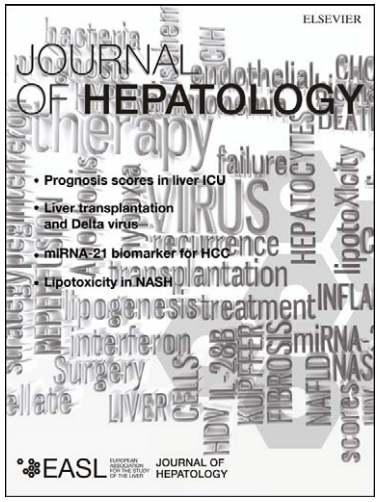

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Antiviral activity of TMC435 monotherapy in patients infected with HCV genotypes 2 to 6: TMC435-C202, a phase IIa, open-label study

(112/130 characters)

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Abbreviations:

HCV, hepatitis C virus; PegIFN, peginterferon; RBV, weight-based ribavirin; SVR, sustained virologic response; AE, adverse event; DAA, direct-acting antiviral; *q.d.*, once daily; RVR, rapid virologic response; IC, inhibitory concentration; ECG, electrocardiogram; t_{max}, time to reach the maximum plasma concentration; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; C_{0h}, pre-dose plasma concentration; AUC_{24h}, area under the plasma concentration-time curve from time of administration up to 24 hours post-dosing; SE, standard error; CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

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Conflict of interest:

C. Moreno was paid for speaking at symposia by Bristol-Myers Squibb and Schering-Plough; is an investigator for Boehringer, Gilead Sciences, Janssen, Novartis, Roche and Schering-Plough; received a research grant from Roche and Schering-Plough; is an adviser for Bristol-Myers Squibb, Janssen and Schering-Plough; and is a consultant for Janssen and Schering-Plough.

T. Berg is a member of advisory boards and/or speaker for Abbott, Bristol-Myers Squibb, Boehringer, Gilead, Janssen/Tibotec, Merck, Novartis, Roche/Genentech and Vertex.

T. Tanwandee is an investigator for Janssen/Tibotec, Merck Sharp & Dohme, Novartis and Roche.

S. Zeuzem is a consultant for Abbott, Achillion, Anadys, Bristol-Myers Squibb, Boehringer, Gilead, iTherX, Janssen/Tibotec, Merck, Novartis, Pharmasset, Pfizer, Roche/Genentech, Santaris and Vertex.

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Abstract (250/250 words)

Background & Aims

TMC435 is an investigational, once-daily, oral NS3/4A protease inhibitor currently in phase III development for the treatment of hepatitis C virus (HCV) infection. Phase I and II studies in patients infected with HCV genotype 1 have demonstrated that TMC435 is generally well tolerated, has a pharmacokinetic profile that supports once daily dosing, and demonstrates potent antiviral activity. This phase IIa study (TMC435-C202; NCT00812331) was conducted to investigate the antiviral activity, safety, tolerability, and pharmacokinetics of TMC435 in treatment-naïve patients infected with HCV genotypes 2 to 6.

Methods

The study consisted of 7 days of monotherapy with TMC435 (200 mg once daily). Patients could begin treatment with pegylated interferon/ribavirin from Day 8 with a follow-up period up to Days 37–42.

Results

Thirty-seven patients were enrolled in Germany, Belgium and Thailand. For the primary endpoint at Day 8, the mean (±standard error) change in plasma HCV ribonucleic acid (log_{10} IU/mL) from baseline was greatest for genotypes 6 (-4.35±0.29) and 4 (-3.52±0.43), followed by genotypes 2 (-2.73±0.71) and 5 (-2.19±0.39). No antiviral activity was evident for genotype 3. Viral breakthrough occurred in six patients during the monotherapy phase and in six additional patients

during PegIFN/RBV-only period. All adverse events were mild or moderate and there were no discontinuations during the TMC435 monotherapy period.

Conclusions

The results of this phase IIa proof-of-concept trial provide evidence that TMC435 has a spectrum of activity against multiple HCV genotypes, except for genotype 3. In this study, TMC435 was generally safe and well tolerated.

Keywords: HCV, TMC435, genotype, antiviral, monotherapy

1. Introduction

The hepatitis C virus (HCV) is a single-stranded RNA virus and one of the leading causes of chronic liver disease worldwide [1]. It is estimated that 130–170 million people are infected with HCV, constituting 2.2-3.0% of the global population [2].

HCV can be classified into six major genotypes based on sequence divergence of 30% [3]. Genotype 1 has a broad global distribution [4–10]. Genotype 2 is prevalent in North America, Europe and Japan (subtypes 2a and 2b), Northern Italy (2c) [11], and Western Africa [12]. Genotype 3 is noted for its wide distribution among intravenous drug users in a number of countries [13–15], and is also predominant in India and Pakistan [16]. Genotype 4 is responsible for >90% of HCV infections in Egypt, where it is associated with the re-use of needles during mass administration of parenteral antischistosomal therapy until the 1980s, and is also prevalent in other regions of the Middle East and sub-Saharan Africa [3,17–19]. In Europe, its prevalence has recently increased due to immigration and transmission between intravenous drug users [17]. Genotype 5 is found most commonly in South Africa, as well as in four regions in France, Spain, Syria and Belgium [3,17]. Genotype 6 is found in South East Asia and surrounding regions where overall HCV prevalence is high [3,20,21].

Recommended treatment for patients infected with non-genotype 1 HCV is pegylated interferon and ribavirin (PegIFN/RBV). Treatment for different genotypes differs slightly, with PegIFN alpha (α) plus weight-based RBV for 48 weeks recommended for genotypes 1, 4 and 6, and PegIFNα plus low-dose RBV (800 mg) for 24 weeks for genotypes 2 and 3 [22–27]. Of note, given the recent approval of the HCV NS3/4A protease inhibitors boceprevir and telaprevir [28,29] the standard of care for genotype 1 is expected to change [27,30].

