CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205123Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 205123
Drug Name:	Simeprevir 150mg capsules
Indication(s):	treatment of chronic hepatitis C genotype-1 infection, in combination with peginterferon-alfa and ribavirin, in adult patients with compensated liver disease, including cirrhosis, who are treatment-naive or who have failed previous interferon and ribavirin therapy
Applicant:	Janssen Research & Development
Date(s):	Received Date: March 28, 2013 Filing Date: May 27, 2013 MidCycle Date: July 9, 2013 PDUFA Due Date: November 27, 2013
Review Priority:	Priority
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Keywords:

Chronic Hepatitis C (CHC), Genotype 1 infection, simeprevir, TMC435, peginterferon alfa (PEG), ribavirin (RBV), Q80K.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

On March 28, 2013, Janssen submitted the NDA 205123 to seek the agency's approval of Simeprevir (TMC435) 150 mg capsule taken once daily in combination with peginterferon alfa and ribavirin. The desired indication is treatment of chronic hepatitis C (CHC) genotype 1 infection, in adult patients with compensated liver disease (including cirrhosis) who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin.

The statistical reviewer evaluated the efficacy results from Study 208 and Study 216, two pivotal phase III, randomized, double-blind, placebo-controlled studies in treatment-naïve genotype 1 hepatitis C-infected population. Another phase III, randomized, double-blind, placebo-controlled study (Study 3007) was also reviewed. Study 3007 enrolled genotype 1 hepatitis C-infected patients who had relapsed after previous interferon-based therapy. Efficacy results from Study 206, a phase IIb study, were also reviewed to investigate the efficacy of Simeprevir in prior null responders and partial responders.

In Study 208, the percentage of patients achieving sustained virologic response 12 weeks after the end of treatment (SVR12) was 51% (66/130) in the control arm and 80% (210/264) in the Simeprevir (TMC435) arm. The treatment difference for SVR12 was 29% with 95% confidence interval (CI) of (19%, 38%). The superiority of Simeprevir to the control was demonstrated in Study 208.

In Study 216, the percentage of patients achieving SVR12 was 50% (67/134) in the control arm and 81% (209/257) in the Simeprevir (TMC435) arm. The treatment difference for SVR12 was 32% (95% CI: 23%, 41%). The superiority of Simeprevir to the control was demonstrated in Study 216.

By integrating the data from Study 208 and Study 216 for the treatment-naïve population, the percentage of patients achieving SVR12 was 50% (133/264) in the control arm and 80% (419/521) in the Simeprevir (TMC435) arm. The treatment difference for SVR12 was 30% (95% CI: 24%, 37%).

In Study 3007, the proportion of patients that achieved SVR12 was 36% (48/133) in the control arm and 79% (206/260) in the Simeprevir arm. The treatment difference was 44% (95% CI: 35%, 53%). The superiority of Simeprevir to control was again demonstrated in the relapser population with regard to SVR12.

Based on the data from Study 206, the SVR12 rate for null responders was 46% (15/33) in patients treated with Simeprevir for 12 weeks and 19% (3/16) for the control arm. The treatment difference was 27% and was not statistically significant (p-value 0.11). For partial responders, the SVR rate was 70% (32/46) in patients treated with Simeprevir for 12 weeks and 9% (2/23) for the control arm. The treatment difference (61%) was statistically significant (p-value <0.0001). For relapsers, the SVR rate was 85% (45/53) in patients treated with Simeprevir for 12

weeks and 37% (10/27) for the control arm. The treatment difference was 48% and was also significant (p-value <0.0001).

Although Simeprevir has demonstrated treatment benefit in treatment-naïve patients, relapsers, and partial responders, little benefit was shown in patients with the Q80K polymorphism at baseline. Q80K is considered to be a clinically important prognostic factor. This lack of benefit was noted first by the applicant in replicon culture studies. The presence of Q80K was associated with an approximately 10-fold reduction in susceptibility to simeprevir. A statistically significant treatment by Q80K polymorphism at baseline interaction (p-value of 0.0002) was observed with regard to SVR12 in the treatment-naïve patients. In the control arm, the efficacy endpoints were quite similar between the patients with and without Q80K at baseline. The SVR12 rate was 49% (104/214) for patients without Q80K at baseline and 55% (24/44) for patients with Q80K at baseline. However in the Simeprevir arm, the proportion of patients that achieved SVR12 was 85% (363/429) for patients without Q80K at baseline and only 59% (51/86) for patients with Q80K at baseline. There appeared to be no improvement in SVR12 for those patients with Q80K at baseline when adding TMC435 to their treatment regime compared with the Q80K patients in the control arm. A similar trend was also shown in the relapser population. Again, a statistically significant treatment by Q80K polymorphism at baseline interaction (p-value=0.04) with regard to SVR12 was detected. In the control arm, SVR12 rate was 37% (42/113) for the patients without Q80K at baseline and 30% (6/20) for the patients with Q80K at baseline. However in the Simeprevir arm, the proportion of patients achieving SVR12 was 83% (188/226) for patients without Q80K at baseline and only 48% (15/31) for patients with Q80K at baseline.

