Telaprevir

Abstract

Telaprevir (LY 570310; LY-570310; LY570310; MP 424; MP-424; VX 950; VX-950) is an orally administered peptidomimetic inhibitor of the hepatitis C virus (HCV) protease NS3/4A. It is being developed by Vertex Pharmaceuticals and its licensees for the treatment of HCV infections and has recently been submitted to the US FDA for approval. As the first ever HCV protease inhibitor in phase III development, it is being studied in trials in combination therapy with pegylated interferon alfa-2a and ribavirin in Europe, the US, Australia, Canada, and Puerto Rico in treatment-naive and treatment-experienced patients with HCV genotype 1 infection. Phase III trials of telaprevir as combination therapy are also in progress in Japan. This review discusses the key development milestones and therapeutic trials of this drug to date.

1. Introduction

Telaprevir is an orally administered peptidomimetic inhibitor of the hepatitis C virus (HCV) protease NS3/4A. It is being developed by Vertex Pharmaceuticals and its licensees, Janssen Pharmaceutica, Tibotec, as well as Mitsubishi Tanabe Pharma Corporation (formerly Mitsubishi Pharma Corporation), for the treatment of HCV infections. A rolling new drug application (NDA) submission is underway in the US in this indication. Telaprevir is the first ever HCV protease inhibitor to begin phase III development. The agent is being studied in phase III trials as part of combination therapy with pegylated interferon (peg-IFN) alfa-2a and ribavirin (RBV) in Europe, the US, Australia, Canada, and Puerto Rico in treatment-naive and treatment-experienced patients with HCV genotype 1 infection, the most difficult-to-treat variant of the disease. Phase III trials of telaprevir as combination therapy are also in progress in Japan. A phase II study of telaprevir in combination with the HCV NS5B polymerase inhibitor VX 222 is in progress in the US. Phase II development of telaprevir as a monotherapy is also ongoing in various countries.

NS3/4A protease activity is essential for viral replication and is partially responsible for the ability of HCV to evade clearance by the immune system of the host. Therefore, protease inhibition could offer a double hit strategy against HCV.

1.1 Company Agreements

In June 2006, Vertex entered into a license, development, manufacturing, and commercialization agreement with Janssen Pharmaceutica (a subsidiary of Johnson & Johnson). Under the collaboration agreement, Vertex will collaborate with Janssen to develop and commercialize telaprevir.
previr. Under the terms of the collaboration agreement, Vertex will retain exclusive commercial rights to telaprevir in North America (the US, Canada, and Mexico) and will continue to lead the development plan for telaprevir in North America and the Janssen territories. Janssen received exclusive rights to commercialize telaprevir outside of North America and the Far East. Another subsidiary of Johnson & Johnson, Tibotec, will lead the development and commercialization of telaprevir for Janssen. However, Vertex will continue to lead the global development plan for telaprevir. Each company will be responsible for the supply of telaprevir in their respective territories. Tibotec has the exclusive rights to telaprevir in Europe, South America, Middle East, Africa, India, Australia, and New Zealand. Under the agreement, Janssen agreed to pay Vertex a total of $US250 million in aggregate milestone payments for the development and launch of telaprevir in the EU. Vertex announced in July 2009 that it intends to sell its rights to these milestone payments. Later, in September 2009, Vertex announced that it will receive $US155 million cash related to future telaprevir milestone payments. Of this $US155 million, approximately $US120 million is for the issuance of notes repayable no later than October 2012; the remaining $US35 million is for the sale of rights to potential future milestones tied only to the European launch of telaprevir, which Vertex is eligible to receive from Janssen.

In June 2004, Vertex and Mitsubishi Pharma Corporation (Mitsubishi Tanabe Pharma Corporation since October 2007) entered into an agreement providing the latter with exclusive rights to develop and commercialize telaprevir in Japan and certain Far East countries. Under this agreement, Mitsubishi Tanabe was required to pay royalties to Vertex on commercial sales of telaprevir in its territories. The agreement provided certain development and commercial rights to telaprevir as a monotherapy agent for the treatment of hepatitis C. In July 2009, the agreement was amended. This amendment grants Mitsubishi a licence to commercialize telaprevir as part of a combination regimen with IFN and RBV to treat hepatitis C in Japan and the Far East. Vertex retains exclusive development and commercial rights to telaprevir in North America.

In November 2003, Vertex entered into a non-exclusive licensing agreement with Chiron Corporation (now Novartis), granting Vertex a license to discover, develop, and commercialize small-molecule therapeutic agents against certain hepatitis C drug targets. In return, Chiron received limited rights to review telaprevir for potential licensing. The agreement may provide Chiron with certain developmental milestone payments and royalty payments based on future sales of telaprevir, if approved. Chiron was subsequently acquired by, and merged into, Novartis in April 2006.

Telaprevir originated from a research collaboration between Vertex and Eli Lilly. The agreement was restructured in 2003 such that Vertex obtained the worldwide rights to compounds identified during the collaboration and Eli Lilly retained a financial interest in telaprevir and other HCV protease compounds through royalties on net product sales.

In February 2009, Vertex secured $US320 million in a stock offering. The funds will be used partly to advance the development of telaprevir.

1.2 Key Development Milestones

In mid-2010, Vertex submitted the non-clinical and the chemistry, manufacturing, and controls sections of its rolling NDA to the US FDA, for telaprevir in the treatment of HCV infections. The company expects to complete the NDA submission by the end of 2010.

Telaprevir has been evaluated in three pivotal phase III trials that included more than 2200 patients in the US and Europe. Two of the trials (ADVANCE [A New Direction in HCV Care: A Study of Treatment-Naive Hepatitis C Patients with telaprevir] and ILLUMINATE) were studies in treatment-naive patients, whereas the third trial (REALIZE [Re-treatment of Patients with Telaprevir-based Regimen to Optimize Outcomes]) is a study in patients who have failed previous therapy. Sustained viral response (SVR) data have been reported for the ADVANCE and ILLUMINATE studies, and efficacy and safety data for REALIZE are expected to be available.
in September 2010. These results will support NDA and MAA submissions in the US and Europe, respectively.[5,13,14] In December 2005, the FDA granted fast-track designation to telaprevir for the treatment of HCV infections.[15] In Japan, telaprevir is also in phase II development as a monotherapy.

1.2.1 Treatment-Naive Patients with Hepatitis C Virus (HCV)

In the fourth quarter of 2010, Vertex and Tibotec plan to initiate a phase IIIb trial to evaluate twice-daily telaprevir (1125 mg) compared with three-times-daily telaprevir (750 mg, every 8 hours). The trial will enroll 700 patients in the US, the EU, and other countries. Based on advice from regulatory authorities in the US and the EU, the trial will not include a control arm of peg-IFN and RBV.[13]

Vertex and Tibotec have reported SVR data from the pivotal, phase III, ADVANCE Study (NCT00627926), which is being conducted at sites in the US, EU, and certain other countries. This study has completed enrollment of 1050 treatment-naive patients with HCV genotype 1 infections, and will evaluate two 24-week telaprevir-based regimens (in combination with standard doses of peg-IFN alfa-2a and RBV) in comparison with a 48-week control arm (peg-IFN + RBV alone). The primary endpoint of the study is SVR (defined as undetectable HCV RNA [<10 IU/mL]) 24 weeks after completion of treatment; interim results showed that 75% of patients treated with telaprevir for 12 weeks achieved SVR. All patients in the ADVANCE trial have completed dosing of all study drugs.[16-21]

A phase III trial, ILLUMINATE, of telaprevir-based treatment for 24 weeks, or extended treatment to 48 weeks, in patients with chronic hepatitis C began in September 2008 (NCT00758043; VX08-950-111). Approximately 500 patients were recruited at sites in the US, Belgium, the Netherlands, and Puerto Rico. Telaprevir was administered as 750 mg three times daily for 12 weeks, in combination with RBV (1000–1200 mg/day) and peg-IFN (180 μg/week) for either 24 or 48 weeks. The aim of the study was to determine the relative benefits of 24 or 48 weeks of total treatment in patients that respond quickly to a telaprevir-based treatment. Results were released in August 2010.[17,22]

In March 2010, Vertex initiated a phase II combination trial of telaprevir and VX 222 in treatment-naive patients with HCV genotype 1 infection. The primary endpoint of the randomized, dose-ranging trial is to assess the safety and tolerability of the combination therapy. The trial will also evaluate SVR rates as a secondary endpoint. Approximately 100 patients will be enrolled at 20 clinical trial sites, mainly in the US, and treatment duration will be 12 weeks. All patients will receive telaprevir 1125 mg twice daily; VX 222 will be administered as 100 mg or 400 mg twice daily. Some patients will receive follow-on therapy with peg-IFN and RBV.[17,23] On-treatment data from this trial are expected in the second half of 2010.[13,24]

In October 2009, Vertex and Tibotec initiated a phase IIa study in patients with HIV/HCV co-infection.[25] The two-part, randomized, double-blind, placebo-controlled, parallel-group, multicenter study (NCT00983853) will evaluate telaprevir in combination with peg-IFN alfa-2a (Pegasys®) and RBV (Copegus®) in treatment-naive patients with chronic HCV who are co-infected with HIV-1 infection. Patients are being recruited in the US, France, and Germany. Study completion is expected in June 2012.

