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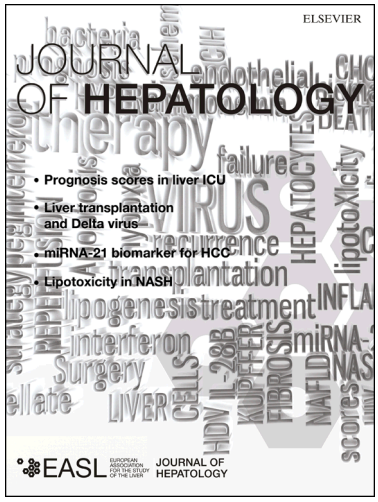

Randomized trials of ombitasvir/paritaprevir/r+dasabuvir±ribavirin vs telaprevir+pegIFN/ribavirin in adults with genotype 1 HCV

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Randomized trials of ombitasvir/paritaprevir/r+dasabuvir±ribavirin vs telaprevir+pegIFN/ribavirin in adults with genotype 1 HCV

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Abbreviations: HCV, hepatitis C virus; GT, genotype; TPV, telaprevir; pegIFN, pegylated interferon; RBV, ribavirin; SVR, sustained virologic response; DAA, direct-acting antiviral agents; OBV, ombitasvir; PTV, paritaprevir; r, ritonavir; DSV, dasabuvir; IL28B, interleukin 28B; RNA, ribonucleic acid; MEMS, Medication Event Monitoring System; PCR, polymerase chain reaction; LLOQ, lower limit of quantitation; SF-36v2, Short Form–36 version 2 Health Survey; PRO, patient-reported outcome; MCS, mental component summary; PCS, physical component summary; WPAI-HCV, work productivity and impairment questionnaire specific for HCV; ANCOVA, analysis of covariance; CI, confidence interval; OATP, organic anion-transporting polypeptide.

Keywords: Hepatitis C virus, telaprevir, interferon-free therapy, direct-acting antivirals, sustained virologic response.

Conflicts of interest

Gregory Dore: Advisory Board Membership: Roche, Merck, Janssen, Gilead, Bristol-Myers Squibb, Abbvie; Research Grants: Roche, Merck, Janssen, Gilead, Bristol-Myers Squibb, Vertex, Boeringher Ingelheim, Abbvie; Travel Sponsorship: Roche, Merck, Janssen, Gilead, Bristol-Myers Squibb, Abbvie

Brian Conway: Research and Grant support, Participation in Advisory Boards: AbbVie, Bristol Myers Squibb, Gilead, Janssen, Merck

Ewa Janczewska: Consultant/speaker/investigator for: AbbVie, BMS, Gilead, Janssen, Vertex, MSD, Roche

Brygida Knysz: Advisory Board Membership: BMS, AbbVie, speaker for AbbVie, BMS, Gilead, Janssen Cilag, MSD, principal investigator: AbbVie, BMS

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Adrian Streinu-Cercel: Speaker/principal investigator: AbbVie, Boehringer Ingelheim, BMS, Janssen, Merck, and Vertex Pharmaceuticals Inc.

Florin Alexandru Caruntu: Consultancy/Advisory Board and speaker: BMS, MSD, Roche, AbbVie, Janssen.

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Richard Skoien: Consultancy/Advisory Board, travel support and speaker: AbbVie, Bayer Australia Ltd, MSD, Roche, Janssen-Cilag Pty Ltd, Gilead.

Wayne Ghesquiere: Research support: AbbVie, BMS, Boehringer Ingelheim, Merck, Roche; Consultant/speaker: Gilead, BMS, Roche.

Wlodzimierz Mazur: Consultancy/ Advisory Board and speaker/ investigator for AbbVie, BMS, Gilead, Janssen Cilag, Roche, and MSD.

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Francisco Fuster: Speaker for BMS, and advisory boards for BMS and AbbVie.

Susan Greenbloom: Advisory Board: Abbvie, Investigator: Abbvie, Gilead, Roche

Adriana Motoc: Investigator Abbvie, Roche, BMS; Speaker Merk, Janssen, Roche

Victoria Arama: Speaker/Principal investigator for: MSD, Roche, BMS, Janssen, AbbVie.

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David Shaw: Nothing to disclose.

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Olav Dalgard: Research support from Merck and Gilead. Advisory board: Abbvie, Gilead, and Medivir.

Yan Luo, Yan Liu, Danielle Sullivan, Xuan Liu, Mudra Kapoor, Andrew Campbell, and Thomas Podsadecki: AbbVie employees and may hold AbbVie stock or options.

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Author contributions

GD, BC, EJ, BK, AS-C, FAC, MC, RS, WG, WM, AS, FF, SG, AM, VA, DS, IT, JS, and OD contributed to patient recruitment and data collection and were investigators in this study. DS and XL contributed to data analysis. GD, BC, Y Luo, EJ, BK, Y Liu, AS-C, FAC, MC, RS, WG, WM, AS, FF, SG, AM, VA, DS, IT, JS, and OD, DS, XL, MK, AC, and TP contributed to the data interpretation. Y Luo, Y Liu, DS, XL, MK, AC, and TP contributed to the study design. GD, BC, Y Luo, EJ, BK, Y Liu, AS-C, FAC, MC, RS, WG, WM, AS, FF, SG, AM, VA, DS, IT, JS, and OD, DS, XL, MK, AC, and TP contributed to the writing and review of this report.

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Abstract

Background & Aims Telaprevir plus peginterferon/ribavirin(TPV+pegIFN/RBV) remains a therapeutic option for chronic HCV genotype(GT) 1 infection in many regions. We conducted two open-label, phase 3b trials comparing safety and efficacy of all-oral ombitasvir/paritaprevir/ritonavir and dasabuvir+/-ribavirin(OBV/PTV/r+DSV+/-RBV) and TPV+pegIFN/RBV.

Methods Treatment-naïve(MALACHITE-I) or pegIFN/RBV-experienced(MALACHITE-II) non-cirrhotic, chronic HCV GT1-infected patients were randomized to OBV/PTV/r+DSV +weight-based RBV, OBV/PTV/r+DSV (treatment-naïve, GT1b-infected patients only), or 12 weeks of TPV+pegIFN+weight-based RBV and 12-36 additional weeks of pegIFN/RBV. Primary endpoint was sustained virologic response 12 weeks post-treatment(SVR_{12}). Patient-reported outcome questionnaires evaluated mental and physical health during the studies.

Results 311 treatment-naïve and 148 treatment-experienced patients were randomized and dosed. Among treatment-naïve patients, SVR_{12} rates were 97%(67/69) and 82%(28/34), respectively, in OBV/PTV/r+DSV+RBV and TPV+pegIFN/RBV-treated GT1a-infected patients; SVR_{12} rates were 99%(83/84), 98%(81/83), and 78%(32/41) in OBV/PTV/r+DSV+RBV, OBV/PTV/r+DSV, and TPV+pegIFN/RBV-treated GT1b-infected patients. Among treatment-experienced patients, SVR_{12} rates were 99%(100/101) and 66%(31/47) with OBV/PTV/r+DSV+RBV and TPV+pegIFN/RBV. Mental and physical health were generally better with OBV/PTV/r+DSV+/-RBV than TPV+pegIFN/RBV. Rates of discontinuation due to adverse events (0-1% and 8-11%,

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respectively, $P<0.05$) and rates of hemoglobin decline to<10g/dL(0-4% and 34-47%, respectively, $P<0.05$) were lower for OBV/PTV/r+DSV+/-RBV than TPV+pegIFN/RBV.

Conclusions Among non-cirrhotic, HCV GT1-infected patients, SVR_{12} rates were 97-99% with 12-week, multi-targeted OBV/PTV/r+DSV+/-RBV regimens and 66-82% with 24-48 total weeks of TPV+pegIFN/RBV. OBV/PTV/r+DSV+/-RBV was associated with generally better mental and physical health, more favorable tolerability, and lower rates of treatment discontinuation due to adverse events.