In order to address the concerns and mitigate risk, the applicant proposed an alternative treatment algorithm (b) (4)

(b) (4)

Given that subjects in the pivotal Phase III studies who were infected with HCV genotype 1a and had the Q80K polymorphism at baseline were less likely to benefit from TMC435 in combination with pegylated interferon and ribavirin than subjects infected with other HCV polymorphic variants, there is a high prevalence of the Q80K polymorphism in genotype 1a patients in the U.S. population, and there are concerns regarding the generation of cross-resistance to the approved HCV protease inhibitors in TMC435 treatment failures (i.e., R155K), the review team recommends that the applicant screen all genotype 1a patients for the Q80K

polymorphism prior to initiation of TMC435 with the objective of excluding patients from treatment if the polymorphism is present. The applicant's proposed treatment algorithm can also be simplified. One of the options is:

- All patients in the naïve and relapser populations would receive a fixed 24 week course of pegylated interferon and ribavirin in conjunction with 12 weeks of TMC435.
- All patients in the partial- and null-responder populations would receive a fixed 48 week course of pegylated interferon and ribavirin in conjunction with 12 weeks of TMC435.

Based on this proposal, the reviewer's estimated SVR12 would be 83% for the naïve population and 81% for the relapsers. The applicant has accepted this proposal.

An Advisory Committee meeting occurred October 24, 2013. The following were questions posed to the committee and topics of discussion:

1. DISCUSSION: Please comment on the safety profile of simeprevir focusing on rash and photosensitivity reactions reported during the clinical trials.

a. Does the committee agree that a discussion of the photosensitivity reaction, including a recommendation for sun-protection measures, should be included in the Warnings and Precautions section of the simeprevir prescribing information?
b. There are apparent differences related to both the clinical presentation and prevention/management strategy for photosensitivity reactions versus rash. Does the committee agree that a separate discussion of rash should be included in the Warnings and Precautions section of the simeprevir prescribing information?

2. VOTE: Considering the overall risks and benefits, do the available data support approval of simeprevir in combination with pegylated interferon and ribavirin for treatment of HCV genotype 1 infection?

3. DISCUSSION: DAVP intends to recommend screening all subjects with GT1a infection for the Q80K viral polymorphism prior to initiation of simeprevir (in combination with pegylated interferon and ribavirin) and that alternative treatment options be considered for patients with this baseline polymorphism. Does the committee agree with DAVP's proposed approach to managing the reduction in efficacy apparent in the setting of the Q80K polymorphism?

4. DISCUSSION: Are there postmarketing studies that should be conducted to further define risks or to optimize use of simeprevir?
The committee voted unanimously in favor of simpeprevir in combination with pegylated interferon and ribavirin for the treatment of HCV genotype 1 infection.

2 INTRODUCTION

2.1 Overview

TMC435 is an inhibitor of the HCV NS3/4A protease and was developed for the treatment of chronic HCV infection. According to the applicant, an in vitro study demonstrated the anti-HCV effect of TMC435 in genotype 1 and genotype 4 patients. It also showed the anti-HCV effect of TMC435 was reduced by amino acid substitution Q80K. The anti-HCV activity was low in genotype 2 and 3 patients.

Different doses and treatment durations were tested in phase I and phase II studies. Based on the results of phase II studies, the proposed dose regimen of TMC435 150 mg once daily (q.d.) for a duration of 12 weeks in combination with peginterferon and ribavirin (PegIFN/ RBV) followed by another 12 or 36 weeks PegIFN/ RBV alone (response-guided duration for treatment with PegIFN/RBV for subjects who are treatment-naïve or relapsed after prior IFN-based therapy) was recommended for phase III studies.