Sustained virologic response (SVR, undetectable HCV RNA in patient plasma 24 weeks after treatment end) is achieved in approximately 75% of patients infected with genotypes 2 and 3 [31]. Rates with genotypes 4, 5 or 6 are 43–70% [17]. Furthermore, PegIFN/RBV therapy is poorly tolerated in some patients. In randomised trials of PegIFNα/RBV, influenza-like and neuropsychiatric symptoms occurred in up to 24–64% of patients [22,32], adverse events (AEs) led to study discontinuation in 14–32% and dose reduction in 11–42% [22,32], and anemia or neutropenia led to dose reduction in 9-22% and 18–20%, respectively [22,32].

It is, therefore, clear that novel direct-acting antivirals (DAAs) are required to address issues of sub-optimal efficacy, poor tolerability and compliance failures, and to reduce treatment duration. Boceprevir and telaprevir have demonstrated significantly improved virologic outcomes in both treatment-naïve and -experienced genotype 1 patients [28,29]. However, their thrice daily dosing schedule (with food) and increased rates of AEs including anemia and rash, in comparison to PegIFN/RBV, suggest that there is still room for improvement. Furthermore, activity in other genotypes has not been extensively investigated.

TMC435 is an investigational, once-daily oral NS3/4A protease inhibitor currently in phase III clinical development for the treatment of HCV infection. Phase I and II trials in patients infected with HCV genotype 1 have demonstrated that TMC435 is generally well tolerated, has a pharmacokinetic profile that supports once daily (*q.d.*) dosing, and demonstrates potent antiviral activity and efficacy [33–36].

Given sub-optimal responses to existing treatment options and the worldwide distribution of genotype 1, this genotype is the current focus of the TMC435 clinical development program. A phase IIa study (TMC435-C202; NCT00812331) was also

performed in patients infected with genotypes 2 to 6 to assess the antiviral activity of TMC435 against these genotypes. Data from biochemical protease assays available before the study start indicated that TMC435 is a potent NS3/4A protease inhibitor in genotypes 2, 4, 5 and 6, with a medium inhibitory concentration (IC_{50}) of <13 nM for all HCV NS3/4A enzymes tested [37]. IC_{50} for genotype 3 was 37 nM [37]. This study assessed antiviral activity, safety, tolerability and pharmacokinetics of TMC435 (200 mg *q.d.* administered for 7 days as monotherapy) in treatment-naïve patients infected with HCV genotypes 2 to 6.

2. Patients and methods

2.1 Patient population

The study was conducted in treatment-naïve patients infected with HCV genotypes 2 to 6. HCV genotype was determined using Trugene, Versant LIPAv2 and/or NS5B sequence-based assays. Patients were male or female, aged 18–70 years old, with documented chronic genotype 2 to 6 HCV infection, with or without cirrhosis (up to Child Pugh A liver disease), and an HCV RNA level of ≥100,000 IU/mL at screening. Staging of fibrosis/cirrhosis was performed according to nationally accepted procedures including Metavir score, fibroscan and fibrotest.

Exclusion criteria included prior treatment (including investigational treatment) for HCV infection; evidence of decompensated liver disease defined as a prior or current history of ascites, hepatic encephalopathy, oesophageal or gastric varices; drug- or alcohol-related cirrhosis; co-infection with hepatitis A or B, HIV-1 or HIV-2; or active tuberculosis at screening.

2.2 Study design

The open-label proof-of-concept study was performed by 12 investigators in three countries (Belgium, Germany and Thailand). The target number of patients to be included in the trial was eight patients of each HCV genotype. Patients were categorised by genotype into five cohorts, and TMC435 (200 mg *q.d.*) was administered to each patient for 7 days as monotherapy (Fig. 1). Patients could begin treatment with PegIFN/RBV from Day 8 onwards, as decided by the patient and their treating physician. There was a follow-up period up to Day 42 (35 days after the last TMC435 administration) which included two specific time points for assessment:

follow-up 1 (Day 21) and follow-up 2 (Days 37–42). Patients participating in the study were not hospitalised, either for enrolment or for therapy.

A 200 mg dose was selected as this was the highest dose previously administered to patients infected with HCV genotype 1 in the TMC435-C201 trial [35], had previously exhibited a good safety and tolerability profile, and also maximised the potential for antiviral activity across all genotypes.

2.3 Antiviral activity

Serum samples were obtained at baseline, pre-TMC435 dose Days 1–11, follow-up 1 and follow-up 2. HCV RNA levels were quantified using a COBAS Taqman HCV v2 assay (linear range from 25 to 391,000,000 IU/mL with a limit of quantification of 25 IU/mL).

The primary endpoint was change from baseline in HCV RNA at Day 8. Secondary efficacy endpoints included change from baseline in HCV RNA at other time points during the monotherapy period, the proportion of patients with HCV RNAbelow the lower limit of quantification (<25 IU/mL) but with traces of HCV RNA detectable at all time points, the proportion of patients with HCV RNA <25 IU/mL undetectable at all time points, and the proportion of patients experiencing viral breakthrough (defined as >1 $\log_{10}$ IU/mL increase in HCV RNA level from nadir, or >100 IU/mL in those with a prior HCV RNA level of <25 IU/mL undetectable).

Viral breakthrough was defined as an increase >1 $\log_{10}$ IU/mL in plasma HCV RNA concentration from the lowest reached, or HCV RNA >100 IU/mL in patients whose HCV RNA was previously <25 IU/mL undetectable or detectable.