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Introduction

HCV genotype(GT) 1 is the most prevalent HCV GT worldwide[1]. In treatment-naïve GT1-infected patients, triple therapy with the first generation HCV NS3/4A protease inhibitor telaprevir and peginterferon/ribavirin(TPV+pegIFN/RBV) results in sustained virologic response(SVR) rates of approximately 75%[2]. Among patients who previously failed to achieve SVR with pegIFN/RBV therapy, retreatment with TPV+pegIFN/RBV results in SVR rates of 31-84% depending on type of previous response[3]. TPV+pegIFN/RBV therapy requires up to 48 weeks of treatment and results in significant adverse events such as influenza-like symptoms, depression, rash, nausea, and pancytopenia, leading to a high discontinuation rate[2, 4-6]. Many patients are pegIFN-intolerant or have contraindications to pegIFN/RBV therapy that preclude the treatment. New direct-acting antiviral(DAA) therapies that provide a significant advancement in chronic HCV treatment are approved and have replaced TPV/+pegIFN/RBV in many areas. However, TPV+pegIFN/RBV is still widely available and remains the choice treatment in regions including Latin America and Asia. There is a lack of direct comparison between the IFN-free DAA regimens and previous standard of care such as TPV+pegIFN/RBV.

The 3-DAA combination regimen of ombitasvir(OBV), paritaprevir coadministered with ritonavir(PTV/r), and dasabuvir(DSV)+/-RBV is approved for treatment of HCV GT1-infected patients with or without cirrhosis in areas including the United States, Canada, and European Union[7]. OBV is an NS5A inhibitor, PTV is an HCV NS3/4A protease inhibitor, and DSV is a nonnucleoside NS5B polymerase inhibitor[8]. In phase 3 trials, these 3-DAA regimens resulted in SVR_{12} rates of 95-100% in GT1a- and GT1b-infected

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187 treatment-naïve and pegIFN/RBV-experienced, non-cirrhotic and cirrhotic patients;
188 discontinuation due to adverse events occurred in 0-2% of patients[7, 9-13]. Here, we
189 report results of the first trials performing head-to-head comparisons of the safety and
190 efficacy of a pegIFN-free regimen(OBV/PTV/r+DSV+/-RBV) and previous standard of
191 care(TPV+pegIFN/RBV) in treatment-naïve(MALACHITE-I) and treatment-
192 experienced(MALACHITE-II) HCV GT1-infected patients without cirrhosis.

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Patients and methods

Study design and participants

MALACHITE-I and MALACHITE-II(Clinicaltrials.gov, NCT01854697 and NCT01854528) are phase 3b, randomized, open-label studies. MALACHITE-I enrolled patients in Australia, Canada, Europe, and South America. MALACHITE-II enrolled patients in Australia, Europe, and South America. Patients were 18-65 years of age with chronic HCV GT1 infection and HCV RNA >10,000 IU/mL. Exclusion criteria included positive hepatitis B surface antigen or anti-HIV antibody screen, and current or past evidence of cirrhosis. In MALACHITE-I, patients with previous use of anti-HCV therapy were excluded. Patients in MALACHITE-II had documentation of adherence with prior pegIFN/RBV therapy with a prior relapse (undetectable HCV RNA at the end of therapy with HCV RNA detectable within 52 weeks of treatment follow-up), partial response(≥2 $\log_{10}$IU/mL reduction in HCV RNA at week 12 of therapy, but HCV RNA detectable at the end of treatment), or null response(<2 $\log_{10}$IU/mL reduction in HCV RNA at week 12 of treatment or<1 $\log_{10}$IU/mL reduction in HCV RNA at week 4 of therapy). Details are in the Supplement.

Ethics committee approval was obtained. Each patient provided written informed consent. The study was conducted in accordance with International Conference on Harmonization guidelines and Declaration of Helsinki ethical principles.

Randomization

In MALACHITE-I, HCV GT1a-infected patients were randomized 2:1 to OBV/PTV/r+DSV+RBV(arm A) or TPV+pegIFN/RBV(arm B). HCV GT1b-infected

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patients were randomized 2:2:1 to OBV/PTV/r+DSV+RBV(arm C), OBV/PTV/r+DSV(arm D), or TPV+pegIFN/RBV(arm E). Randomization was stratified by IL28B genotype(CC, non-CC). In MALACHITE-II, patients were randomized 2:1 to OBV/PTV/r+DSV+RBV or TPV+pegIFN/RBV. Randomization was stratified by HCV subgenotype(1a, non-1a) and previous response to pegIFN/RBV treatment(relapsers, partial responders, null responders). Random allocation sequences were computer-generated by the sponsor and interactive response technology was utilized for randomization of patients to treatment. Treatment allocation was open-label.

Procedures

Patients received 12 weeks of co-formulated OBV/PTV/r(25mg/150mg/100mg once daily) and DSV(250mg twice daily) with or without weight-based RBV or 12 weeks of TPV(750mg every 8 hours) co-administered with pegIFN(pegIFN alpha-2a, 180μg subcutaneously weekly) and weight-based RBV with an additional 12 or 36 weeks of pegIFN/RBV, depending on virologic response at treatment week 4-12. Total daily dose of RBV was 1000mg for body weight<75kg or 1200mg for body weight≥75kg, administered in 2 daily doses. All patients are being followed for 48 weeks post-treatment. Adherence was assessed by pill and syringe counts and Medication Event Monitoring System(MEMS) caps, which record daily dosing history.

HCV RNA was measured at screening, baseline, and at visits throughout the treatment and post-treatment periods. RNA extraction and determination of plasma HCV RNA levels were performed by a central laboratory. The Roche High Pure System Viral Nucleic Acid Kit was used for RNA extraction. Plasma HCV RNA level determination

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was by the Roche COBAS TaqMan® real-time reverse transcriptase-PCR assay v2.0(lower limit of detection[LLOD] and lower limit of quantitation[LLOQ] are 15 IU/mL and 25 IU/mL, respectively). On-treatment virologic failure was defined as confirmed HCV RNA≥lower limit of quantitation(LLOQ) after HCV RNA<LLOQ during treatment, a confirmed increase in HCV RNA from nadir>1 $\log_{10}$IU/mL during treatment, or failure to achieve HCV RNA<LLOQ by week 6(OBV/PTV/r+DSV+/-RBV arms) or week 16(TPV+pegIFN/RBV arms). Post-treatment relapse was defined as confirmed HCV RNA≥LLOQ after the end of treatment in a patient who completed treatment with HCV RNA<LLOQ at final treatment visit. Resistance-associated variant(RAV) testing was by population sequencing at baseline and population and/or clonal sequencing at post-baseline.

Patients completed the Short Form–36 version 2 Health Survey(SF-36v2), a self-administered patient-reported outcome(PRO) questionnaire assessing functional health and well-being. Scores are aggregated into a Mental Component Summary(MCS) and a Physical Component Summary(PCS), with higher scores indicating better health. The SF-36v2 was completed at baseline and every 4-12 weeks. Patients also completed a Work Productivity and Activity Impairment questionnaire specific for HCV(WPAI-HCV, details in supplement).

Treatment-emergent adverse events were defined as those occurring between treatment day 1 and 30 days post-treatment. Clinical laboratory testing was performed at screening, baseline, and at visits throughout the treatment and post-treatment periods.

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Outcomes

In both studies, the primary endpoint was percentage of patients with SVR_{12}(HCV RNA<LLOQ 12 weeks after the last dose of study drug). Secondary endpoints included mean change from baseline to final treatment visit in the SF-36v2 MCS and PCS and percentages of patients with on-treatment virologic failure and post-treatment relapse.