Before the NDA submission, the statistical reviewer evaluated the statistical analysis plan for the pooling of the efficacy data, and comments were sent to the applicant. The reviewer indicated that the applicant had to follow the original method that was pre-specified in the protocols and analysis plans. The applicant was informed that the newly proposed (b) (4) could not be used to make a labeling claim. Janssen acknowledged the agency's feedback and stated that SVR12 would be the primary efficacy endpoint. All other endpoints would be ordered to support submission to other health authorities and for publication of key results. The agency stated that the additional endpoints could be submitted, but they would not be considered for labeling purposes.
The applicant submitted the results of their clinical studies to support the indication for treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease who are treatment-naïve or who have failed previous interferon therapy(pegylated or non-pegylated) with or without ribavirin.

The statistical review focused on the below listed studies. Complete study report for Study 206 was submitted. For the Phase III studies (208, 216 and 3007), 60 weeks interim results were submitted.

Table 1: List of all studies included in analysis

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects Total (ITT population)	Study Population
208	Phase 3	24/48 weeks	24 weeks	394 (ratio: 1:2)	HCV Genotype1 naïve patients
216	Phase 3	24/48 weeks	24 weeks	391 (ratio: 1:2)	HCV Genotype1 naïve patients
HPC3007	Phase 3	24/48 weeks	24 weeks	393 (ratio: 1:2)	HCV Genotype1 experienced patients (relapser)
206	Phase 2	24/48 weeks	24 weeks	462 (ratio: 1:1:1:1:1:1:1)	HCV Genotype1 experienced patients

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2.2 Data Sources

The NDA is located at:
\\CDSESUB1\EVSPROD\NDA205123\0000
Both SDTM and ADAM datasets were submitted. Some of the SAS programs were also submitted.

The SDTM datasets for Study 208 are located in the following directory:
\\CDSESUB1\EVSPROD\ NDA205123\0000\m5\datasets\tmc435-tidp16-c208\tabulations\sdtm
The ADAM datasets of Study 208 are under the following directory:
\\CDSESUB1\EVSPROD\ NDA205123\0000\m5\datasets\tmc435-tidp16
c208\analysis\adam\datasets

The SDTM datasets of Study 216 are located in the following directory:
\\CDSESUB1\EVSPROD\ NDA205123\0000\m5\datasets\tmc435-tidp16-c216\tabulations\sdtm
The ADAM datasets of Study 216 are under the directory of:
\\CDSESUB1\EVSPROD\ NDA205123\0000\m5\datasets\tmc435-tidp16-
c216\analysis\adam\datasets

The SDTM datasets of Study 3007 are under the directory of:
\\CDSESUB1\EVSPROD\ NDA205123\0000\m5\datasets\tmc435hpc3007\tabulations\sdtm
The ADAM datasets of Study 3007 are under the directory of:
\\CDSESUB1\EVSPROD\ NDA205123\0000\m5\datasets\
tmc435hpc3007\analysis\adam\datasets

The SDTM datasets of Study 206 are under the directory of:
\\CDSESUB1\EVSPROD\ NDA205123\0000\m5\datasets\tmc435-tidp16-c206\tabulations\sdtm
The ADAM datasets of Study 206 are under the directory of:
\\CDSESUB1\EVSPROD\ NDA205123\0000\m5\datasets\tmc435-tidp16
c206\analysis\adam\datasets

The statistical reviewer's analyses were primarily based on the raw (SDTM) datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant submitted data of good quality. However, the derivation of the efficacy variables were not described in detail in the **define** files. The review's analyses were based on the raw datasets and the methods described in Section 3.2.2.2. Statistical analysis plans were also submitted.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The study design, objective and primary endpoints are described in the sections below for each study. The phase III studies were designed appropriately to meet the primary objective.

3.2.1.1 Study 208

Study 208 was a Phase III, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of TMC435 as part of a treatment regimen including peginterferon alfa-2a and ribavirin (PegIFNα-2a/RBV) in treatment-naïve, genotype 1 hepatitis C-infected subjects. The primary objective of this study was to demonstrate the superiority of TMC435 compared to placebo as part of a treatment regimen including PegIFNα-2a/RBV with respect to the proportion of subjects with sustained virologic response (SVR) 12 weeks after the planned end of treatment.

Subjects with documented chronic genotype 1 HCV infection, who were treatment-naïve and had a screening plasma HCV ribonucleic acid (RNA) level of > 10,000 IU/mL, were randomly assigned in a 2:1 ratio to receive TMC435 or placebo, stratified by HCV genotype 1 subtype and *IL28B* genotype.

