reduction in nasopharyngeal swabs analyzed by qt-PCR. Encouragingly, an antiviral effect was noted in patients who were found to have plasma levels of drug that exceeded the EC_{90} for a short period of time. Unfortunately, administration of the compound required a high-fat meal to improve exposure and the resulting drug exposure was too variable across the trial participants for the target endpoint to be met. No further development has been reported for this compound.

Lung transplant patients offer another immunosuppressed patient population for performing RSV treatment trials and have been used in the efficacy trials of aerosolized ALN-RSV01. A total of 521 transplant recipients were followed for RSV infection and 24 were eventually enrolled into the initial study from 22 sites in four countries. Owing to differences in the baseline viral loads of placebo- and drug-treated arms and time from symptom onset, it was not possible to determine a statistically significant antiviral effect. Mean daily symptom scores were lower in the treated group and the cumulative symptom score was significantly lower. At day 90 following treatment, the incidence of new or progressive BOS was significantly reduced compared with placebo. Encouraged by these initial results, a follow-on study of ALN-RSV01 in lung transplant patients was performed. This second study enrolled 87 lung transplant recipients by recruiting from 33 centers in six countries. The study narrowly missed its primary endpoint of reduction in new or progressive BOS at 180 days in the confirmed RSV-infected intention-to-treat group (Alnylam press release, 31 May 2012).

One method for mitigating the difficulty in recruitment of sufficient RSV-infected patients is to utilize the RSV season in both the northern and southern hemispheres. This strategy was used for clinical trial of tamiflu. Many of the trials to date have done this to boost the numbers. One advantage of performing studies in immunosuppressed patients is the ability to monitor disease progression from the upper to the lower respiratory tract. The primary endpoint in the ribavirin trial in HSCT patients was the progression of disease to clinical pneumonia, as determined by chest radiographs and blinded symptom evaluations.[77] Furthermore, in subjects with confirmed pneumonia, bronchoalveolar lavage was performed at the discretion of the patient's physician to provide details of RSV lung infection. This type of information is not readily accessible in other patient groups. Despite the hurdles, it is likely that clinical trials will continue in immunosuppressed patients, but large registrational trials powered for statistical significance will remain logistically challenging. More likely, smaller trials analogous to those described above will provide initial POC promoting drug developers to invest further toward registrational trials in an alternative population, such as infants.

2.6.2 Clinical Studies in COPD or CHF Patients

An alternative adult population for consideration of natural infection RSV trials are the frail elderly, especially those with underlying conditions of COPD and CHF. In the USA and Western Europe, there are more deaths due to RSV infection in the elderly population than in other patient groups and, therefore,