Statistical analysis

In MALACHITE-I, the primary efficacy analysis tested non-inferiority of SVR_{12} rates for OBV/PTV/r+DSV+RBV to TPV+pegIFN/RBV in GT1a-infected patients(arm A versus B) and OBV/PTV/r+DSV to TPV+pegIFN/RBV in GT1b-infected patients(arm D versus E). Because a previous trial demonstrated non-inferiority of OBV/PTV/r+DSV to OBV/PTV/r+DSV+RBV in GT1b-infected patients, arm D rather than arm C was compared with arm E in the primary efficacy analysis in GT1b-infected patients per protocol[11]. The percentage of patients achieving SVR_{12} in each arm and a 2-sided 95% confidence interval(CI) for the difference in SVR_{12} rates(arm A-B, arm D-E) were calculated. If the lower bound of the CI for the difference was above the non-inferiority margin(–10.5%), OBV/PTV/r+DSV+/-RBV was considered non-inferior to TPV+pegIFN/RBV in that subgenotype. In secondary endpoint analyses, mean changes in SF36-v2 MCS and PCS scores from baseline to final treatment visit were compared in arm A versus B and arm D versus E using an ANCOVA model with treatment arm as a factor and baseline SF-36v2 MCS or PCS score, respectively, and region as covariates. SVR_{12} rates in arm A versus B and arm D versus E were compared using a logistic regression model with treatment arm, baseline log_{10} HCV RNA level, and IL28B

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genotype(CC, non-CC) as predictors at the α=0.05 significance level. If the logistic regression failed to converge, a stratum-adjusted Mantel Haenszel approach was used. Mean changes from baseline to final treatment visit in SF-36v2 MCS and PCS scores were compared between regimens in all treatment-naïve patients (1a- and 1b-infected) in post-hoc analyses.

In MALACHITE-II, the primary efficacy analysis compared the percentage of patients achieving SVR_{12} between treatment arms using a logistic regression model with treatment arm, baseline log_{10} HCV RNA level, HCV subgenotype(1a, non-1a), and previous pegIFN/RBV treatment response(relapser, partial responder, null responder) as predictors at the α=0.05 significance level. In secondary efficacy analyses, mean changes in SF-36v2 MCS and PCS scores from baseline to final treatment visit were compared between treatment arms using an ANCOVA model with treatment arm as a factor and baseline SF36-v2 MCS or PCS score, respectively, and region as covariates.

Each study used a fixed-sequence testing procedure for primary and secondary efficacy analyses to control the type I error rate. In MALACHITE-I, the testing procedure was conducted in GT1a- and 1b-infected patients separately; the order of analyses within each subgenotype was: SVR_{12} non-inferiority, SF-36v2 MCS, SF-36v2 PCS, and SVR_{12} superiority. In MALACHITE-II, the order of analyses was SVR_{12} analysis, SF-36v2 MCS analysis, and SF-36v2 PCS analysis. Details of efficacy endpoint analyses and sample size determination for each study are in the Supplement.

Demographic, efficacy, and safety analyses were on the modified intention-to-treat population, defined as all patients who were randomized and received $\geq$1 dose of study

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304 drug. SAS®(SAS Institute, Inc., Cary, NC) for the UNIX operating system was used for
305 all analyses. All statistical tests and CIs were 2-sided with an α level of 0.05. CIs were
306 calculated using normal approximation to the binomial distribution unless the point
307 estimate was 0% or 100%, in which case Wilson score method was used. Frequencies
308 of treatment-emergent adverse events and post-baseline laboratory abnormalities were
309 compared between treatment groups by Fisher's exact test.

310 *Roles of the funding source*

311 The sponsor contributed to trial design, data analysis and interpretation, and the
312 decision to submit this report for publication. The first draft of this report was written by a
313 sponsor-employed medical writer and revised critically by all authors. All authors had full
314 access to the data. The corresponding author had final responsibility for the decision to
315 submit the manuscript for publication.

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Results

In the treatment-naïve study, 404 patients were screened; 311 were randomized and received study drug(Figure 1, Supplemental Figure 1). In the treatment-experienced study, 222 patients were screened, 154 were randomized, and 148 received study drug (Figure 1, Supplemental Figure 2). Reasons for exclusion are in Supplemental Tables 1&2. Patient characteristics are in Table 1. In each study the majority of patients(≥95% receiving OBV/PTV/r+DSV+/-RBV and ≥86% receiving TPV+pegIFN/RBV) were adherent with planned dosing of each study drug. Among 75 treatment-naïve patients receiving TPV+pegIFN/RBV, 59 received 24 weeks of pegIFN/RBV while 16 received 48 weeks. Among 47 treatment-experienced patients receiving TPV+pegIFN/RBV, 10 received a 24-week regimen(all prior relapsers) and 37 received a 48-week regimen(2 relapsers, 12 partial responders, 23 null responders).

Efficacy

Treatment-naïve patients(MALACHITE-I)

Among HCV GT1a-infected patients, 97%(67/69)(95% CI 93-100) receiving OBV/PTV/r+DSV+RBV and 82%(28/34)(95% CI 69-96) receiving TPV+pegIFN/RBV achieved SVR_{12}(Figure 2). The SVR_{12} rate difference of 15%(95% CI 1-28) demonstrated protocol-defined non-inferiority of OBV/PTV/r+DSV+RBV to TPV+pegIFN/RBV in GT1a-infected patients. Among HCV GT1b-infected patients, 98%(81/83)(95% CI 94-100) receiving OBV/PTV/r+DSV and 78%(32/41)(95% CI 66-91) receiving TPV+pegIFN/RBV achieved SVR_{12}. The difference of 20%(95% CI 6-33) demonstrated protocol-defined non-inferiority of OBV/PTV/r+DSV to TPV+pegIFN/RBV

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in GT1b-infected patients. The SVR_{12} rate for OBV/PTV/r+DSV was also superior to TPV+pegIFN/RBV(*P*=0.005). The SVR_{12} rate of 99%(83/84)(95% CI 97-100) in OBV/PTV/r+DSV+RBV-treated, GT1b-infected patients was non-inferior(difference=21%, 95% CI 8-34%) and superior(*P*=0.002) to that for TPV+pegIFN/RBV.

Four of 236 patients(2%) receiving OBV/PTV/r+DSV+/-RBV versus 9 of 75 patients(12%) receiving TPV+pegIFN/RBV met protocol-specified criteria for on-treatment virologic failure or post-treatment relapse(Table 2). Available data showed the 3 patients receiving OBV/PTV/r+DSV+/-RBV with on-treatment virologic failure were adherent to study drugs. At the time of failure, these patients had variants at resistance-associated positions in the amino acid sequences for NS3, NS5A, and/or NS5B that were not present at baseline. One GT1b-infected patient receiving OBV/PTV/r+DSV+RBV met the criteria for post-treatment relapse but had GT2a infection, consistent with reinfection. Most patients in the TPV+pegIFN/RBV arm who experienced virologic failure had RAVs present in NS3 at the time of failure.

Treatment-experienced patients(MALACHITE-II)

A total of 100 of 101 patients receiving OBV/PTV/r+DSV+RBV achieved SVR_{12}(99%, 95% CI 97-100%)(Figure 2). Thirty-one of 47 patients receiving TPV+pegIFN/RBV achieved SVR_{12}(66%, 95% CI 53-79%). SVR_{12} rate was significantly different between treatment arms(odds ratio=54, 95% CI 7-430; *P*<0.001). SVR_{12} rates were numerically higher with OBV/PTV/r+DSV+RBV than TPV+pegIFN/RBV in subgroups of patients based on genotype or prior treatment experience(Supplemental Table 4). SVR_{12} rates

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were 100%(49/49) and 57%(13/23) in prior null responders receiving OBV/PTV/r+DSV+RBV and TPV+pegIFN/RBV, respectively.

There were no on-treatment failures or post-treatment relapses with OBV/PTV/r+DSV+RBV; the 1 patient not achieving SVR_{12} had missing data, but had HCV RNA<LLOQ at the end of treatment(Table 2). Among patients receiving TPV+pegIFN/RBV, 23% met protocol-specified criteria for virologic failure. Most patients receiving TPV+pegIFN/RBV who experienced virologic failure had RAVs present in NS3 at the time of failure.

