Introduction
Studies to investigate new treatments to prevent acute kidney allograft rejection are typically active controlled studies with a primary endpoint of Month 6 biopsy-proven acute rejection (BPAR). When designing these studies, there is a strong desire to monitor the study in an on-going fashion and use formal stopping rules to stop the study quickly if the rejection risk with the experimental treatment is unacceptably high. However, because the endpoint can be 6 months from randomization, stopping rules based on the observed data meeting the primary endpoint at Month 6 can be inefficient. We desired a model and stopping rule that allowed for some incorporation of historical control data and that does not require waiting until subjects reach the Month 6 endpoint. To this end we examined stopping criteria based on estimates from a Bayesian time to event model for BPAR.

Our approach is presented in the context of a Phase 2 study investigating CP-690,550, an immunosuppressive agent being developed for the prevention of kidney allograft rejection and other autoimmune diseases.

Current Study Design
A Phase 2, randomized, multicenter, partially blinded, active-comparator controlled parallel-group trial. Approximately 300 patients were to be randomized to one of two CP-690,550 regimens or cyclosporine (CsA).

Study Objective: To compare the incidence of clinical BPAR of combination regimens of CP-690,550 and mycophenolate mofetil (MMF) / mycophenolate sodium (MPS) versus a cyclosporine (CsA)-based regimen in first renal allografts at Month 6 post-transplant.

Methods
Without accrual pauses to follow patients until each has reached their endpoint at 6 months, analyses must utilize partial information from many patients.

To accomplish this we incorporated a time-to-event model for BPAR. Since no subjects will have reached the Month 6 endpoint early in recruitment, a Bayesian model facilitated predictions of Month 6 BPAR early in the study.

Bayesian time-to-event model
A review of the published literature identified 4 studies with designs and dosing regimens matching the study control regimen [(1) – (4)]. Review of the Kaplan-Meier time-to-event curves from these and other studies suggested dividing the 6 month treatment interval into 3 time periods with approximately constant hazard rates: Days 0-7, Days 8-28 and Days 29-182. An example K-M curve is shown below (6).