Future Medical Treatments for Congenital Hyperinsulinism

Dr Antonia Dastamani

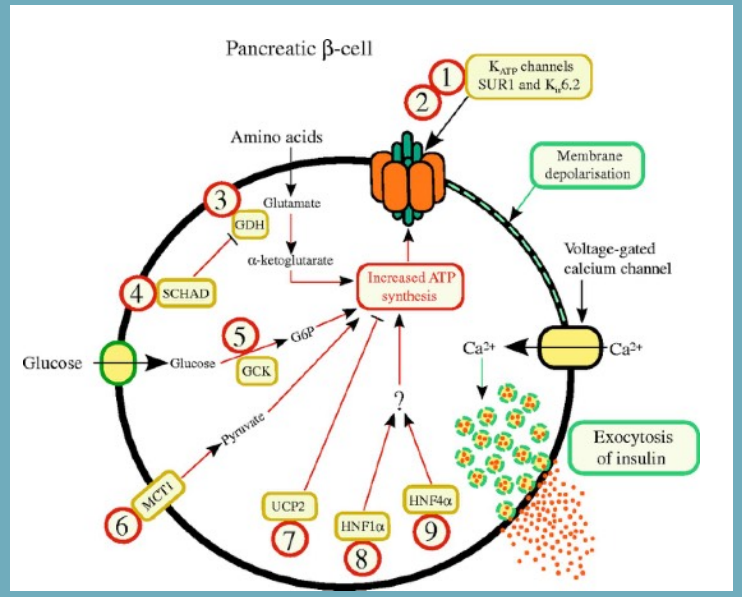
Consultant of Pediatric Endocrinology and Diabetes
Lead of Congenital Hyperinsulinism NHS Highly Specialized Service

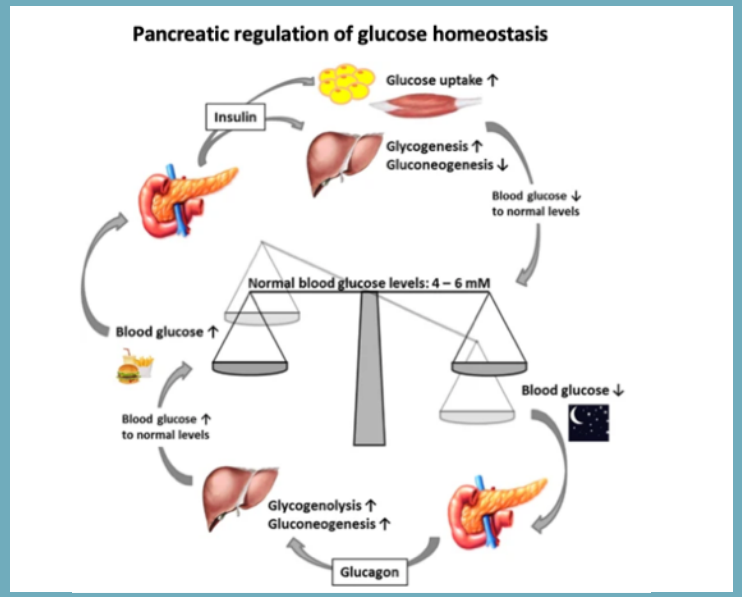
Great Ormond Street Hospital for Children NHS Foundation Trust London, England

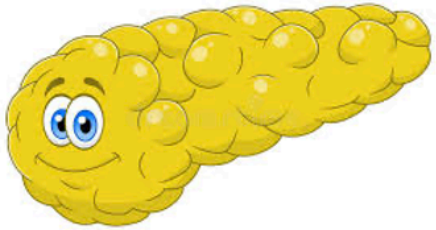
DISCLOSURES

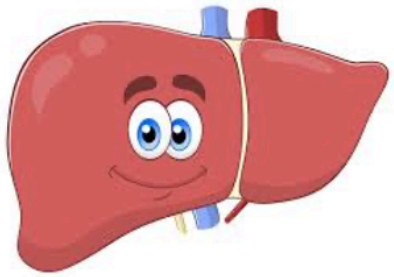
I am PI in studies of Zealand, Rezolute, Hanmi

The investigational drugs will be presented according to their phase in the research and development process









