DEVELOPMENT OF AVEXITIDE (EXENDIN 9-39) FOR TREATMENT OF CONGENITAL HYPERINSULINISM

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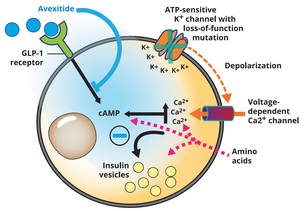
ABSTRACT

Avexitide (formerly known as exendin 9-39) is a first-in-class glucagon-like peptide-1 receptor (GLP-1r) antagonist[1,2] and inverse agonist[3,4] under development by Eiger BioPharmaceuticals for treatment of hyperinsulinemic hypoglycemia. Avexitide is the chemically synthesized N-terminus 31-amino-acid fragment of exendin-4, a 39 amino-acid naturally occurring peptide of the Gila monster, *Heloderma suspectum*[5,6].

The most common and severe form of congenital hyperinsulinism (HI) results from inactivating mutations in genes encoding the sulfonylurea receptor 1 (SUR-1) and K+-selective pore-forming subunit (Kir6.2), which together form the ATP-sensitive potassium channel (K_{ATP} channel)[7,8]. Loss of K_{ATP} channel activity leads to persistent beta-cell membrane depolarization and insulin degranulation regardless of plasma glucose levels.

In vitro, in vivo, and clinical data generated at Children's Hospital of Philadelphia (CHOP) in animal models of K_{ATP}-HI[4] and in patients with HI[9] over the past decade have elucidated the role of the GLP-1r in HI and provided proof-of-concept that avexitide administered by intravenous infusion can effectively mitigate fasting and postprandial hypoglycemia, and reduce glucose infusion rates in patients with HI. By binding to the GLP-1r, avexitide reduces basal and amino-acid induced cAMP accumulation and decreases calcium-stimulated insulin secretion[4,9] (Figure 1). To date, 39 patients with HI (10 adolescents and adults, 16 children, and 13 neonates) have received intravenous infusion of avexitide at CHOP across multiple clinical studies. An overview of clinical studies conducted to-date evaluating the use of avexitide for the treatment of HI will be presented.

Figure 1: Pancreatic Beta Islet Cell



Adapted from De Leon et al. J Biol Chem. 2008;283(38):25786–25793 and Velasco et al. Mol Pharmacol. 2016;90:341–357.

BACKGROUND

Avexitide (chemical name: exendin 9-39) is a first-in-class glucagon-like peptide-1 receptor (GLP-1r) antagonist[1,2] with inverse agonist properties[3,4] under development by Eiger Biopharmaceuticals, Inc. (Eiger). Avexitide is the chemically synthesized N-terminus 31-amino-acid fragment of exendin-4, a 39-amino- acid naturally occurring peptide isolated from the Gila monster, Heloderma suspectum[5,6]. Eiger is developing avexitide for the treatment of hyperinsulinemic hypoglycemia, including HI and post-bariatric hypoglycemia (PBH).

Preclinical studies conducted in a mouse model of K_{ATP} HI[4] and in pancreatic islets from patients with HI[9] have demonstrated an important role for GLP-1r signaling in catalysing calcium-mediated insulin degranulation in K_{ATP} HI. GLP-1r signaling activates adenylyl cyclase and generation of cyclic adenosine monophosphate (cAMP). Inhibition of GLP-1r signaling with avexitide has been shown to reduce cAMP accumulation and insulin degranulation, thereby demonstrating a critical role for GLP-1r signaling in the pathophysiology of K_{ATP} HI[4,9].

Clinical proof-of-concept has been demonstrated with the use of avexitide in the treatment of hyperinsulinemic hypoglycemia, including HI and post-bariatric hypoglycemia (PBH) (Table 1). Eiger has developed a stable, solution formulation for subcutaneous injection (Avexitide Injection), which has been well-tolerated when administered over 28 days in adults with PBH. This formulation may be used in future studies in patients with HI.

Presented is an overview of the 3 clinical investigations conducted to date in patients with K_{ATP} HI, including the "Adolescent and Adult Study," the "Children Study" and the "Neonate and Infant Study."

Table 1: Overview of Clinical Development of Avexitide

Route of Administration		Formulation*	Dosing Duration	Patient Number and Age Cohort	Hyperinsulinemic Hypoglycemia Indication
IV Infusion	Studies conducted by Eiger	Lyophilized Formulation	Single Dose	10 adolescent & adult	Congenital Hyperinsulinism
		Lyophilized Formulation	Single Dose	16 children	Congenital Hyperinsulinism
		Lyophilized Formulation	Single Dose	13 neonates & infants	Congenital Hyperinsulinism
SC Injection	Studies conducted by Eiger	Lyophilized Formulation	Single Ascending Dose	8 adults	Post-bariatric Hypoglycemia
		Lyophilized Formulation	Single Ascending Dose	8 adults	Post-bariatric Hypoglycemia
		Lyophilized Formulation: 15 patients Solution Formulation: 5 patients	Multiple Ascending Dose Up to 3 Days Twice Daily Injection	20 adults	Post-bariatric Hypoglycemia
		Solution Formulation	Single Ascending Dose; Multiple Ascending Dose 3 Days Twice Daily Injection	40 adults	Healthy Volunteers
		Solution Formulation	28 Days Outpatient Administration Once and Twice Daily Injection	18 adults	Post-bariatric Hypoglycemia