2.4 Safety and tolerability

AEs, defined as any untoward medical occurrence in a patient participating in the study that does not necessarily have a causal relationship with the treatment, were recorded throughout the study. All AEs were followed until values returned to baseline or stabilisation occurred. Vital signs, electrocardiogram (ECG) recordings and clinical laboratory tests were performed up to 2 hours pre-dose on Days 1, 7, 8 and at follow-up 2. In the German study centre, additional ECG assessments were performed 6 hours post-dose on Days 1 and 7 (protocol amendment).

2.5 Pharmacokinetics

Blood samples were taken up to 96 hours post-dose following seven days of TMC435 dosing to determine TMC435 steady-state plasma pharmacokinetics. Pharmacokinetic analysis was performed using non-compartmental methods using the WinNonlin Professional^{TM} (Version 4.1; Pharsight Corporation, Mountain View, CA, USA). Calculated parameters included time to reach the maximum plasma concentration (t_{max}), maximum plasma concentration (C_{max}), minimum plasma concentration (C_{min}), pre-dose plasma concentration (C_{0h}) and area under the plasma concentration-time curve from time of administration up to 24 hours post-dosing (AUC_{24h}).

2.6 Statistical analysis

Demographic, antiviral activity, virology, and safety and tolerability data were summarised using descriptive statistics and frequency tabulation. Previous trials indicate that residual error on change from baseline in plasma HCV RNA is unlikely to be >1. Assuming a residual error of 1 and a 2-sided significance level of 5%, a comparison of eight patients receiving TMC435 treatment per genotype cohort had

90% power to detect a difference of 1.8 $\log_{10}$. Increased power was obtained when change in HCV RNA per genotype cohort was compared with baseline. A total of eight patients was sufficient to detect a difference with baseline of 1.3 $\log_{10}$.

3. Results

3.1 Patient demographics and baseline characteristics

The trial was conducted from 3 March to 18 November 2009. A total of 37 patients were enrolled (Fig. 1) across Germany, Belgium and Thailand. No major differences in demographics and baseline disease characteristics were observed, except that all patients with genotype 6 were Asian, and median age of patients with genotype 5 was higher compared with other genotype cohorts (Supplementary Table 1). Overall, 11% of patients in the study had cirrhosis (Metavir score F4), including patients infected with genotype 2 (n=1), genotype 3 (n=1) and genotype 5 (n=2). Multiple subtypes were included in cohorts for genotype 2 (2b, 2c, 2i, 2k), genotype 4 (4, 4c, 4d) and genotype 6 (6a, 6c-l, 6j, 6n) (Table 1).

Following the 7-day TMC435 treatment period, all patients started PegIFN/RBV therapy. Thirty-one patients began PegIFN/RBV on Day 8 or 9, whereas one patient with genotype 3 and five with genotype 6 began PegIFN/RBV after Day 9.

3.2 Antiviral activity

3.2.1 Change in plasma HCV RNA from baseline

An initial rapid decline in HCV RNA from baseline at Day 3 of TMC435 monotherapy was evident for all patients infected with HCV genotypes 4 to 6, and for three out of six patients with genotype 2 (Figs 2 and 3). Of these three patients, those who responded were infected with subtypes 2b and 2c.

At Day 3, the mean (±standard error [SE]) change from baseline in plasma HCV RNA (log_{10} IU/mL) was greatest for genotypes 6 (-3.57±0.197) and 4 (-3.43±0.167), followed by genotypes 5 (2.71±0.335) and 2 (-2.02±0.625). For the primary endpoint at Day 8, the mean (±SE) change from baseline was greatest for genotypes 6 (-4.35±0.29) and 4 (-3.52±0.43) cohorts, followed by genotypes 2 (-2.73±0.71) and 5 (-2.19±0.39) (Figs 1 and 2). However, no clear antiviral activity was evident for patients with genotype 3 (change from baseline at day 3 and 8; Figs 2 and 3). At Day 8, four patients (two patients with genotype 4 and two with genotype 6) achieved HCV RNA levels of <25 IU/mL detectable. No patients achieved HCV RNA levels of <25 IU/mL undetectable at Day 8.

From Day 8 to the end of follow-up 2 (Days 37–42), when patients had been treated with PegIFN/RBV only for up to 35 days, mean HCV RNA declined in all genotypes, with the exception of genotype 4 where mean HCV RNA began to increase (Fig. 2). By the end of follow-up 2, HCV RNA change from baseline was -5.19±0.37 for genotype 2, -4.96±0.37 for genotype 3, -3.26±0.77 for genotype 4, -3.89±0.60 for genotype 5 and -5.46±0.32 for genotype 6. HCV RNA was <25 IU/mL detectable for 5/6 (83%), 6/8 (75%), 5/8 (63%), 2/7 (29%) and 7/8 (88%) of patients with genotypes 2, 3, 4, 5 and 6, respectively. HCV RNA <25 IU/mL undetectable was achieved by 5/6 (83%), 3/8 (38%), 5/8 (63%), 1/7 (14%) and 6/8 (75%) of patients with genotypes 2, 3, 4, 5 and 6, respectively.

3.2.2 Viral breakthrough

One patient infected with genotype 3, two with genotype 4 and three with genotype 5 experienced viral breakthrough during the TMC435 monotherapy period. In addition,

another 6 patients experienced viral breakthrough during the follow-up period, whilst being treated with PegIFN/RBV only, suggesting lack of activity of PegIFN/RBV treatment in these patients: two infected with genotype 2, one with genotype 3, one with genotype 4, and two with genotype 6.

