15 mg/kg bid
5 mg/kg bid

**ABSTRACT**

Melanin-concentrating hormone (MCH) is a cyclic neuropeptide involved in appetite regulation and energy homeostasis. Antagonists of the MCH receptor have been shown to be promising new mediators of weight loss in animal models. ALB-127158(a), a selective, high affinity antagonist of the human MCH1 receptor, demonstrated significant reductions in food intake and body weight in a 28-day feeding study in hyperinsulinemic male diet-induced obese (DIO) C57BL/6J mice. At twice daily oral doses of 5 and 15 mg/kg and a once daily oral dose of 30 mg/kg, ALB-127158(a) reduced food intake (12.4%, 18.9%, 20.2%, respectively), body weight (12.3%, 17.9%, 18.1%), and fasting plasma insulin levels (25.7%, 30.3%, 29.0%), respectively relative to control animals. An oral glucose tolerance test (OGTT) performed after 28 days of dosing also demonstrated improvements in glucose tolerance and insulin sensitivity. Reductions in plasma insulin were observed 15 minutes (-17%, 38.6%, 49.4%), 30 minutes (19.1%, 23.2%, 37.2%), and 60 minutes (22.3%, 29.6%, 31.2%) after challenge and reductions in plasma glucose were observed 15 minutes (8.1%, 9.8%, 23.4%), 30 minutes (18.4%, 9.9%, 14.6%) and 60 minutes (22.7%, 13.6%, 17.1%) after challenge, respectively. ALB-127158(a) was identified as safe and well tolerated in a Phase I clinical study. The preclinical efficacy and clinical data support the continued development of ALB-127158(a) as a potential once daily treatment for obesity and related disorders.

**INTRODUCTION**

Obesity is a growing concern for public health in industrialized nations across the globe. In the United States alone, over 60% of the population is overweight and over 30% of these people are obese. Obesity is associated with a variety of comorbidities such as diabetes, dyslipidemia, coronary heart disease, stroke and certain cancers. Current pharmacological treatments suffer from weak efficacy and significant side effects that limit their use. Therefore, a major need exists for safer, more effective weight loss agents.

ALB-127158(a) was identified by AMRI as a selective, high affinity MCH1 receptor antagonist and has recently completed a Phase I clinical study. Selected preclinical in vitro and in vivo properties of ALB-127158(a) are presented that lead to positive effects on food intake, body weight, insulin sensitivity and glucose tolerance in obese mice.

**METHODS**

The affinity for the MCH1 receptor (Fig. 1) was determined using a binding assay with [3H]AMAR-MCH1 and cloned human MCH1 receptors. The functional antagonism was established with an agonist-based cell2^3 mobilization assay (carried out by Euroscreen). A panel of more than 80 GPCRs, ion channels and cytochrome P450s was used to demonstrate the selectivity for the MCH1 receptor (based on the Cerep high throughput profiling panel). Selectivity against the hERG potassium channel was established using a mini-patch clamp assay.

In the in vivo efficacy was demonstrated in a chronic, 28-day feeding study with male dietary-induced obese (DIO) C57BL/6J mice. The mice were group housed and given free access to a high fat diet (D12451 45% of Kcal derived from fat). Research Diets, New Jersey, USA) and tap water for 14 weeks to induce obesity. At the end of the 14 week period, the animals were singly housed for an additional two week period and placed on reverse phase lighting (lights off for 8 h from 09:30 – 17:30 h). On the day prior to the OGTT, animals were fasted at 16:00 h. On the day of the OGTT, each animal was dosed with vehicle or test compound and 60 minutes later was dosed with D-glucose (Fig. 4) and further blood samples were taken 15, 30 and 60 minutes post glucose administration (Fig. 5).

**CONCLUSIONS**

- ALB-127158(a) is a selective, high affinity MCH1 receptor antagonist.
- ALB-127158(a) causes gradual, sustained weight loss in obese mice, accompanied by reduction in food intake.
- ALB-127158(a) improves insulin sensitivity and glucose tolerance in obese mice.
- ALB-127158(a) was found to be safe and well tolerated in a Phase I clinical study with no dose limiting cardiovascular, ECG or behavioral adverse events observed. Reductions in ‘Hunger’ and ‘Desire to eat’ using a visual analogue scale and food intake were observed.
- These data support the continued development of ALB-127158(a) as a potential treatment for obesity and related disorders.

**REFERENCES**