Patient-Reported Outcomes(PROs)

Mean changes from baseline to final treatment and post-treatment week 12 visit in SF-36v2 MCS and PCS in treatment-naïve and treatment-experienced patients are in Figure 3. When GT1a- and GT1b-infected treatment-naïve patients were analyzed separately, mean changes at the final treatment visit in MCS and PCS with OBV/PTV/r+DSV+/-RBV versus TPV+pegIFN/RBV were significantly different in GT1b-infected patients(P<0.05). Mean change in MCS was not significantly different for OBV/PTV/r+DSV+RBV versus TPV+pegIFN/RBV in GT1a-infected patients, preventing statistical testing of subsequent secondary endpoints in GT1a-infected patients per protocol. In a post-hoc analysis, mean changes at the final treatment visit in SF-36v2 MCS and PCS were significantly different between patients receiving OBV/PTV/r+DSV+/-RBV and TPV+pegIFN/RBV in the overall population of treatment-naïve patients(P<0.05). Similarly, mean changes in SF-36v2 MCS and PCS were significantly different between patients receiving OBV/PTV/r+DSV+/-RBV and

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TPV+pegIFN/RBV in the overall population of treatment-experienced patients(*P*<0.05). Overall, mean changes at post-treatment week 12 in MCS and PCS were not significantly different between OBV/PTV/r+DSV+/-RBV and TPV+pegIFN/RBV in treatment-naïve or -experienced patients. Across the two studies, 46% and 58% of patients receiving OBV/PTV/r+DSV+/-RBV showed numerical improvement over baseline at final treatment visit in MCS and PCS, respectively; 27% and 22% of patients receiving TPV+pegIFN/RBV showed numerical improvement in MCS and PCS, respectively. Overall, the difference between the two regimens in the changes from baseline in MCS and PCS throughout the treatment and post-treatment periods in both treatment-naïve and treatment-experienced patients favored the OBV/PTV/r+DSV+/-RBV regimen(Figure 4). Comparable differences in WPAI-HCV between regimens were observed(Supplemental Figure 3).

Adverse events

Safety data were combined according to treatment regimen within each study. Adverse event frequency was lower with OBV/PTV/r+DSV+/-RBV versus TPV+pegIFN/RBV(*P*<0.05)(Table 3). The majority of treatment-emergent adverse events observed were mild with OBV/PTV/r+DSV+/-RBV and moderate with TPV+pegIFN/RBV. Notably, rash occurred less frequently with OBV/PTV/r+DSV+/-RBV versus TPV+pegIFN/RBV(*P*<0.05). One treatment-naïve patient receiving TPV+pegIFN/RBV but none receiving OBV/PTV/r+DSV+/-RBV experienced toxic skin eruption. The rates of adverse events commonly associated with RBV, such as anemia, pruritus, rash, nausea, and asthenia, were lower with OBV/PTV/r+DSV+RBV versus TPV+pegIFN/RBV(*P*<0.05). Depression was also less frequent with OBV/PTV/r+DSV+/-

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RBV than TPV+pegIFN/RBV(0-2% versus 6-9%, *P*<0.05). In treatment-naïve GT1b-infected patients, the frequencies of these adverse events were numerically lower with OBV/PTV/r+DSV than OBV/PTV/r+DSV+RBV, consistent with their known association with RBV.

In both studies the rates of serious adverse events and treatment discontinuation due to adverse events were lower with OBV/PTV/r+DSV+/-RBV versus TPV+pegIFN/RBV(*P*<0.05). Serious adverse events occurred in 2 patients receiving OBV/PTV/r+DSV+RBV(one treatment-naïve[1%] and one treatment-experienced[1%]), no patient receiving OBV/PTV/r+DSV, and 14 patients receiving TPV+pegIFN/RBV(9 treatment-naïve[12%], 5 treatment-experienced[11%]). One treatment-naïve patient(1%) receiving OBV/PTV/r+DSV+RBV and no patient receiving OBV/PTV/r+DSV discontinued treatment due to adverse events, versus 6 treatment-naïve patients(8%) and 5 treatment-experienced patients(11%) receiving TPV+pegIFN/RBV. Details are in Supplemental Tables 5&6.

Decreased hemoglobin levels

Among treatment-naïve patients, 3 receiving OBV/PTV/r+DSV+RBV(2%), none receiving OBV/PTV/r+DSV, and 35 receivingTPV+pegIFN/RBV(47%) had hemoglobin declines to<10g/dL(*P*<0.05, versus TPV+pegIFN/RBV)(Table 3). Among treatment-experienced patients, 4 receiving OBV/PTV/r+DSV+RBV(4%) versus 16 receiving TPV+pegIFN/RBV(34%) had hemoglobin declines to<10g/dL(*P*<0.05). Five treatment-naïve patients(3%) and 2 treatment-experienced patients(2%) receiving OBV/PTV/r+DSV+RBV modified RBV dose due to anemia; all achieved SVR_{12}. Thirty-

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two treatment-naïve patients(43%) and 15 treatment-experienced patients(32%) receiving TPV+pegIFN/RBV modified RBV dose due to anemia; SVR_{12} rates were 84% and 93% in treatment-naïve and treatment-experienced patients, respectively. Twelve patients receiving TPV+pegIFN/RBV(6 treatment-naïve, 6 treatment-experienced) had a blood transfusion, and one treatment-experienced patient received erythropoietin.

Other laboratory abnormalities

No patient discontinued OBV/PTV/r+DSV+/-RBV due to laboratory abnormalities. Six treatment-naïve patients(4%) and one treatment-experienced patient(1%) receiving OBV/PTV/r+DSV+RBV had total bilirubin elevations>3X the upper limit of normal(ULN)(Table 3). These elevations were comprised mainly of indirect bilirubin, peaked at week 1 of treatment, and normalized or stabilized thereafter. Total bilirubin elevations>3X ULN occurred in 2 treatment-naive patients(3%) and 1 treatment-experienced patient(2%) receiving TPV+pegIFN/RBV.

One treatment-naïve patient(1%) receiving OBV/PTV/r+DSV+RBV had isolated elevations of aminotransferases>5X ULN within the first month of treatment that led to study drug interruption for 14 days. Aminotransferase levels normalized by post-treatment week 4. The patient had no other liver function test abnormalities, and achieved SVR_{12}. One(1.0%) treatment-experienced patient receiving OBV/PTV/r+DSV+RBV and 3(6.4%) receiving TPV+pegIFN/RBV had at least one alanine aminotransferase measurement>5X ULN. In the patient receiving OBV/PTV/r+DSV+RBV this elevation was concurrent with an elevation in aspartate aminotransferase>5X ULN. These values declined without treatment interruption or

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450 discontinuation and normalized at post-treatment week 4; this patient had no clinically
451 significant bilirubin elevation.

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Discussion

Significant advances have occurred rapidly in chronic HCV treatment with approval of new DAAs. Studies of DAA regimens in HCV GT1-infected patients have demonstrated higher SVR rates and better tolerability profiles than previously reported for first generation protease inhibitors co-administered with pegIFN/RBV[2, 9-18]. However, evidence-based policy centers have highlighted the lack of direct comparative trials demonstrating the efficacy and safety benefits of IFN–free regimens versus pegIFN-containing regimens[19]. This is the first report of head-to-head studies of an all-oral, DAA(OBV/PTV/r+DSV+/-RBV) and a pegIFN-containing(TPV+pegIFN/RBV) regimen that quantitatively compares efficacy and safety benefits in treatment-naïve and treatment-experienced HCV GT1-infected patients.

As expected based upon results of previous trials, SVR_{12} rate was numerically higher with OBV/PTV/r+DSV+/-RBV than TPV+pegIFN/RBV regardless of subgenotype or prior treatment status[2, 9-13, 17]. The efficacy difference between the regimens persisted despite numerically higher SVR rates for TPV+pegIFN/RBV than previously reported[2, 13]. The higher SVR rates of TPV+pegIFN/RBV may be related to exclusion of cirrhotic patients and absence of black patients, who are less likely to respond to TPV+pegIFN/RBV, and improved management of adverse events associated with TPV-containing regimens by experienced healthcare providers[2, 17, 20, 21].