In genotype 2 and 3-infected patients with viral breakthrough, viral sequencing did not reveal emerging mutations. However, for most genotype 4, 5, and 6 patients with viral breakthrough, emerging mutations were detected. The most frequently observed emerging mutations in the NS3 protease domain were R155K, D168E and D168V (data not shown).

3.3 Safety and tolerability

The type and incidence of AEs (all Grade 1–2) during the 7-day TMC435 monotherapy period was similar across all cohorts in the study (Table 2) and the most common AEs were influenza-like illness and headache. There were no clinically relevant changes in laboratory parameters, and no clinically significant findings in terms of vital signs, physical examinations or ECG recordings. Mild elevations in bilirubin (total, direct and indirect) levels were observed in all cohorts. Mean change from baseline to Day 8 was 1.38 µmol/L (95% confidence interval [CI] 0.88, 1.87) for direct and 3.06 µmol/L (95% CI 1.51, 4.61) for indirect bilirubin. These returned to baseline value after completion of TMC435 dosing and were not associated with clinical symptoms or elevations in aspartate aminotransferase, alanine aminotransferase or alkaline phosphatase (Supplementary Table 2).

On Day 8 (after the 7-day dosing period with TMC435 was completed), one patient experienced an SAE of Grade 1 ileitis not considered related to TMC435 therapy. The

patient discontinued from the study and recovered after 4 days. No other discontinuations due to AEs occurred during the trial.

3.4 Pharmacokinetics

Steady-state TMC435 C_{0h}, C_{min}, C_{max} and AUC_{24h} were similar for the genotype 4, 5 and 6 cohorts, though lower values were observed for the genotype 2 and 3 cohorts with the lowest values in the genotype 3 cohort (Supplementary Table 3). T_{max} values were generally similar for all genotype cohorts (Supplementary Table 3). Exposure did not differ according to race or cirrhosis (data not shown).

4. Discussion

The results of this phase IIa proof-of-concept trial provide evidence that TMC435 has a broad spectrum of activity against multiple HCV genotypes, with the exception of genotype 3.

Monotherapy with oral TMC435 200 mg *q.d.* for 7 days was associated with potent antiviral activity in patients infected with genotypes 2, 4, 5 and 6. The greatest antiviral activity was observed among patients infected with genotypes 4 and 6, followed by genotypes 2 and 5. Of note, potent activity was observed in three patients with genotype 2, with limited activity observed in the other three patients in this cohort. No antiviral activity was seen against genotype 3. Viral breakthrough (protocol defined: plasma HCV RNA increase >1 $\log_{10}$ IU/mL from the lowest reached, or >100 IU/mL in patients whose HCV RNA was previously <25 IU/mL undetectable or detectable) occurred in six patients during the monotherapy phase. Six additional patients had viral breakthrough during the PegIFN/RBV-only period, and could therefore be considered viral rebound after cessation of treatment with TMC435. In this study, TMC435 was generally safe and well tolerated. All AEs were mild to moderate and during the 7-day period of TMC435 monotherapy there were no discontinuations or untoward changes in biochemical parameters.

This is the first study in which an HCV protease inhibitor has demonstrated antiviral activity in genotypes 5 and 6. Furthermore, data for genotypes 2, 3 and 4 are limited for other investigational agents. In a phase IIa study, telaprevir combined with PegIFN/RBV showed substantial activity against genotype 2, modest activity against genotype 4 [38] and limited activity against genotype 3 [39]. Of note, unlike

nucleotide inhibitors, NS3 protease inhibitors are generally considered to have limited activity in certain genotypes. However, results of this study suggest that the protease inhibitor TMC435 could be efficacious across multiple genotypes, though additional clinical data are required to provide further support.

A limitation of this study relates to the high subtype diversity in genotypes 2, 4 and 6 (such diversity is not observed in genotypes 3 and 5). Not all subtypes were included in this study and the number of patients per subtype was sometimes limited. Importantly, no difference in efficacy between included subtypes was observed in genotypes 4 or 6. The difference in antiviral activity between patients infected with genotype 2 may be caused by the different subtypes, as HCV RNA change from baseline at Day 3 in patients infected with 2b and 2c was -3.19 to -3.61- $\log_{10}$ IU/mL, compared with -0.26 to -0.99 in those infected with 2, 2k and 2i. In addition to this limitation, the sample size in each cohort was relatively small. It should also be noted that a TMC435 dose of 200 mg *q.d.* was administered in this trial, whereas a dose of 150 mg is currently in phase III development.

The lack of antiviral activity against genotype 3, compared with other genotypes, is consistent with the lower IC_{50} value of TMC435 against a genotype 3 isolate in an *in vitro* biochemical assay [37]. It is suggested that this may be due to the presence of a naturally occurring D168Q polymorphism at baseline, which is present in most genotype 3a isolates known to date and was observed in all genotype 3a patients included in this study (data not shown). A D168Q mutation alone has been shown to reduce TMC435 activity in a genotype 1b replicon assay by >700 fold [40]. TMC435 exposure (as indicated by C_{0h}, C_{min}, C_{max} and AUC_{24h}) was lower in genotypes 2 and 3 than in genotypes 4, 5 and 6, though it is suggested that this may be due to chance due

to the small number of patients in this study. Furthermore, as mean AUC values were <3 fold lower in the genotype 3 cohort compared to genotype 6 but *in vitro* susceptibility of genotype 3 isolates was >700 fold lower, the lower exposure observed in this cohort does not explain the lack of antiviral activity against genotype 3.

In patients infected with HCV genotype 4, mean change from baseline in HCV RNA began to increase after Day 5. Prior to Day 8, this was driven by two patients who experienced viral breakthrough under TMC435 monotherapy. The further increase in HCV RNA after Day 8 is thought to reflect a lack of response to PegIFN/RBV.

