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A phase 3b study of sofosbuvir plus ribavirin in Taiwanese patients with chronic genotype 2 hepatitis C virus infection

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Abstract

Background & Aims: In Taiwan, patients with chronic hepatitis C virus (HCV) infection are currently treated with pegylated interferon-alpha plus ribavirin, but interferon-based regimens can be poorly tolerated, especially by those with advanced liver disease and the elderly. Sofosbuvir, an oral nucleotide analogue inhibitor of HCV NS5B polymerase, is approved in Europe, the USA and Japan for treating chronic HCV infection. This phase 3b study examined the efficacy and safety of sofosbuvir plus ribavirin in Taiwanese patients with chronic genotype 2 HCV infection ± compensated cirrhosis. *Methods:* In this multicentre, open-label, phase 3b (NCT02021643) study, 87 patients (n = 43, treatment-naive; n = 44, treatment-experienced) received 12 weeks of treatment with sofosbuvir plus weight-based ribavirin. The primary efficacy endpoint was the proportion of patients with sustained virological response 12 weeks after treatment discontinuation (SVR12). Safety and pharma-

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Abbreviations

AE, adverse event; AUC_{tau}, area under the plasma/serum concentration vs. time curve over the dosing interval; CI, confidence interval; CL/F, oral clearance; C_{max}, maximum concentration; C_{tau}, drug concentration at the end of the dosing interval; GLSM, geometric least-squares mean; HCV, hepatitis C virus; LLOQ, lower limit of quantitation; NS5B, nonstructural 5B; RAV, resistance-associated variant; RT-PCR, reverse transcription polymerase chain reaction; SVR, sustained virological response; ULN, upper limit of the normal range.

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cokinetic data were also collected. *Results:* All 87 patients (100%; 95% confidence interval, 92–100%) achieved SVR12, including the 13 patients with compensated cirrhosis. The most common treatment-emergent adverse events (AEs) were insomnia (16%, 14/87) and upper respiratory tract infection (16%, 14/87). No grade 3 or grade 4 AE was reported. There was one serious AE (biliary colic), which was deemed unrelated to study treatment. Laboratory abnormalities other than ribavirin-related reductions in haemoglobin were uncommon. *Conclusions:* The results from this phase 3b study demonstrate that 12 weeks of treatment with the interferon-free regimen sofosbuvir plus ribavirin is effective and well tolerated in both treatment-naive and treatment-experienced Taiwanese patients with chronic genotype 2 HCV infection.

Keywords
genotype 2 – hepatitis C virus (HCV) – ribavirin – sofosbuvir – Taiwan

Key points

- Interferon-based regimens, the standard of care for treating chronic HCV infection in many Asian countries including Taiwan, can be poorly tolerated
- Sofosbuvir, an oral nucleotide analogue inhibitor of HCV NS5B polymerase, is approved in Europe, the USA and Japan for treating chronic HCV infection
- In this phase 3b study, 12 weeks of sofosbuvir plus ribavirin resulted in an SVR12 rate of 100% in treatment-naive and treatment-experienced Taiwanese patients with chronic genotype 2 HCV infection ± compensated cirrhosis
- Sofosbuvir plus ribavirin, an interferon-free regimen, was well tolerated. No grade 3 or grade 4 AE was reported

In Taiwan, approximately 578 000 people are estimated to be chronically infected with the hepatitis C virus (HCV) (1). Community-based cohort studies in Taiwan have shown that individuals seropositive for HCV have a greater risk of developing hepatocellular carcinoma and of dying than individuals who are HCV-seronegative (2, 3). Genotype 2a is second only to genotype 1b in terms of seroprevalence, accounting for 32.7% of all HCV infections in Taiwan (4). The relative seroprevalence of genotype 2a HCV infection is inversely correlated to age, with an age-specific prevalence of 41.4% in those younger than 30 years and 23.0% in those older than 60 years (4).

