Liver targeted insulin:
A novel long lasting insulin for NASH patients

- **Long-lasting insulins** are used in the treatment of Diabetes Mellitus (DM) to control fasting glucose. Administered subcutaneously, they do not replicate the physiological delivery of insulin.
- Insulin lipogenic activity generates **non-alcoholic steatohepatitis** (NASH) and weight gain, worsening insulin resistance.
- A new **proprietary fusion protein has been** developed combining a single chain insulin and a scaffold protein, with the following properties:
  - Liver targeted, enabling physiological control of DM.
  - Prolonged half-life in circulation.
  - Reduced lipogenic activity.
- **Primary Indication**: glucose management in diabetic patients with NASH.

Scope of the problem

- The prevalence of type 2 diabetes mellitus (T2DM) is approaching epidemic proportions due to physical inactivity and obesity.
- Despite the improvements observed with basal insulin analogs, their time-action profiles are not completely flat and are shorter than 24 hours in many patients. Moreover, severe hypoglycemia remains a concern, particularly in patients with type 1 DM.
- Long-lasting insulins do not replicate the physiological delivery of insulin, generating an imbalance that contributes to chronic insulin resistance and vascular complications.
- Insulin lipogenic activity generates hepatic steatosis and weight gain, worsening insulin resistance.

Patient Need Addressed

Safer and more efficacy insulin analogues are needed to improve glucose management in diabetic patients with NASH.

Current Standard of Care & Market Scope

- Insulin preparations differing both in their time of onset and duration of action are available for insulin substitution therapy.
- Current regimens try to mimic physiological insulin secretion by injection of delayed action insulin for basal insulin supply and rapid-acting insulins for prandial control.
- The modern insulins market as a whole is forecast to grow over the next 10 years, with basal insulins having the largest market share. The US has the largest contribution and is forecast to reach sales of $12bn in 2020.

Product Profile

- A recombinant fusion protein of a single chain insulin and a scaffold protein (apolipoprotein-AI).
- The fusion protein has a longer half-life in circulation (50-fold) than insulin (Fig. 1).
- The hypoglycemic activity is prolonged more than 12 hours in streptozotocin-induced diabetic mice (Fig. 2).
- The fusion protein is preferentially retained in liver and kidney (Fig. 3).
- The hypoglycemic activity in diabetic db/db mice is similar to an analogous of insulin degludec.

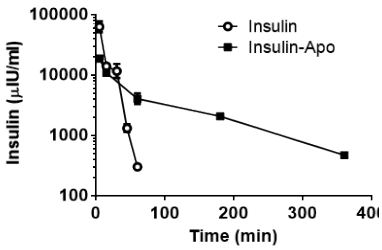

Fig. 1: C57BL/6 mice received 55 nmol/kg of insulin or, insulin\Apo intravenously.

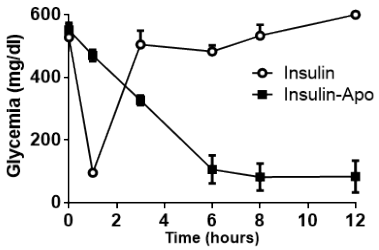

Fig. 2: Streptozotocin\induced diabetic C57BL/6 mice received 139 nmol/kg Insulin\Apo or Insulin intravenously.

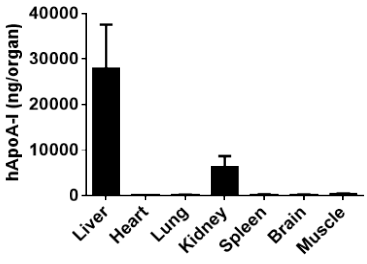

Figure 3: C57Bl/6 mice received 139 nmol/kg Insulin-Apo intravenously. Three hours after administration, mice were sacrificed and several organs were removed.

Intellectual Property

Apo-A conjugates for the administration of biologically active compounds. WO2009150284.

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