Nevertheless, the observation that patients with higher drug exposure above the EC_{90} had a larger drop in viral load is very promising. Novartis is continuing clinical trials.[69]

YM53403: Yamanouchi reported RSV inhibitor (**30**) with submicromolar potency and a detailed MOA study suggested a post-entry (L-protein) mechanism.[71]

Gilead WO/2011/005842: Gilead Sciences recently claimed a series of RSV inhibitors that have structural features of the YM series (**31**).[72] No further data regarding MOA and development status were disclosed.

Boehringer-Ingelheim (BI): Novel L-protein inhibitors with activity in the low double-digit nanomolar range were identified by BI (**32**). The L-protein is part of the rather complex RSV polymerase complex. The authors suggested a novel mechanism by which the synthesis of RSV m-RNA is blocked *via* inhibition of guanylation of viral transcripts.[73,74]

ALN-RSV01: Alnylam is developing an RNAi therapeutic targeting the RSV N-protein.[75,76] Phase 1 studies in 2006 and 2007 established the safety and tolerability of ALN-RSV01 and in 2012 results from a Phase 2b trial of ALN-RSV01 in adult lung transplant patients for the treatment of RSV infection were reported. ALN-RSV01 treatment was associated with a clinically meaningful treatment effect, although the primary endpoint of reduced progressive bronchiolitis obliterans syndrome (BOS) in an 'intention-to-treat' (ITTc) analysis was narrowly missed (Alnylam press release, 30 May 2012).

2.6 Options for the Clinical Development of RSV Fusion Inhibitors

Following ribavirin (**1**), only a handful of compounds targeted for the treatment of RSV infection have progressed into clinical trials and none have reached formal Phase 3 registrational trials. This fact alone testifies to the difficulty associated with developing treatments for RSV. A few clinical programs have been reported in Phase 2 and these include the small molecule RSV-604, the siRNA drug ALN-RSV01 and a γ-globulin enriched with RSV neutralizing antibodies, RI-001. None of these products, however, are small-molecule fusion inhibitors, which, despite being more plentiful than other inhibitor classes for RSV, as described earlier, have often stumbled in Phase 1 trials. The early fusion inhibitor VP-14637 (**26**) was discontinued in Phase 1, as was the more recent BTA-9881 fusion inhibitor. Therefore, at the time of writing, only one small-molecule fusion inhibitor is currently in clinical development for RSV, which is the above-mentioned VP-14637 (**26**) in a dry powder formulation using the MicroDose inhaler technology (MDT-637). This inhaler is based on a high-frequency piezo transducer inhaler, avoiding the earlier ethanol based formulation of **26**. Clinical development is sponsored by Gilead (Gilead Science press release, 20 April 2011). Antibody or antibody-based therapeutics such as ADMA-001 are competitors to the approved prophylactic monoclonal antibody Synagis, but can also be considered as