The current standard-of-care regimen for treating chronic genotype 2 HCV infection in Taiwan is 24 weeks of once-weekly subcutaneous pegylated interferon-alpha plus daily oral ribavirin (5). Sustained virological response (SVR) rates to interferon-containing treatment regimens are higher in Taiwanese patients with chronic genotype 2 HCV infection than in those with chronic genotype 1 HCV infection (6, 7). While younger age has been associated with a more favourable response to pegylated interferon-alpha plus ribavirin in Taiwanese patients with chronic genotype 2 HCV infection (7), this may be a reflection of treatment adherence, for interferon-containing regimens can be poorly tolerated, especially by the elderly. In a prospective, case–control study of Taiwanese patients with chronic HCV infection, rates of dose modification and treatment discontinuation were significantly higher in patients aged at least 65 years vs. those aged 50–64 years (8, 9). Thus, treatment regimens that are not only effective but well tolerated are urgently needed in Taiwan for patients with chronic genotype 2 HCV infection.

Sofosbuvir, an oral nucleotide analogue inhibitor of HCV nonstructural 5B (NS5B) polymerase, is approved in the European Union, the USA and Japan. Sofosbuvir is indicated for the treatment of chronic genotype 1, 2, 3, 4, 5 or 6 HCV infection in Europe (10), chronic genotype 1, 2, 3 or 4 HCV infection in the USA (11), and chronic genotype 2 in Japan (12). In four Western phase 3 studies of sofosbuvir plus ribavirin administered for 12 weeks to patients with chronic genotype 2 HCV infection, sustained virological response 12 weeks after treatment discontinuation (SVR12) rates ranged from 86 to 97% (13–15). Moreover, in an open-label, phase 3 study undertaken in Japan, SVR12 rates following 12 weeks of treatment with sofosbuvir plus ribavirin in previously treatment-naive and treatment-experienced patients with chronic genotype 2 HCV infection were 98 and 95% respectively (12). Across these phase 3 studies, rates of treatment discontinuation due to adverse events (AEs) and the incidence of grade 3–4 AEs, serious AEs and laboratory abnormalities were low (12–15). In this report, we describe the results of a phase 3b study that examined the efficacy and safety of 12 weeks of treatment with sofosbuvir plus ribavirin in treatment-naive and treatment-experienced Taiwanese patients with chronic genotype 2 HCV infection ± compensated cirrhosis.

Patients and methods

Patients

Eligible patients were aged 20 years or older, with a body weight of at least 40 kg. Patients were required to have chronic genotype 2 HCV infection, with HCV RNA levels $\geq 10^4$ IU/ml at screening. Patients could have been either treatment-naive or treatment-experienced (see online supplement for definitions). Up to 20% of those enrolled could have had compensated cirrhosis

(Child-Pugh A). A patient was considered to have cirrhosis if liver biopsy showed cirrhosis (Metavir score 4 or Ishak score ≥5) or if FibroScan® (Echosens, Paris, France) indicated cirrhosis (value >12.5 kPa). For patients who did not have cirrhosis, further fibrosis staging was not protocol-specified; these patients could have had a fibrosis stage between Metavir F0–F3. Patients were also required to have alanine aminotransferase and aspartate aminotransferase levels ≤10× upper limit of the normal range (ULN), direct bilirubin levels ≤1.5× ULN, platelets counts ≥50 000 cells/μl, haemoglobin ≥12 g/dl for men and ≥11 g/dl for women, albumin levels ≥3 g/dl and creatinine clearance ≥50 ml/min per the Cockcroft–Gault equation (16). See online supplement for comprehensive inclusion/exclusion criteria.

Study design and treatment

This international, multicentre, open-label, phase 3b (ClinicalTrials.gov, NCT02021643) study was conducted in Korea, Taiwan, China, Hong Kong and Vietnam. The results from the 12 Taiwan study sites (Table S1) are reported here. Results from the Korean study sites have been published (17). Patients received 12 weeks of treatment with once-daily sofosbuvir 400 mg plus twice-daily, weight-based ribavirin (1000 or 1200 mg). The protocol was approved by the ethics committees/institutional review boards of participating centres and conformed to Good Clinical Practice guidelines and Declaration of Helsinki principles. All participants provided written informed consent.