Tibotec has completed a phase II trial (VX-950-TiDP24-C208; NCT00528528) of twice-daily versus three-times-daily dosing of telaprevir. The trial was initiated at sites in Belgium and Germany with the intention to include additional sites in France, Italy, the Netherlands, and Spain. Enrollment of 161 treatment-naive patients with chronic HCV genotype 1 infection has been completed. Patients are receiving either telaprevir (1125 mg every 12 hours) or telaprevir (750 mg every 8 hours) for 12 weeks in combination with standard therapy. Interim results reported in July 2008 and final data presented in October 2009 showed that more than 80% of patients had undetectable HCV RNA at weeks 4 and 12 in both dosing arms, with no substantial differences in safety observed between the two dosing regimens.[4,26-29]
A phase II viral kinetics study of telaprevir (VX-950-TiDP24-C209; NCT00561015) was completed in Europe by Tibotec in the first half of 2009. This trial recruited treatment-naive patients with HCV genotype 2/3 infections.[29]

Vertex initiated a 28-day phase II trial of telaprevir in combination with peg-IFN and RBV in 12 treatment-naive patients with HCV infection in December 2005. Positive preliminary results have been reported. This study was not designed to evaluate SVRs in telaprevir recipients.[30,31]

1.2.2 Treatment-Experienced Patients with HCV

Tibotec is conducting the pivotal phase III REALIZE trial (VX-950-TiDP24-C216; NCT-00703118) to assess the efficacy, safety, and tolerability of telaprevir in combination with peg-IFN alfa-2a and RBV in patients who have failed prior standard of care treatment (peg-IFN alfa-2a plus RBV). The REALIZE trial has enrolled approximately 650 patients with HCV genotype 1 infections and is being conducted in Australia, Canada, Puerto Rico, the EU, and the US. The trial is designed to evaluate two 48-week telaprevir-based regimens in comparison with a 48-week control arm (standard doses of peg-IFN and RBV). Telaprevir will be dosed for 12 weeks; the primary endpoint of the trial is SVR.[25,32,33] All patients in the REALIZE trial have completed dosing of all study drugs. A phase III roll-over trial (NCT01054573) providing telaprevir to patients from the control group in this study who failed treatment for virologic reasons began enrollment in March 2010.

An observational, follow-up study began in mid-2009 in patients with hepatitis C who had previously been treated with telaprevir (NCT00916474). The expected completion date is mid-2013.

A non-blind, rollover, phase II trial of telaprevir plus standard therapy (RBV plus peg-IFN alfa-2a) has been conducted in the US, Canada, and the EU in patients who participated in the control arms of studies VX06-950-106, VX05-950-104, and VX05-950-104EU and did not respond to therapy; this study is identified as VX06-950-107 (Study 107; NCT00535847; n = 170).[34,35] The study has been completed, and results have been reported.[36-38]

1.2.3 PROVE Trials

Vertex has completed the PROVE 3 (Investigation of HCV PROtease Inhibition for Viral Eradication 3) phase IIb trial in the US, Canada, Germany, the Netherlands, and Puerto Rico (NCT00420784; VX06-950-106). This trial included 453 patients with HCV genotype 1 who had responded poorly to previous treatment. Final results from PROVE 3 were positive, demonstrating that adding telaprevir to the patient’s treatment regimen resulted in cure of approximately 50% of this difficult-to-treat population whose therapy had failed and for whom no other options currently exist.[39-42] PROVE 3 was initiated in January 2007 and completed in April 2009.

In December 2006, Vertex announced interim safety and antiviral analyses of PROVE 1 (Study 104; NCT00336479), a phase II US trial of telaprevir in 260 treatment-naive patients with genotype 1 infection. This generated a milestone payment of $US15 million to Vertex from Janssen. The second phase II trial in this program, PROVE 2 (Study 104EU; NCT00372385), was initiated in June 2006 in Europe and was completed in 2008. Preliminary results from PROVE 2 were consistent with the findings from PROVE 1. The PROVE 1 and PROVE 2 trials evaluated the SVR rates, optimal treatment duration, and the role of RBV in telaprevir-based therapy.[43,44] Final results from the PROVE 1 and PROVE 2 trials have been reported.[14,18,45-48]

1.2.4 Development in Japan

In October 2008, Mitsubishi Tanabe initiated phase III registration trials of telaprevir in Japan. These trials will evaluate 12 weeks’ treatment with telaprevir in combination with peg-IFN alfa-2a plus RBV in both treatment-naive patients with HCV genotype 1 infection (NCT00780416) and in treatment-experienced patients (NCT00781274, NCT00780910). All three trials have completed enrollment. Other clinical trials of telaprevir have been initiated in Japan by Mitsubishi Tanabe Pharma Corporation (a phase I trial, NCT00591214, and a phase II trial, NCT00621296) to assess the safety and efficacy of telaprevir monotherapy in treatment-naive patients with chronic genotype 1b hepatitis C.[7]
1.2.5 Miscellaneous Studies

Other phase I studies have been completed that assessed the effects of severe renal impairment (NCT00903773), and co-administration of ciclosporin and tacrolimus (NCT01038167), in subjects treated with telaprevir. Another phase I study (VX-950-TiDP24-C136; NCT00973388) has also been completed to assess the effect of telaprevir on electrocardiogram results in healthy volunteers.

1.3 Patent Information

Vertex has received a US patent (No. 6 117 639) for the technology to screen compounds for activity against HCV protease, using a cell-based assay. The invention is a proprietary tool that can be used to accelerate the discovery of HCV protease inhibitors for the treatment of HCV infection, and is also broadly applicable for drug discovery against other protease enzyme targets.

2. Scientific Summary

2.1 Pharmacokinetics

2.1.1 Clinical Studies

Telaprevir (750 mg every 8 hours or 1125 mg every 12 hours) plus peg-IFN alfa-2 plus RBV and telaprevir (750 mg every 8 hours or 1125 mg every 12 hours) plus peg-IFN alfa-2 plus RBV were associated with similar total telaprevir exposure levels (measured as area under the concentration-time curve over 24 hours [AUC\textsubscript{24}]) according to a pharmacokinetic/pharmacodynamic analysis of data from a randomized, open-label, phase IIa trial (NCT00528528, C208) in 161 treatment-naïve patients with chronic genotype 1 hepatitis C.[26]

Single-dose telaprevir was orally bioavailable and achieved desired blood concentrations at and above the middle range of the doses tested (25–1250 mg) among healthy volunteers in phase Ia study. Blood concentrations of telaprevir exceeded the concentrations known to demonstrate antiviral activity in preclinical studies. At certain dose levels, these target concentrations were maintained for more than 12 hours. Analysis of combined clinical and preclinical pharmacokinetic results for telaprevir, based on its antiviral activity in the replicon assay, indicated that average liver concentration values were up to 57-fold above the replicon 90% inhibitory concentration and 113-fold above the 50% inhibitory concentration.[49,50]

Results from a phase I study in 25 healthy male volunteers showed that the apparent elimination half-life (t\textsubscript{1/2}) value of telaprevir (25–1000 mg)

| Table I. Features and properties |
|----------------------------------|
| Alternate names                  | LY 570310; LY-570310; LY570310; MP 424; MP-424; VX 950; VX-950 |
| Originator                       | Eli Lilly |
| Highest development phase        | Preregistration (US) |
| Active development-indications   | Hepatitis C |
| Class                            | Oligopeptides, small-molecules |
| Mechanism of action              | Hepatitis C virus NS3 protein inhibitors, hepatitis C virus NS4 protein inhibitors |
| Chemical name                    | Cyclopenta(c)pyrrole-1-carboxamide, (2S)-2-cyclohexyl-N-(pyrazinylcarbonyl)glycyl-3-methyl-L-valyl-N-((1S)-1-((cyclopropylamino)oxoacetyl)butyl)octahydro-, (1S, 3aR, 6aS)- |
| Molecular formula                | C36 H53 N7 O6 |
| CAS registry number              | 402957-28-2 |
| Route of administration          | PO |
| Pharmacodynamics                 | Inhibits HCV protease expressed in vivo; decreases steatosis induced by wild type HCV protease |
| Antimicrobial activity           | Exhibits antiviral activity in vitro; amino acid substitutions that confer resistance to telaprevir in HCV genotype 1 also appear to confer improved fitness to the resistant variants |
| Drug interactions                | Increases exposure to tenofovir disoproxil fumarate by about 30%; increases plasma exposure to VX 222 |
| ATC Codes                        | WHO ATC code: J05A-E (protease inhibitors) |
|                                 | EphMRA ATC code: J5B1 (viral hepatitis products) |
ranged from 2 to 6 hours in the ≥450 mg dose range and 1.5–3 hours in the 25–300 mg dose range.\textsuperscript{51}

Results from a clinical study in 34 patients with genotype 1 HCV infection showed that telaprevir (450–1250 mg) accumulated to steady state with a median accumulation index of 1.8. The drug induced a biphasic HCV RNA decline, with a rapid slope at day 1, followed by a second slower slope. The average steady state trough concentration was 781.1, 1054.6, and 675.5 ng/mL for the 450, 750, and 1250 mg doses, respectively.\textsuperscript{52}

2.1.2 Animal Studies
Telaprevir has demonstrated good potency, bioavailability, and pKa values. Telaprevir was nontoxic in laboratory studies and in some animal studies.\textsuperscript{53}

2.2 Adverse Events

2.2.1 Monotherapy Trials

Phase II: There were no treatment discontinuations or serious adverse events (AEs) reported in a phase II trial, according to preliminary results.\textsuperscript{54}

Phase I: Single oral dose administration of telaprevir (25–1250 mg) was well tolerated at all dose levels and was not associated with any serious AEs among healthy volunteers in a phase Ia study. In addition, there did not appear to be an increase in AEs with increasing dose levels. No dose-limiting toxicities were identified and a maximum tolerated dose was not reached.\textsuperscript{49,50}

Results from a phase I study in 25 healthy male volunteers showed telaprevir (25–1000 mg) to be well tolerated with no serious or severe AEs reported. Most AEs were mild and non-specific in nature.\textsuperscript{51}

