This study links the hepatoprotective effects of AR and sFas to the improvement in liver function, as suggested by decreased Bili and lower MELD than the population as a whole. The improvement in liver function, suggest that the observed improvement in 91-day survival in these pre-identified patients is related to hepatoprotective factors delivered during ELAD treatment.

**RESULTS**

**Demographics of Evaluated Subjects**

ELAD and Control subjects in this pre-defined subset were not significantly different at screen, for demographic, diagnostic criteria for ACLF (associated with organ failure) and mortality rate, concentration of AR, concentration of sFas, or MELD (Table 1).

**Changes in Bilirubin and 90-day Survival in this Subset of Subjects**

Bili levels significantly increased in ELAD-treated subjects at days 3, 5, and 7 compared to both screen and control subjects (p<0.011, D3; p<0.031, D5; p<0.043, D7, ELAD vs. Control). Both AR and sFas increased significantly in subject plasma, relative to screen, during ELAD treatment. The same factors either did not increase (i.e., AR), or did not increase significantly (i.e. sFas) in Control subjects during the same time period.

**DISCUSSION (cont.)**

To date, the majority of the data supporting this model was produced in vitro. However, this study measured changes in protein concentrations in the plasma of twenty-five subjects from the VTL 208 trial with sAH, but without ELAD, concurrent with both AR and sFas increased significantly in subject plasma, relative to screen, during ELAD treatment. These different factors either did not increase (i.e., AR), or did not increase significantly (i.e. sFas) in Control subjects during the same time period. These results are consistent with the hypothesis that the cell-based model is predictive of measurable clinical outcomes and that the benefit provided to the pre-specified subject subset may be due in part to hepatoprotective factors delivered during ELAD treatment. Importantly, early changes in Bili levels (ECBL) are proposed as a surrogate endpoint predictive of survival in AH.1,5,6 Although, ECBLs are not significant in control subjects, significantly more ELAD-treated subjects in the pre-specified VTL 208 subset had a 20% ECBL and survived to 91 days.7,8 Oxidative stress is another hepatoprotective mechanism noted in our cell-based models, 10,11 Identification and quantification of circulating biomarkers of oxidative stress in support of results of our in vitro work is the subject of current investigation. Additional work demonstrating anti-inflammatory mechanisms have already been made, but not yet published.

**CONCLUSIONS**

Subjects on ELAD experienced increases in AR and sFas during treatment, with corresponding early changes in Bili levels, which others have previously shown to be prognostic of survival. These data suggest hepatoprotection occurs during ELAD treatment, perhaps by inhibiting apoptosis through EGR activation, competition for Fas ligand, and reducing oxidative stress, as was previously demonstrated using vitro primary human hepatocyte models.12,13,14 These clinical biomarker data and decreases in Bili, as a measure of liver function, support that ELAD treatment provides the necessary tools for improving outcomes in these pre-defined ELAD subsets. These studies are likely a part of a multi-therapeutic approach via cell-based treatment.

**ACKNOWLEDGEMENTS**

Thank you to Licia Li for her assistance in clinical data organization.

**REFERENCES**