Novel agents for the treatment of genotypes 4 to 6 would be advantageous as SVR rates are low [17,31], and together with genotype 1 these groups are considered 'difficult to treat'. Antiviral activity against genotypes 4 to 6 observed in this study suggests that TMC435 could provide a clinical benefit, particularly for patients infected with genotypes 4 and 6. For genotype 5, the mean decline in HCV RNA from baseline over the 7 day monotherapy period was slightly lower compared to genotypes 4 and 6, suggesting that the TMC435 activity was somewhat lower in this group. Due to SVR rates of ≥70% in genotype 2 and 3 patients following treatment with PegIFN/RBV, there is perhaps a less urgent need for novel agents to treat infection with these genotypes, though patients who do not respond to treatment could benefit from regimens including novel DAAs. TMC435 showed antiviral activity in 3/6 patients infected with genotype 2, and no activity against genotype 3.

Of note, given the high sequence variability between the different genotypes and subtypes, further work is ongoing to investigate the role of naturally occurring

baseline polymorphism in variation in virologic response, and to fully characterise viral variants observed in patients with viral breakthrough.

In spite of study limitations outlined above, the results of this phase IIa study in 37 treatment-naïve patients suggest that this investigational agent may be a future candidate for treatment of infection with HCV genotypes 4, 5 and 6, and potentially particular subtypes of genotype 2.

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Tables

Table 1. HCV subtype defined using NS5B sequence-based assay or Versant LIPAv2.*

HCV subtype, n (%)	**Genotype 2 (*N*=6)**	**Genotype 3 (*N*=8)**	**Genotype 4 (*N*=8)**	**Genotype 5 (*N*=7)**	**Genotype 6 (*N*=8)**
2	1 (16.7)				
2b	2 (33.3)				
2c	1 (16.7)				
2i	1 (16.7)				
2k	1 (16.7)				
3a		8 (100)			
4			1 (12.5)*		
4a			4 (50)		
4c			2 (25)		
4d			2 (25)		
5a				7 (100)	
6a					1 (12.5)
6b					1 (12.5)
6c-l					3 (37.5)*

6j	1 (12.5)
6 n	2 (25.0)

*NS5B assay failed in four patients. LIPAv2 assay determined genotypes were genotype 4 (one patient) and genotype 6c-l (three patients)

Table 2

Adverse events occurring in more than two patients, during the TMC435 treatment period, by genotype cohort

Preferred term, *n* (%)	**Genotype 2 (*N*=6)**	**Genotype 3 (*N*=8)**	**Genotype 4 (*N*=8)**	**Genotype 5 (*N*=7)**	**Genotype 6 (*N*=8)**	**Overall (*N*=37)**
Any AE	5 (83.3)	6 (75.0)	8 (100)	4 (57.1)	5 (62.5)	28 (75.7)
Influenza-like illness	2 (33.3)	1 (12.5)	4 (50.0)	1 (14.3)	1 (12.5)	9 (34.3)
Headache	2 (33.3)	1 (12.5)	2 (25.0)	0	0	5 (13.5)
Diarrhoea	2 (33.3)	1 (12.5)	1 (12.5)	0	0	4 (10.8)
Fatigue	2 (33.3)	1 (12.5)	0	0	1 (12.5)	4 (10.8)
Pruritus	1 (16.7)	1 (12.5)	1 (12.5)	1 (14.3)	0	4 (10.8)
Anorexia	1 (16.7)	2 (25.0)	0	0	0	3 (8.1)
Back pain	0	1 (12.5)	1 (12.5)	0	1 (12.5)	3 (8.1)
Myalgia	0	2 (25.0)	1 (12.5)	0	0	3 (8.1)

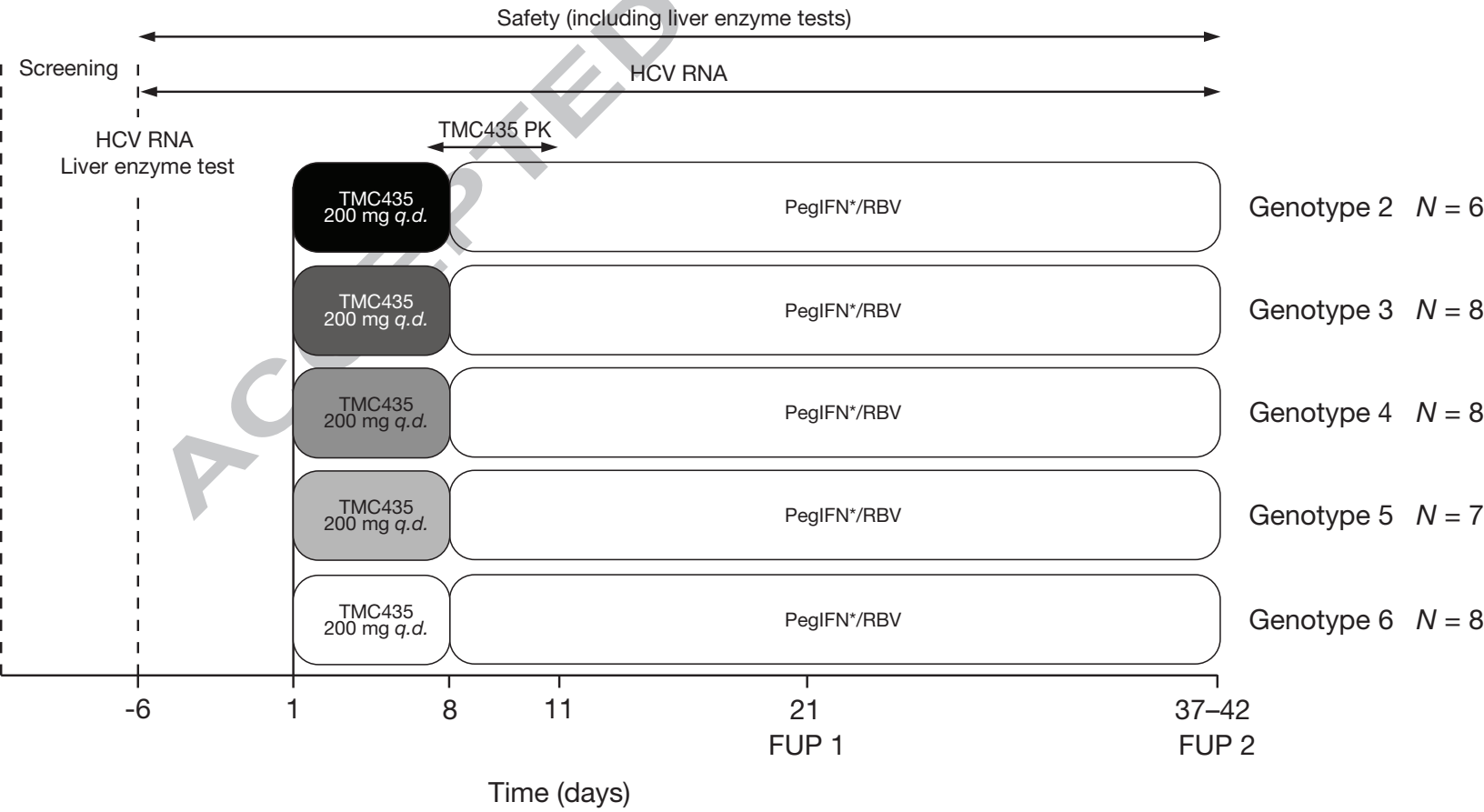
AE, adverse event.

