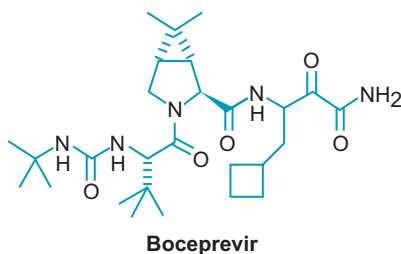


The vital need for the NS3/4A protease in the viral life cycle inspired the development of a new class of anti-viral compounds that are protease inhibitors. Drugs that inhibit the HCV NS3/4A protease include boceprevir and telaprevir, approved by the FDA in May 2011, and other drugs. Boceprevir and telaprevir have similar structures and similar mechanisms of action (9). The similar mechanisms of action of these two drugs are vividly illustrated by the following fact. Naturally occurring mutations in the HCV NS3/4A protease that confer resistance to either boceprevir or telaprevir tend to be identical in the case of the two drugs (10,11,12). For example, one mutation leading to resistance to boceprevir and telaprevir is valine-36 mutated to alanine-36 (V36A).

According to the package insert for boceprevir (13) FDA approval was granted for administering boceprevir in combination with both pegylated interferon-alpha and ribavirin. Clinical trials on boceprevir include those of Poordad et al. (14) and Bacon et al. (15) while those on telaprevir include those of Hezode et al. (16) McHutchison et al. (17) and McHutchison et al. (18). The efficacy of these new protease inhibitors in treating HCV, when used according to the package insert, is dramatically better than the previous standard of care, namely, the combination of interferon-alpha plus ribavirin. The structure of boceprevir is shown below. The drug is a peptide analogue.



- ⁹ Venkatraman S, Velazquez F, Wu W, Blackman M, Madison V, Njoroge FG. Potent ketoamide inhibitors of HCV NS3 protease derived from quaternized P1 groups. *Bioorg Med Chem Lett.* 2010;20:2151–2155.
- ¹⁰ Hofmann WP, Zeuzem S. A new standard of care for the treatment of chronic HCV infection. *Nat Rev Gastroenterol Hepatol.* 2011;8:257–264.
- ¹¹ Kieffer TL, Sarrazin C, Miller JS, et al. Telaprevir and pegylated interferon- α -2a inhibit wild-type and resistant genotype 1 hepatitis C virus replication in patients. *Hepatology.* 2007;46:631–639.
- ¹² Bartels DJ, Zhou Y, Zhang EZ, et al. Natural prevalence of hepatitis C virus variants with decreased sensitivity to NS3.4A protease inhibitors in treatment-naïve subjects. *J Infect Dis.* 2008;198:800–807.
- ¹³ Package insert. Merck and Co. Victrelis® (boceprevir) capsules. May 11, 2011 [25 pages].
- ¹⁴ Poordad F, McCone J Jr, Bacon BR, et al. Boceprevir for untreated chronic HCV genotype 1 infection. *New Engl J Med.* 2011;364:1195–1206.
- ¹⁵ Bacon BR, Gordon SC, Lawitz E, et al. Boceprevir for previously treated chronic HCV genotype 1 infection. *New Engl J Med.* 2011;364:1207–1217.
- ¹⁶ Hézode C, Forestier N, Dusheiko G, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. *New Engl J Med.* 2009;360:1839–1850.
- ¹⁷ McHutchison JG, Everson GT, Gordon SC, et al. Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection. *New Engl J Med.* 2009;360:1827–1838.
- ¹⁸ McHutchison JG, Manns MP, Muir AJ, et al. Telaprevir for previously treated chronic HCV infection. *New Engl J Med.* 2010;362:1292–1303.