SA-PO635

Sparsentan Pharmacokinetics and Pharmacodynamics as the Basis of Dose Selection for Primary Focal Segmental Glomerular Sclerosis (FSGS)

Michael D. Karol,[1] Xin-Ru Pan-Zhou,[1] Sarah Tuller,[1*] Radko Komers[1]
[1]Retrophin, Inc., Cambridge, MA, USA

Introduction

- Focal segmental glomerulosclerosis (FSGS) is a rare glomerular disorder that may result in extreme proteinuria and progression to end-stage kidney disease (ESKD). It is a leading and growing cause of nephrotic syndrome[1] and accounts for 4% of the prevalence of ESKD.[2] The incidence of FSGS appears to be rising,[3] and the etiology and pathogenesis of the syndrome are just beginning to be understood.[4]
- Reduction in proteinuria is widely regarded to be beneficial in the management of FSGS and is considered the primary goal of treatment.[1] Endothelin receptor antagonists have been shown to lower proteinuria in clinical trials in diabetic nephropathy[5,6] and have been speculated to be effective in FSGS.[7]
- Sparsentan (RE-021) is a first-in-class, potent, oral, dual-acting angiotensin II type 1 receptor blocker plus an endothelin type A receptor antagonist. It is anticipated that sparsentan, as a dual antagonist, will provide an optimal balance between reversal of the underlying podocytopathy and any adverse effects on hemodynamics.
- Sparsentan is currently being tested for the treatment of primary FSGS.

Objective

- To select an optimal sparsentan dose for the phase 3 DUPLEX study.

Methods and Materials

- The phase 2 DUET study (NCT01613118)[8] measured sparsentan-induced changes from baseline to Week 8 in urine protein/creatinine ratio (Up/C) in patients assigned to receive 200 (n=13), 400 (n=21), or 800 (n=30) mg/day.
- The relationship between sparsentan dose or area under the curve (AUC) and change in Up/C was assessed.
- Pharmacokinetic/pharmacodynamic (PK/PD) analyses were based on actual doses received, accounting for dose reductions and resulted in PK/PD sample sizes of 17 (400 mg/day), 23 (400 mg/day), and 22 (800 mg/day) patients.

Results

- **Figure 1** shows medians (black horizontal lines), means (black diamonds), interquartile ranges (colored boxes), 95% confidence intervals for the medians (hourglasses), data ranges (whiskers), and outliers (small circles) for AUC by dose. Medians and means were not distinguishable by dose.
- **Figure 2** shows the same box-whisker plot horizontally and aligned with a plot of changes in Up/C by AUC on Day 56 (Week 8). The black line represents a linear regression, and the yellow curve represents a smoothing function (LOESS). Blue lines highlight the data range. The plot is grayed out where data are very sparse. This figure shows an apparent diminishing variability with increasing AUC.
- **Figure 3** shows changes from baseline in Up/C as a function of sparsentan dose. As in **Figure 2**, variability in Up/C diminishes with increasing dose. For the 800 mg dose, only 1 patient had an undesirable change (increase) in Up/C.
- **Figure 4** shows the shape of the AUC distributions for the 400 and 800 mg groups, aligned with the previously described box-whisker dose vs. AUC plot. A greater proportion of the AUC is toward the higher range with the 800 mg dose.

Figure 1. Box-whisker plot of sparsentan AUC by dose

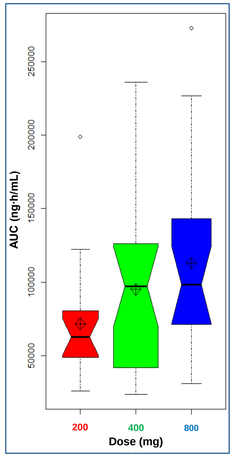


Figure 2. Change in Up/C from baseline vs. sparsentan AUC on Day 56 (Week 8) with box-whisker plot of AUC by dose, aligned by AUC

