A Fixed-Dose Combination of Olmesartan Medoxomil (OM), Amlodipine (AML), and Hydrochlorothiazide (HCTZ): Use of Modeling and Simulation to Support an Understanding of the Dose Response of Intermediate Dose Combinations not Included in the Pivotal Phase 3 Study

Timothy J. Carrothers, ScD¹; Michelle Green, PhD¹; Helen Moore, PhD¹; Shashank Rohatagi, PhD¹; SuHeum Song, PhD¹; James Lee, PhD¹; Antonia Wang, PhD¹; Reinilde Heyman, MD²; Daniel E. Salazar, PhD²

¹Thrasight Corporation, Mountain View, CA; ²Gaelsich Sankys Pharma Development, Edison, NJ

Objectives

- To characterize the PK and exposure-response of the fixed-dose combinations planned for marketing.
- To support an understanding of the dose response of intermediate dose combinations not included in the pivotal Phase 3 study.

Primary Study for Analysis

- Primary efficacy analysis period (Week 8 in CS8663-A-U301; Week 12 in CS8635-A-U301).

Data and Methods

- Study Phase N M:F

Demographic Summary of Exposure-Response

- Table 1. Demographic Summary of PK Subjects

Population Pharmacokinetic Modeling Results

- Table 2. Demographic Summary of Exposure-Response Subjunct Subjects

Results from Simulation Models

- Table 4. Predicted and Observed BP Lowering Effects (CS8663-A-U301) Mean (SD)

Results from Exposure-Responses Modeling of Blood Pressure

- Table 5. Predicted BP Lowering Effect of CS-8635 – (Amlodipine to Benicar HCT) Mean (SD)

Exposure-Response Analysis for Seated Systolic Blood Pressure

- Table 6. Predicted BP Lowering Effect of CS-8635 – (HCTZ to AZOR®) Mean (SD)

Conclusions

- The concentrations of each drug were successfully described by a mammillary two-compartment model with first order elimination. The concentrations dose-normalized to 40mg were used for the post-predictive check for the pivotal studies. The results from the post-predictive check for CS8663-A-U301 and CS866-318 were in good agreement with the observed data. For CS8635-A-U301, the results were also in good agreement with the observed data. The post-predictive check for Phase 1 studies showed that the model was able to predict the exposure-response relationships for the four fixed-dose combinations planned for marketing. The model was able to predict the exposure-response relationships for the four fixed-dose combinations planned for marketing. The model was able to predict the exposure-response relationships for the four fixed-dose combinations planned for marketing.