Figure legends

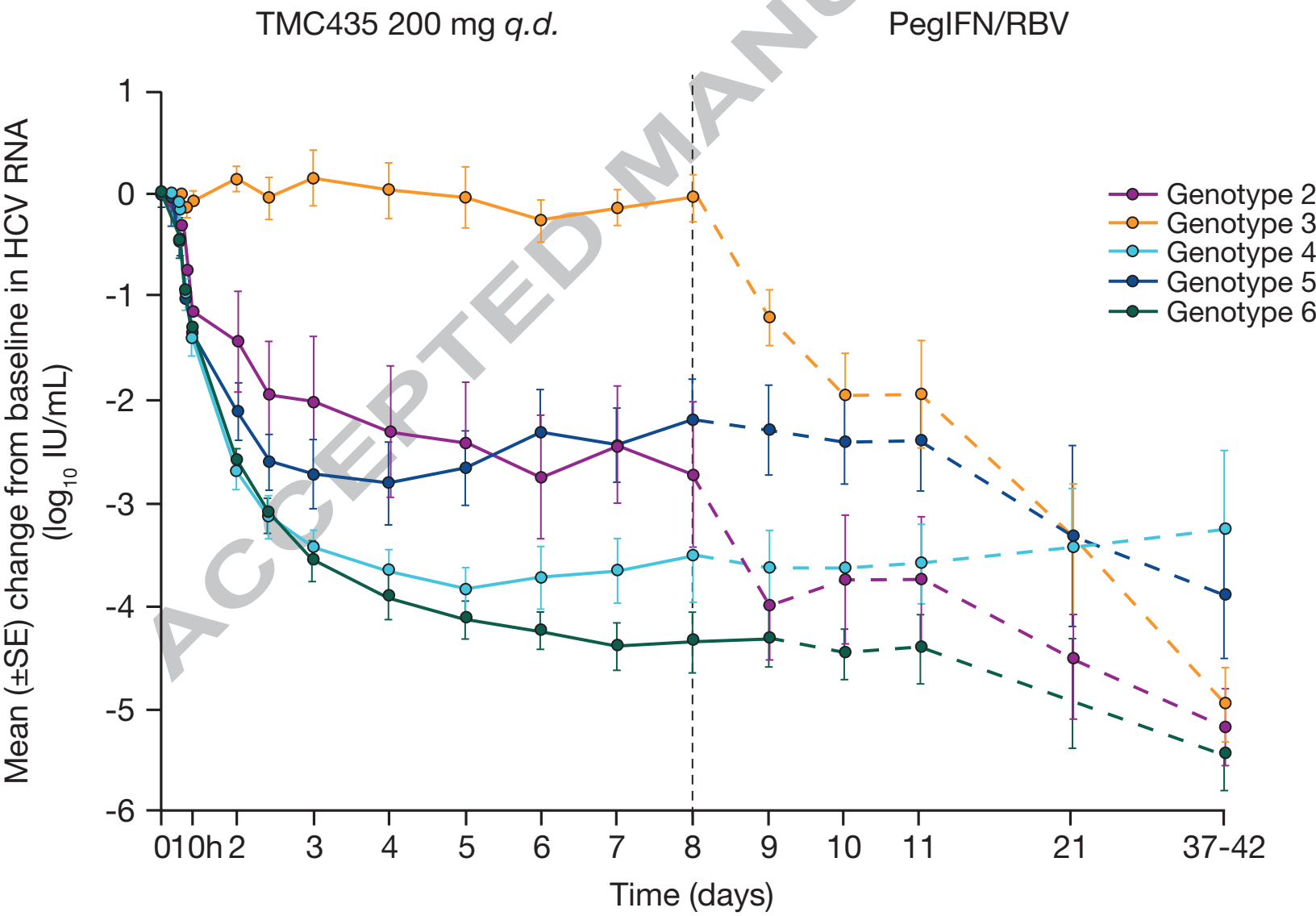
Fig. 1. TMC435-C202 study design.