**Lyophilized Formulation= lyophilized avexitide reconstituted prior to intravenous or subcutaneous administration; Solution Formulation = stable, sterile solution formulation of avexitide for subcutaneous injection.*

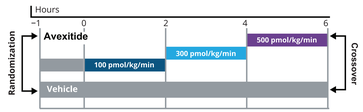
METHODS

1 ADOLESCENT AND ADULT STUDY

A Randomized, Two-Period, Crossover Study in 10 Adolescents and Adults with K_{ATP}HI to Evaluate the Effects of a Single, Intravenous Infusion of Avexitide on Glucose Metabolism

Adolescents and adults with a confirmed K_{ATP}HI diagnosis were randomly assigned to one of two IV infusion treatment sequences: an initial 1-hour infusion of vehicle followed by infusion of avexitide at infusion rates that ascended from 100 to 500 pmol/kg/min over the course of 6 hours on one day followed the next day by a 7-hour infusion of vehicle or vice versa.

Figure 2: Adolescent and Adult Study Design



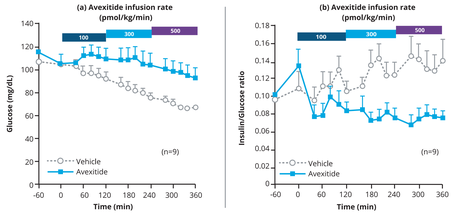
RESULTS

Avexitide Increased Fasting Glucose, Decreased Requirement for Rescue, and Decreased Insulin/Glucose Ratio

Nine patients, ages 15-47 (6 female, 3 male) were included in the analysis. Three of the 9 evaluated patients had undergone subtotal pancreatectomy as infants.

In all patients fasting blood glucose levels were statistically significantly higher during avexitide infusion compared with vehicle (Figure 3a). Eight patients had hypoglycemia (blood glucose <70 mg/dL) during vehicle infusion, of which 3 patients required an IV infusion of dextrose for symptomatic hypoglycemia and blood glucose concentrations <60 mg/dL. No patients experienced hypoglycemia during avexitide infusion. The insulin/glucose AUC was reduced during avexitide infusion as compared with vehicle (29.2 vs. 43.6, respectively, $p = 0.053$), with greater reductions in insulin/glucose AUC ratios observed with higher infusion rates (100 pmol/kg/min: 6.7 vs. 8.9, $p = 0.11$; 300 pmol/kg/min: 6.2 vs. 10.3, $p = 0.016$; and 500 pmol/kg/min: 6.0 vs. 10.7, $p = 0.045$) (Figure 3b).

Figure 3: Blood Glucose and Insulin/Glucose Ratio During Avexitide vs Vehicle Infusion[9]



Adolescent and Adult Study Summary

Avexitide infusion:

- Significantly raised fasting glucose concentrations
- Reduced the requirement for glycemic rescue
- Reduced the fasting insulin/glucose AUC

METHODS

2 CHILD STUDY

A Placebo-Controlled, Randomized, Crossover Study in 16 Children with K_{ATP}HI to Evaluate the Effect of Avexitide on Fasting and Protein-induced Hypoglycemia

Children with a confirmed K_{ATP}HI diagnosis and persistent hypoglycemia requiring medical treatment were randomly assigned to one of two treatment sequences: either an initial 6-hour IV infusion of avexitide on Day 1 followed by a 6-hour IV infusion of vehicle on Day 2, or vice versa (Figure 4). Avexitide was infused at 300, 500, 300 pmol/kg/min over the course of 6 hours, or 300, 100, 300 pmol/kg/min over the course of 6 hours. Dextrose infusion was initiated if blood glucose levels fell below 55 mg/dL. On Days 3–4 (Figure 5), a subset of 8 patients were evaluated during and after a mixed meal tolerance test (MMTT) and a protein tolerance test (PTT) during IV infusion of vehicle or avexitide infused at a rate of 500 pmol/kg/min. At T = 0 min the treatment infusion began and the patient ate breakfast; 3 hours later patients ingested protein.

Figure 4: Evaluation of Fasting Blood Glucose Levels

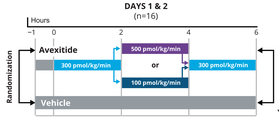
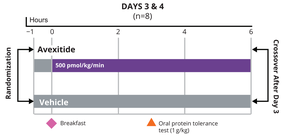


Figure 5: Evaluation of Protein-Induced Hypoglycemia

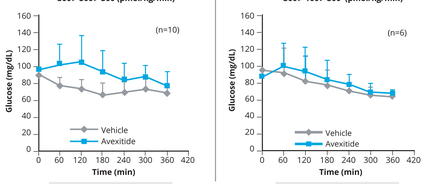


RESULTS

Avexitide Raised Fasting Glucose and Lowered Fasting Insulin and C-peptide

On Days 1 and 2, avexitide infusion resulted in higher fasting plasma glucose levels, and lower fasting insulin and c-peptide levels compared with vehicle.