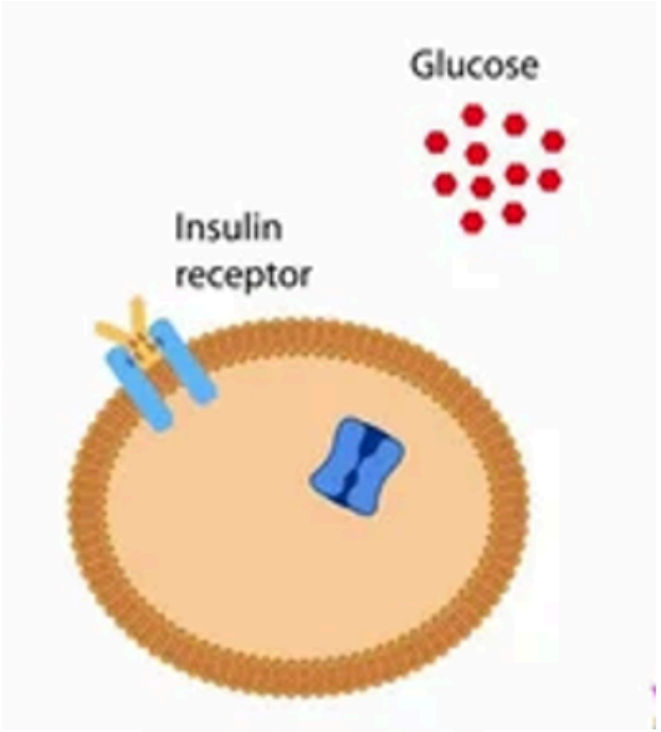
Dasiglucagon

HM15136

ZEALAND PHARMA

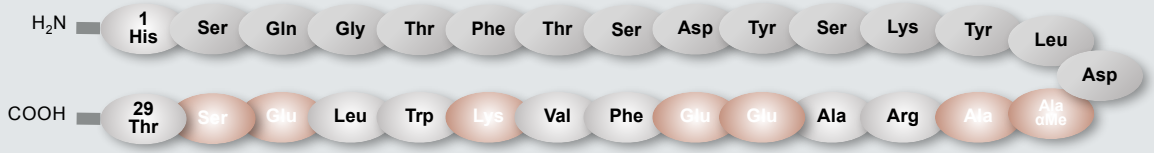
Hanmi

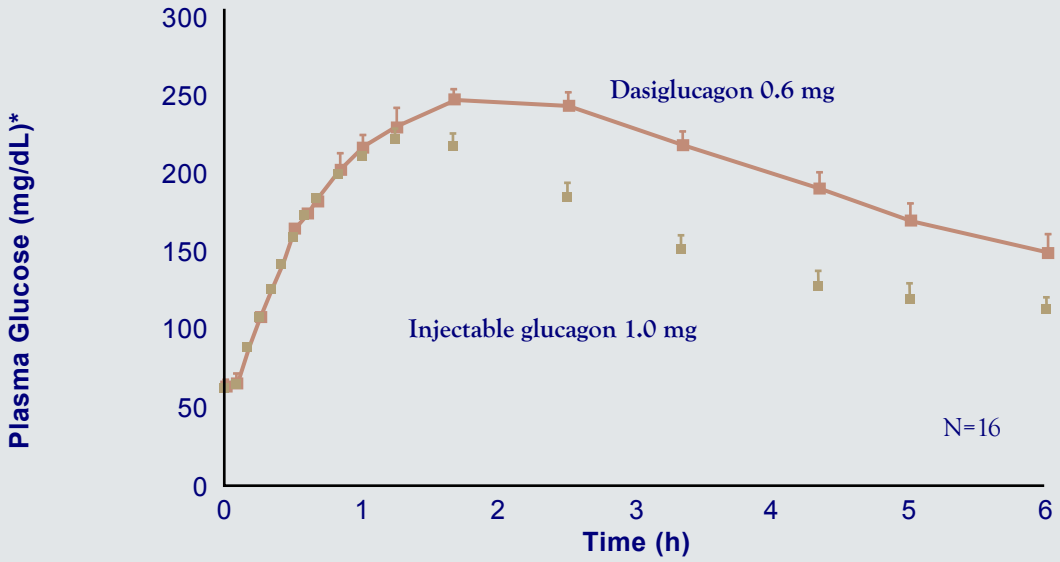
Selective Somatostatin-Analogue
GLP-1 Antagonist
IRDye700DX



RZ358

Dasiglucagon





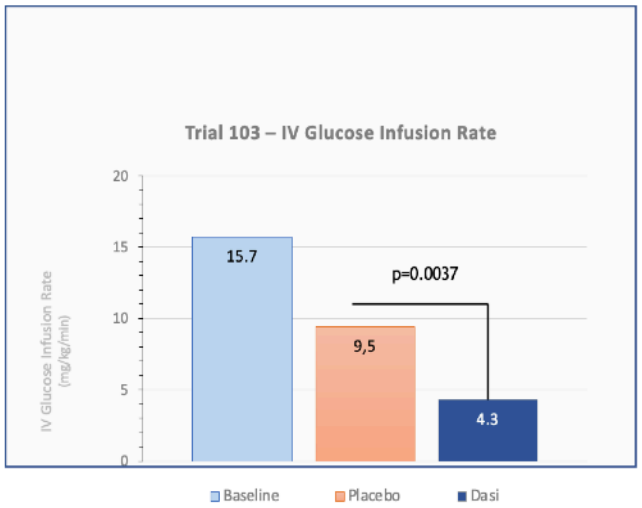
- ✓ **Mimics the action of glucagon, a hormone produced by the pancreas that helps regulate blood glucose levels by stimulating glucose production in the liver and breaking down glycogen (a stored form of glucose) into a form the body can use**
- ✓ **Stable, non-fibrillating glucagon analogue. Soluble in aqueous solution and suitable for continuous SC infusion**
- ✓ **Shown to raise plasma glucose in a dose dependent manner**