Fig. 2. Mean (±SE) change from baseline in plasma HCV RNA (log_{10}IU/mL) for each genotype cohort.

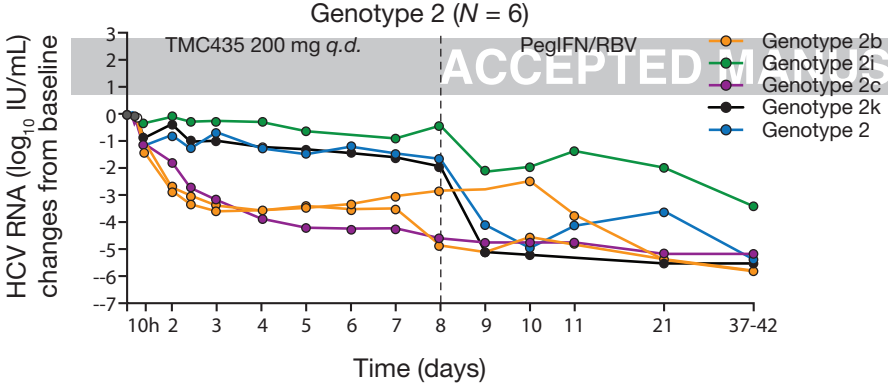
Fig. 3. Individual changes from baseline in plasma HCV RNA (log_{10}IU/mL) over time for each genotype cohort.

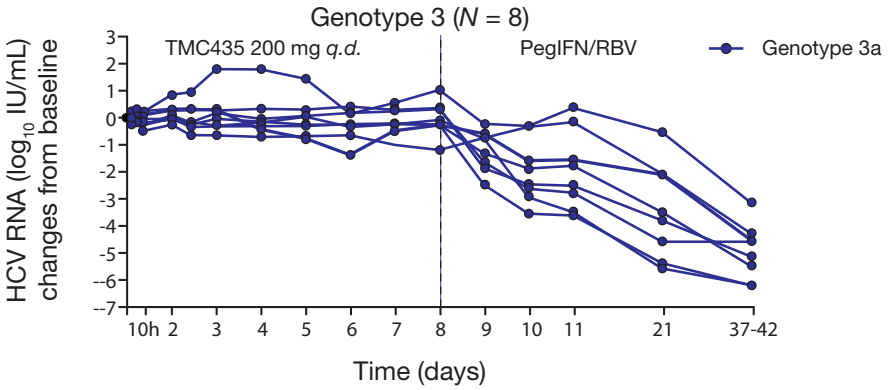


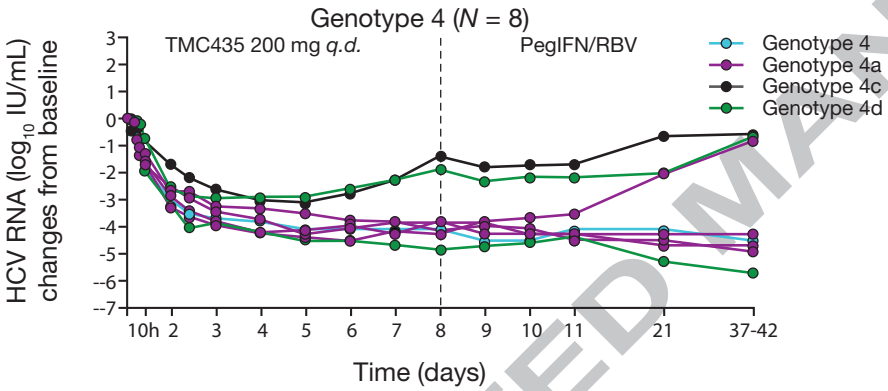
*Patients could start treatment with either PegIFNα-2a or PegIFNα-2b in combination with RBV.
HCV, hepatitis C virus; FUP, follow-up; GT, genotype; PegIFN, pegylated interferon; PK, pharmacokinetics; *q.d.*, once daily; RBV, ribavirin; RNA, ribonucleic acid.