Assessments and endpoints

Screening assessments included HCV RNA levels (Roche COBAS® TaqMan® HCV Test, version 2.0 for use with the High Pure System assay; Pleasanton, CA, USA), HCV genotype and subtype (Siemens VERSANT® HCV Genotype INNO-LiPA 2.0 Assay; Tarrytown, NY, USA), *IL28B* genotyping (rs12979860), and other standard laboratory and clinical tests, as measured by the central laboratories (Covance Central Laboratory Services, Inc. Indianapolis, IN, USA, and Covance [Asia] Pte Ltd., Singapore). The assessments performed at each visit are presented in Table S2. The primary efficacy endpoint was the proportion of patients with SVR12, which was defined as HCV RNA levels below the lower limit of quantitation (LLOQ, 25 IU/ml) 12 weeks after discontinuation of study treatment. All AEs were coded using the Medical Dictionary for Regulatory Activities, Version 17.0 (MedDRA, McLean, VA, USA).

For viral resistance monitoring, the coding regions of HCV NS5B were amplified by DDL Diagnostic Laboratory (Rijswijk, Netherlands) using standard reverse transcription polymerase chain reaction (RT-PCR) on a subgroup of study participants ($n = 62$) for whom HCV subtype could not fully be assigned by the screening LiPA assay. RT-PCR products were then deep sequenced by DDL Diagnostic Laboratory using the Illumina MiSeq® Platform (Illumina, San Diego, CA, USA). The threshold for detecting resistance-associated variants (RAVs) was 1%.

For the pharmacokinetic analyses, a single blood sample was collected from all patients at weeks 1, 2, 4, 6, 8, 10 and 12 and at the early termination visit (if applicable). Plasma concentrations of sofosbuvir and the sofosbuvir metabolite GS-331007 were determined by QPS, Inc. (Newark, DE, USA) using fully validated high-performance liquid chromatography/tandem mass spectrometry bioanalytical methods (data on file). Pharmacokinetic parameters including maximum concentration (C_{max}), area under the plasma/serum concentration vs. time curve over the dosing interval (AUC_{tau}), and drug concentration at the end of the dosing interval (C_{tau}) in genotype 2 HCV-infected Taiwanese patients were estimated using established population pharmacokinetic models and compared with the phase 2/3 population of HCV-infected patients used to support the New Drug Application for sofosbuvir in the USA. Pharmacokinetic equivalence in exposure was concluded if the 90% confidence interval (CI) for the geometric least-squares mean (GLSM) ratio remained within the bounds of 70–143%. The effects of intrinsic factors on pharmacokinetic exposures were also evaluated.

Statistics

The efficacy and safety analyses included all patients who received at least one dose of study drug. For the efficacy analysis, data were analysed for the total patient cohort and by prior treatment experience (treatment-naive or treatment-experienced). Point estimates with two-sided, 95% exact CIs using the binomial distribution (18) were constructed for SVR12 rates. For the safety analysis, data from all study participants were grouped together and summarised using descriptive statistics. The pharmacokinetic analysis dataset was composed of all patients who received at least one dose of study drug and had analyte concentration data available.

Results

Patients

Of the 102 patients screened in Taiwan, 87 (treatment-naive, $n = 43$; treatment-experienced, $n = 44$) were enrolled between December 25, 2013 and March 11, 2014. Of the 15 patients who failed screening, seven did not meet protocol-specified laboratory thresholds, five did not have definitive genotype 1, 2, 3 or 6 HCV infection, two had HCV RNA levels $\geq 10^4$ IU/ml, one was co-infected with HBV or HIV, and one was using prohibited concomitant medications (patients could have violated ≥1 inclusion/exclusion criterion). All enrolled patients completed study treatment and the post-treatment visit at Week 12. All patients were Taiwanese (100%), and 59% were female. The mean age was

