

GLP-1R Antagonist Antibodies for Rare Metabolic Diseases, Primed for Development

First-in-class antibodies for the potential treatment of hypoglycemia and hyperinsulinism

The Unmet Medical Need

Severe and persistent hypoglycemia (low blood glucose) due to excess insulin secretion from pancreatic β -cells can result in serious clinical outcomes including seizures, brain damage, and death. There are limited therapeutic options for this metabolic dysfunction, which can be caused by certain medical conditions:

- **Post-bariatric hypoglycemia (PBH):** A complication of bariatric surgeries (250K/year in the U.S.), in which 14% to 34% of Roux-en-Y gastric bypass or vertical sleeve gastrectomy patients report postprandial symptoms.
- **Congenital hyperinsulinism (CHI):** A rare pediatric genetic disorder affecting 1 in 50K newborns.
- **Insulinoma:** Pancreatic tumors that overexpress GLP-1R and cause hypoglycemia in 1 to 4 people out of 1M of the population.

Target Rationale: Glucagon-Like Peptide 1 Receptor (GLP-1R) for Hypoglycemia and Hyperinsulinism

Glucose-dependent insulin secretion is mediated through the binding of GLP-1 to GLP-1R. Excessive signaling through this pathway increases insulin secretion, resulting in hypoglycemia. GLP-1R antagonism is a promising therapeutic strategy for treating hypoglycemia.

An antagonistic therapeutic antibody targeting GLP-1R offers enhanced specificity, efficacy, and advantageous pharmacokinetics. Inhibiting GLP-1R may also offer a better safety profile than inhibiting the insulin receptor, and GLP-1R is a viable target for all forms of hyperinsulinism.

Twist's GLP-1R Antagonist Antibody: TB01-3

Twist has identified a high-affinity, potent GLP-1R antagonist, TB01-3, from our expertly designed and proprietary GPCR library. TB01-3 is a fully human IgG2 antibody and its function, pharmacokinetics, and *in vivo* efficacy have been characterized¹. TB01-3 acts as a dose-dependent competitive antagonist of GLP-1 and stabilizes higher blood glucose concentrations *in vivo* (Figure 1), making it an attractive candidate for further pre-clinical development. Twist has also characterized seven additional GLP-1R antagonists with EC_{50} s in the low nM range that are ready for additional testing.

Additional Advantages

- First anti-GLP-1R antibody for hypoglycemia
- Potent nM antagonist; $EC_{50} = 10.4$ nM
- Long half-life of ~ 1 week (in rats)
- Promising pre-clinical efficacy

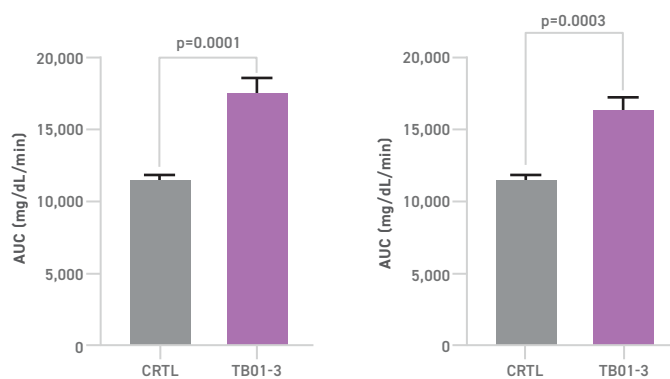


Figure 1. TB01-3 stabilizes higher blood glucose levels in an insulin tolerance test using a 6 hour (left) and 19+2 hour (right) dosing regimen.

PARTNER ON GLP-1R WITH TWIST BIOPHARMA

If you are interested in learning more or licensing Twist antibodies, please contact biopharma@twistbioscience.com