potential treatments. Along these lines, the nanobody ALX-0171, the antigen site of which is part of the fusion protein, was reported to be in Phase 1 development in late 2011 (Ablynx press release, 13 December 2011). Both monoclonal antibodies, Synagis and Numax, have also been studied as potential treatments for RSV in hospitalized infant trials.[41,43]

Programs that successfully negotiate Phase 1 safety and PK analyses can initiate treatment-based efficacy studies in one of several naturally infected patient populations, the immunosuppressed, especially hematopoietic stem cell (HSCT) and lung transplant patients, young infants below 2 years of age and the frail elderly with underlying conditions such as COPD or congestive heart failure (CHF). However, each of these diverse patient groups carries significant challenges to prospective pharmaceutical companies for developing RSV therapeutics. An alternative to evaluating efficacy in natural infected populations is to use normal healthy volunteers (NHVs) experimentally infected with virus, which is discussed in Section 2.6.4.

2.6.1 Clinical Trials in Immunosuppressed Patients

RSV infection in immunosuppressed patients is a major concern, since progression to lower respiratory tract infection and pneumonia carries significant risks, including high mortality rates of 70–80%.[77] Most immunosuppressed patients presenting to a healthcare facility having contracted an upper respiratory tract infection, and within 1 week 40–50% will progress to pneumonia. Improvements in managed care and isolation of RSV outbreaks in the main transplant centers over the years have reduced the risk of RSV spreading and also mortality. Therefore, one of the main challenges in conducting efficacy studies in immunosuppressed patients is the difficulty in powering trials without invoking a large geographically diverse set of study sites.[77] For example, aerosolized ribavirin (**1**) was studied in HSCT patients with the intention of enrolling up to 90 subjects, but the trial was discontinued after 5 years owing to low enrollment numbers.[77] The main reasons cited for this problem were the reduced incidence of RSV as a result of improved care practices as described above and the complexity of the study design, which required hospitalization of patients in the trial and daily blinded analysis by investigators. Despite insufficient patient accrual leading to a lack of statistical significance, subjects who were treated with ribavirin were found to have lower serial viral load in nasal wash samples as detected by qt-PCR (quantitative polymerase chain reaction). Furthermore, a trend towards reduced pneumonia was noted following radiographic analysis. Additional ribavirin-based studies in HSCT patients have been reported in which dosing regimens and alternative routes of administration, oral *versus* inhaled, are under investigation. Once again, these trials appear to recruit only small numbers of subjects over many years. The small-molecule RSV604 was also studied in HSCT patients and, not surprisingly, similar recruitment difficulties complicated the study. Altogether 20 patients were enrolled in 1 year from 10 sites in the USA, Europe and Australia.[69] The primary endpoint for the study was a $2\log_{10}$ viral load