Table 1. Baseline demographics and disease characteristics

Characteristic	Treatment-naive (n = 43)	Treatment-experienced (n = 44)	Total (N = 87)
Mean age (range), yrs	53 (22–73)	54 (29–71)	53 (22–73)
Age ≥65 yrs, *n* (%)	8 (19)	5 (11)	13 (15)
Male, *n* (%)	12 (28)	24 (55)	36 (41)
Taiwanese, *n* (%)	43 (100)	44 (100)	87 (100)
Mean BMI (range), kg/m^2	24 (18–32)	27 (21–37)	25 (18–37)
BMI ≥25 kg/m^2, *n* (%)	20 (47)	28 (64)	48 (55)
HCV genotype*, *n* (%)			
2a	30 (70)	27 (61)	57 (66)
2b	13 (30)	17 (39)	30 (34)
Cirrhosis, *n* (%)	4 (9)	9 (20)	13 (15)
IL28B genotype (rs12979860), *n* (%)			
CC	37 (86)	40 (91)	77 (89)
CT	6 (14)	3 (7)	9 (10)
TT	0 (0)	1 (2)	1 (1)
HCV RNA			
Mean (SD), $\log_{10}$ IU/ml	6.0 (1.01)	6.8 (0.51)	6.4 (0.91)
≥800 000 IU/ml, *n* (%)	24 (56)	43 (98)	67 (77)
ALT >1.5× ULN, *n* (%)	20 (47)	18 (41)	38 (44)
Mean platelet count (range), ×10^3/μl	202 (90–365)	186 (60–305)	194 (60–365)
Mean neutrophil count (range), ×10^3/μl	2.91 (1.66–4.94)	3.20 (1.15–7.38)	3.06 (1.15–7.38)
Mean estimated GFR (range), ml/min†	99 (59–177)	102 (66–158)	101 (59–177)
Interferon eligibility status‡, *n* (%)			
Eligible	24 (56)	N/A	24/43 (56)
Ineligible	0 (0)	N/A	0/43 (0)
Unwilling	19 (44)	N/A	19/43 (44)
Response to prior HCV treatment§, *n* (%)			
Relapse/breakthrough	N/A	30 (68)	30/44 (68)
Nonresponder	N/A	12 (27)	12/44 (27)
Interferon-intolerant	N/A	2 (5)	2/44 (5)

ALT, alanine aminotransferase; BMI, body mass index; GFR, glomerular filtration rate; HCV, hepatitis C virus; N/A, not applicable; SD, standard deviation; ULN, upper limit of normal.

*Subtypes that were unable to be differentiated by the VERSANT® HCV Genotype Assay (Version 2 [LiPA 2.0]) underwent sequence analysis of baseline samples; combined results for the LiPA 2.0 and sequencing analyses are reported.

†Per the Cockcroft–Gault equation (16).

‡Interferon eligibility was reported for treatment-naive patients.

§Response to prior HCV treatment was reported for treatment-experienced patients.

53 years (range, 22–73 years), with 15% aged 65 years or older. Most patients were infected with genotype 2a HCV (66%), had viral loads of 800 000 IU/ml or higher (77%), and had the *IL28B* CC genotype (89%). A total of 15% of patients had compensated cirrhosis at baseline (Table 1). Compared with treatment-naive patients, more treatment-experienced patients were male (55% vs 28%), younger than 65 years (89% vs 81%), and had a body mass index (BMI) of at least 25 kg/m^2 (64% vs 47%), compensated cirrhosis (20% vs 9%), and baseline HCV RNA levels of at least 800 000 IU/ml (98% vs 56%) (Table 1).

Efficacy

All 87 patients (100%; 95% CI, 92–100%) achieved SVR12 (Table 2), including the four treatment-naive and nine treatment-experienced patients with compensated cirrhosis at baseline. Since all patients achieved SVR12, it was not possible to determine the relationship (if any) between on-treatment viral kinetics and achieving SVR12 (Table 2). Although of limited value (because all patients achieved SVR12), response rates in clinically relevant patient subgroups, including those stratified by age (<65 years vs ≥65 years) and *IL28B* genotype, are presented in Table S3.

Virology

Deep-sequencing data were obtained for 62 of the 87 patients for whom HCV subtype was not fully determined by the LiPA assay at screening. No HCV nucleoside inhibitor resistance-associated variants (L159F, S282T or V321A) in NS5B were detected in any of the 62 study participants with available sequencing data at baseline.

