys are commonly used animal species. The toxicity characteristics in rats mainly include the following aspects: decreased body weight and food consumption, decreased Retic count, decreased concentrations of triglycerides, creatinine, total protein, albumin and α1-globulin, and slightly increased in urea concentration in clinical pathological indicators. Decreased weight of various organs was observed. Histopathology analysis include duodenal intestinal gland hypertrophy, thymic atrophy, mild acinar cell atrophy of the pancreas, pancreatic zymogen depletion and persistent lobular atrophy associated with persistently decreased amylase. With analysis of the abnormal changes mentioned above, it is believed that they are mainly caused by the pharmacological effects of the test articles and the secondary changes, as well as the distribution of GLP-1 receptors on the organs.

RESULTS

The toxicity characteristics in cynomolgus monkeys mainly include the following aspects: gastrointestinal reactions, dehydration, and decreased activity, decreased body weight and food consumption,. decreased Erythrocyte count and its related indicators, increased/decreased Retic count, slightly decreased blood glucose, and increased bilirubin in clinical pathological indicators. Increased weight of various organs and decreased weight of thymus. Increased heart rate and left bundle branch block. Gross observation shows right ventricular epicardial pallor, and histopathological examination shows thymic atrophy, pancreatic zymogen granule decreased, slight myocardial vacuolization and degeneration, inflammatory cell infiltration of the kidney or gastric pylorus, mild gastrointestinal bleeding and local irritation of the injection site. Based on the abnormal changes mentioned above, it is believed that they are mainly caused by the pharmacological effects of the test article and the secondary changes, as well as the distribution of GLP-1 receptors on the organs. Of these, cardiac-related changes are considered possibly toxic reactions.

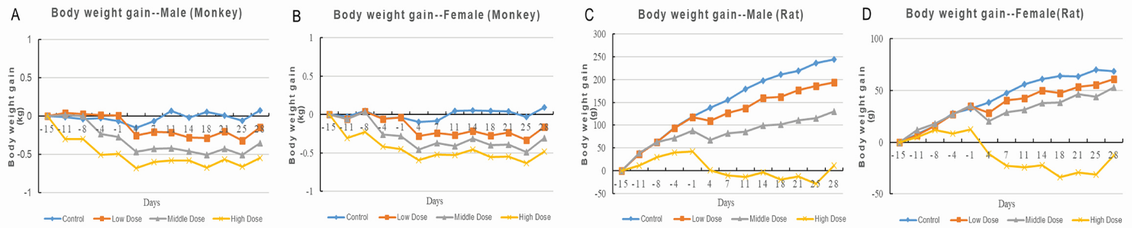

Figure 1. Body weight changes during 6-week dosing. (A) Body weight changes in male monkeys (n=10) (B) Body weight changes in female monkeys (n=10). (C) Body weight change in male rats (n=10). (D) Body weight gain in female rats (n=10).

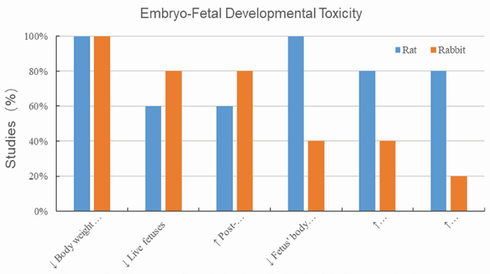

Figure 2. Changes for clinical pathological indicators in the repeat-dose toxicity studies (n=20).

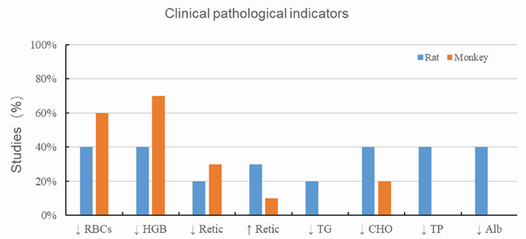

Figure 3. Changes for Embryo-fetal developmental toxicity of 10 studies.

Reproductive and Development Toxicity Characteristics:
Fertility and early embryonic development toxicity characteristics of rats mainly included the following aspects: decreased body weight or weight gain, decreased food consumption, prolonged female estrous cycle, decreased number of corpora lutea, implantations and live fetuses. No abnormality in male fertility is detected except for slightly decreased sperm motility and decreased reproductive organ weight. There were no histopathological abnormalities of reproductive organs in males.

Embryo-fetal developmental toxicity characteristics mainly included the following aspects: In SD rats decreased maternal body weight or body weight gain, and decreased food consumption, decreased number of live fetuses, increased post-implantation loss, decreased fetal weight, decreased body length and tail length, skeletal development retardation, significant increases in skeletal and visceral variation or malformations. In NZ rabbits, significantly decreased body weight and food consumption or even death, abortion or pre-mature delivery, decreased number of live fetuses, increased post-implantation loss, decreased fetal body weight, skeletal development retardation, and slightly increases in skeletal and visceral variation or malformations. In cynomolgus monkeys, decreased maternal body weight or body weight gain, and decreased food consumption, and no significant embryo-fetal developmental toxicity and teratogenicity were noted.

Pre- and postnatal developmental toxicity characteristics of rats included the following aspects: decreased body weight or weight gain, decreased food consumption and slightly delayed or normal parturition in F0 generation, decreased birth weight in F1 generation, which may not return to normal till adulthood, some abnormal developmental indicators, possible abnormal behavioral function and no abnormality of reproductive capacity. Based on the above reproductive toxicity changes, it is believed that they are mainly caused by the pharmacological effects of the test articles, the effects on fetal development secondary to the decreased maternal body weight gain during pregnancy, and direct drug exposure.

CONCLUSION

This abstract summarizes the results of the toxicity studies of GLP-1 RA conducted in our facility, combined with the toxicity characteristics of similar marketed products. No new toxicity was found in the test articles in the facility, and their toxicity characteristics are similar to those of marketed products, providing a reference basis for the non-clinical safety evaluation and toxicity analysis of such products.