PRO assessments provide patients' perspective on the impact of treatment on daily life and work. PROs were evaluated using the SF-36v2 and WPAI-HCV instruments, which are standard PRO tools for general diseased and HCV-infected populations,

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475 respectively. In general, mean changes in SF-36v2 MCS and PCS scores from baseline
476 were numerically or significantly different between OBV/PTV/r+DSV+/-RBV and
477 TPV+pegIFN/RBV throughout the treatment period, with the difference indicating better
478 mental and physical health in patients receiving OBV/PTV/r+DSV+/-RBV. Decreases in
479 health-related quality of life through treatment week 12 and return to baseline after
480 treatment have previously been reported for patients receiving TPV+pegIFN/RBV[22].
481 The largest differences in mental and physical health between the two regimens were
482 observed at treatment week 12. SF-36v2 MCS in patients on all regimens and PCS
483 scores in patients on TPV+pegIFN/RBV were near baseline levels by post-treatment
484 week 12; improvement in PCS scores over baseline was observed as early as treatment
485 week 8 in patients on OBV/PTV/r+DSV+/-RBV. Similarly, mean changes in WPAI-HCV
486 scores indicate that patients receiving OBV/PTV/r+DSV+/-RBV were better able to
487 perform work during treatment than patients receiving TPV+pegIFN/RBV. These
488 findings indicating improved health-related quality of life in patients receiving an IFN-
489 free versus an IFN-containing regimen are consistent with previous reports examining
490 regimens separately[2, 23-26].

491 While PROs were evaluated using standard PRO tools for this population, these
492 analyses had limitations. The impact of knowledge of treatment efficacy on PRO
493 measures is not known, as there were no specific instructions to investigators on
494 informing patients of their virologic response before PRO questionnaire completion.
495 Furthermore, the studies were not specifically designed to assess the potential impact
496 of physiological differences(e.g. anemia associated with IFN or RBV use) on changes in
497 PRO measures.

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Safety data support better tolerability of OBV/PTV/r+DSV+/-RBV than TPV+pegIFN/RBV regardless of subgenotype or prior treatment status. Across groups of patients receiving OBV/PTV/r+DSV+/-RBV there were up to 4 adverse events with a frequency of>10% while across groups of patients receiving TPV+pegIFN/RBV there were up to 24 adverse events with a frequency of>10%, demonstrating the contrast in breadth of symptoms experienced by patients on the regimens. While the frequency of common adverse events was numerically higher with OBV/PTV/r+DSV+RBV than the RBV-free regimen in treatment-naïve GT1b-infected patients, OBV/PTV/r+DSV+RBV was well-tolerated and discontinuation due to adverse events was infrequent, consistent with previous reports[11].

The adverse event profile of RBV is being redefined in the era of pegIFN-free therapies. The numerically higher frequencies of adverse events such as anemia, nausea, pruritus, rash, insomnia, and asthenia in treatment-naïve patients receiving OBV/PTV/r+DSV+RBV versus the RBV-free regimen suggest that these are more likely associated with RBV use. Rates and severity of these adverse events were significantly lower with OBV/PTV/r+DSV+RBV versus TPV+pegIFN/RBV. Hemoglobin declines were less frequent and severe with OBV/PTV/r+DSV+RBV than TPV+pegIFN/RBV. The greater frequency and severity of anemia with the pegIFN-containing regimen may reflect bone marrow suppressant effects of IFN that prevent compensatory reticulocytosis[27, 28]. Hemoglobin declines in patients receiving OBV/PTV/r+DSV+RBV were managed by RBV dose modification alone while some patients receiving TPV+pegIFN required blood transfusion or erythropoietin. The high

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520 SVR_{12} rates among patients who reduced RBV are consistent with previous reports
521 indicating RBV reduction does not impact efficacy of either regimen[9-11, 13, 29].

522 The most common laboratory abnormality with OBV/PTV/r+DSV+/-RBV was a transient
523 elevation in bilirubin(predominantly indirect bilirubin), consistent with the known roles of
524 PTV as an inhibitor of the OATP1B1 and OATP1B3 transporters and RBV-induced
525 hemolysis[18, 30]. Alanine aminotransferase and bilirubin elevations observed with
526 OBV/PTV/r+DSV+/-RBV were infrequent and generally isolated abnormalities that
527 recovered without drug discontinuation, consistent with previous studies[10-12].

528 The trials were designed as open-label because the well-known adverse event profile of
529 TPV+pegIFN/RBV prevented effective blinding of investigators and patients. While the
530 open-label design may have influenced reporting of adverse events, it would not affect
531 objective endpoints such as SVR_{12} and laboratory abnormalities. Adverse event profiles
532 were consistent with those reported in blinded trials[2, 10, 11, 13, 17]. Because patients
533 in the United States had significant access to all-oral DAA therapies through clinical
534 trials at the time of enrollment, United States sites were not included. The trials were
535 limited by the exclusion of cirrhotic patients. The safety and efficacy of
536 OBV/PTV/r+DSV+RBV was previously characterized in a phase 3 trial dedicated to
537 patients with compensated cirrhosis(N=380); 12-24 weeks of treatment achieved SVR
538 rates of 92-97%[12]. In cirrhotic patients, TPV+pegIFN/RBV therapy generally has a
539 total duration of 48 weeks with reduced efficacy compared to non-cirrhotic patients[2, 3,
540 17]. Therefore, exclusion of cirrhotic patients should not change the general
541 conclusions.

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The treatment-experienced study was limited by the low number of GT1a-infected patients enrolled. This resulted from the dominance of GT1b infection in Europe, one of the major study locations. However, 96%(166/173) of GT1a-infected patients receiving 12 weeks of OBV/PTV/r+DSV+RBV achieved SVR_{12} in a phase 3 trial in non-cirrhotic, treatment-experienced patients in Australia, North America, and Europe[13]. Because phase 2 data were available for treatment-naïve but not treatment-experienced GT1b-infected patients receiving OBV/PTV/r+DSV without RBV at the time of study design, the treatment-experienced study did not include an arm with GT1b-infected patients receiving the RBV-free regimen[31]. More recently available phase 3 data demonstrated SVR_{12} rates of 100%(91/91) in treatment-experienced, GT1b-infected patients receiving a RBV-free OBV/PTV/r+DSV regimen[9].

In HCV GT1-infected patients without cirrhosis, all-oral 12-week combination regimens of OBV/PTV/r+DSV+/-RBV demonstrate SVR_{12} rates of 97-99%, while 12 weeks of TPV with 24-48 weeks of pegIFN/RBV achieves SVR_{12} rates of 66-82%. OBV/PTV/r+DSV+/-RBV is associated with generally better mental and physical health and tolerability, with lower rates of severe and serious adverse events and treatment discontinuation due to toxicity, compared to TPV+pegIFN/RBV. OBV/PTV/r+DSV+/-RBV represents a significant advancement over pegIFN-based regimens with first generation protease inhibitors. Taken together, data from the MALACHITE-I and –II studies support the preferential use of IFN-free regimens, where available, for the treatment of HCV infection in this patient population.

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669 Author names in bold designate shared co-first authorship.

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671 **Tables**

672 Table 1. Demographic and baseline characteristics.

	Treatment-naive(MALACHITE-I)					Treatment-experienced(MALACHITE-II)	
	Arm A OBV/PTV/r+DSV +RBV GT1a N=69	Arm B TPV +pegIFN/RBV GT1a N=34	Arm C OBV/PTV/r+DSV +RBV GT1b N=84	Arm D OBV/PTV/r+DSV GT1b N=83	Arm E TPV +pegIFN/RBV GT1b N=41	OBV/PTV/r+DSV +RBV N=101	TPV+ pegIFN/RBV N=47
Male sex	48(70%)	17(50%)	38(45%)	40(48%)	17(41%)	55(54%)	28(60%)
White race	62(90%)	30(88%)	80(95%)	82(99%)	38(93%)	101(100%)	47(100%)
Hispanic or Latino ethnicity	12(17%)	3(9%)	12(14%)	15(18%)	3(7%)	12(12%)	2(4%)
Age, years	46.1(12.3)	44.5(14.1)	46.2(11.3)	47.1(11.3)	45.9(10.8)	46.9(12.2)	45.0(10.4)
Body-mass index, kg/m^2	26.6(4.9)	25.8(3.6)	25.5(3.6)	25.4(4.0)	25.2(3.6)	25.9(4.0)	26.4(4.1)
HCV genotype 1a 1b	 69(100%) 0	 34(100%) 0	 0 84(100%)	 0 83(100%)	 0 41(100%)	 19(19%) 82(81%)	 7(15%) 40(85%)
IL28B genotype, non-CC	50(72%)	23(68%)	70(83%)	69(83%)	34(83%)	93(92%)	41(87%)
Fibrosis stage F0-F1 F2 ≥F3	 49(72%) 12(18%) 7(10%)	 24(71%) 7(21%) 3(9%)	 70(83%) 7(8%) 7(8%)	 60(72%) 11(13%) 12(14%)	 31(76%) 4(10%) 6(15%)	 79(78%) 17(17%) 5(5%)	 32(68%) 11(23%) 4(9%)
HCV RNA, log_{10} IU/mL	6.29(0.8)	6.37(0.8)	6.36(0.6)	6.33(0.6)	6.23(0.7)	6.37(0.50)	6.39(0.50)
Type of response to previous pegIFN/RBV treatment Relapse Partial response Null response	NA	NA	NA	NA	NA	 27(27%) 25(25%) 49(49%)	 12(26%) 12(26%) 23(49%)