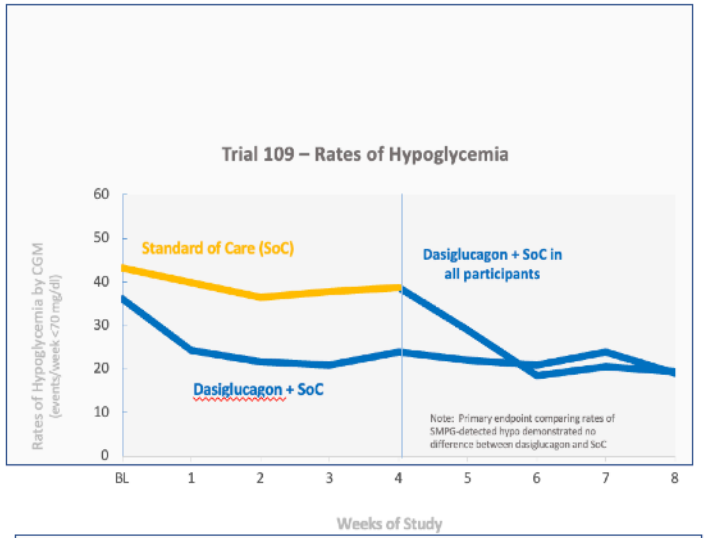
Hovelmann et al. Diabetes Care. 2018;41:531-537.

ZEALAND PHARMA

Phase 3 program of dasiglucagon in CHI:

Results of Pivotal Clinical Trials





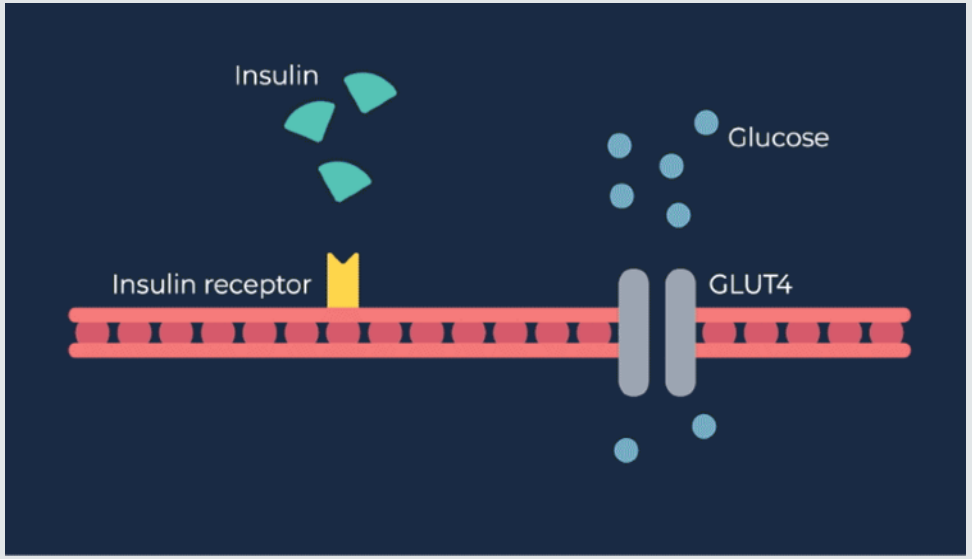
- Reduced IV glucose infusion rate by ~55% (as compared to placebo)
- 7 of 12 subjects discontinued IV glucose over 25 days of treatment (without pancreatectomy)

- Meaningful reductions in CGM measures of hypoglycemia
- No significant effect on hypoglycemic events as measured by SMPG

Key Phase 3 Results

- ✓ 44 patients recruited
- ✓ NEWBORNS
  - ✓ Significantly reduced the requirement for IV glucose support
  - ✓ Reduced the total daily carbohydrate requirement
- ✓ CHILDREN
  - ✓ Reduced both hypoglycemic events and time in hypoglycemia (by CGM) when compared with SoC alone
  - ✓ Support use of more frequent monitoring using CGM to detect hypoglycemic events
- ✓ Over 3 years safety and efficacy data
- ✓ The most frequently reported adverse events in both trials were skin reactions and gastrointestinal disturbances