In a double-blind, placebo-controlled, phase Ib trial, telaprevir was well tolerated across three different dose groups. No serious AEs were reported and there were no treatment discontinuations. In the trial 34 patients with chronic genotype 1 HCV were randomized to receive telaprevir 450 mg every 8 hours, 1250 mg every 12 hours, or 750 mg every 8 hours, or placebo for 14 days.\textsuperscript{55,56} Prior to the phase Ib trial in patients with HCV, Vertex completed dosing in 24 healthy volunteers. No serious AEs or treatment discontinuations were reported, and the most common potentially drug-related AEs were headache (5 of 24), diarrhea (3 of 24), frequent urination (2 of 24), sleepiness/drowsiness (2 of 24), and nausea (2 of 24). Healthy volunteers were randomized to the same treatment regimens as patients with HCV.\textsuperscript{57}

Final results from the phase I trial (known as VX04-950-101) in 24 patients showed that telaprevir was well tolerated after 5 days of multiple dosing. All drug-related AEs were mild in severity. No serious AEs were reported, and no subjects discontinued treatment due to AEs.\textsuperscript{58}

2.2.2 Combination Therapy Trials

Phase III: In the phase III ILLUMINATE study, the most frequently reported AEs were fatigue, pruritus, nausea, anemia, rash, and headache, the majority of which were mild or moderate in severity. ILLUMINATE compared the effects of treatment continuation to either 24 or 48 weeks in approximately 500 previously treatment-naïve patients who achieved a virologic response at 4 and 12 weeks of therapy with telaprevir in combination with peg-IFN and RBV. The incidence of AEs leading to treatment withdrawal was 6.9%, and more specifically, the rates of withdrawal due to anaemia and rash were 1.1% and 0.6%, respectively.\textsuperscript{24}

The safety and tolerability profile of telaprevir was consistent with that observed in previous phase II trials, in the phase III ADVANCE trial in patients with chronic, genotype 1 HCV infections. In this double-blind trial, patients were randomized to one of two telaprevir arms (8 or 12 weeks therapy with telaprevir 750 mg every 8 hours plus peg-IFN and RBV) or the control arm (peg-IFN plus RBV for 48 weeks). After the completion of the telaprevir treatment phase, patients in the 12-week telaprevir arm received either 12 or 36 weeks treatment with peg-IFN and RBV) or the control arm (peg-IFN plus RBV for 48 weeks). After the completion of the telaprevir treatment phase, patients in the 12-week telaprevir arm received either 12 or 36 weeks treatment with peg-IFN and RBV alone, and patients in the 8-week arm received either 16 or 40 weeks treatment with peg-IFN and RBV alone; both based on response to treatment at weeks 4 and 12. Compared with previous trials of the agent, an improvement in treatment discontinuation rates due to AEs, including
rash and anemia, was observed. The most common AEs in the telaprevir arms were fatigue, rash, pruritus, nausea, headache, and anemia; of which, anemia, rash, pruritus, and nausea occurred more frequently in the telaprevir arms than in the control arm (peg-IFN plus RBV). The majority of these AEs were mild to moderate in nature. AEs leading to discontinuation of all study drugs occurred in 6.9%, 7.7%, and 3.6% of patients in the telaprevir 12-week, telaprevir 8-week and control arms, respectively; discontinuations due to anemia were observed in 0.8%, 3.3%, and 0.6% of patients in each of the respective arms.\footnote{16}

**Phase II:** In a phase IIa trial, C209, the overall incidence of AEs was similar across arms and the most common AEs in the telaprevir arms were skin-related events, nausea, influenza-like illness, and asthenia in-line with previous reports. One genotype 2 patient in T2/PR24 discontinued telaprevir due to rash. The trial enrolled subjects with genotype 2/3 hepatitis C who were randomized to receive 15 days of telaprevir (750 mg every 8 hours) followed by peg-IFN (180 mg every 8 hours) for 24 weeks (T2&PR24), telaprevir and peg-IFN plus RBV followed by 22 weeks of peg-IFN plus RBV (TPR2&PR22), or placebo/peg-IFN plus RBV followed by 22 weeks of peg-IFN plus RBV (Pbo/PR24).\footnote{26,27}

Data from a phase II trial (VX05-950-102) of telaprevir in combination with peg-IFN alfa-2a and RBV have shown that no serious AEs were seen in patients with chronic genotype 1 HCV infection who completed dosing. Telaprevir was administered in a tablet formulation at a dose of 750 mg every 8 hours for 28 days, in combination with standard doses of peg-IFN alfa-2a and RBV. The most common AEs observed in the study were flu-like illness, fatigue, headache, nausea, anemia, depression, itching, and rash. All of these AEs were mild to moderate in severity, except for one headache that was graded as severe. The AEs reported were considered typical of peg-IFN alfa-2a plus RBV treatment. The most common AEs reported, including patients who did not receive telaprevir, and regardless of possible relationship to drug, have been headache, frequent urination, gastrointestinal symptoms, myalgias (muscle pain in AE table), skin disorders, and chills.\footnote{30,60}

The phase II, C208 study, evaluated a twice-daily telaprevir dosing regimen versus a three-times daily regimen; treatment-naive patients with genotype 1 HCV received telaprevir in combination with RBV plus peg-IFN alfa-2a (Pegasys\textsuperscript{®}) or peg-IFN alfa-2b (Pegintron\textsuperscript{®}). Four patients (10%) in the three-times-daily peg-IFN alfa-2a and two patients (5%) in the three-times-daily peg-IFN alfa-2b arms discontinued due to AEs and one patient (3%) and three patients (7%), respectively, experienced virologic breakthrough. In the twice-daily peg-IFN alfa-2a and twice-daily peg-IFN alfa-2b arms, four patients (10%) and three patients (8%), respectively, discontinued due to AEs, and two patients (5%) and three patients (8%), respectively, experienced virologic breakthrough.\footnote{18}

According to the intent-to-treat (ITT) analysis data from the study C208, the most frequently reported AEs were pruritus, nausea, rash, anemia, flu-like symptoms, fatigue, and headache. These events were similar in patients receiving either 8-hourly or 12-hourly telaprevir-based regimens. Five percent (8 of 161) of patients discontinued treatment because of serious AEs, including rash (3%, 4 of 161) and anemia (2%, 3 of 161).\footnote{26,27}

Data from a phase II rollover study (VX06-950-107 or Study 107; NCT00535847) have shown that ten of 117 patients (9%) discontinued all therapy due to AEs, four due to rash and two to anemia. Grade 3 rash and grade 3 anemia were observed in 5% and 5% patients, respectively. AEs reported in this study were similar to those reported in prior phase II trials of telaprevir. The most common AEs reported were rash (all types), fatigue, pruritus, and headache. Study 107 was an open-label study of patients who did not achieve SVR after receiving peg-IFN and RBV in the control arms of the phase II PROVE trials (PROVE 1, PROVE 2, or PROVE 3) of telaprevir. Patients in Study 107 were characterized as null responders, partial responders, relapers or breakthroughs, based on their antiviral response documented as a result of their participation in the control arms of the PROVE trials. A total of 117 patients enrolled in Study 107, including 51 patients with prior treatment null response, 29 patients with prior treatment partial response, eight patients with prior treatment viral
breakthrough, and 29 patients with prior treatment relapse. When Study 107 first began, all patients were to receive 12 weeks of telaprevir in combination with peg-IFN plus RBV followed by an additional 12 weeks of Peg-IFN plus RBV, for a total of 24 weeks of therapy. In 2008, Study 107 was amended and underwent several changes, most notably to the duration of treatment. Following these amendments, only patients who did not achieve HCV RNA ≤100 IU/mL at week 4 were required to stop therapy. In addition, prior treatment null responder patients were to receive a 48-week telaprevir-based treatment regimen. Patients with prior treatment relapse, prior treatment viral breakthrough, and prior treatment partial response were eligible to receive a response-guided, 24-week telaprevir-based treatment regimen if they achieved undetectable HCV RNA at week 4 and 12, otherwise these patients would receive a 48-week regimen. These results were consistent with interim data from 94 of total 117 patients enrolled in Study 107.

2.2.3 PROVE (Phase IIb) Trials

PROVE 1

Final data from the phase IIb, US-based PROVE 1 trial have shown that treatment-naive patients with chronic hepatitis C genotype 1 infection who received telaprevir in combination with peg-IFN alfa-2a plus RBV, the most common AEs were rash (37% with mild rash, 15% with moderate rash, 7% with severe rash), pruritus, nausea, and diarrhea. However, the proportion of patients who discontinued treatment because of an AE was higher in the three telaprevir-based treatment arms (21%), compared with control group (11%); this was predominantly due to the incidence of drug-related rash. The median time to treatment discontinuation because of rash in the telaprevir groups was 73 days (range 8–88) after the start of treatment. Serious AEs were reported in 22 patients during treatment (4 control recipients and 18 telaprevir recipients); 15 of these events were considered to be related to the study drug. PROVE 1 was a phase IIb, randomized, double-blind, placebo-controlled trial that enrolled and treated 250 treatment-naive patients with HCV genotype 1 infection at 37 clinical trial sites in the US. Patients received telaprevir 750 mg (or placebo) orally every 8 hours, based on treatment arm, and a once-weekly 180 µg injection of peg-IFN alfa-2a, as well as a 1000 mg or 1200 mg weight-based daily oral dose of RBV. PROVE 1 consisted of the following four treatment arms: (i) a 24-week telaprevir-based arm consisting of 12 weeks of telaprevir in combination with peg-IFN and RBV, followed by an additional 12 weeks of peg-IFN and RBV alone; (ii) a 48-week telaprevir-based arm consisting of 12 weeks of telaprevir in combination with peg-IFN and RBV, followed by an additional 36 weeks of peg-IFN and RBV alone; (iii) a 12-week telaprevir-based arm consisting of 12 weeks of telaprevir in combination with peg-IFN and RBV; and (iv) a control arm consisting of 12 weeks of placebo in combination with peg-IFN and RBV alone. These results were consistent with earlier reported findings. After 12 weeks of treatment, the percentage of patients who had discontinued treatment due to AEs was 11% of those treated with telaprevir-based regimen versus 3% of control patients. Serious AEs were noted in 3% and 1% of patients in the telaprevir and control groups, respectively.