Safety

In total, 75% of patients experienced at least one AE during this study (Table 3), and 34% had a treatment-

Table 2. Response during and after treatment with sofosbuvir plus ribavirin

Response	Treatment-naive	Treatment-experienced	Total
HCV RNA <LLOQ*			
During treatment, *n/N* (%) 95% CI			
At week 2	43/43 (100)	35/44 (80)	78/87 (90)
	92–100	65–90	81–95
At week 4	43/43 (100)	44/44 (100)	87/87 (100)
	92–100	92–100	96–100
At week 12	43/43 (100)	44/44 (100)	87/87 (100)
	92–100	92–100	96–100
Post-treatment, *n/N* (%) 95% CI			
At week 4	43/43 (100)	44/44 (100)	87/87 (100)
	92–100	92–100	96–100
At week 12	43/43 (100)	44/44 (100)	87/87 (100)
	92–100	92–100	96–100
On-treatment virological failure, *n*	0	0	0
Relapse, *n*	0	0	0

CI, confidence interval; HCV, hepatitis C virus; LLOQ, lower limit of quantitation.

*The LLOQ was 25 IU/ml.

Table 3. Treatment-emergent AE frequency and severity

Patients, *n* (%)	Total (*N* = 87)
Any treatment-emergent AE	65 (75)
Treatment-related AE	30 (34)
Any-grade AE reported in ≥5% of patients	
Insomnia	14 (16)
Upper respiratory tract infection	14 (16)
Pruritus	12 (14)
Cough	9 (10)
Fatigue	9 (10)
Rash	9 (10)
Headache	7 (8)
Dizziness	7 (8)
Grade 3 or 4 AE	0 (0)
Serious AE	1 (1)*
AE leading to permanent discontinuation of study drug	0 (0)
AE leading to interruption of sofosbuvir	1 (1)†
Death	0 (0)

AE, adverse event.

*One patient experienced biliary colic.

†One patient experienced toothache, which led to an interruption in treatment with sofosbuvir (and ribavirin).

related AE. The most common treatment-emergent AEs were insomnia (16%) and upper respiratory tract infection (16%). All AEs were mild or moderate; no grade 3 or grade 4 AE was reported. One patient reported a serious AE (biliary colic) that was considered by the investigator to be unrelated to study treatment. Four (5%) patients experienced grade 3 laboratory abnormalities, all of which were grade 3 decreases in haemoglobin. One patient had a post-baseline absolute haemoglobin value <10 g/dl, and none had a post-baseline absolute haemoglobin value <8.5 g/dl. Ribavirin dose was reduced only in the patient with a post-baseline absolute haemoglobin value <10 g/dl. All four patients with grade 3 laboratory abnormalities continued treatment with sofosbuvir, and haemoglobin levels rebounded in the post-treatment period. One (1%) additional study participant, who had low neutrophil levels at baseline (1.15×10^3/μl), experienced grade 4 neutrophil count decrease.

Pharmacokinetics

Pharmacokinetic data were available from all 87 study participants. Exposures to sofosbuvir and GS-331007 in the present cohort were within the pharmacokinetic equivalence boundaries for the population of phase 2/3 study participants used to support the New Drug Application for sofosbuvir in the USA (Table S4). Subgroup analyses showed that creatinine clearance was the only statistically significant intrinsic covariate to affect the oral clearance (CL/F) of GS-331007, which is renally excreted (Table S5). The creatinine clearance of GS-331007 was inversely correlated with the AUC_{tau} and C_{max} of GS-331007, which decreased by approximately 30 and 19% respectively. These decreases in exposure were not considered clinically relevant. Creatinine clearance did not affect the CL/F of sofosbuvir, which is not eliminated via the kidneys. No other intrinsic covariate examined affected exposures to sofosbuvir or GS-331007 (Table S5).

Discussion

In this multicentre, open-label, phase 3b study, all 87 Taiwanese patients achieved SVR12 following 12 weeks of treatment with sofosbuvir plus weight-based ribavirin. The 100% SVR12 rate is comparable with rates reported in the phase 3 study undertaken in Japan and in the Korean cohort of this study, where overall SVR12 rates of 97% were reported (12, 17). In phase 3 studies of Western patients with chronic genotype 2 HCV infection, responses to 12 weeks of treatment with sofosbuvir plus ribavirin were numerically lower, with SVR12 rates ranging from 86 to 97% (13–15). The numerical difference in SVR12 rates between Asian and Western patients may be attributable to the more favourable baseline and disease characteristics of Asian patients, including younger age, lower BMI and predominance of CC *IL28B* alleles (19–24).