The clinical trial data support that dasiglucagon represents an effective and safe potential treatment option for infants/children with CHI to limit hypoglycemia risk and dependence on supplemental glucose/CHO

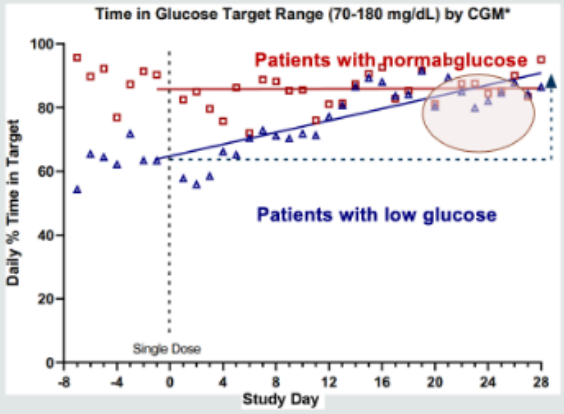


- ✓ Fully humanized, IgG2 monoclonal antibody which binds to the insulin receptor at a non-competitive site, normalizing insulin activity to prevent hypoglycemia
- ✓ Highly selective to the insulin receptor (does not bind to the IGF-1 receptor)
- ✓ Works downstream from the pancreas and agnostic to genetic cause, developed specifically for CHI disease

RZ358: Monoclonal Antibody Therapy
Key Phase 1, 2a studies Results

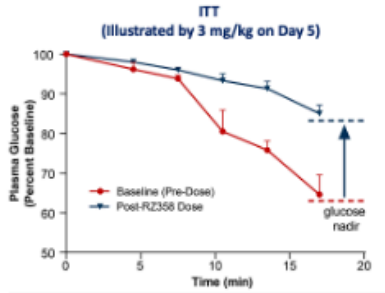
- ✓ 30-minute IV infusion
- ✓ Dose dependent and predictable PK/PD lasting 2-4 weeks
- ✓ 6 clinical RZ358 studies completed, 75 participants have received RZ358 , *26 pediatric patients with congenital HI (including 16 patients ages 2-6 years old)*
- ✓ Safe and well tolerated overall. No identified safety risks thus far
- ✓ Improved hypoglycemia, without clinically-significant hyperglycemia
- ✓ Data support potential 2x/monthly or even monthly 30 min IV infusion

Time in Glucose Target Range (70-180 mg/dL) by CGM*

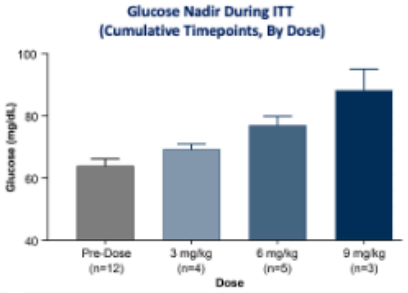


Glucose normalization achieved after two weeks with single dose of RZ358 in Congenital HI patients

Insulin Tolerance Test (ITT)



- Conducted at: baseline and on days 1, 2, 3, 5, 7, 11, and 22 at the 3, 6, and 9 mg/kg dose
- On each ITT day, insulin administered at T_0 and glucose measured serially until nadir
- RZ358 blunted insulin-induced hypoglycemia
- No hyperglycemia observed

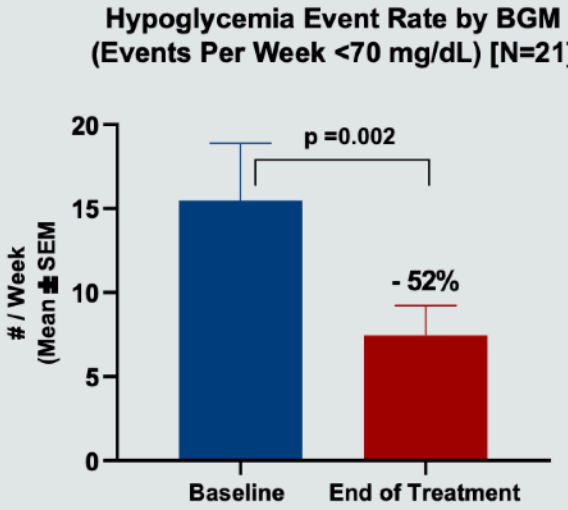


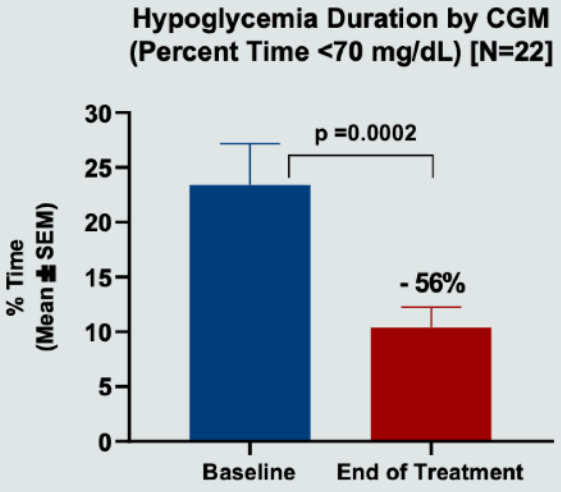
- PK-PD (dose-response) correlation observed
- Effect persisted for 2 weeks
- PK/PD model shows potential for 1-2x monthly dosing

