Simeprevir (TMC435) With Peginterferon/Ribavirin for Treatment of Chronic HCV Genotype-1 Infection in Treatment-Naive Patients: Results From QUEST–2, a Phase III Trial

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Background and aims: Simeprevir is a potent, once-daily, oral, investigational HCV NS3/4A protease inhibitor. QUEST–2 (NCT01290679) is a Phase III, randomized, double-blind, placebo-controlled trial assessing the efficacy, safety, and tolerability of simeprevir versus placebo as part of a regimen including peginterferon-α2a (pegIFNα2a-2a) or pegIFNα2b-2b/ribavirin (PR) in treatment-naive patients chronically infected with genotype-1 HCV. Safety and SVR12 results from a primary (Week 45) analysis are presented. Methods: Patients (n=532), randomised 2:1 by stratified by HCV genotype-1 subtype and host IL28B genotype, received simeprevir (150 mg QD) or placebo/PR for 12 weeks, followed by PR alone. Total treatment duration was 24 weeks (simeprevir group) or 48 weeks (placebo group). Results: Simeprevir/PR was superior to placebo/PR; SVR12 81% vs 42% (p<0.001). The majority (91%) of patients receiving simeprevir was able to shorten therapy to response-guided therapy (RGT) criteria (HCV RNA <25 IU/mL Week 4 and undetectable Week 12 or 48 weeks [placebo group]). Results: Simeprevir/PR was superior to placebo/PR; SVR12 81% vs 50%, respectively (p<0.001). The majority (91%) of simeprevir-treated patients met RGT criteria and completed treatment at Week 24. Overall, 79% of simeprevir- and 13% of placebo-treated patients achieved VR treatment with simeprevir/PR led to lower rates of on-treatment failure and relapse compared to placebo/PR (7 vs 32% and 13 vs 24%, respectively). The incidence of AEs was similar between groups, regardless of the pegIFN used. The most common AEs were fatigue, influenza-like illness, pruritus and headache. The majority of patients had bridging fibrosis (METAVIR F3; 15%) or cirrhosis (METAVIR F4; 15%). A slightly higher proportion of simeprevir patients experienced rash and photosensitivity, compared to placebo (27 vs 20% and 4 vs 1%, respectively). There was no difference in the proportion of patients experiencing anemia. Conclusions: Simeprevir 150 mg QD was well tolerated, leading to a high SVR12 rate of 81% when administered with either pegIFN α2a-2a or pegIFNα2b-2b. The majority of patients (91%) receiving simeprevir was able to shorten therapy to 24 weeks.

Simeprevir (TMC435) With Peginterferon/Ribavirin for Treatment of Chronic HCV Genotype 1 Infection in Patients Who Relapsed After Prior Interferon-Based Therapy: Results From PROMISE, a Phase III Trial

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Background and aims: Simeprevir is a potent, once-daily, oral, investigational HCV NS3/4A protease inhibitor currently in Phase III clinical development for the treatment of HCV infection. PROMISE (TMC435–IHP–3007, NCT01281830) is a Phase III, randomized, double-blind, placebo-controlled trial assessing the efficacy, safety and tolerability of simeprevir plus peginterferon-α2a/ribavirin (PR) versus placebo/PR in chronically infected, genotype 1 HCV patients who relapsed after previous interferon-based therapy. Safety and SVR12 results from a primary analysis at Week 60 are presented. Methods: Patients (N=939) were randomized (2:1) to receive simeprevir (130 mg QD) plus PR (n=260) or placebo plus PR (n=433) for 12 weeks, followed by PR alone. Patients were stratified by HCV genotype 1 subtype and IL28B genotype. Total treatment duration was 24 or 48 weeks based on response-guided therapy (RGT) criteria (simeprevir group, HCV RNA <25 IU/mL Week 4 and undetectable Week 12 or 48 weeks [placebo group]). Results: Simeprevir/PR was superior to placebo/PR; SVR12 80% vs 37%, respectively (p<0.001). A significant proportion of patients had bridging fibrosis (METAVIR F3), 15% or cirrhosis (METAVIR F4, 15%), 42% were infected with HCV genotype 1a, and 24% were CC IL28B genotype. The majority (93%) of simeprevir-treated patients met RGT criteria and completed treatment at Week 24. Overall, 77% of simeprevir- and 3% of placebo-treated patients achieved VR treatment. With simeprevir/PR also led to a lower on-treatment failure rate and a lower relapse rate, compared to placebo/PR (3% vs 27% and 19% vs 48%, respectively). The most common adverse events were fatigue, influenza-like illness, pruritus and headache. Rates of anemia and neutropenia in the simeprevir group compared to placebo were 17% vs 20% and 18% vs 22%, respectively. Rates of pruritus and rash were comparable between simeprevir and placebo (27% vs 27.8% and 23.3% vs 22.6%, respectively). Conclusions: Simeprevir 150 mg QD, in combination with PR, was generally safe and well tolerated in patients with prior relapse after previous PR therapy, leading to SVR12 rates of 80% overall, 83% in those meeting RGT criteria and 74% in F3–F4 patients. The majority of patients (93%) receiving simeprevir was able to shorten therapy to 24 weeks.