673 Data are mean(SD) or n(%). OBV, ombitasvir; PTV, paritaprevir; DSV, dasabuvir; RBV,
674 ribavirin; TPV, telaprevir; pegIFN, peginterferon; NA, not applicable. Fibrosis stage was
675 assessed by liver biopsy scores, FibroScan scores, or FibroTest scores(Supplemental
676 Table 3). Fibrosis stage was missing for one treatment-naïve HCV GT1a-infected
677 patient receiving OBV/PTV/r+DSV+RBV.

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678 Table 2. Reasons for nonresponse.

	Treatment-naive(MALACHITE-I)					Treatment-experienced (MALACHITE-II)	
	Arm A OBV/PTV/r+DSV +RBV GT1a N=69	Arm B TPV +pegIFN/RBV GT1a N=34	Arm C OBV/PTV/r+DSV +RBV GT1b N=84	Arm D OBV/PTV/r+DSV GT1b N=83	Arm E TPV +pegIFN/RBV GT1b N=41	OBV/PTV/r+DSV +RBV N=101	TPV +pegIFN/RBV N=47
On-treatment failure	2/69, 3% (0-7)	2/34, 6% (0-14)	0 (0-4)	1/83, 1% (0-4)	5/41, 12% (2-22)	0 (0-4)	9/47, 19% (8-30)
Post-treatment relapse	0 (0-6)	0 (0-12)	1/84,* 1% (0-4)	0 (0-5)	2/32, 6% (0-15)	0 (0-4)	2/32, 6% (0-15)
Failure to achieve SVR12 due to other reasons†	0	4/34, 12%	0	1/83, 1%	2/41, 5%	1/101, 1%	5/47, 11%

679 Data are n/N, % (95% CI) or n/N, %. OBV, ombitasvir; PTV, paritaprevir; DSV,

680 dasabuvir; RBV, ribavirin; TPV, telaprevir; pegIFN, peginterferon, GT, genotype.

681 *This patient had GT2a infection upon recurrence of viremia, consistent with reinfection.

682 †Other reasons were missing SVR_{12} data or premature study drug discontinuation.

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684 Table 3. Numbers of patients with treatment-emergent adverse events.

	Treatment-naive(MALACHITE-I)			Treatment-experienced(MALACHITE-II)	
	Arm A+C OBV/PTV/r+DSV +RBV N=153	Arm D OBV/PTV/r+DSV N=83	Arm B+E TPV +pegIFN/RBV N=75	OBV/PTV/r+DSV +RBV N=101	TPV +pegIFN/RBV N=47
Any adverse event	115(75%)*	41(49%)*	74(99%)	63(62%)*	43(91%)
Severe adverse event	5(3%)*	0*	14(19%)	1(1%)	2(4%)
Moderate or severe adverse event	47(31%)*	13(16%)*	61(81%)	18(18%)*	34(72%)
Serious adverse event†	1(1%)*	0*	9(12%)	1(1%)*	5(11%)
Adverse event leading to discontinuation of study treatment‡	1(1%)*	0*	6(8%)	0*	5(11%)
Adverse events occurring in ≥20% of patients in any group					
Headache	41(27%)	16(19%)	23(31%)	29(29%)	21(45%)
Nausea	32(21%)*	7(8%)*	30(40%)	10(10%)*	20(43%)
Pruritus	19(12%)*	5(6%)*	26(35%)	13(13%)*	19(40%)
Fatigue	21(14%)*	4(5%)*	23(31%)	12(12%)	12(26%)
Anemia	10(7%)*	1(1%)*	34(45%)	3 (3%)*	16(34%)
Rash	12(8%)*	0*	17(23%)	3 (3%)*	12(26%)
Asthenia	11(7%)*	2(2%)*	15(20%)	8 (8%)*	16(34%)
Decreased appetite	6(4%)*	1(1%)*	17(23%)	3 (3%)*	8(17%)
Pyrexia	4(3%)*	2(2%)*	16(21%)	2 (2%)*	15(32%)
Anal pruritus	1(1%)*	0*	10(13%)	0*	12(26%)
Neutropenia	0*	0*	14(19%)	1 (1%)*	12(26%)
Cough	11(7%)	1(1%)*	9(12%)	7 (7%)*	12(26%)
Insomnia	14(9%)	0*	7(9%)	6 (6%)*	10(21%)
Post-baseline abnormalities in laboratory values					
Hemoglobin 8-<10 g/dL <8 g/dL	 2/153(1%) 1/53(1%)	 0/83 0/83	 32/74(43%) 3/74(4%)	 4/101 (4%) 0/101	 12/47(26%) 4/47(9%)
Alanine aminotransferase >5X ULN	1/153(1%)	0/83	0/74	1/101(1%)	3/47(6%)
Aspartate aminotransferase >5X ULN	1/153(1%)	1/83(1%)	0/74	1/101(1%)	1/47(2%)
Total bilirubin >3X ULN	6/153(4%)	0/83	2/74(3%)	1/101(1%)	1/47(2%)

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Data are n (%).ULN, upper limit of normal; OBV, ombitasvir; PTV, paritaprevir; DSV, dasabuvir; RBV, ribavirin; TPV, telaprevir; pegIFN, peginterferon. In treatment-naïve patients, the OBV/PTV/r+DSV+RBV group includes patients from arms A and C, the OBV/PTV/r+DSV group includes patients from arm D, and the TPV+pegIFN/RBV group includes patients from arms B and E. Adverse events occurring in $\geq$10% of patients in any group and additional data on laboratory values are in Supplemental Tables 7&8. *Statistically significant difference versus the TPV+pegIFN/RBV group of the same prior treatment status(P<0.05).

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693 **Figure Legends**

694 **Fig 1. Study designs.**

695 GT, genotype; OBV, ombitasvir; PTV, paritaprevir; DSV, dasabuvir; RBV, ribavirin; TPV,
696 telaprevir; pegIFN, peginterferon. Gray bars indicate post-treatment follow-up period.
697 Diamonds indicate time of SVR_{12} analysis.
698 *PegIFN/RBV was administered without TPV for an additional 12-36 weeks, per local
699 prescribing information.

700 **Fig. 2. SVR_{12} rates.**

701 OBV, ombitasvir; PTV, paritaprevir; DSV, dasabuvir; RBV, ribavirin; TPV, telaprevir;
702 pegIFN, peginterferon, GT, genotype. Bars indicate 95% confidence intervals.
703 *P* value shown for arm C versus E is based on logistic regression. *P* value shown for
704 arm D vs E is based on a stratum-adjusted Mantel Haenszel approach. SVR_{12} rate was
705 not compared between arms A and B by logistic regression analysis as the fixed-
706 sequence testing procedure concluded with the failure of the SF-36v2 MCS analysis in
707 GT1a-infected patients. In treatment-experienced patients *P* value is based on a logistic
708 regression.

