

non-1 genotypes ($>2\mu\text{M}$). They exhibit favorable PK profiles and good distribution to the liver (liver/plasma ratio ranging from 10 in dogs to 70 in rats and monkeys at 12 h for ABT-072).⁸⁴

ABT-072 and ABT-333 were evaluated in parallel in Phase 2a studies where treatment-naive patients were treated for 12 weeks with either 100, 300 or 600 mg qd of ABT-072 or 400 mg or 800 mg bid of ABT-333, both in combination with PegIFN/RBV following 3 days of monotherapy with one of the two drugs alone. SVR_{12} was achieved in up to 86% of subjects in the ABT-072 high-dose group, while similar 63% SVR_{12} was obtained with both ABT-333 doses, although these studies had fewer than 10 patients per treatment arm and larger studies are required to elucidate response rates in a broader population.⁸⁵

Having demonstrated *in vitro* that combinations of ABT-333 with either NS3/4A protease or NS5A inhibitors produced additive to synergistic effects and were effective at increasing the genetic barrier to resistance, Abbott initiated Phase 2 studies on IFN-free combinations of ABT-072 (400 mg qd) or ABT-333 (400 mg bid) with a ritonavir-boosted PI (ABT-450) and RBV. Treatment-naive gt1-HCV patients who were administered ABT-072 for 12 weeks achieved 91% SVR_{24} and 82% SVR_{36} . Two ABT-333 (400 mg bid) arms in combination with either 250/100 mg ABT450/r qd or 150/100 mg ABT-450/r qd achieved 95% and 93% SVR_{12} , respectively. In the case of treatment-experienced patients, treatment with ABT-450/r (150/100 mg qd) + ABT-333 (400 mg bid) + RBV resulted in a lower SVR_{12} rate of 47%, with 6/17 patients experiencing viral breakthrough.⁸⁶

The third benzothiadiazine palm site 1 compound currently in Phase 2 clinical development is setrobuvir (ANA598). Anadys initiated a Phase 1 study of setrobuvir in 2008 and the drug was reported to be well tolerated, achieving 2.4, 2.3 and 2.9 \log_{10} reductions in HCV RNA at doses of 200, 400 and 800 mg administered tid for 4 days to gt1 HCV patients.⁸⁷ An ongoing Phase 2b study is investigating the safety, tolerability and efficacy of setrobuvir (200 and 400 mg bid) in combination with PegIFN and RBV in TN gt1-HCV subjects. Twelve week data have been reported for the setrobuvir 200 mg bid dose group, for which 78% of treatment-naive patients had undetectable HCV RNA (cEVR). Partial responders and relapsers experienced similar outcomes (cEVR = 76%). Viral breakthrough rates were very low ($\sim 3\%$) in both patient categories.⁸⁸

The structure of the fourth clinical candidate, IDX375 (**60**, Figure 8.14; Idenix Pharmaceuticals) was recently disclosed.⁸⁹ This palm site 1 NS5B inhibitor features some significant structural departures from the original benzothiadiazine scaffold. The left-hand side of the molecule is a monocyclic tetramic acid derivative whereas the benzothiadiazine moiety was modified to a phosphorus isostere. The compound exhibits high antiviral potency in the gt1b replicon ($\text{EC}_{50} = 2.3\text{ nM}$) and a 2.7-fold shift ($\text{EC}_{50} = 6.2\text{ nM}$) against gt1a. IDX375 showed adequate exposure in preclinical PK, favorable liver distribution and moderate bioavailability ranging from 16 to 42%. In a first-in-man study, **60** was well tolerated and well absorbed with long elimination