

Sample Size

Given the small sample size, the information available for safety decisions will be imperfect. Two types of sampling errors are possible:

- 1) At a dose level whose true probability of an AE is unacceptable, the sample data may pass the safety criteria;
- 2) At a dose level whose true rate probability of an AE is warranted by the potential benefits of the medication, the sample data may fail the safety criteria.

The extent to which the safety criteria are subject to these errors can be assessed by examining various hypothetical “true” rates of the occurrence of an AE, if the study medication were used extensively among the study population at the dose level under question. The hypothetical situations presented below range from conditions under which the dose level would cause a high incidence of AEs to conditions under which AE toxicities would be relatively rare. For each of these hypothetical situations, we assume that an initial sample of three volunteers is drawn from the defined population and that the algorithm for adjusting the dose, described above, is applied. The following table presents the probability that the sample will pass the safety criteria, under each of the hypothetical true rates of AEs, in the single-dose cohort (n = 3-6) or the multiple-dose cohort (n = 6). Two scenarios are considered: 1) where the team will decide to escalate only if no AEs are observed; 2) where the team will escalate if no or only 1 AE is observed.

Table 4. Probability of Dose Escalation to the next Cohort under Potential Probabilities of an AE

True Probability of an AE	Probability of Dose Escalation to the Next Cohort			
	Single-Dose Cohorts		Multiple-Dose Cohorts	
	Scenario 1	Scenario 2	Scenario 1	Scenario 2
.50	0.12	.17	0.02	0.11
.40	0.22	.31	0.05	0.23
.20	0.51	.71	0.26	0.66
.10	0.73	.91	0.53	0.89
.03	0.91	.99	0.83	0.98

This table shows that, for example, in a single-dose cohort where AEs will be assessed by the team to continue escalation if no or only 1 AE is observed, there will be a 17% chance that a sample will result in a dose escalation at a dose whose true probability of an AE is 50%. Conversely, there is a 99% probability of dose escalation at a dose whose true probability of an AE is 3%.

The estimated maximum sample size will be 42 evaluable volunteers, assuming that 5 single and 2 multiple-dose levels are tested. This may vary, depending upon: 1) the number of doses that must be tested in order to find the optimal dose, and 2) the number of occasions in which 3 additional volunteers must be added to the initial 3 volunteers, in applying the algorithm specified above. The cohort of volunteers who will receive a single dose following a standardized meal will be drawn from volunteers who have completed other cohorts and are not counted again in this estimated sample size.