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Surrogate Versus Clinical End Points and Venture Capital Companies: The Doubts of a Clinician

To the Editor:

In their editorial about the trial by Lewis et al[1] of sulodexide for microalbuminuria in diabetic nephropathy, House and Weir[2] comment on the relationship between surrogate and clinical end points and suggest that a treatment may provide important benefits with respect to clinical end points while not affecting or perhaps even worsening surrogate end points. Importantly, concurrent with the sulodexide microalbuminuria trial published in the *American Journal of Kidney Diseases*[1] was a sulodexide phase 4 clinical end points trial for patients with macroalbuminuria[3]; this trial was terminated after the negative results of the microalbuminuria trial[1] became evident and an interim analysis for the Drug Safety and Monitoring Committee of the phase 4 trial that showed that sulodexide did not reduce proteinuria.[4] The termination therefore was based on a surrogate end point, proteinuria, and occurred even though the prespecified criterion for stopping the trial was the composite clinical end point of doubling of baseline serum creatinine level, development of end-stage renal disease, or creatinine level ≥6.0 mg/dL.[3,4] In addition, the venture capital company sponsoring the study stated in the press release announcing the termination of the sulodexide phase 4 trial that "our ability to successfully adjust our strategy and reduce our operating expenses in order to properly support the trials of our other drug candidates . . .",[4] which may reveal that there also were financial considerations in terminating the study.

Considering that no safety issues had occurred and all patients were continuing treatment with appropriate renin-angiotensin system blockade, the suspension of the sulodexide study is perplexing and leaves the question of the benefit of sulodexide on clinical end points unanswered, which is concerning for clinicians.

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In Reply to 'Discounting the Efficacy of Sulodexide in Diabetic Nephropathy Is Premature' *and* 'Surrogate Versus Clinical End Points and Venture Capital Companies: The Doubts of a Clinician'

We thank Dr Gambaro[1] and Drs Gaddi and Benedetto[2] for their comments regarding our editorial.[3] Their efforts in the development of sulodexide make their disappointment understandable.

We have no meaningful response to the argument that the sulodexide preparation used in the SUN-MICRO study of Lewis et al[4] was either unabsorbable or inactive. This cannot be investigated, so debate would be entirely speculative. However, the SUN-MICRO pilot study, which used the same agent and manufacturer, suggested some drug effect.[5]

The concerns raised about the characteristics of patients enrolled in SUN-MICRO warrant discussion. Although the mean estimated glomerular filtration rates reported in SUN-MICRO and the Diabetic Nephropathy and Albuminuria Study (DiNAS) differed (78 vs 85 mL/min/1.73 m^2, respectively), the difference was small.[4,6] More relevant is the similarity between study patients and those encountered in clinical practice. Considering the degree of decrease in kidney function and the underlying disease, both SUN-MICRO and DiNAS enrolled patients for whom adjuvant antiproteinuric therapy was reasonable. Because patients in SUN-MICRO received appropriate renin-angiotensin system blockade,[7,8] its results better generalize to clinical practice.

The discontinuation of the subsequent SUN-MACRO trial was disappointing, more so because termination was by the sponsor for a lack of surrogate outcome signal, not by the Data and Safety Monitoring Committee for safety or efficacy concerns.[9] This illustrates the tension between optimal science and shrewd business practice. Nonetheless, with more than 2,200 patients randomly assigned in SUN-MACRO and SUN-MICRO, the bar has been set high for investigators wishing to demonstrate the utility of sulodexide in diabetic nephropathy.

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