Sustained Virologic Response (SVR) in Prior PegInterferon/ribavirin (PR) Treatment Failures After Retreatment with Bocprevir (BOC) + PR: Final results of the PROVIDE Study

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Purpose: Patients in the PK control arms of BOC Phase 2/3 studies who did not achieve SVR were eligible for retreatment with BOC + PR in the PROVIDE study. The purpose of this presentation is to report the final efficacy and safety results from the PROVIDE study.

Methods: The study enrolled 168 patients of which 164 received BOC (800 mg TID with food) plus P 1.5 g/m²/kg/week and weight-based R (600–1400 mg/day BID) for up to 44 weeks. Patients with >2 weeks since end of treatment in the previous study received PR lead-in for 4 weeks before adding BOC. Four subjects discontinued the study during the 4-week lead-in phase. Protocol specified analyses include only patients who received at least one dose of BOC (N=164). Results: Most patients were male (67%), white (84%), had baseline viral load >800,000 IU/mL (77%) and had genotype 1a infection (62%) 10% of patients were cirrhotic. At baseline, mean age was 52 years, mean BMI was 27.9 kg/m² and mean viral load was 6.26 log₁₀ IU/mL. The proportion of patients with undetectable HCV RNA at various time points during the study is shown in the table. SVR was achieved by 43% of prior null responders (<2 log₂ decline in HCV-RNA at TW12 in prior study), 67% of prior partial responders and 96% of prior relapsers. In total, 156 patients completed the 4-week PR lead-in. SVR was achieved by 31 of 64 (48%) patients with <1 log₂ decline at end of lead-in and by 70 of 92 (78%) patients with a ≥1 log₂ drop or undetectable HCV-RNA at end of lead-in. In total, 8% of patients discontinued due to AEs. Anemia (49%), dysgeusia (35%), and neutropenia (23%) were frequently reported AEs. Conclusions: SVR rates with BOC + PR were high in all patient subgroups, even among patients who were documented to be null responders to prior PR treatment (41%). The highest SVR rates were observed in the prior relapser group (96%). No patients who were interferon-responsive after the 4-week PR lead-in demonstrated a higher SVR rate (76%) than poorly interferon-responsive patients (48%). The safety profile was similar to that previously reported for BOC + PR.

ProspSixpective validation of ASGE criteria for the evaluation of patients with suspected choledocholithiasis

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Aim: To prospectively validate the ASGE criteria for the evaluation of suspected choledocholithias.

Methods: From September 2011 to January 2013, we evaluated 402 consecutive patients referred to a tertiary care hospital for suspected common bile duct stone. We recorded clinical, radiographic and biochemical data from the time of presentation and excluded 69 patients with incomplete data. We determined the presence of biliary stones or stone fragments based on endoscopic retrograde cholangiography (ERC) with or without sphincterotomy or biliary balloon sweep. We examined the prevalence of choledocholithiasis within the ASGE categories and evaluated individual predictors using multivariate logistic regression.

Results: Of 3033 patients in the final analysis, 254 met criteria for high risk of choledocholithiasis, among whom 192 had choledocholithiasis at the time of ERC, yielding a positive predictive value (PPV) of 75% (95%CI 70–81%). Among 77 patients in the intermediate risk group, 38 had choledocholithiasis giving a PPV of 49% (95%CI 38–61%). Two patients met the low risk criteria and neither had choledocholithiasis (PPV 0% (95%CI 0–21%)). The high risk category predicted choledocholithiasis with sensitivity of 83.3% (95%CI

*Slower incidence of disease in the Roche TaqMan assay = 9.3 IU/mL. 2 patients didn't meet the criteria of one of the predefined categories and are qualified as “others” and included in the “total” column. The 4 patients who discontinued during the 4-week lead-in are not included in this table.

EOF = end of treatment; EOF = end of follow-up, time point for SVR24.