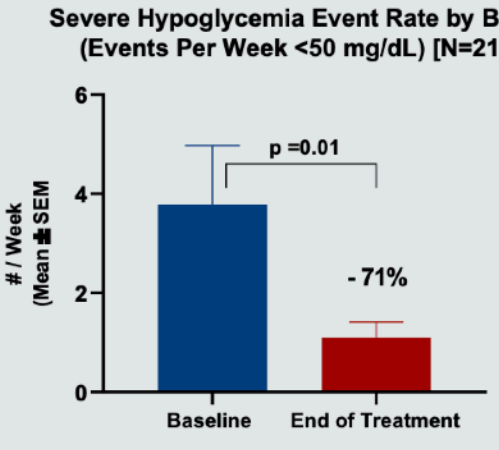
Key Phase 2b Results

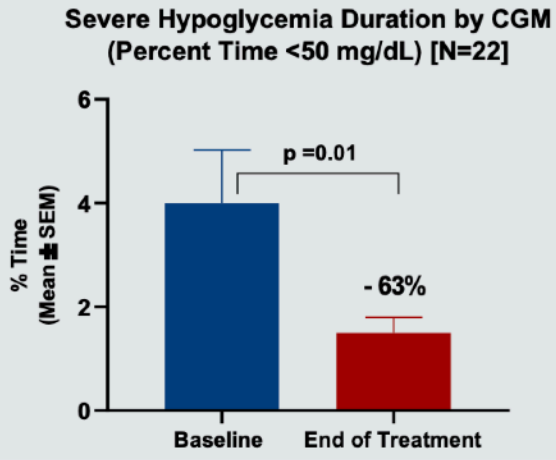
- ✓ **Safety: RZ358 was generally safe and well-tolerated. Reported AEs not dose-dependent and were generally mild and unrelated to study drug. No study discontinuations or adverse drug reactions, not immunogenic**
- ✓ **PK: Predictable and dose-dependent RZ358 concentrations achieved**
- ✓ **Efficacy: After eight weeks of treatment with RZ358 demonstrated:**
  - **Hypoglycemia correction of ~50% across all doses and cohorts; ~75% at the 6 mg/kg and 9 mg/kg and at severe thresholds**
  - **Dose and exposure-dependent responses**
  - **100% patient response rate with > 50% Hypoglycemia correction at the top dose**

Expectations of ≥ 25% Hypoglycemia Correction (Time, Events) were met and exceeded across multiple metrics