PROVE 2

Final results from the phase IIb, EU-based PROVE 2 trial (n = 323) confirmed that treatment with 24-week, telaprevir-based therapy was generally well tolerated in treatment-naive patients with genotype 1 hepatitis C. The AE profile of the drug was generally consistent with that seen in the PROVE 1 trial. The most frequent AEs were pruritus, headache, rash, fatigue, weakness (or asthenia), and anemia. Additionally, 14% of patients receiving a 24-week telaprevir-based regimen discontinued all drugs due to AEs versus 7% in the 48-week control arm. The discontinuation rate due to severe rash (grade 3) for all treatment in the telaprevir-based arms was approximately 7%. Although rash and pruritus were frequently reported in this study, they did not always occur in combination; both of these AEs regressed after withdrawal of telaprevir and administration of appropriate therapy. PROVE 2 was another
arm. The incidence of anemia was 32% in the telaprevir arm versus 22% in the placebo arm. The incidence of severe rash was 8% in the telaprevir arm versus 1% in the placebo arm. Grade 3 anemia was observed in 0% of patients in the 12-week telaprevir arm, 24% in the 24-week telaprevir arm, and 1% in the 24-week peg-IFN-alfa arm, respectively. Grade 3 rash was observed in 0% of patients in the peg-IFN-alfa arm, 3% in the peg-IFN-alfa plus RBV arm, and 0% of patients in the peg-IFN-alfa plus RBV arm. The incidence of severe rash was 8% in the pooled telaprevir arm versus 1% in the pooled control arm. The incidence of anemia was 32% in the telaprevir arm versus 22% in the control arm.

In these trials, the most common AEs reported more frequently in the telaprevir treatment arms, compared with the placebo arms, were gastrointestinal events, skin events (rash, pruritus), and anemia. Other AEs reported were similar in type and frequency to those seen with currently approved peg-IFN plus RBV treatment. The most common AE leading to discontinuation in the telaprevir arms was rash in approximately 7% of patients across both PROVE 1 and PROVE 2. Investigators have reported that rash AEs were reversible upon discontinuation of treatment, and a rash management plan was implemented as part of subsequent telaprevir clinical trials.[14]

PROVE 3

Interim results showed that skin and gastrointestinal disorders were more common in patients receiving telaprevir-based therapy than standard therapy alone (peg-IFN-alfa plus RBV; PR) in the PROVE 3 trial in patients with genotype 1 hepatitis C who did not achieve SVR with prior standard therapy. In the double-blind trial, 453 such patients were randomized to treatment with the following four regimens: (i) peg-IFN alfa-2a 180 μg once daily on day 1 and then 750 mg (or placebo) orally every 8 hours, based on treatment arm, a once-weekly 180 μg injection of peg-IFN alfa-2a, as well as a 1000 mg or 1200 mg weight-based daily oral dose of RBV. PROVE 2 consisted of the following four treatment arms: (i) a 24-week telaprevir-based arm consisting of 12 weeks of telaprevir in combination with peg-IFN and RBV, followed by an additional 12 weeks of peg-IFN and RBV alone; (ii) a 12-week telaprevir-based arm consisting of 12 weeks of telaprevir in combination with peg-IFN and RBV; (iii) a 12-week telaprevir-based arm consisting of 12 weeks of telaprevir in combination with peg-IFN (no RBV); and (iv) a control arm consisting of 12 weeks of placebo in combination with peg-IFN and RBV, followed by 36 weeks of peg-IFN and RBV alone.[14,18,47,48,64]

**PROVE 1 and PROVE 2 Pooled Analysis**

Two identical treatment regimen arms were pooled: 12 weeks of telaprevir with 24 weeks of peg-IFN alfa-2a and RBV, and 48 weeks of peg-IFN alfa-2a and RBV (control group). AEs (telaprevir group vs control group) included fatigue (54% vs 46%), rash (54% vs 32%), nausea (51% vs 32%), flu-like symptoms (47% vs 44%), headache (41% vs 50%), and pruritus (24% vs 48%). The incidence of severe rash was 8% in the pooled telaprevir arm versus 1% in the pooled control arm. The incidence of anemia was 32% in the telaprevir arm versus 22% in the control arm.[45]

In these trials, the most common AEs reported more frequently in the telaprevir treatment arms, compared with the placebo arms, were gastrointestinal events, skin events (rash, pruritus), and anemia. Other AEs reported were similar in type and frequency to those seen with currently approved peg-IFN plus RBV treatment. The most common AE leading to discontinuation in the telaprevir arms was rash in approximately 7% of patients across both PROVE 1 and PROVE 2. Investigators have reported that rash AEs were reversible upon discontinuation of treatment, and a rash management plan was implemented as part of subsequent telaprevir clinical trials.[14]
received TDF 300 mg once-daily monotherapy, telaprevir 750 mg every-8-hours monotherapy, and a combination of both drugs in three separate 7-day treatment periods. Two subjects discontinued the study: one withdrew consent, the other due to a non drug-related AE.[66]

2.3 Drug Interactions

TDF did not influence the pharmacokinetic properties of telaprevir in a phase I study of telaprevir in 18 healthy volunteers. Exposure to TDF however, was increased by about 30% during co-administration with telaprevir. The least squares mean ratio (ratio of TDF plus telaprevir to TDF alone, 90% CI) for the minimum and maximum plasma concentrations and AUC values of TDF were 1.41, 1.30, and 1.30, respectively. Similar observations have been reported during combination treatments of TDF with antiretroviral drugs. In the study, the subjects received TDF 300 mg once-daily monotherapy, telaprevir 750 mg every-8-hours monotherapy, and a combination of both drugs, in three separate 7-day treatment periods. Sixteen of 18 subjects completed the study.[66]

In a phase I trial in approximately 20 healthy volunteers, the plasma exposure of VX 222 was increased when it was administered over 10 days in combination with telaprevir, whereas the plasma exposure of telaprevir was not affected when administered in combination with VX 222. For VX 222, doses of 100 mg twice daily and 400 mg twice daily, given in combination with telaprevir, were expected to result in plasma exposures similar to those noted in previous studies with doses of 250 mg twice daily and 750 mg twice daily, respectively, when administered as monotherapy in patients with hepatitis C.[23]

2.4 Antimicrobial Activity

2.4.1 Viral Infections

Analysis of clinical isolates from patients with HCV genotype 1 infection who were treated with a combination of telaprevir, peg-IFN alfa-2b and RBV and experienced disease breakthrough during therapy or post-treatment relapse showed complex mixtures of viral variants bearing amino acid substitutions conferring resistance to telaprevir. In addition, the amino acid substitutions appeared to confer improved fitness to telaprevir-resistant variants.[67]

Dominant mutation(s) selected in the laboratory against telaprevir remained sensitive to ciluprevir, a protease inhibitor which has shown antiviral activity in HCV patients, and ciluprevir resistant mutants remained sensitive to telaprevir. Analysis of minor mutations that were cross-resistant to telaprevir and ciluprevir in the laboratory, and showed that enzymatic activity of the cross-resistant HCV protease was reduced approximately 4- to 7-fold, a condition that could impair the ability of the virus to grow.[68]

Telaprevir exhibits potent and sustained antiviral activity in vitro. In these studies, HCV replicon cells, which mimic the intracellular replication of HCV, were treated with telaprevir and were evaluated at multiple timepoints. In one experiment, treatment with telaprevir for 9 days reduced HCV RNA by almost 10 000-fold (4 log_{10}). In another experiment, HCV replicon cells treated with telaprevir for 13 days exhibited viral clearance at day 13, and no rebound of HCV viral RNA was observed at day 27.[69]

In vitro, telaprevir inhibited HCV RNA replication in a time- and dose-dependent fashion. In a 2-day HCV replicon assay, telaprevir showed a 50% inhibitory dose of 0.35 μmol/L and a 50% cytotoxicity dose of 83 μmol/L. Various combinations of telaprevir, merimepodib, and IFN-α often led to synergistic effects or at least additive effects in reducing HCV RNA. Conditions were also identified where telaprevir alone or in combination with IFN-α was able to completely clear HCV RNA, with no rebound effect observed after withdrawal of the drug.[70]

2.5 Pharmacodynamics

2.5.1 Viral Infections

A novel preclinical HCV protease expression model was used to stringently evaluate the ability of telaprevir to inhibit HCV protease in liver tissue. Telaprevir dosed orally resulted in a significant, dose-dependent inhibition of an HCV-protease enzyme-dependent signal. In untreated control models, high concentrations of active
HCV protease enzyme over 7 days were associated with significant liver damage. However, treatment with telaprevir for the initial 3 days of the experiment resulted in sharply reduced liver damage.[69]

A decrease in steatosis was observed in mice expressing wild type HCV protease after treatment with VX 950.[71]

Results from a clinical study in 34 patients with genotype 1 HCV infection showed that telaprevir (450–1250mg) dose-dependently inhibited viral production with the median antiviral efficacy exceeding 0.999 for the 750 mg dose regimen.[52]

2.6 Therapeutic Trials

2.6.1 Viral Infections

**Monotherapy**

**Phase II:** Preliminary results from a phase II trial demonstrated that at the end of week 2, plasma HCV RNA was <30 IU/mL in 11 of 12 patients and <10 IU/mL in 3 of 12 patients and at the end of week 3, levels were <30 IU/mL in 12 of 12 and <10 IU/mL in 9 of 12. At the end of the 28 day trial, 12 of 12 patients had levels <10 IU/mL. No patients demonstrated evidence of viral breakthrough while receiving treatment.[54]

