## Hepatic-Directed Vesicle Insulin: A Review of Formulation Development and Preclinical Evaluation

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## Abstract

Hepatic-directed vesicle insulin (HDV-I), a novel investigational vesicle (<150 nm diameter) insulin delivery system that carries insulin and a specific hepatocyte-targeting molecule (HTM) in its phospholipid bilayer and has the ability to mimic a portal vein insulin infusion remotely [subcutaneous (SC) HDV-I] and noninvasively (oral HDV-I), has been developed. This review summarizes formulation development, subsequent refinements, and results of preclinical evaluation studies, including biodistribution, mechanistic, and toxicology studies of predominantly SC HDV-I, in various animal models. Studies conducted to date have confirmed the hepatocyte specificity of HDV and HDV-I and revealed that HDV-I can stimulate the conversion of hepatic glucose output to uptake at a dose that is <1% of the dose of regular insulin (RI) required for liver stimulation; suggest that the enhanced antihyperglycemic effect of HDV-I is due to hepatic glucose uptake; and in pancreatectomized dogs during an oral glucose tolerance test, HDV-I normalized blood glucose curves when compared to control curves in intact dogs and prevented secondary hypoglycemia in contrast to the same dose of RI. A 28-day SC HDV toxicity study in rats revealed no clinical, clinical laboratory, or histopathological findings, and the battery of three genetic toxicology studies was negative. Results support the hypothesis that HDV-I works by stimulating hepatic glucose uptake and/or glycogen storage in insulin-deficient animals. The ability to target the delivery of HDV-I to the liver reestablishes the liver as a major metabolic modulator of glucose metabolism. The future of HDV-I depends on the results of ongoing development and longer term clinical trials.

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Abbreviations: (AUC) area under the concentration-time curve, (DGDG) digalactosyl diglyceride, (HDV) hepatic-directed vesicle, (HDV-I) hepatic-directed vesicle insulin, (HTM) hepatocyte-targeting molecule, (OGTT) oral glucose tolerance test, (PE) phosphatidylethanolamine, (PPG) postprandial plasma glucose, (RI) regular insulin, (SC) subcutaneous

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