**Sample Size and Power Calculations**

The primary endpoint of this study is the counting of graded pulmonary exacerbations, and it will be analysed using a negative binomial model. The method proposed by Keene et al (2007) was used for the determination of the sample size based on a negative binomial model.

The baseline exacerbation rate was assumed to be two events per year based on the reports from previous clinical studies. A dispersion parameter of 0.6 was also assumed for the negative binomial model based on the literature review (Keene et al, 2007). Therefore, a sample size of 378 patients (189 per group) will be sufficient to provide 80% power to detect a 27% reduction in event rates (mannitol vs placebo control) at the significance level of 0.05. Allowing for 20% early withdrawal, this study will recruit a total of 474 patients (237 per group). This result was confirmed by simulation.