**Phase I:** Results from a double-blind, placebo-controlled, phase Ib trial demonstrated that treatment with oral suspension telaprevir resulted in significantly reduced plasma HCV RNA levels. In the trial, 34 patients with chronic genotype 1 HCV infection were randomized to receive telaprevir 450 mg every 8 hours, 1250 mg every 12 hours, 750 mg every 8 hours, or placebo over a period of 14 days. After 2 days of treatment, the 26 of 28 patients who completed the trial, achieved an HCV RNA reduction of >3 log_{10} regardless of dose level. A further reduction was observed between days 3 and 14 in the group receiving 750 mg every 8 hours, with mean reductions of 4.4 log_{10} at day 14. The highest trough plasma concentrations were observed in the 750 mg every 8 hour group. In the other dose groups, maximal effects were observed between 3 and 7 days of treatment, after this an increase in median HCV RNA levels of approximately 1 log_{10} between days 7 and 14 was observed in both of these groups. At the end of dosing, five patients across all dose groups tested HCV RNA negative in the quantitative Roche COBAS TaqMan® assay (<30 IU/mL). Twenty-eight days after treatment completion, two patients had viral levels of >1 log_{10} below pretreatment levels.[55,57,72]

In a 14-day study, treatment with telaprevir resulted in a median serum ALT level decline of 25–32 U/L in all dose groups, compared with an 8 U/L increase in the placebo group. Following telaprevir treatment, 83% of patients who had elevated ALT levels at baseline achieved normalization of ALT levels by day 14, compared with none of the patients in the placebo group. Treatment with telaprevir also reduced mean serum levels of neopterin.[73]

The rate of SVR may be increased in patients with chronic genotype 1 hepatitis C who receive a telaprevir-based regimen, compared with conventional regimens, according to final results of a phase I trial (VX04-950-103). SVR was attained in 9 of 15 such patients who were treated with telaprevir alone or telaprevir plus peg-IFN alfa-2a for 14 days, followed by peg-IFN alfa-2a plus RBV for 24 or 48 weeks in total. In contrast, SVR was achieved in 1 of 4 patients who received peg-IFN alfa-2a alone over 2 weeks, followed by 48 weeks of peg-IFN alfa-2a plus RBV. At week 12, HCV DNA could not be detected in all eight patients in the telaprevir plus peg-IFN alfa-2a group and five of seven patients who received telaprevir alone. At week 24, HCV was not detectable in all 15 recipients of telaprevir. Telaprevir 750 mg was administered orally as tablets, three times daily; peg-IFN alfa-2a was administered once weekly.[74,75]

**2.6.2 Combination Therapy**

**Phase III:** Extending telaprevir therapy to 48 weeks did not provide additional benefit over 24 weeks of therapy in treatment-naive patients with hepatitis C who had achieved a virologic response at 4 and 12 weeks in the phase III ILLUMINATE study. In this study, approximately 500 patients who had undetectable HCV levels at weeks 4 and 12 of treatment with telaprevir in combination with peg-IFN alfa-2a and RBV were randomized to receive either 24 or 48 weeks of additional...
therapy. The SVR rates were 92% and 88% in the 24- and 48-week treatment groups, respectively. Relapse rates were 5.7% and 1.9%, respectively.\[24\]

A total of 75% of patients with chronic genotype 1 HCV infections achieved a SVR after 12 weeks of treatment with a telaprevir-based combination regimen, in the phase III ADVANCE trial. In this double-blind study, patients (n = 1095) were randomized to receive either telaprevir for 8 or 12 weeks, in combination with peg-IFN and RBV, or peg-IFN and RBV alone. Following the completion of the telaprevir treatment phase, patients in the 12-week telaprevir arm received peg-IFN and RBV for a subsequent 12 or 36 weeks, based on response to treatment at weeks 4 and 12; and patients in the 8-week telaprevir arm, received peg-IFN and RBV for a subsequent 16 or 40 weeks, based on response to treatment at weeks 4 and 12. Patients in the control arm received a total of 48 weeks treatment with peg-IFN and RBV. The SVR rates observed were 75%, 69%, and 44% for the telaprevir 12-week, telaprevir 8-week and control arms, respectively (p < 0.0001 for both telaprevir arms compared with control). A total of 68%, 66%, and 9% of patients in each of the respective treatment arms, had undetectable HCV RNA levels 4 weeks after the initiation of treatment (defined as rapid viral response; RVR). Furthermore, viral relapse (defined as the proportion of patients who achieved undetectable HCV RNA at the completion of treatment but relapsed during post-treatment follow-up) was observed in 8.6%, 9.5%, and 28% of the telaprevir 12-week, 8-week and control arms, respectively.\[116\]

**Phase II:** Preliminary results of a proof-of-concept, phase IIa (C210; NCT00580801) study indicated that telaprevir plus peg-IFN alfa-2a plus RBV showed greater antiviral activity than telaprevir monotherapy or peg-IFN alfa-2a plus RBV alone in treatment-naive patients with hepatitis C genotype 4.\[76,77\]

Among hepatitis C genotype 2 and genotype 3 subjects receiving telaprevir monotherapy in a phase IIa study, six and three patients, respectively, developed a viral breakthrough by day 15; no viral breakthroughs were observed in the TPR2&PR22 arm. Viral breakthroughs were associated with viral variants with decreased susceptibility to telaprevir. Three genotype 2 and one genotype 3 patients with viral breakthroughs who continued treatment with peg-IFN plus RBV achieved a SVR. SVR rates in genotype 2/3-infected subjects were 56%/50%, 100%/67%, and 89%/44% for arms A, B, and C, respectively. Among genotype 2/genotype 3 subjects receiving telaprevir monotherapy, six of nine and three of eight patients, respectively, developed a viral breakthrough by day 15; no viral breakthroughs were observed in arm B. The trial enrolled subjects with genotype 2/3 hepatitis C who were randomized to receive 15 days of telaprevir (750 mg every 8 hours) followed by peg-IFN (180 μg/week) and RBV (800 mg/day) for 24 weeks (T2&PR24), telaprevir and peg-IFN plus RBV followed by 22 weeks of peg-IFN plus RBV (TPR2&PR22), or placebo and peg-IFN plus RBV followed by 22 weeks of peg-IFN plus RBV (Pbo/PR24).\[59,77-79\]

Analysis of the natural prevalence of hepatitis C variants in patients prior to combination treatment in two phase II trials, revealed that treatment with telaprevir plus peg-IFN alfa-2a plus RBV is effective against the V36M and R109K variants.\[80\]

When administered with peg-IFN plus RBV, telaprevir appeared to have considerable activity against genotype 1 hepatitis C, based on the 4-week interim analysis of Study C208. In this non-blind, phase II trial, 161 treatment-naive patients were randomized to receive one of four different regimens (arms A–D) combining telaprevir, administered 8-hourly or 12-hourly, with peg-IFN alfa-2a or peg-IFN alfa-2b, plus RBV, for 12 weeks. The numbers of patients were 40, 42, 40, and 39 in arms A, B, C, and D, respectively. Telaprevir was administered as 750 mg every 8 hours (arms A and B) or as 1125 mg every 12 hours (arms C and D). Patients received peg-IFN alfa-2a 180 μg/week and RBV 1000–1200 μg/day in arms A and C, and peg-IFN alfa-2b 1.5 μg/kg/week and RBV 800–1200 μg/day in arms B and D. The proportions of patients achieving undetectable HCV RNA at week 4 were greater for study arms A and C (82% and 85%, respectively) than for arms B and D (71% and 68%, respectively); the differences in HCV RNA clearance between arms
A and C, and arms B and D were not statistically significant. Viral breakthrough was reported in, at most, two patients in any study arm, and discontinuation rates were similar in all arms.\textsuperscript{[18,81,82]} According to the ITT analysis data, SVR rates in the study C208 were 82\% and 83\% in patients receiving 12-hourly telaprevir-based regimen (peg-IFN plus RBV), respectively, and 81\% and 85\% in patients in an 8-hourly telaprevir-based regimen, respectively. The majority of patients achieved these SVR rates within a 24-week telaprevir-based regimen.\textsuperscript{[26,27]}

Results of a non-blind study indicated that patients with genotype 1 hepatitis C who do not respond to peg-IFN alfa-2a plus RBV can achieve treatment response with a regimen based on telaprevir. Patients who did not achieve SVR in the peg-IFN alfa-2a plus RBV control arms of the PROVE studies received telaprevir 750 mg every 8 hours and peg-IFN alfa-2a plus RBV at standard doses for 12 weeks, followed by peg-IFN alfa-2a plus RBV for 12 weeks (relapsers or partial responders in PROVE) or 36 weeks (null responders in PROVE). Seventy-two patients received at least one dose of the study drugs; 60, 36, and 16 patients had been treated for 4, 8, and 12 weeks, respectively. In PROVE, null responders were defined by a decrease in HCV RNA of $<1\log_{10}$ at week 4 or $<2\log_{10}$ at week 12, partial responders by $\geq2\log_{10}$ decrease in HCV RNA at week 12 and detectable HCV RNA at week 24, and relapers by an end-of-treatment response but with relapse after 48 weeks of treatment with peg-IFN alfa-2a plus RBV.