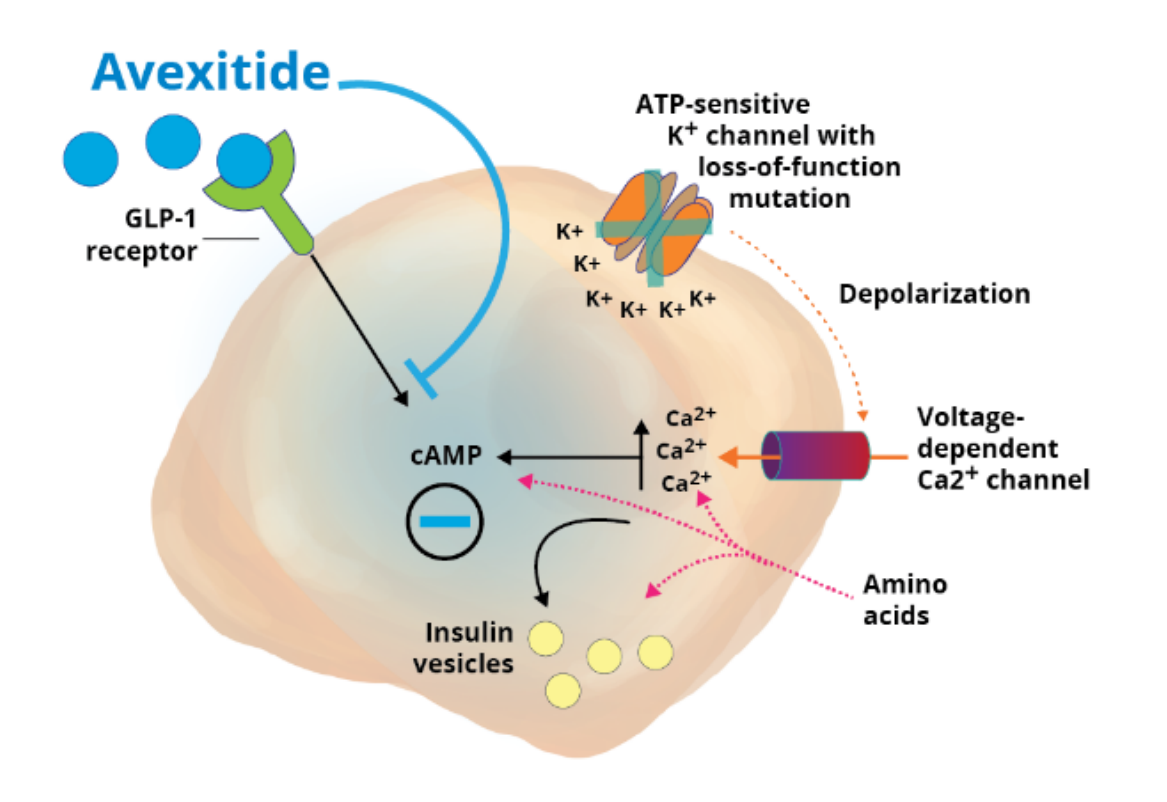








Phase 3 study ongoing



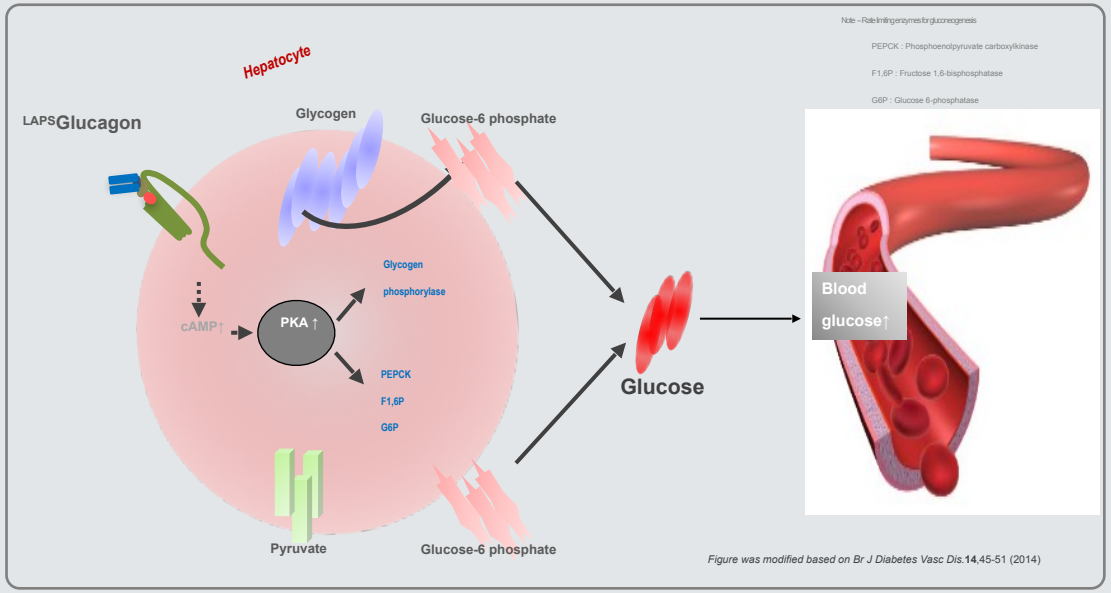
- ✓ GLP-1 receptor antagonist, which lowers basal cAMP levels and decreases Ca2+-stimulated insulin secretion
- ✓ Preclinical studies (mouse model of HI and in pancreatic islets from HI patients) have demonstrated critical role of GLP-1r in HI
- ✓ Reduce fasting and amino-acid stimulated hypoglycemia in clinical trials

Key Phase 2 Results

- ✓ Phase 2 studies (n=3)
  - ✓ Newborns and infants (n=13) significantly reduced the glucose infusion rate with dose-dependent improvements
  - ✓ Children (n=16) reduced the likelihood of fasting hypoglycemia by up to 84% and reduced the likelihood of protein-induced hypoglycemia by 82% among a subset of patients (n=8)
  - ✓ Adolescent and Adult Study Results (n=9) increased fasting glucose and decreased requirement for rescue

Hanmi

HM15136 (^{LAPS}Glucagon Analogue, Efpegerglucagon)

