isoforms ($IC_{50} > 30\,\mu M$) and had good solubility at pH 6.2 ($2.55\,mg\,mL^{-1}$). The cross-species PK profile of **38** suggested that this compound was amenable to a twice-daily dosing regimen.[52] Filibuvir was tested in a panel of genotype 1 isolates in which it displayed an average $EC_{50} = 75\,nM$ and modest shifts were observed in the presence of human serum (3.5-fold). Amino acid positions associated with resistance to filibuvir include M423, M426 and I482. M423 substitutions confer a 715- to >2200-fold increase in EC_{50}, confirming the importance of this residue for interaction with dihydropyrones. Filibuvir was weakly active against non-genotype 1 HCV polymerases ($IC_{50} \geq 1\,\mu M$) and not active against human DNA and RNA polymerases. Despite its initial structural similarity to tipranavir, it was not significantly active against HIV protease and a panel of human aspartyl and serine proteases.[52] In the light of its broad-spectrum antiviral activity against genotype-1 HCV and favorable PK profile in preclinical animal species, in 2007 Pfizer initiated clinical trials with filibuvir in genotype-1 HCV patients. At a dose of 450 mg administered bid for 8 days, filibuvir was well tolerated and after 48 h produced a $1.74\log_{10}$ mean maximal reduction in viral load in TN gt1 HCV patients. A 450 mg bid dose provided similar results in TE patients. In agreement with *in vitro* studies, resistance to filibuvir in HCV-infected patients was observed and primary mutations identified at amino acid M423.[53] Filibuvir is a weak time-dependent inhibitor and inducer of CYP3A4 and potential for drug–drug interactions has been evaluated in clinical trials where ketoconazole and midazolam both had measurable effects on the PK of filibuvir.[54]

In a Phase 2a study, filibuvir was tested for 4 weeks in combination with the SOC (PegIFN-α2a and RBV), followed by SOC for an additional 44 weeks. Filibuvir significantly increased the proportion of patients achieving undetectable HCV RNA levels at week 4 compared with SOC alone (up to 75% RVR in the 300 mg bid group). However, a high rate of virological breakthrough was observed (20–50% of patients with undetectable levels at week 48 relapsed by week 60) such that SVR_{12} was similar for the filibuvir- and placebo-treated groups.[55] These observation suggest that a longer treatment duration is required. A 24 week Phase 2b trial assessing the safety and efficacy of filibuvir in combination with SOC was completed, but the outcome has not yet been reported.

In summary, filibuvir is a non-nucleoside inhibitor of HCV polymerase that binds in the thumb domain of NS5B (thumb pocket 2) and likely interferes with protein conformational changes that are required for initiating RNA synthesis. The resistance signature for this compound is characterized by mutations at M423. The main advantage of the drug is its potency against major 1a/1b HCV genotypes. Weaknesses of this compound include its drastically reduced potency against non-1 virus, potential for drug–drug interactions and low barrier to resistance within 4 week therapy in combination with SOC. NS5B inhibitors are currently positioning themselves to be used in combination with complementary DAAs in IFN-free regimens rather than SOC, and no information is available suggesting that this compound is being considered for any such strategy.