Final results showed that 51\% and 53\% of patients achieved a SVR after treatment with telaprevir as part of 24- and 48-week regimens, respectively. The SVR rate in the control group was 14\%.\textsuperscript{[83]} Previous interim data showed that, in the non-blind study at week 4, HCV RNA was $<10\text{IU/mL}$ in 8 of 24 null responders (week 4), five of ten null responders (week 12), 15 of 19 partial responders and four of five relapers. At week 12, HCV RNA was $<10\text{IU/mL}$ in eight of nine null responders (week 4), three of three null responders (week 12), one of one partial responders and two of two relapers. Two patients (both null responders at week 4 in PROVE) experienced viral breakthrough ($>1\log_{10}$ increase above the nadir of HCV RNA, or $>100\text{IU/mL}$ HCV RNA) at week 2.\textsuperscript{[34,35,84]} Additional interim data from 104 enrolled patients showed that a high proportion of treatment-failure patients with HCV genotype 1 infection had a rapid viral response to treatment with telaprevir. These patients maintained undetectable levels of HCV RNA ($<10\text{IU/mL}$) through 24 weeks of treatment.\textsuperscript{[18]}

Telaprevir in combination with peg-IFN alfa-2a plus RBV has strong antiviral activity in patients with hepatitis C, according to results from a phase II study (VX05-950-102). Twelve treatment-naive patients with genotype 1 hepatitis C received 750 mg of oral telaprevir every 8 hours plus standard schedules of peg-IFN alfa-2a plus RBV, for 28 days. After completing this regimen, all patients received follow-on peg-IFN alfa-2a plus RBV treatment. At 28 days, all 12 patients had undetectable plasma HCV RNA levels ($<10\text{IU/mL}$), and no patients showed evidence of viral breakthrough while receiving telaprevir. At week 12 of the follow-on therapy, 11 patients still had undetectable hepatitis C viral RNA levels. Final results showed that SVR was achieved in seven of seven patients who completed 48 weeks of treatment. Two patients had viral breakthroughs after 12 and 24 weeks of treatment. Two patients who were lost to follow-up had undetectable hepatitis C viral RNA levels. Data from a phase II rollover study (VX06-950-107 or Study 107; NCT00535847) have shown that 59\% of patients overall who received telaprevir-based combination therapy achieved SVR after failing to achieve SVR with at least one prior course of HCV therapy. Specifically, 56\% of null-responders to prior therapy (n = 27) achieved SVR after treatment with a 48-week telaprevir-based combination regimen, and 97\% of prior treatment relapers (n = 29) and 55\% of prior treatment partial responders (n = 29) achieved SVR after treatment with a 24-week or 48-week telaprevir-based combination regimen. The overall relapse rate in this study was 16\%. Study 107 was an open-label study of patients who did not achieve SVR after receiving peg-IFN alfa-2a plus RBV in
the control arms of the phase II PROVE trials (PROVE 1, PROVE 2, or PROVE 3) of telaprevir. Patients in Study 107 were characterized as null responders, partial responders, relapsers, or breakthroughs, based on their antiviral response documented as a result of their participation in the control arms of the PROVE trials. A total of 117 patients enrolled in Study 107, including 51 patients with prior treatment null response, 29 patients with prior treatment partial response, eight patients with prior treatment viral breakthrough, and 29 patients with prior treatment relapse. When Study 107 first began, all patients were to receive 12 weeks of telaprevir in combination with peg-IFN plus RBV followed by an additional 12 weeks of peg-IFN plus RBV, for a total of 24 weeks of therapy. In 2008, Study 107 was amended and underwent several changes, most notably to the duration of treatment. Following these amendments, only patients who did not achieve HCV RNA $\leq$100 IU/mL at week 4 were required to stop therapy. In addition, prior treatment null responder patients were to receive a 48-week telaprevir-based treatment regimen. Patients with prior treatment relapse, prior treatment viral breakthrough and prior treatment partial response were eligible to receive a response-guided, 24-week telaprevir-based treatment regimen. Patients who received the 24-week telaprevir-based regimen (arm 1) versus control regimen had a SVR rate of 61% versus 41%, an RVR rate of 81% vs 11%, and a relapse rate of 2% versus 23%. The relapse rate in treatment arm 1 reflected only those patients who achieved an RVR and remained undetectable through week 20. Of the small subgroup of African American patients enrolled in PROVE 1, SVR was achieved by 44% of patients in the telaprevir arms versus 11% in the control group. SVR rates in African Americans are typically lower than in other ethnic groups. African Americans are also disproportionately infected with HCV, compared with other ethnic groups.[14,46]

These final data were consistent with earlier reported interim results, which showed that 88% of patients receiving telaprevir plus peg-IFN alfa-2a plus RBV had an undetectable level of HCV RNA ($<10$IU/mL). Fifty-five percent of patients who received placebo plus peg-IFN alfa-2a plus RBV demonstrated an undetectable level of HCV
RNA. Six of nine patients treated with telaprevir continued to have undetectable HCV RNA levels 20 weeks after stopping treatment. In addition, nine patients stopped treatment after 12 weeks after achieving a RVR (<10 IU/mL) at week 4 and maintenance of this viral response at week 10 of treatment. Of these patients, six continued to have an undetectable HCV RNA at week 20.

Further interim PROVE 1 data showed that 79% of 182 patients with genotype 1 hepatitis C who received telaprevir plus peg-IFN alfa-2a plus RBV had non-detectable HCV RNA at week 4 (RVR), compared with 11% of 81 patients who received only peg-IFN alfa-2a plus RBV (p < 0.001). At week 12, the respective percentages were 70% and 39% (p < 0.001). Viral breakthroughs in the first 12 weeks of treatment were noted in 12 of 175 patients who received telaprevir plus peg-IFN alfa-2a and RBV. Of nine patients with a RVR who received a further 12 weeks treatment with peg-IFN alfa-2a plus RBV, six achieved SVR; the other three relapsed with telaprevir-resistant variants of HCV.[62] After 48 weeks, the percentage of patients with non-detectable HCV RNA was respectively 65% and 45% in recipients of 12 weeks’ treatment with telaprevir, peg-IFN alfa-2a and RBV. Of nine patients with a RVR who received a further 12 weeks treatment with peg-IFN alfa-2a plus RBV, six achieved SVR; the other three relapsed with telaprevir-resistant variants of HCV.[62] After 48 weeks, the percentage of patients with non-detectable HCV RNA was respectively 65% and 45% in recipients of 12 weeks’ treatment with telaprevir, peg-IFN alfa-2a plus RBV followed by 36 weeks’ treatment with peg-IFN alfa-2a plus RBV and a control group that received 48 weeks’ treatment with peg-IFN alfa-2a plus RBV only.[85]

PROVE 2

Final results from the PROVE 2 study confirmed final data from the PROVE 1 trial – that telaprevir significantly improved the proportion of treatment-naive patients who were cured of HCV genotype 1 infection, and also shortened the duration of HCV therapy from 48 to 24 weeks for the majority of patients. PROVE 2 was another phase IIb, randomized, partially double-blind, placebo-controlled trial that enrolled and treated 323 treatment-naive patients with HCV genotype 1 infection at 28 clinical trial sites in France, Germany, the UK, and Austria. As in PROVE 1, patients in PROVE 2 received telaprevir 1250 mg as a single dose on day 1 and then 750 mg (or placebo) orally every 8 hours, based on treatment arm, a once-weekly 180 μg injection of peg-IFN alfa-2a, as well as a 1000 mg or 1200 mg weight-based daily oral dose of RBV. PROVE 2 consisted of the following four treatment arms: (i) a 24-week telaprevir-based arm consisting of 12 weeks of telaprevir in combination with peg-IFN and RBV, followed by an additional 12 weeks of peg-IFN and RBV alone; (ii) a 12-week telaprevir-based arm consisting of 12 weeks of telaprevir in combination with peg-IFN and RBV; (iii) a 12-week telaprevir-based arm consisting of 12 weeks of telaprevir in combination with peg-IFN (no RBV); and (iv) a control arm consisting of 12 weeks of placebo in combination with peg-IFN and RBV, followed by 36 weeks of peg-IFN and RBV alone. Patients who received the 24-week telaprevir-based regimen (arm 1) versus control regimen had a SVR rate of 69% versus 46%, an RVR rate of 69% versus 13%, and a relapse rate of 14% versus 22%. For patients in treatment arm 1 who achieved an RVR and remained undetectable through week 12, the relapse rate was 7%.[14,18,47,48,64,86]

PROVE 1 and PROVE 2 Pooled Analysis

A pooled subgroup analysis of PROVE 1 and 2 showed that telaprevir-based triple therapy improved SVR rates in patients predicted to have low virologic response to current standard treatment. Two identical treatment regimen arms were pooled: 12 weeks of telaprevir with 24 weeks of peg-IFN alfa-2a plus RBV, and 48 weeks of peg-IFN alfa-2a plus RBV (control group). Overall SVR rates were 65% for the pooled telaprevir arm and 44% for the pooled control arm (p = 0.0001). By logistic regression analysis, treatment group, baseline HCV RNA level, age group, and race were predictors of SVR.[45]

PROVE 3

Final results from a phase IIb study (PROVE 3) involving 453 patients with HCV genotype 1 infection who failed prior treatment with peg-IFN plus RBV have shown that SVR rates in all treatment groups who received telaprevir-based therapy were significantly higher than those who received peg-IFN alfa-2a plus RBV. In this study, telaprevir was given at a single oral dose of 1250 mg for the first dose followed by a 750 mg dose every 8 hours for the predefined treatment
period. peg-IFN alfa-2a was administered at 180 μg each week by subcutaneous injection. RBV was administered twice daily at 1000 mg/day for patients weighing <75 kg and 1200 mg/day for patients weighing ≥75 kg. Patients received either telaprevir plus peg-IFN alfa-2a plus RBV for 12 weeks followed by placebo and peg-IFN alfa-2a plus RBV for 12 weeks (T12PR24 group; n = 115); or telaprevir plus peg-IFN alfa-2a plus RBV for 24 weeks followed by peg-IFN alfa-2a plus RBV for 24 weeks (T24PR48 group; n = 113); or telaprevir plus peg-IFN alfa-2a for 24 weeks PR48 (T24P24 group; n = 111); or placebo plus peg-IFN alfa-2a plus RBV for 24 weeks (control; n = 114). SVR rates (primary endpoint) were 51% in the T12PR24 group, 53% in the T24PR48 group, 24% in T24P24 group, versus 14% in the control group; the differences between the telaprevir-based regimens versus control were all statistically significant. Among prior relapsers, SVR rates were 69% in the T12PR24 group, 76% in the T24PR48 group, 42% in the T24P24 group, and 20% in the control group. Among prior non-responders, SVR rates were 39% in the T12PR24 group, 38% in the T24PR48 group, 11% in the T24P24 group, and 9% in the control group. Viral breakthrough rates through week 24 were 13% in the T12PR24 group, 12% in the T24PR48 group, 32% in the T24P24 group, and 3% in the PR48 group. In all telaprevir-based treatment groups, the majority of patients with viral breakthrough were prior nonresponders. All patients who received telaprevir and achieved virologic response maintained it for 48 weeks after the end of the treatment. Adding telaprevir to the treatment regimen resulted in cure of approximately 50% of this patient population who have failed therapy and for which no other options currently exist.[40,87-89]