709 **Fig. 3. Mean changes in SF-36v2 mental and physical component summary**
710 **scores from baseline to end of treatment and to post-treatment week 12.**
711 OBV, ombitasvir; PTV, paritaprevir; DSV, dasabuvir; RBV, ribavirin; TPV, telaprevir;
712 pegIFN, peginterferon; BL, baseline; EOT, end of treatment (final treatment visit);
713 PTW12, post-treatment week 12. Bars show mean scores at baseline (determined for
714 patients with end of treatment data), end of treatment, and post-treatment week 12.
715 Numbers over bars are mean changes (standard deviation). Mean changes and

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716 standard deviations for post-treatment week 12 are based on the baseline for patients
717 who had post-treatment week 12 data. Thus, in some cases, this baseline differs from
718 the baseline presented (for patients with end of treatment data), but does not impact the
719 interpretation. Analyses in all treatment-naïve patients were not pre-specified. Mean
720 change in PCS was not compared between arms A and B by logistic regression
721 analysis as the fixed-sequence testing procedure concluded with the failure of the SF-
722 36v2 MCS analysis in GT1a-infected patients.
723 *, **, *** indicates *P*<0.05, *P*<0.01 and *P*<0.001, respectively, for comparison to
724 TPV+pegIFN/RBV arm.

725 **Fig. 4. Mean changes from baseline during the treatment and post-treatment**
726 **periods in SF-36v2 mental and physical component summary scores.**
727 OBV, ombitasvir; PTV, paritaprevir; DSV, dasabuvir; RBV, ribavirin; TPV, telaprevir;
728 pegIFN, peginterferon; BL, baseline; W, treatment week; PTW, post-treatment week.

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Figure 1.

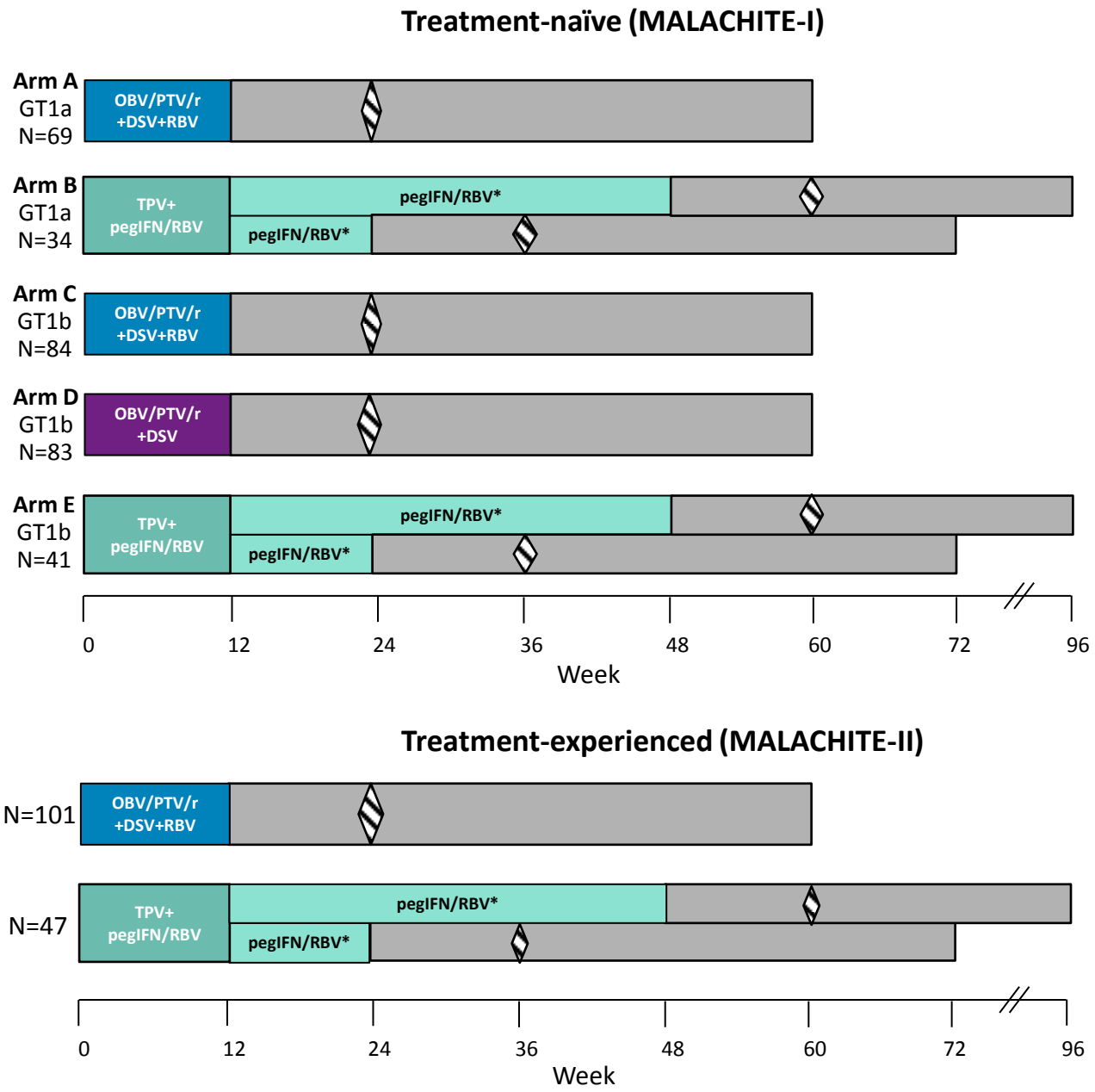

Treatment-naïve (MALACHITE-I)
Arm A
GT1a
N=69
OBV/PTV/r
+DSV+RBV
Arm B
GT1a
N=34
TPV+
pegIFN/RBV
pegIFN/RBV*
pegIFN/RBV*
Arm C
GT1b
N=84
OBV/PTV/r
+DSV+RBV
Arm D
GT1b
N=83
OBV/PTV/r
+DSV
Arm E
GT1b
N=41
TPV+
pegIFN/RBV
pegIFN/RBV*
pegIFN/RBV*
0
12
24
36
48
60
72
96
Week
Treatment-experienced (MALACHITE-II)
N=101
OBV/PTV/r
+DSV+RBV
N=47
TPV+
pegIFN/RBV
pegIFN/RBV*
pegIFN/RBV*
0
12
24
36
48
60
72
96
Week

Figure 2.

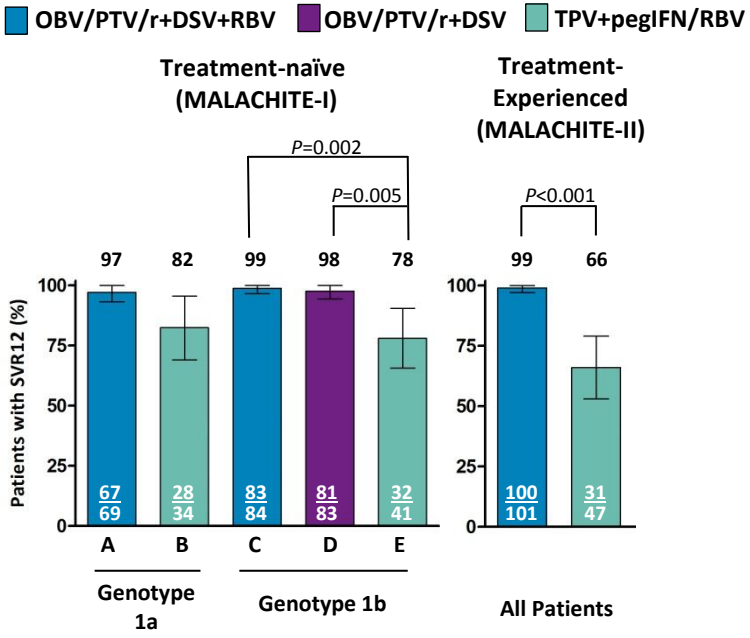

OBV/PTV/r+DSV+RBV
OBV/PTV/r+DSV
TPV+pegIFN/RBV
Treatment-naïve (MALACHITE-I)
Treatment-Experienced (MALACHITE-II)
P=0.002
P=0.005
P<0.001
97
82
99
98
78
99
66
Patients with SVR12 (%)
100
75
50
25
0
67/69
28/34
83/84
81/83
32/41
100/101
31/47
A
B
C
D
E
Genotype 1a
Genotype 1b
All Patients

Figure 3 (Revised).

