Pharmacology of ALB-127158(a), an antagonist of the MCH1 receptor for the treatment of obesity

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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 pharmaceutical 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. Melanin concentrating hormone (MCH) is a cyclic, 19 amino acid neuropeptide expressed in the zona incerta and lateral hypothalamus that regulates food intake and body weight. Antagonism of the MCH1 receptor has been shown to be a promising new approach for the treatment of obesity.

ALB-127158(a) (formerly AMR-MCH-22) was identified by AMRI as a selective, high affinity MCH1 receptor antagonist and has recently advanced into Phase I clinical trials. Selected preclinical in vitro and in vivo properties of ALB-127158(a) are presented.

METHODS and RESULTS for ALB-127158(a)

The affinity for the MCH1 receptor (Fig. 1) was determined using a binding assay with [3H]MCH-1 and cloned human MCH1 receptors. The functional antagonism was established with an equinorin-based Ca2+ 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. Selectivity against the MCH1 receptor channel was established using a mini-patch clamp assay. The in vivo efficacy was demonstrated in a chronic, 28-day feeding study with male diabetic-induced obese (DIO) C57BL/6J DIO Mice (Fig. 2). 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 4 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 feeding (light on for 8 h from 09:30 - 17:30 h). After a 14-day baseline run in period with di-saccarides feeding, animals were treated with ALB-127158(a) twice daily (at 08:45 h and 14:45 h) by oral gavage at doses of 5 and 15 mg/kg or once daily with 30 mg/kg at 08:45 h; vehicle at 14:45 h). Changes in body weight and food intake were compared to positive control subcutaneous. Unlike sibutramine, which showed rapid onset of weight loss followed by significant weight loss gain, ALB-127158(a) was characterized by gradual weight loss that was maintained throughout the course of the four week study. Measurement of food intake showed a sustained reduction in the groups treated with ALB-127158(a) (Fig. 3). In contrast, subcutaneous reduced food intake in the first week, and then increased food consumption in weeks two through four. An oral glucose tolerance test on days 29 and 30 showed improvements in insulin sensitivity and glucose tolerance (Fig. 4). Following termination, analysis of body composition (water, fat, protein and ash content) demonstrated that the weight loss caused by ALB-127158(a) was associated with selective reduction in fat mass (Fig. 5). Analysis of terminal plasma samples revealed significant improvements in plasma leptin and adiponectin levels concomitant with fat loss (Fig. 6). Also following the DIO mouse study, coronal sections of the brain containing the caudate putamen were removed and used to determine the ex vivo MCH1 receptor occupancy (Fig. 7).

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.
• Weight loss is associated with selective reduction in fat mass and accompanied by improvements in circulating plasma leptin and adiponectin levels.
• Weight loss correlates well with MCH1 receptor occupancy.
• ALB-127158(a) improves insulin sensitivity and glucose tolerance in obese mice.
• ALB-127158(a) is currently in Phase I clinical trials.

REFERENCES