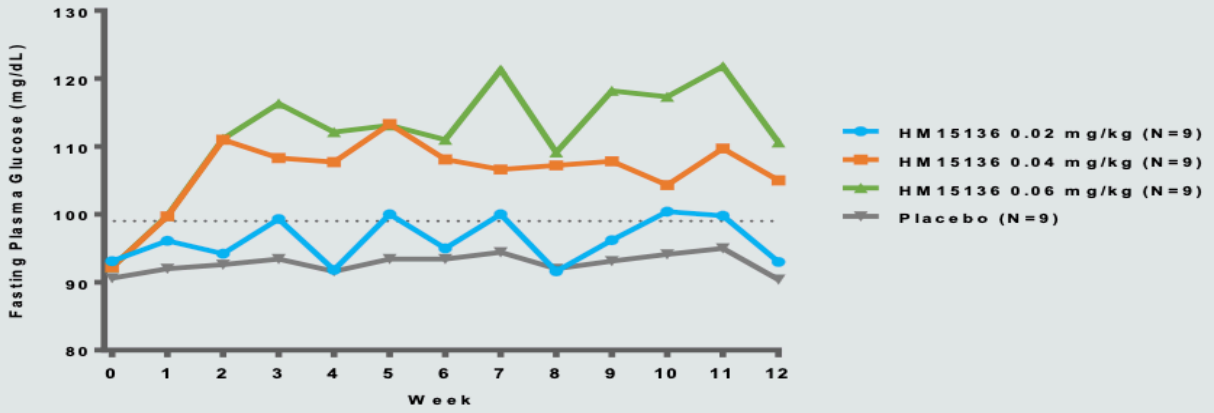


- ✓ Acts like glucagon
- ✓ Ready-to-inject soluble long-acting glucagon for weekly subcutaneous injection

Key Phase 1 Results

- ✓ **Safety: The safety and tolerability of HM15136 demonstrated in Phase 1 studies**
- ✓ **PK: Extended half-life ranging from 77 to 167 hours was observed in Phase 1 studies (weekly dosing). It is significantly greater than that of native glucagon**
- ✓ **Efficacy: The dose dependent FPG increase was observed after multiple administrations of HM15136 in multiple ascending dose**

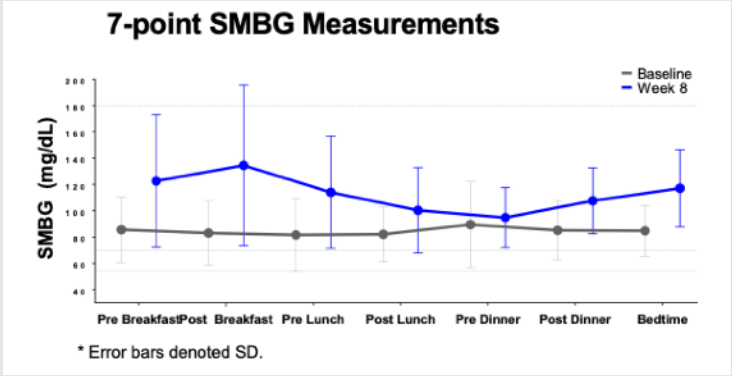
Fasting plasma glucose after multiple weekly HM15136 dosing

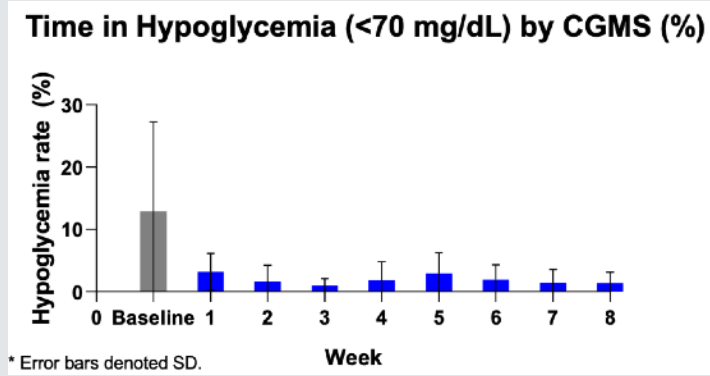


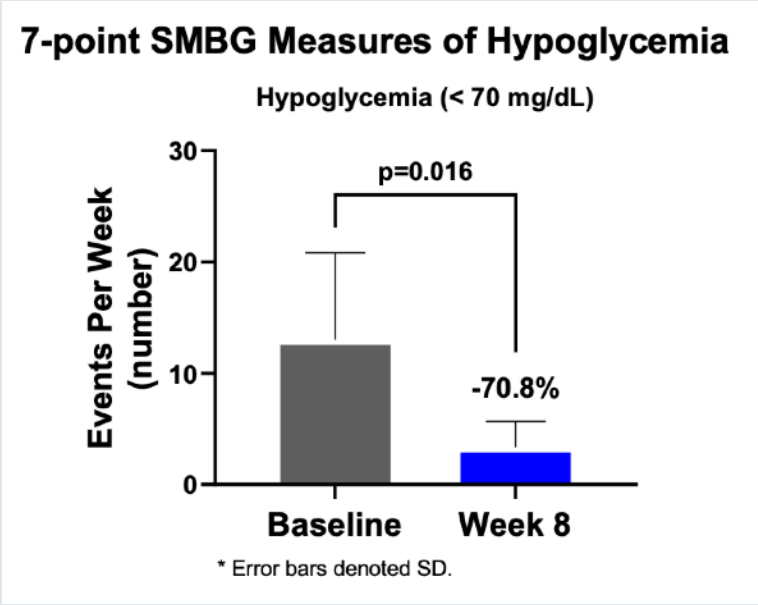
Phase 1 Single Ascending Dose study (HM-GCG-101), ADA 2020
Phase 1 Multiple Ascending dose study (HM-GCG-102), ENDO 2022