In the first 24 weeks, subjects received 12 weeks TMC435 150 mg or placebo q.d. with PegIFNα-2a/RBV, followed by 12 weeks of PegIFNα-2a/RBV alone. As part of a response-guided treatment duration, HCV therapy was stopped at Week 24 in subjects in the TMC435 treatment group when they achieved HCV RNA levels < 25 IU/mL (detectable or undetectable) at Week 4 and < 25 IU/mL undetectable HCV RNA levels at Week 12. All other subjects continued PegIFNα-2a/RBV until Week 48. In the control group, all subjects continued PegIFNα-2a/RBV alone until Week 48.

The complete virologic stopping criteria used in Study 206 and all the phase III studies were:
Stop TMC435/placebo and continue with PegIFN and RBV if HCV RNA is >1000 IU/mL at Week 4.
Stop PegIFN and RBV if HCV RNA reduction is less than 2 log10 at Week 12 compared to baseline; confirmed detectable at Week 24 and confirmed detectable at Week 36.

The primary efficacy endpoint was the proportion of subjects in each treatment group achieving sustained virologic response 12 weeks after the planned end of therapy (SVR12).

3.2.1.2 Study 216

Study 216 was a Phase III, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of TMC435 versus placebo as part of a treatment regimen including peginterferon α-2a (Pegasys®) and ribavirin (Copegus®) or peginterferon α-2b (PegIntron®) and ribavirin (Rebetol®) in treatment-naïve,genotype 1, hepatitis C-infected subjects. The primary objective of this study was to demonstrate the superiority of TMC435 as part of a treatment regimen including PegIFNα-2a/RBV or PegIFNα-2b/RBV, with respect to the proportion of treatment-naïve genotype 1 HCV-infected subjects with sustained virologic response 12 weeks after the planned end of treatment.
Subjects with documented chronic genotype 1 HCV infection, who were treatment-naïve and had a screening plasma HCV RNA level of > 10,000 IU/mL, were randomly assigned in a 2:1 ratio to receive TMC435 or placebo, stratified by HCV genotype 1 subtype and *IL28B* genotype.

In the first 24 weeks, subjects received 12 weeks TMC435 150 mg or placebo q.d. along with PegIFNα- 2a/2b and RBV, followed by 12 weeks of PegIFN/RBV alone. As part of a response-guided treatment duration, HCV therapy was stopped at Week 24 in subjects in the TMC435 treatment group when they achieved HCV RNA levels < 25 IU/mL (detectable or undetectable) at Week 4 and < 25 IU/mL undetectable HCV RNA levels at Week 12. All other subjects continued PegIFN/RBV alone until Week 48. In the control group, all subjects continued PegIFN/RBV alone until Week 48.

The use of PegIFNα-2b was limited to a selected number of countries. A maximum of 30% of the overall study population was randomized to a PegIFNα-2b containing regimen. In these countries, subjects were randomized in a 1:1 ratio to PegIFNα-2a/RBV or PegIFNα-2b/RBV.

The primary efficacy endpoint was the proportion of subjects in each treatment group achieving SVR12.

3.2.1.3 Study 3007

Study 3007 was a Phase III, randomized, double-blind, placebo controlled study to investigate the efficacy, safety and tolerability of TMC435 as part of a treatment regimen including PegIFNα-2a/RBV in hepatitis C, genotype 1 infected subjects who relapsed after previous interferon-based therapy. The primary objective of this study was to demonstrate the superiority of TMC435 as part of a treatment regimen including PegIFNα-2a/RBV, with respect to the proportion of subjects with sustained virologic response 12 weeks after the planned end of treatment.

Subjects with documented chronic genotype 1 HCV infection, who relapsed after previous

Peg-IFN-based therapy and had a screening plasma HCV ribonucleic acid (RNA) level of > 10,000 IU/mL, were randomized in a 2:1 ratio to receive TMC435 or placebo, stratified by HCV genotype 1 subtype and *IL28B* genotype.

In the first 24 weeks, subjects received 12 weeks TMC435 150 mg or placebo q.d. along with PegIFNα-2a/RBV, followed by 12 weeks of PegIFNα-2a/RBV alone. As part of a response-guided treatment duration, HCV therapy was stopped at Week 24 in subjects in the TMC435 treatment group when they achieved HCV RNA levels < 25 IU/mL (detectable or undetectable) at Week 4 and < 25 IU/mL undetectable HCV RNA levels at Week 12. All other subjects continued PegIFNα-2a/RBV until Week 48. In the control group, all subjects would continue PegIFNα-2a/ RBV alone until Week 48.

