In the DIO study, the effect of 28 day LOR treatment on cardiac function was assessed using echocardiography. Secondary efficacy measures of food and water intake were also recorded. At the completion of the treatment phase (LOR) in obese patients, provides opportunity to back-translate to preclinical obesity models. We have investigated the effect of LOR administered twice daily for 28 days in two rat obesity models. The publication of multiple clinical reports detailing the clinical effects of the recently approved 5-HT2C agonist lorcaserin (LOR) in obese patients, provides opportunity to back-translate to preclinical obesity models. We have investigated the effect of LOR administered twice daily for 28 days in two rat obesity models.

### Characterisation of the DIO and Zucker rats as models of obesity

**DIO-induced obesity model**: Male, Sprague-Dawley rats, 7 weeks age (body weight range: 170-200g) at the start of the experiment. Rat's that were randomly allocated into high fat (DIO) group. Food and water intake and body weight was recorded. At the completion of the 28 days treatment phase, body weight was recorded. Blood glucose levels (fasted 0.5-1.7h) throughout the study. A variety of measures including QMR and MRI imaging, behaviour and clinical biomarkers (blood cholesterol, triglycerides, glucose) were made to characterise each obesity model. A comparative summary is presented below.

**Zucker rat model**: Male, Zucker rats (approximate age 7 months) were randomly allocated into 2 groups, one designated vehicle control (N=6 rats) and a separate group of lorcaserin treated rats (N=6 rats). Daily food/water intake, and body weight was recorded. At the completion of the treatment phase (28 days LOR), body weight was recorded. Blood glucose levels (fasted 0.5-1.7h) throughout the study. A variety of measures including QMR and MRI imaging, behaviour and clinical biomarkers (blood cholesterol, triglycerides, glucose) were made to characterise each obesity model. A comparative summary is presented below.

### Summary and Conclusions

1. In the DIO rat model, lorcaserin administered at a dose regimen of 1-2mg/kg SC x2daily (equivalent to plasma [drug] 14-160ng/ml [1mg/kg], 30-260ng/ml [2mg/kg]) produced a decline in % body weight change of 3.0-5.2% compared to vehicle controls.

2. Lorcaserin produced this weight change through reduction in fat, not lean mass. Modest effects on lipid biomarkers (blood cholesterol) were found.

3. In the Zucker rat model, lorcaserin at a dose regimen of 3mg/kg SC x2daily produced a decline in % body weight of ~4% compared to vehicle controls. Effects on food intake and lipid biomarkers were also noted.

4. In sum, these studies show an effect of lorcaserin in both the DIO and Zucker models, which in the context of the primary endpoint measure of % body weight change was similar to that reported clinically (i.e. 3.2%; see Chan et al. (2013) Lorcaserin Phase III obesity trial meta-analysis).

5. No evidence for cardiac valvulopathy was evident following this dose regimen of lorcaserin. 28 day treatment with 5HT4R did produce a detectable effect.

6. The present studies highlight the translational value of obesity models such as the DIO model, and suggest that assuming calibration is paid to non-specific drug effects such as malaise, the DIO and Zucker models show reasonable forward translational value to help predict clinical outcomes of a new chemical entity (see also Vickers et al., 2012). The chronic nature of these studies design provides opportunity to combine with safety assessments.

### Lorcaserin: DIO model

Male Sprague-Dawley rats (approximate age 5 months) were placed on a high fat diet (Research diet D12451; 24 kcal%) for 3 months prior to study. DIO rats were then randomly allocated into 3 groups (Veh; N=10; LOR; N=8). LOR (2.4 mg/kg SC) was administered twice daily for 28 days. Treatments were administered SC, 2x daily. Daily food/water intake, and body weight was recorded. At the completion of the 28 days treatment phase, body weight was recorded. Blood glucose levels (fasted 0.5-1.7h) throughout the study. A variety of measures including QMR and MRI imaging, behaviour and clinical biomarkers (blood cholesterol, triglycerides, glucose) were made to characterise each obesity model. A comparative summary is presented below.

### Lorcaserin: Zucker model

Male Zucker rats (approximate age 7 months) were randomly allocated into 2 groups, one designated vehicle control (N=6 rats) and a separate group of lorcaserin treated rats (N=6 rats). Following a 3 day baseline period, the rats were treated 2x daily for 28 days. Daily food and water intake, and body weight was recorded. At the completion of the 28 day treatment phase, body weight was recorded. Blood glucose levels (fasted 0.5-1.7h) throughout the study. A variety of measures including QMR and MRI imaging, behaviour and clinical biomarkers (blood cholesterol, triglycerides, glucose) were made to characterise each obesity model. A comparative summary is presented below.

### Summary and conclusions

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