Key Phase 2 Preliminary Results

- ✓ 6 patients recruited
- ✓ Safety: HM15136 was safe and well tolerated, with no significant changes in vital signs, physical examinations, safety laboratory tests, or ECG.The most common adverse event was gastrointestinal disorders such as upper abdominal pain and diarrhea
- ✓ PK: The mean elimination half-life at Week 8 was 146 hours, which supports the weekly dosing interval
- ✓ Efficacy: After eight weeks of treatment with HM15136, patients with CHI demonstrated clinically significant reductions in hypoglycemia events

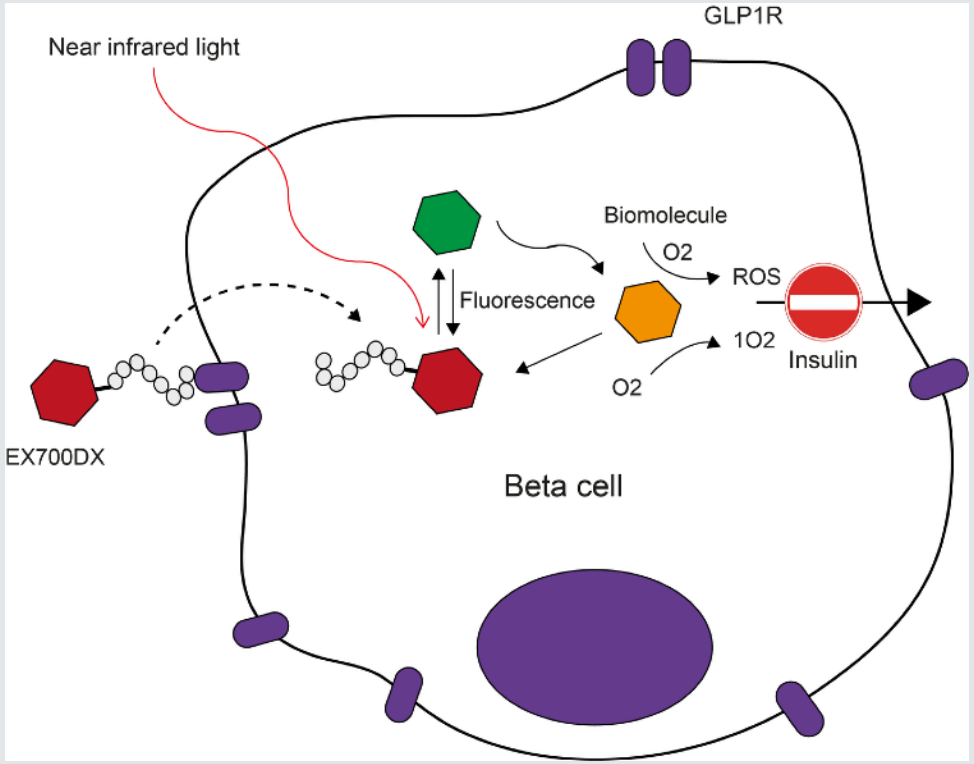






Phase 2 study ongoing

LightCure



- **Exendin 4, EX binds to the GLP-1R specifically expressed on the beta cells**
- **EX labeled with radionuclides or fluorescent dyes, shows high accumulation in beta cells in vivo while not accumulating in the rest of the pancreas.**
- **In clinical trials Ga-68-NODAGA-EX for PET imaging of fCHI and insulinomas, performed superior to all current state-of-the-art imaging modalities**
- **Deliver an EX bound photosensitizer (IRDye700DX) to the beta cells (via i.v. injection). 700DX can then be activated by light of a specific wavelength, leading to production of radical oxygen species (ROS) functionally impairing/damaging over-functioning beta cells or, if required induce apoptosis, while preserving all other cells. This highly specific therapeutic principle is called "targeted photodynamic therapy" (tPDT).**
- **Available preclinical trials in animal models (rodents and pigs)**

A few more on the horizon

Somatostatin analogues -New formulations
Pharmacological trafficking chaperones

Gene therapy

Thank you


Patients
& their families
Researchers
Pharmaceutical companies
Committees