The above results were consistent with previously reported results. An ITT analysis of a phase IIb study (PROVE 3; study VX06-950-106) showed that telaprevir-based regimen produced superior SVR, compared with peg-IFN alfa-2a plus RBV alone, in patients with genotype 1 hepatitis C who did not achieve SVR with prior peg-IFN alfa-2a plus RBV therapy; 51% and 52% of patients achieved SVR in the 24- and 48-week telaprevir-based regimens, respectively, compared with 14% in 48-week peg-IFN alfa-2a plus RBV therapy (control); 69% and 76% of prior relapsers in the 24- and 48-week telaprevir arm, respectively, achieved SVR as compared with 20% in control; 39% and 38% of prior nonresponders in the 24- and 48-week telaprevir arms, respectively, achieved SVR as compared to 9% in the control. A sub-analysis showed that 53% and 45%, respectively, of patients with cirrhosis in the 24- and 48-week telaprevir arms achieved SVR compared with 8% in the control arm. An overall response rate was observed in 10 of 76 and 26 of 87 patients in 48- and 24-week telaprevir arm, respectively. The relapse rates were 2 of 53 and 22 of 80 patients who completed 48- and 24-week telaprevir treatment respectively, compared with 17 of 33 in control.[41,90]

Viral breakthrough rates were 11%, 10%, 21%, and 3% in the 12-week telaprevir/24-week peg-IFN alfa-2a plus RBV arm, 24-week telaprevir/48-week peg-IFN alfa-2a plus RBV arm, 24-week telaprevir/peg-IFN alfa-2a arm, and control arm, respectively. Relapse rates were 28%, 4%, 53%, and 52% in those groups, respectively, 24 weeks after treatment. No late relapses occurred 48 weeks after treatment in the telaprevir regimens.[39]

Interim results showed that telaprevir-based therapy appeared to be effective in the PROVE 3 trial in patients with HCV genotype 1 failed to achieve SVR with prior peg-IFN alfa-2a plus RBV therapy. In the double-blind trial, 453 such patients were randomized to treatment with the following four regimens: (i) peg-IFN alfa-2a 180 μg/day once weekly plus RBV 1000–1200 mg/day for 48 weeks; telaprevir 750 mg three times daily in combination with peg-IFN alfa-2a plus RBV for 12 weeks, followed by 12 weeks of peg-IFN alfa-2a plus RBV alone; telaprevir 750 mg three times daily in combination with peg-IFN alfa-2a for 24 weeks, followed by 24 weeks of peg-IFN alfa-2a plus RBV alone; and telaprevir 750 mg three times daily plus peg-IFN alfa-2a for 24 weeks. Between 41% and 72% of patients randomized to receive treatment with a 24-week telaprevir-based regimen maintained undetectable viral load at 12 weeks post-treatment.[65] Earlier interim results of PROVE 3 had shown that 60
| Date               | Comment                                                                                                                                                                                                 |
|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 13 August 2010     | inThought analysis for hepatitis C updated                                                                                                                                                              |
| 10 August 2010     | Efficacy and adverse events data from the phase III ILLUMINATE trial in hepatitis C released by Vertex Pharmaceuticals[24]                                                                                   |
| 28 July 2010       | Preregistration for hepatitis C (treatment-experienced patients) in the US (PO)                                                                                                                                 |
| 28 July 2010       | Preregistration for hepatitis C (treatment-naive patients) in the US (PO)                                                                                                                                    |
| 26 May 2010        | Efficacy and adverse event data from the phase III ADVANCE trial in hepatitis C virus infections released by Vertex Pharmaceuticals[16]                                                                  |
| 20 April 2010      | Efficacy and adverse events data from three phase II trials in hepatitis C presented at the 45th Annual Meeting of the European Association for the Study of the Liver (EASL-2010)[59,61,76,87] |
| 16 April 2010      | Efficacy and adverse events data from a phase II rollover trial (Study 107) in treatment-experienced patients with hepatitis C presented at the 45th Annual Meeting of the European Association for the Study of the Liver (EASL-2010)[36,37] |
| 9 April 2010       | Final efficacy data added from the phase IIb trial (PROVE 3) in patients with hepatitis C who have failed prior therapy[88,89]                                                                                   |
| 6 April 2010       | Vertex and Tibotec complete a phase I trial in healthy volunteers to assess effect of telaprevir on pharmacokinetics on tacrolimus and ciclosporin in the US                                                                 |
| 26 March 2010      | Tibotec completes a phase I trial (NCT00903773) in hepatitis C in Ireland                                                                                                                                  |
| 24 March 2010      | Tibotec and Vertex initiate enrollment in a roll-over trial for the REALIZE trial for hepatitis C virus infection in the US, EU, South America, and Australia.                                                                 |
| 17 March 2010      | Tibotec and Vertex complete enrollment in a phase I trial in healthy volunteers to evaluate the effects of telaprevir on the pharmacokinetics of ciclosporin and tacrolimus in the US                                                                                  |
| 2 March 2010       | Tibotec completes enrollment in a phase I study in subjects with renal impairment in Ireland                                                                                                                                 |
| 1 March 2010       | Drug interactions data from a phase-I trial in healthy volunteers released by Vertex Pharmaceuticals[25]                                                                                                |
| 1 March 2010       | Vertex Pharmaceuticals initiates a phase-II trial of combination therapy with VX 222 for hepatitis C in treatment-naive patients in the US                                                                        |
| 5 February 2010    | All patients in the phase III ADVANCE, ILLUMINATE, and REALIZE trials have completed dosing of all study drugs[17]                                                                                             |
| 29 January 2010    | Tibotec and Vertex initiate enrollment in a phase I trial in healthy volunteers to evaluate the effects of telaprevir on the pharmacokinetics of ciclosporin and tacrolimus in the US                                           |
| 3 November 2009    | Final efficacy and adverse events data from the phase IIb PROVE 3 trial in hepatitis C presented at the 60th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD-2009)[35,40] |
| 3 November 2009    | Pooled efficacy and adverse events data from the phase IIb PROVE 1 and PROVE 2 trials in hepatitis C presented at the 60th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD-2009)[45] |
| 31 October 2009    | Efficacy, adverse events and pharmacokinetics data from a phase II study (C208) in hepatitis C presented at the 60th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD-2009)[26,27] |
| 30 October 2009    | Interim safety and efficacy data from Study 107 in hepatitis C released by Vertex[38]                                                                                                                                 |
| 6 October 2009     | Phase II clinical trials in treatment-naive hepatitis C (with HIV co-infection) in the US (PO)                                                                                                              |
| 30 July 2009       | Mitsubishi Tanabe Pharma and Vertex Pharmaceuticals amend agreement for the development and commercialization of telaprevir in Asia[7]                                                                     |
| 10 July 2009       | The rights to milestone payments for telaprevir in the EU are available for purchase (http://www.vrtx.com)                                                                                                  |
| 31 May 2009        | Vertex completes the phase II PROVE 3 trial in hepatitis C in the US, Canada, and the EU, and Tibotec completes a phase II viral kinetics study in hepatitis C in Europe                                                                 |
| 29 April 2009      | Final efficacy and adverse events data from two phase IIb trials (PROVE 1 and PROVE 2) in treatment-naive patients with hepatitis C genotype 1 infection released[14,46,47]                                               |
| 26 April 2009      | Antimicrobial data from an in vitro study in hepatitis C presented at the 44th Annual Meeting of the European Association for the Study of the Liver (EASL-2009)[67]                                              |