Cirrhosis has been found to adversely impact responses to pegylated interferon-alpha plus ribavirin (19). Although only 13 patients in this study had compensated cirrhosis at baseline, all achieved SVR12 following treatment with sofosbuvir plus ribavirin. Additional studies are needed to determine if response rates differ in Taiwanese vs. Western patients with chronic genotype 2 HCV infection and cirrhosis.

The interferon-free regimen of sofosbuvir plus ribavirin was well tolerated by Taiwanese patients: none prematurely discontinued sofosbuvir plus ribavirin and no grade 3–4 or treatment-related serious AEs were reported. No patient in the present Taiwanese cohort prematurely discontinued sofosbuvir plus ribavirin, consistent with the low rates of treatment discontinuation in the Western studies and in the Korean cohort of patients recruited to the present study (13–15, 17); no patient participating in the phase 3 Japanese study discontinued treatment due to an AE (12). Moreover, no new safety signals were seen by longer treatment duration. The BOSON study, which recruited Western patients, examined the safety and efficacy of up to 24 weeks of treatment with sofosbuvir plus ribavirin in treatment-experienced patients with chronic genotype 2 HCV infection and cirrhosis ($n = 32$) and treatment-naïve or treatment-experienced patients with genotype 3 HCV infection ($n = 363$); the safety profile of sofosbuvir plus ribavirin was similar in treatment-naïve and treatment-experienced patients (25).

Haemoglobin reductions were the only laboratory abnormality reported in more than one patient and were managed appropriately with ribavirin dose reduction in accordance with the prescribing information (26). The most common AEs were insomnia (16%), which is common with treatment with ribavirin (26), and upper respiratory tract infection (16%). The incidence of upper respiratory infection was higher than rates reported in the Korean cohort of this study (<5%) (17); the VALENCE (<10%), POSITRON (<10%), FUSION (<10%) and FISSION (<15%) studies of Western patients (12–15); and the Japanese phase 3 study (<5%) (12). This study was conducted in the winter months, which may account for the increased prevalence of upper respiratory tract infection. Slightly more Taiwanese than Korean patients participating in the present phase 3b study experienced at least one AE (75% vs 68%) (17). However, headache, an AE associated with sofosbuvir (10, 11), occurred at lower frequency in the Taiwanese vs. Korean cohort (8% vs 18%) (17).

To conclude, we found 12 weeks of treatment with sofosbuvir plus ribavirin to be effective and well tolerated in both treatment-naive and treatment-experienced Taiwanese patients with chronic genotype 2 HCV infection with or without cirrhosis. The results from this study supported the 2015 approval of sofosbuvir (SOVALDI®) in Taiwan. Sofosbuvir, when administered with ribavirin, is the first highly effective and well tolerated interferon-free treatment regimen available to patients with chronic genotype 2 HCV infection. Importantly, this regimen provides patients who are unable to use or who have failed prior interferon-based therapy with an option for treatment.

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Conflict of interest: J-HK has served as a consultant for Abbott, AbbVie, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Johnson & Johnson, Merck Sharp & Dohme, Novartis, and Roche. He has also served on speaker's bureaus for Abbott, Roche, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, and Novartis. R-NC has served as an advisory committee member for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Johnson & Johnson, Merck Sharpe & Dohme, Novartis, and F. Hoffmann-La Roche. He has also served on speaker's bureaus for Bristol-Myers Squibb, Gilead Sciences, Merck Sharpe & Dohme, Roche and Novartis. T-TC, T-HH, G-HL, H-YW, J-JC, I-SS, Y-CH and C-JC have nothing to disclose. C-YP has served as an advisory committee member for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Merck Sharpe & Dohme, and F. Hoffmann-La Roche. JCY, SJK, LH, HM, AM and DMB are employees of Gilead Sciences, Inc. W-LC has served as an advisory board member for Gilead Sciences, AbbVie, and F. Hoffmann La-Roche. He has also served on speaker's bureaus for Gilead Sciences, Bristol-Myers Squibb, Merck Sharpe & Dohme, F. Hoffmann-La Roche, and Novartis.

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Supporting information

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