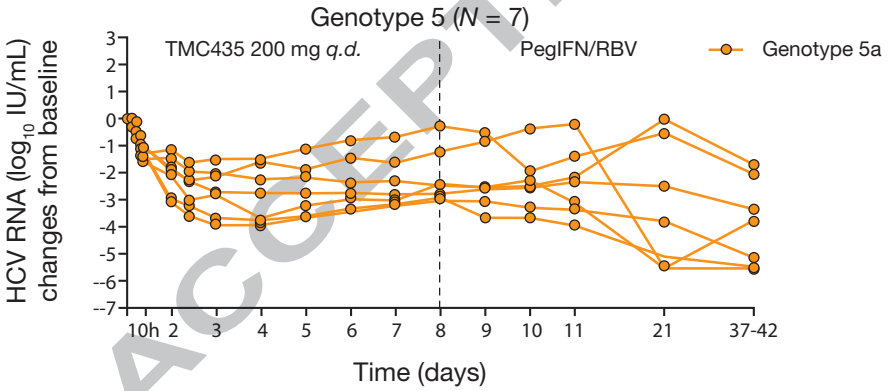


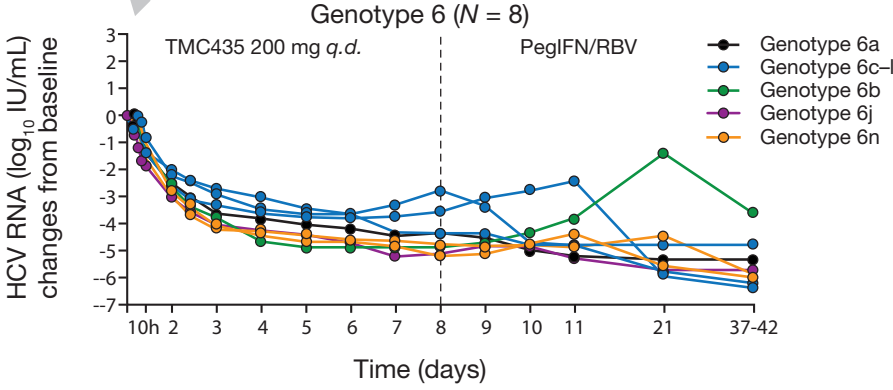
h, hours; HVC, hepatitis C virus; PegIFN, pegylated interferon; RBV, ribavirin; RNA, ribonucleic acid
Serum samples were obtained at baseline, Days 1–11, Day 21 (follow-up 1; 14 days after final TMC435 administration) and Days 37-42 (follow-up 2; 30–35 days after final TMC435 administration).



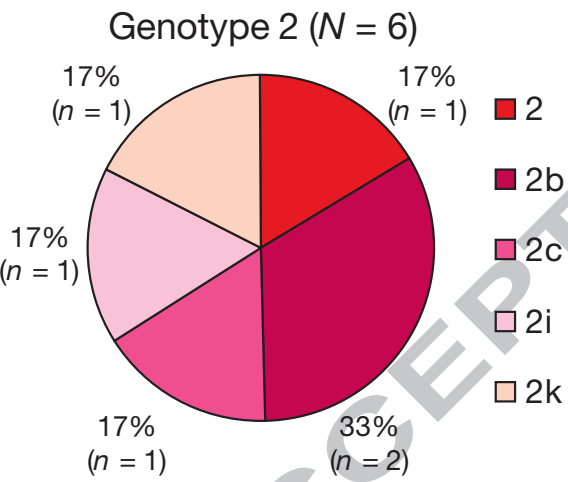


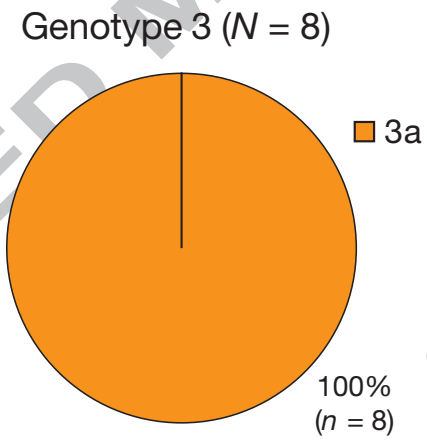


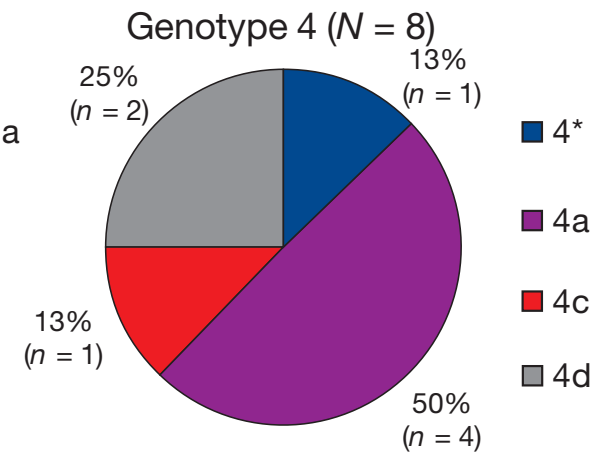


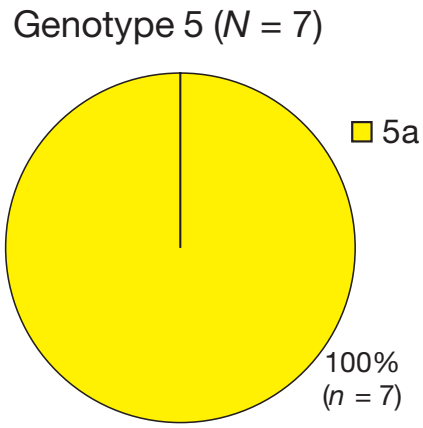


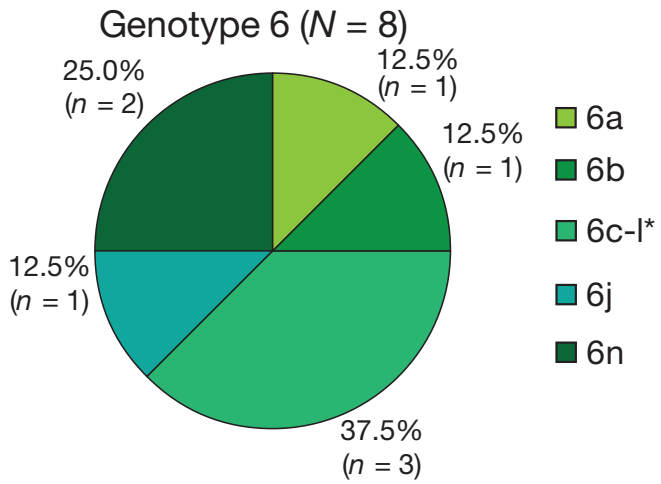
h, hours; HVC, hepatitis C virus; PegIFN, pegylated interferon; RBV, ribavirin; RNA, ribonucleic acid; SE, standard error
Serum samples were obtained at baseline, Days 1–11, Day 21 (follow-up 1; 14 days after final TMC435 administration) and Days 37-42 (follow-up 2; 30–35 days after final TMC435 administration).











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