*Continued next page*
| Date               | Comment                                                                                                                                 |
|--------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| 26 April 2009      | Interim efficacy data from a phase II, C209 trial in hepatitis C presented at the 44th Annual Meeting of the European Association for the Study of the Liver (EASL-2009)[77,79] |
| 26 April 2009      | Interim efficacy data from a phase IIa, C210 trial in hepatitis C presented at the 44th Annual Meeting of the European Association for the Study of the Liver (EASL-2009)[76,77] |
| 25 April 2009      | Efficacy data from an intent-to-treat analysis of a phase II trial (PROVE 3) in hepatitis C presented at the 44th Annual Meeting of the European Association for the Study of the Liver (EASL-2009)[41,90] |
| 31 January 2009    | Vertex and Tibotec complete enrollment in the phase-III trial ILLUMINATE in hepatitis C in the US, Puerto Rico, and the EU, and in an open-label phase IIa trial (VX06-950-107) in hepatitis C in the US, Canada, and the EU |
| 15 December 2008   | New score for hepatitis C (PO)                                                                                                                                                                   |
| 20 November 2008   | Phase III clinical trials in hepatitis C (treatment-experienced patients) in Australia (PO)                                                                                                       |
| 20 November 2008   | Phase III clinical trials in hepatitis C (treatment-experienced patients) in Canada (PO)                                                                                                          |
| 20 November 2008   | Phase III clinical trials in hepatitis C (treatment-experienced patients) in Puerto Rico (PO)                                                                                                     |
| 20 November 2008   | Tibotec initiates enrollment in the phase III, REALIZE trial for hepatitis C (treatment-experienced patients) in Europe                                                                            |
| 4 November 2008    | Interim efficacy and adverse events data from phase II trials in hepatitis C presented at the 59th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD-2008)[85,81,82,84] |
| 1 November 2008    | Final efficacy and safety data from the phase II, PROVE 2 trial in hepatitis C presented at the 59th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD-2008)[18,48] |
| 1 November 2008    | Interim efficacy data from the PROVE 3, C208 and Study 107, phase II trials in hepatitis C presented by Vertex at the 59th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD-2008)[18] |
| 31 October 2008    | Vertex and Tibotec complete enrollment in the phase III ADVANCE trial for hepatitis C in treatment-naive patients                                                                               |
| 30 October 2008    | Phase III clinical trials in treatment-naive and treatment-experienced patients with hepatitis C in Japan (PO)                                                                                   |
| 28 October 2008    | Drug interactions and adverse events data from a phase I trial in healthy volunteers presented at the 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy and 46th Annual Meeting of the Infectious Diseases Society of America (ICAAC/IDSA-2008)[66] |
| 17 October 2008    | Tibotec initiates enrollment in the phase III, REALIZE trial for hepatitis C (treatment-experienced patients) in the US                                                                          |
| 30 September 2008  | Vertex and Tibotec initiate a phase III trial, ILLUMINATE, for hepatitis C in the US, Belgium, the Netherlands, and Puerto Rico                                                              |
| 19 August 2008     | Phase III clinical trials in hepatitis C (treatment-experienced patients) in the EU (PO)                                                                                                          |
| 19 August 2008     | Phase III clinical trials in hepatitis C (treatment-experienced patients) in the US (PO)                                                                                                          |
| 30 June 2008       | Phase III clinical trials in hepatitis C (treatment-naive patients) in the EU (PO)                                                                                                               |
| 9 June 2008        | Interim efficacy data from a phase IIb (PROVE 3) trial in HCV patients who have failed prior treatment released by Vertex[42]                                                                  |
| 27 April 2008      | Efficacy data from three clinical trials presented at the 43rd Annual Meeting of the European Association for the Study of the Liver (EASL-2008)[34,35,80,91]                                           |
| 14 March 2008      | Phase III clinical trials in hepatitis C (treatment-naive patients) in Puerto Rico (PO)                                                                                                           |
| 14 March 2008      | Phase III clinical trials in hepatitis C (treatment-naive patients) in the US (PO)                                                                                                               |
| 14 March 2008      | Vertex Pharmaceuticals and Tibotec initiate patient recruitment in the ADVANCE study in treatment-naive patients with hepatitis C genotype 1 infection in the US and Puerto Rico                              |
| 31 December 2007   | Phase II clinical trials in hepatitis C in Japan (PO)                                                                                                                                             |
| 9 November 2007    | Tibotec initiates enrollment in a phase II trial for hepatitis C treatment in Europe                                                                                                              |
| 6 November 2007    | Efficacy data and adverse event data from phase II trials (including PROVE 1 and PROVE 2) in hepatitis C presented at the 58th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD-2007)[60,62,64,74,85,86] |
| 1 October 2007     | Mitsubishi Pharma Corporation has merged with Tanabe Seiyaku to form Mitsubishi Tanabe Pharma Corporation                                                                                          |
| 12 June 2007       | Vertex completes enrollment in the PROVE 3 trial for hepatitis C in the US, Canada, and the EU                                                                                                |
| 15 April 2007      | Interim efficacy data from a phase II trial in hepatitis C released by Vertex Pharmaceuticals[63]                                                                                                 |
| 5 February 2007    | Vertex initiates enrollment in the PROVE 3 trial for hepatitis C virus in the US, Canada, and the EU                                                                                             |
| 31 January 2007    | Phase II clinical trials (PROVE 3) in hepatitis C (treatment-experienced patients) in Germany (PO)                                                                                               |

Continued next page
| Date                  | Comment                                                                 |
|----------------------|-------------------------------------------------------------------------|
| 31 January 2007      | Phase II clinical trials (PROVE 3) in hepatitis C (treatment-experienced patients) in Netherlands (PO) |
| 31 January 2007      | Phase II clinical trials (PROVE 3) in hepatitis C (treatment-experienced patients) in Puerto Rico (PO) |
| 31 January 2007      | Phase II clinical trials (PROVE 3) in hepatitis C (treatment-experienced patients) in the US (PO) |
| 31 January 2007      | Phase II clinical trials (PROVE 3) in hepatitis C (treatment-experienced) in Canada (PO) |
| 8 January 2007       | Vertex Pharmaceuticals completes enrollment in the PROVE 2 trial in Europe for hepatitis C |
| 15 December 2006     | Interim results from a phase II clinical trial (PROVE 1) in patients with hepatitis C infection added to the adverse events and viral Infections therapeutic trials sections[43] |
| 27 July 2006         | Phase I clinical trials in hepatitis C treatment in Asia (PO) |
| 5 July 2006          | Telaprevir has been licensed to Janssen. Vertex retains the rights for North America |
| 29 May 2006          | Vertex has initiated enrollment in a phase II trial for hepatitis C in the US and Europe |
| 24 May 2006          | Data presented at the Digestive Disease Week 2006 conference (DDW-2006) have been added to the adverse events and viral infections therapeutic trials sections[52] |
| 23 May 2006          | Phase II clinical trials in hepatitis C treatment in Europe (PO) |
| 10 February 2006     | Data from a media release have been added to the adverse events and viral infections therapeutic trials sections[54] |
| 12 December 2005     | Data presented at the 56th Annual Meeting and Postgraduate Course of the American Association for the Study of Liver Diseases (AASLD-2005) have been added to the adverse events, pharmacokinetics and viral infections pharmacodynamics sections[52,58] |
| 8 December 2005      | Telaprevir has received fast track status for hepatitis C virus infection in the US (PO, tablet) |
| 7 December 2005      | Phase II clinical trials in hepatitis C treatment in the US (PO) |
| 21 November 2005     | Data from a media release have been added to the viral infections therapeutic trials section[73] |
| 15 November 2005     | Vertex has filed an IND with the US FDA for hepatitis C |
| 11 November 2005     | Vertex has initiated enrollment in a phase Ib combination trial for hepatitis C in Europe |
| 7 June 2005          | Data presented at the Digestive Disease Week and the 106th Annual Meeting of the Gastroenterological Association (DDW-2005) have been added to the adverse events section[56] |
| 12 May 2005          | Data from a media release have been added to the adverse events and viral infections therapeutic trials sections[55,57] |
| 11 November 2004     | Phase-Ib clinical trials in hepatitis C treatment in Europe (PO) |
| 8 November 2004      | Additional phase Ia data have been added to the adverse events and pharmacokinetics section[49] |
| 3 November 2004      | Data presented at the 55th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD-2004) have been added to the adverse events, pharmacokinetics and viral infections pharmacodynamics sections[51,71] |
| 30 September 2004    | Vertex has completed a phase Ia trial in hepatitis C treatment in Europe |
| 10 September 2004    | Clinical data from a media release have been added to the adverse events and pharmacokinetics sections[50] |
| 9 September 2004     | Vertex has completed patient dosing a phase Ia trial in healthy volunteers in Europe |
| 18 June 2004         | Telaprevir has been licensed to Mitsubishi Pharma in Japan and Far East countries |
| 11 June 2004         | Phase I clinical trials in hepatitis C treatment in Europe (PO) |
| 1 June 2004          | Data presented at the 17th International Conference on Antiviral Research (ICAR-2004) have been added to the viral infections antimicrobial activity section[70] |
| 22 April 2004        | Preclinical data from a media release have been added to the viral infections antimicrobial activity section[68] |
| 7 April 2004         | Vertex is seeking collaborations to support development and commercialization of telaprevir outside of North America |
| 5 November 2003      | Data presented at the 54th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD-2003) have been added to the pharmacodynamics and viral infections antimicrobial activity section[69] |
| 9 January 2003       | Vertex will lead development and commercialization of telaprevir |
| 14 January 2002      | Vertex has received a $US5 million milestone payment from Lilly for the selection of a lead drug candidate for the treatment of hepatitis C virus infection |
| 10 July 2001         | This program is still in active development |
| 6 October 2000       | Vertex has received a US patent covering assay technology to accelerate drug discover targeting hepatitis C protease |
| 8 December 1998      | New profile |
| 8 December 1998      | Preclinical development for hepatitis C in the US (unspecified route) |
of 115 (52%) patients treated with a 24-week telaprevir-based regimen (12 weeks of telaprevir with peg-IFN alfa-2a plus RBV followed by 12 weeks of peg-IFN alfa-2a plus RBV alone) maintained undetectable HCV RNA 12 weeks post-treatment. Of these 60 patients, 27 (of 66) were prior non-responders to peg-IFN and RBV, 29 (of 40) were prior relapers, and 4 (of 9) were prior breakthroughs.[42]

Pooled Analyses (PROVE Trials)
Interim pooled data from the phase II trials PROVE 1 and PROVE 2 demonstrated that a rapid viral response was observed after 4 weeks in 77% of patients with genotype 1 HCV who received telaprevir, peg-IFN alfa-2a plus RBV and in 12% of those in a control group that received peg-IFN alfa-2a plus RBV only. Viral breakthroughs during the first 12 weeks of treatment were noted in 5% of recipients of telaprevir, peg-IFN alfa-2a plus RBV; most of these occurred during the first 4 weeks and were associated with low levels of IFN in blood.[85,91]

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