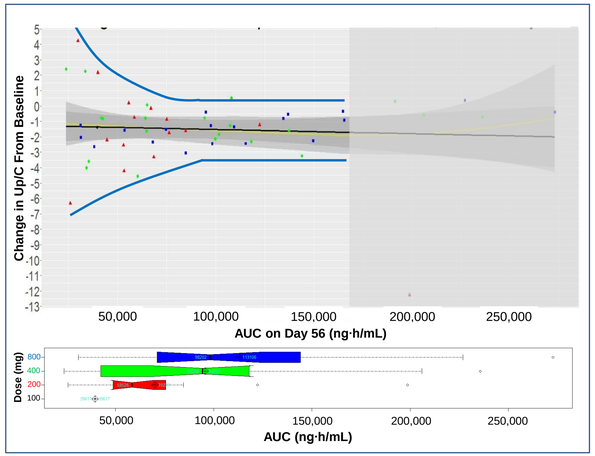
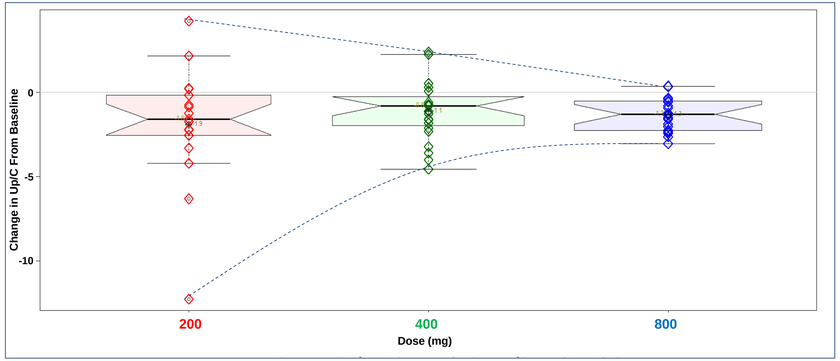
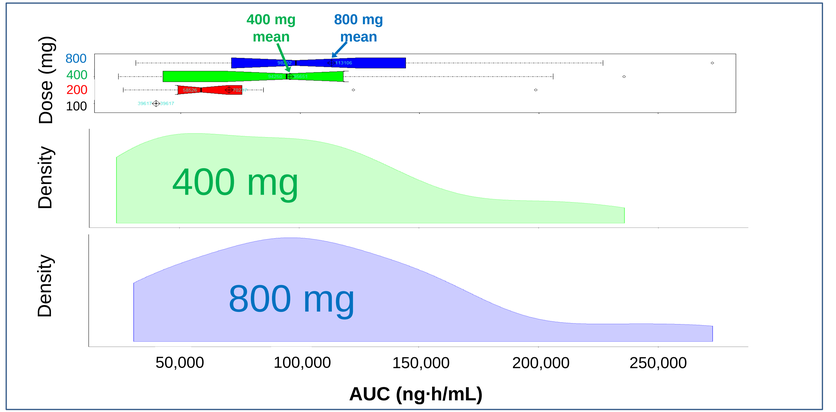


Figure 3. Box-whisker plot of change in Up/C from baseline vs. sparsentan dose on Day 56 (Week 8)



Box-Whisker Plot Key:
Black: 100 mg (n=2); red: 200 mg (n=17); green: 400 mg (n=23); blue: 800 mg (n=22).
Band=median; diamond=mean; hourglass=95% CI; box limit=inner quartile; whiskers=ranges; small circle=outlier (1.5 x inner quartile)

Figure 4. AUC distributions for sparsentan 400 mg and 800 mg aligned with box-whisker plot of sparsentan AUC by dose on Day 56 (Week 8)



Discussion

- In the DUET study, antiproteinuric effects across sparsentan doses were not statistically distinguishable due to the small sample size; however, the likelihood that a patient will have drug exposures resulting in a decrease in Up/C is greater with the 800 mg dose.
- The percentages of patients with decreases in Up/C were 76%, 74%, and 91% for the 200 mg, 400 mg, and 800 mg doses, respectively (**Figure 3**).
- In the DUET study, of the 30 patients assigned to receive the 800 mg dose, 18% experienced early hypotension. Otherwise, this dose of sparsentan was safe and well tolerated, with no clinically significant changes in vital signs or major clinically significant abnormalities in laboratory test results.

Conclusions

- Results of these analyses support the use of sparsentan 800 mg as a target dose for reduction of proteinuria in primary FSGS.
- Achieving this target dose should be preceded by dose titration. This approach increases the likelihood of antiproteinuric effect while ensuring high-dose tolerability.
- Both the therapeutic effect vs. dose or AUC and AUC distribution analyses yielded the same conclusion.

Disclosures

Michael D. Karol, Xin-Ru Pan-Zhou, and Radko Komers are employees of Retrophin, Inc., and may have an equity or other financial interest in Retrophin, Inc. *Sarah Tuller is a former employee of Retrophin, Inc., and may have an equity or other financial interest in Retrophin, Inc.
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