Figure 6: Blood Glucose During Two Different Dosing Schemes of Avexitide vs Vehicle Infusion



Glucose AUC raised by 26%
Insulin AUC lowered by 22%
C-peptide AUC lowered by 21%

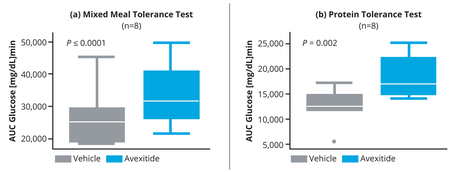
Glucose AUC raised by 8%
Insulin AUC lowered by 10%
C-peptide AUC lowered by 2%

**Data represents combined results from first 3 participants (500 pmol/kg/min) and 7 participants (300>500>300 pmol/kg/min)*

Avexitide Significantly Reduced Protein-Induced Hypoglycemia

On Days 3 and 4, avexitide infused at a continuous rate of 500 pmol/kg/min significantly increased mean AUC glucose concentrations during MMTT (Figure 7a) and PTT provocation ($p \leq 0.0001$ and $p = 0.002$, respectively) (Figure 7b), with substantially lower proportions of patients with glucose <60 mg/dL (37.5% avexitide vs 87.5% vehicle; $p = 0.046$) and glucose < 50 mg/dL (0% avexitide vs 37.5% vehicle; $p = 0.083$).

Figure 7: AUC Glucose in Response to MMTT and PTT During Avexitide During Avexitide vs Vehicle Infusion



- Proportion of patients with glucose <60 mg/dL: 37.5% avexitide; 87.5% vehicle, $p = 0.046$
- Proportion of patients with glucose <50 mg/dL: 0% avexitide; 37.5% vehicle, $p = 0.083$

Child Study Summary

Avexitide infusion:

- Raised fasting glucose concentrations
- Lowered fasting insulin and c-peptide levels
- Significantly reduced protein-induced hypoglycemia
- Higher avexitide infusion rates resulted in a greater treatment effect

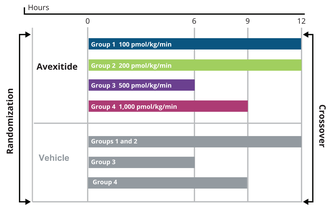
METHODS

3 NEONATE AND INFANT STUDY

Open-label, Randomized, Crossover Study in 13 Neonates and Infants with K_{ATP}HI to Evaluate the Effects of Avexitide Infusion on Glucose Requirements to Maintain Euglycemia

Neonates and infants with confirmed diazoxide unresponsive HI received one of four single ascending doses of avexitide infused at rate ranging from 100 to 1,000 pmol/kg/min over up to 12 hours. Patients maintained regular feedings every 3 hours, and the glucose infusion rate (GIR) was adjusted to maintain glucose in the range of 70-90 mg/dL throughout. The primary efficacy endpoint was the GIR.

Figure 8: Neonate and Infant Study Design

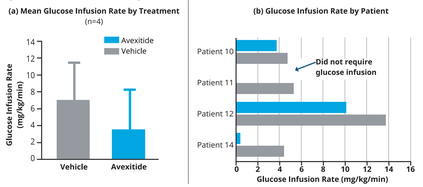


RESULTS

Avexitide Reduced the Mean Glucose Infusion Rate

Thirteen neonates and infants with diazoxide unresponsive HI (10 with focal; 3 with diffuse disease; ages 1 to 35 weeks old) who had not undergone pancreatectomy participated. Higher avexitide infusion rates resulted in greater reductions in GIR. When infused at 1,000 pmol/kg/min, mean GIR was reduced by approximately 60%.

Figure 9: Glucose Infusion Rate During Avexitide vs Vehicle Infusion



Neonate & Infant Study Summary

Avexitide infused at a rate of 1,000 pmol/kg/min reduced the mean GIR by 60%.

CONCLUSIONS

- **Avexitide is a first-in-class GLP-1 receptor antagonist with inverse agonist properties**
- **The GLP-1 receptor plays an important role in the mechanisms mediating K_{ATP}HI**
- **GLP-1r antagonism/inverse agonism represents a targeted therapeutic approach to K_{ATP}HI**
- **Avexitide has been administered by IV infusion to 39 patients with K_{ATP}HI enrolled in 3 POC studies at CHOP, suggesting that avexitide can effectively reduce fasting and postprandial hyperinsulinemic hypoglycemia in patients with K_{ATP}HI**
- **Eiger has developed a stable, solution formulation for subcutaneous injection (Avexitide Injection), which has been well-tolerated in 63 adults, including in 18 patients with PBH who received Avexitide Injection for 28 days in the outpatient setting.**
- **Avexitide Injection for subcutaneous administration may represent a convenient dosing option for use in future clinical studies in HI.**

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