Introduction
Selective agonists at the 5-HT2C receptor have attracted interest as novel therapies for obesity. The most advanced compound of this class, lorcaserin, has recently completed two Phase III trials, the outcomes of which support the potential of this drug class for the treatment of obesity (Smith et al, 2010). It is becoming increasingly recognised that there is considerable overlap in CNS systems that regulate behaviors related to excessive feeding and the intake of drugs of abuse (e.g. Volkow & Wise, 2005; Fletcher & Higgins, 2010). Indeed we have previously demonstrated that the prototypic 5-HT2C agonist, Ro 60-0175, reduces nicotine self-administration and hyperactivity in rats (Grottick et al, 2001). Accordingly in the present series of studies we have evaluated lorcaserin against both the stimulant and reinforcing properties of nicotine. For comparative purposes we have also tested acute effects of lorcaserin in a rat feeding assay.

Methods
Locomotor activity studies: Test subjects were male, Sprague-Dawley rats. Following a defined pretreatment the animals were singly placed within test chambers where locomotor activity (measured as distance travelled) was measured using photocell interruptions. Lorcaserin was evaluated over a 90min test session against a hyperactivity induced by nicotine (0.4 mg/kg s.c.) or on basal activity. Test design was essentially identical across all studies, with the animals first being familiarised to test chambers, before formal tests which were run using a repeated measures design with 2-3 treatment free days between each cycle. In the nicotine hyperactivity studies, test subjects were first sensitised to nicotine by daily injection of 4-5mg/kg s.c. dose over 10 days. Over the course of the locomotor studies the rats continued to be treated with the same dose of nicotine.

Results (cont.)

C. Effect of Lorcaserin against nicotine induced self-administration

D. Effect of Lorcaserin in a model of cue-induced reinstatement of nicotine self-administration

E. Effect of lorcaserin on food intake in 22h deprived rats

Summary and conclusions
1. Lorcaserin is one of the most selective 5-HT2C receptor agonists identified to date, having >20-fold functional selectivity for 2C vs. 2A, and >120-fold functional selectivity for 2C vs. 2B (Thomsen et al, 2008). In vivo this apparent selectivity is demonstrated by the fact that acute effects of this drug in wild type C57BL/6j mice, evident over a 10-fold dose range is completely eliminated in 5-HT2C receptor KO mice across same dose range (Fletcher et al, 2009).
2. In rats habituated to test chamber, lorcaserin produces a modest decrease in distance travelled and rearing at doses of 0.6 mg/kg s.c. and above.
3. Lorcaserin (0.3-1mg/kg s.c.) produces a robust dose dependent decrease in a nicotine hyperactivity. This effect of lorcaserin is blocked by pretreatment with the selective 5-HT2C receptor antagonist, SB-242084.
4. Lorcaserin (0.6-1 mg/kg s.c.) reduces the intravenous self-administration of nicotine. This effect of lorcaserin is blocked by SB-242084.
5. In rats previously extinguished to the self-administration of nicotine, self-administration behaviour (i.e lever pressing on a lever previously associated with nicotine delivery) is reliably reinstated by a compound cue comprising of an experimenter delivered nicotine priming injection and a cue-tone CS previously paired with nicotine delivery. 6. Lorcaserin (0.3-1 mg/kg s.c.) reduces the reinstatement of nicotine self-administration produced by the compound cue. This effect of lorcaserin is blocked by SB-242084.
7. Consistent with its clinical efficacy as a potential treatment for obesity, lorcaserin reduces food intake produced by 22h food deprivation in rats. Drug doses for this effect overlap with those necessary for antagonism of nicotine behaviours.
8. Assuming lorcaserin has a safety profile in the clinic acceptable to regulatory agencies, it may represent a viable approach for the treatment of smoking cessation, either as a stand alone medication, or in conjunction with other treatment approaches. With the recent withdrawal of Chantix® there may be opportunities to test this experimentally.

The selective 5-HT2C receptor agonist, lorcaserin, reduces indices of nicotine reward as well as food intake in the rat