The primary efficacy endpoint was the proportion of subjects in each treatment group achieving SVR12.

3.2.1.4 Study 206

Study 206 was a Phase IIb, randomized, 7-arm, double-blind, placebo-controlled trial to investigate the efficacy, tolerability, safety and pharmacokinetics of TMC435 as part of a treatment regimen including PegIFNα-2a and ribavirin in HCV genotype 1 infected subjects who failed to respond or relapsed following at least 1 course of PegIFNα-2a/b and RBV therapy. The primary objective of the trial was to evaluate the treatment effect of 6 different regimens of TMC435 in combination with PegIFNα-2a/RBV on the proportion of subjects with < 25 IU/mL undetectable HCV RNA 24 weeks after the planned end of treatment (SVR24) compared to the control group receiving PegIFNα-2a/RBV in combination with TMC435-matched placebo.

Subjects were randomized in a 1:1:1:1:1:1:1 ratio to 1 of 7 different treatment arms as described below

- Treatment arms 1 and 2 consisted of 12 weeks triple therapy with 100 mg and 150 mg TMC435 q.d., respectively, along with PegIFNα-2a/RBV followed by 36 weeks of PegIFNα-2a/RBV with TMC435-matched placebo and 24 weeks of post-therapy follow up.
- Treatment arms 3 and 4 consisted of 24 weeks triple therapy with 100 mg and 150 mg

TMC435 q.d., respectively, with PegIFNα-2a/RBV followed by 24 weeks of PegIFNα-2a/RBV with TMC435 matched placebo and 24 weeks of post-therapy follow-up.

- Treatment arms 5 and 6 consisted of 48 weeks triple therapy with 100 mg and 150 mg TMC435 q.d., respectively, with PegIFNα-2a/RBV and 24 weeks of post-therapy follow-up.
- Treatment arm 7 (control arm) consisted of 48 weeks of TMC435-matched placebo plus PegIFNα-2a/RBV and 24 weeks of post-therapy follow up.

Two stratification factors were used in the randomization process: genotype 1 subtype and prior PegIFNα-2a/b and RBV response (i.e. relapsers, partial responders, and null responders).

The primary efficacy endpoint was the proportion of subjects in each treatment group achieving SVR24 defined as having undetectable HCV RNA at the EOT and 24 weeks after the planned EOT, i.e., Week 72.

3.2.2 Statistical Methodologies

3.2.2.1 Applicant's Statistical Methodologies

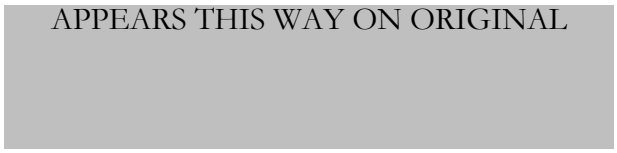
3.2.2.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint and the null hypothesis of three phase III studies were stated by the applicant as follows:

> The primary efficacy endpoint is the proportion of subjects in each treatment group achieving sustained virologic response 12 weeks after the planned end of therapy (SVR12).
>
> The null hypothesis that will be tested to address the primary objective of this trial is that there is no statistically significant difference between the active treatment arm and the control group for the primary efficacy endpoint (SVR12).

The difference in SVR12 rates was calculated using Cochran–Mantel–Haenszel (CMH) method to control stratification factors.

The applicant used the following algorithm to derive SVR12:



SVR12 is defined as follows:

- 1=Success (both of the below conditions were met):
  - at the actual end of treatment (see section 2.1)
    - HCV RNA < 25 IU/ml undetectable or
    - HCV RNA < 25 IU/ml detectable/≥ 25 IU/mL quantifiable, and at the previous measurement < 25 IU/mL undetectable, and the next measurement (either retest or next visit) is available and HCV RNA < 25 IU/mL undetectable for this next visit
  - at the timepoint of SVR
    - < 25 IU/mL undetectable or
    - < 25 IU/mL detectable and
      - the sample obtained at a confirmation visit* OR
      - the sample is the last available HCV RNA measurement OR
      - the next available measurement has HCV RNA < 25 IU/mL (undetectable or detectable)
    - ≥ 25 IU/mL quantifiable and
      - the sample not obtained at a confirmation visit* AND
      - not the last available measurement in the study AND
      - a next measurement is available and HCV RNA < 25 IU/mL (undetectable or detectable) for this next measurement
- 0= failure: otherwise