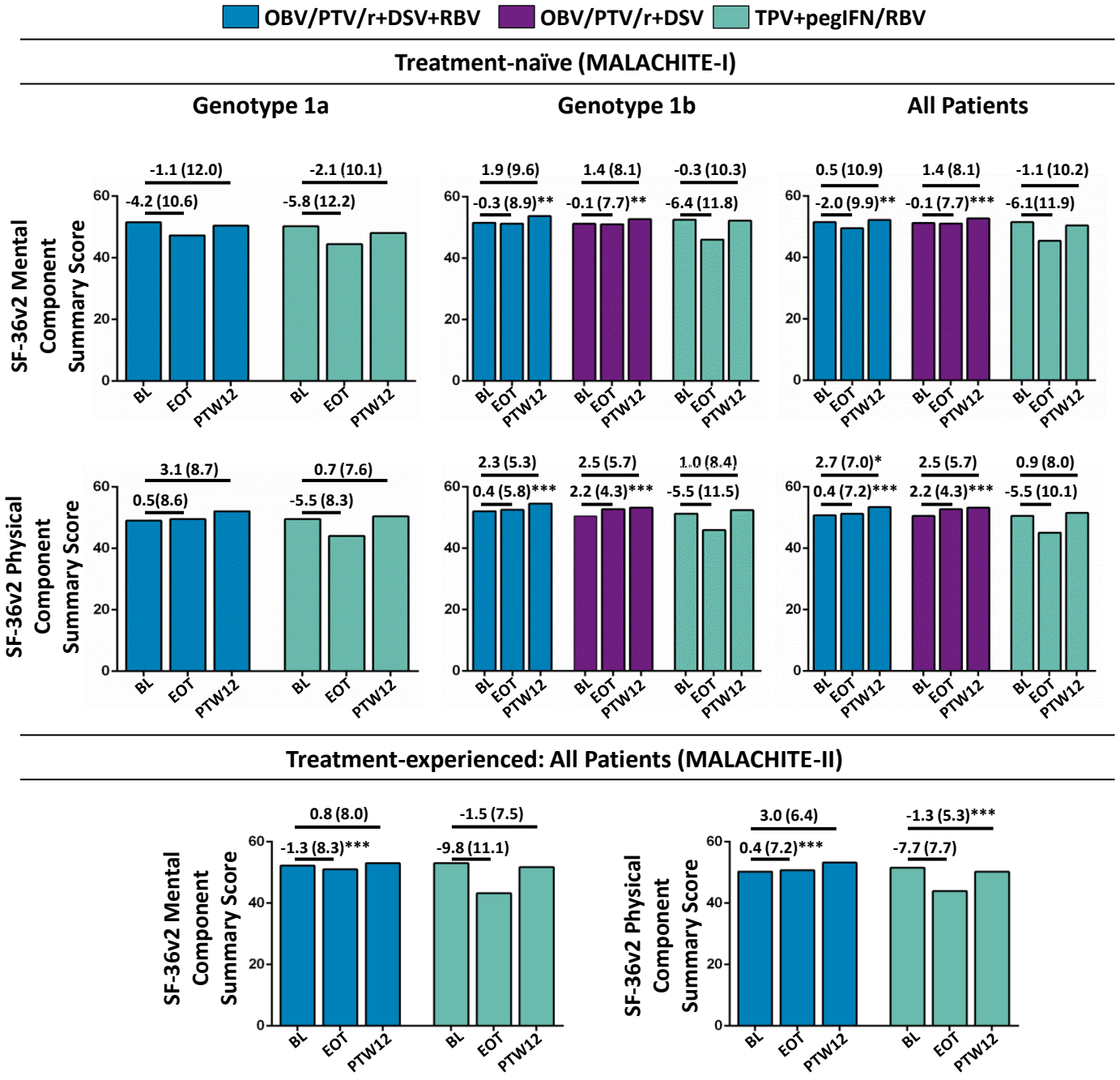
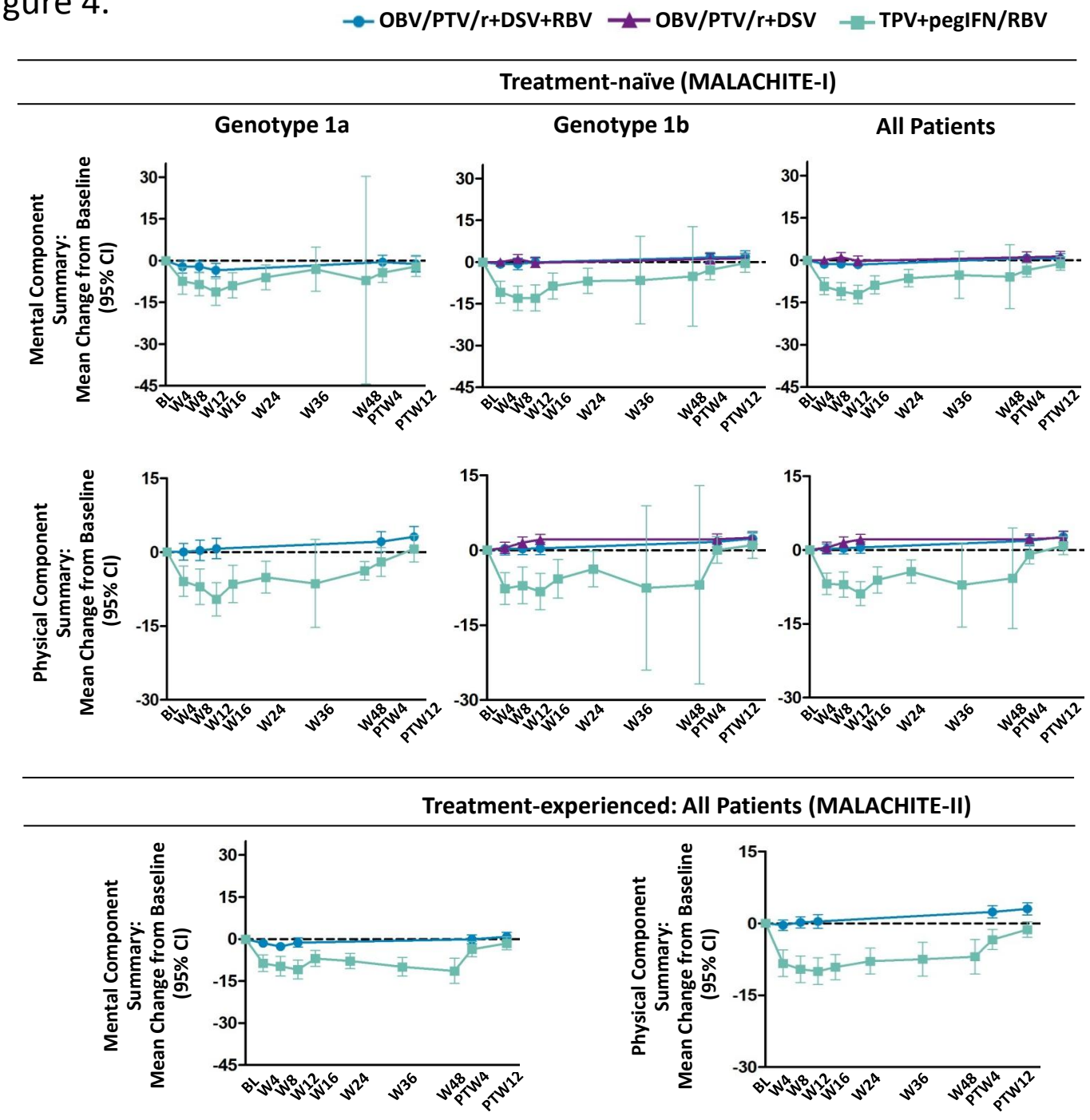


Figure 4.


OBV/PTV/r+DSV+RBV
OBV/PTV/r+DSV
TPV+pegIFN/RBV
Treatment-naïve (MALACHITE-I)
Genotype 1a
Genotype 1b
All Patients
Mental Component Summary: Mean Change from Baseline (95% CI)
Physical Component Summary: Mean Change from Baseline (95% CI)
BL W4 W8 W12 W16 W24 W36 W48 PTW4 PTW12
Treatment-experienced: All Patients (MALACHITE-II)