**Background:**

The 5-HT₃ receptor antagonist alosetron is used for the treatment of IBS-D but its widespread use has been hampered by the development of severe constipation and ischemic colitis in some individuals. Targeting 5-HT₃ receptors remains one of the best prospects to help IBS-D sufferers. One approach to modulating 5-HT₃ receptor activity without abolishing receptor-mediated activity is to develop partial agonists that will dampen the overactive system without abolishing receptor-mediated activity. Thus the dual action of a high affinity, low intrinsic activity 5-HT₃ receptor partial agonist should prevent excessive receptor activation by competitively blocking serotonin without simultaneously providing a low level of receptor stimulation thereby maintaining basal tone.

**Aims:**

Evaluate the in vitro and in vivo functional properties of novel 5-HT₃ receptor partial agonist ALB-137391(a). Select drug properties are also reported.

**Methods:**

ALB-137391(a) and 5-HT were evaluated for their ability to evoke 5-HT₃ receptor mediated agonist responses, assessed by changes in [Ca²⁺]ᵢ at the 5-HT₃ receptor expressed in HEK293 cells. The test compound was also evaluated for its ability to either induce a transient bradycardia reflex following intravenous bolus administration alone or block a 5-HT induced bradycardia reflex in urethane (2250 mg/kg ip) anesthetized male ICR mice (24 ± 2 g; n = 8 per group). For the 5-HT blocking experiment, ALB-137391(a) was dosed 1 hour prior to 5-HT (Figure 4) while animals were pre-treated 1, 2, 4, and 8 hours prior to 5-HT for the duration of action study (Figure 5). The E₂₀₀ dose was used to investigate the duration of action.

**Results:**

- **Binding Assay**
  - Table 1: Drug Profiling Data for ALB-137391(a)
    - | Compound                  | IC₅₀ (nM) | E₅₀ (%) | Hill Coefficient |
    - |---------------------------|----------|---------|-----------------|
    - | 5-HT (serotonin)          |          | 100     |                 |
    - | ALB-137391(a)              |          |         |                 |
    - | ALB-137391(a)              | 175      | 4.0     | 1.3             |
    - | ALB-137391(a)              | 109      | 1.4     | 1.3             |
    - | MDS Pharma LeadProfilingScreen®; MDS Pharma FastPatch, mean IC₅₀ 5-point), [a] IC₅₀ (µM) reported; [b] Mean IC₅₀ (µM) reported; [c] Human microsomal stability (Cl₉₆, µl/min/mg) [d] [Plasma Protein binding]

- **Functional Assay**
  - **Figure 2:** Radioligand Competition Binding Assay Utilizing 5-HT₃A / HEK293 Membranes in a SPA Format.
  - **Figure 3:** Cell-based Functional Assay Monitoring [Ca²⁺]ᵢ in HEK293 Cells Expressing the 5-HT₃A Receptor.
  - **Figure 4:** Inhibition of 5-HT Induced Transient Bradycardia by Oral Administration of ALB-137391(a) in Mice (Reduction in Heart Rate ± SEM). Antagonist properties are demonstrated by oral administration of ALB-137391(a) to mice (n = 8 per group) 1 hour prior to a challenge dose of 5-HT administrated iv.
  - **Figure 5:** Inhibition of 5-HT Induced Transient Bradycardia by Oral Administration of ALB-137391(a). Duration of effect comparing ALB-137391(a) to the 5-HT₃ receptor antagonist, alosetron, at their respective E₂₀₀ doses in mice. (n = 8 per group)
  - **Table 2:** Dog Pharmacokinetics of ALB-137391(a) in vivo. Oral administration of ALB-137391(a) blocks 5-HT₃-induced bradycardia in the von Bezold-Jarisch murine model.

**Conclusions:**

- **In vitro** pharmacology studies demonstrate ALB-137391(a) to be a selective, high affinity 5-HT₃ receptor partial agonist with lower intrinsic activity than 5-HT.
- **In vivo**, oral administration of ALB-137391(a) blocks 5-HT₃-induced bradycardia in the von Bezold-Jarisch murine model.
- Intravenous administration of ALB-137391(a) to mice elicits a transient reflex bradycardia consistent with mild activation of native 5-HT₃ receptors.
- ALB-137391(a) has excellent oral drug properties with an acceptable oral pharmacokinetic profile and a low potential for drug-drug interactions.

**References:**