*Confirmation visit: an unscheduled visit following a measurement with HCV RNA levels which became <25 IU/mL detectable or ≥25 IU/mL after previous undetectability

Timepoint of SVR:

- 12 weeks after the planned EOT (i.e. the last available measurement in the SVR12 analysis window)
- or, if not available, the first available measurement at least 12 weeks after the planned EOT (i.e. the first available measurement after the SVR12 analysis window)
- or, if not available (i.e. no measurement at least 12 weeks after the planned EOT), the subject is considered a failure

3.2.2.1.2 Analysis Set

The applicant defined the *Intent-to-treat (ITT) population* as all randomized subjects who took at least 1 dose of investigational medication (TMC435 or placebo). The applicant also stated that all analyses would be done on the ITT population.

Major protocol deviations were identified prior to database lock. If there were more than 10% of subjects with a major protocol deviation, a per protocol analysis was performed on the primary endpoint excluding these subjects.

3.2.2.1.3 Visit Windows

The Applicant realigned all visits according to the visit windows below. If two visits fell within the same interval, the last measurement within the interval was used for the descriptive statistics/tabulations per time point and graphics in order to have only one evaluation per subject per analysis time point. If there were two measurements on the same day, then the measurement with the highest sequence number was used.

Table 2: On-treatment Visit Windows of the Phase III studies

Trial phase	Target day	Analysis time point (numeric version)	Analysis time point	Time interval (days)[a]
Screening	-∞	-1	Screening	<0
72 weeks study period[c]	1	0	Baseline[b]	<=1
	3	0.3	Day 3	[2,5]
	7	1	Week 1	[6,11]
	14	2	Week 2	[12,21]
	28	4	Week 4	[22,42]
	56	8	Week 8	[43,70]
	84	12	Week 12	[71,98]
	112	16	Week 16	[99,126]
	140	20	Week 20	[127,154]
	168	24	Week 24	[155,182]
	196	28	Week 28	[183,224]
	252	36	Week 36	[225,273]
	294	42	Week 42	[274,315]
	336	48	Week 48	[316,350]
	364	52	Week 52	[351,392]
	420	60	Week 60	[393,476]
	504	72	Week 72	[477,+∞]
	last visit while on study therapy or 3 days after the day of last dose	999	EOT	

[a] the first double-blind medication day is day 1.
[b] If the reldy of the baseline value closest to the target day is less than 0, only the record closest to the target day will be retained in the ADAM dataset, otherwise only the record(s) with reldy 1 will be kept.
[c] The same analysis time points can be used for the other phases (TMC435/PBO + PR, Entire Treatment, PR only, Follow-up). Distinction between the time points of different phases, should be based on the combination of phase and analysis time point.

Plasma HCV RNA values were determined using the Roche COBAS Taqman HCV/HPS v2.0 assay with a linear range from 25-300,000,000 IU/mL, a limit of quantification of 25 IU/mL.

For the purpose of the analysis, HCV RNA results of '<25 IU/mL HCV RNA detected' were set to 24 IU/mL and 'HCV RNA not detected' was set to 9 IU/mL before log transformation.
The visit windows of Study 206 were slightly different from the visit windows of the phase III studies due to more frequent visits.

3.2.2.2 Reviewer's Statistical Methodologies

The statistical reviewer performed all efficacy analyses on the ITT analysis set.
All HCV RNA records including withdrawal visits and unscheduled visits were treated as regular visits and included in the analysis.

3.2.2.2.1 Reviewer's Primary Efficacy Endpoint

The primary efficacy endpoint, SVR12, was modified by the reviewer slightly and was defined as the proportion of subjects in each treatment group achieving sustained virologic response (HCV RNA < 25IU/mL) 12 weeks after the end of therapy. Instead of using the planned end of therapy, the actual date of the end of therapy was used. Missing SVR12 was substituted by SVR24 if available. If both SVR12 and SVR24 were missing, SVR12 was imputed as failure.

The reviewer also defined another important efficacy endpoint, SVR, which was the proportion of subjects in each treatment group achieving sustained virologic response (HCV RNA < 25IU/mL) at least 12 weeks after the end of therapy. If there was more than one record in the follow-up visit window [57, +∞], the last record was taken. This was a more conservative definition to capture the latest available HCV RNA record. Patients that relapsed after Week 12 follow-up were considered as SVR failures by this definition. For patients with missing SVR, SVR was imputed as failure.

For Study 206, the analyses performed were similar to those of the Phase III studies in order to be consistent.

3.2.2.2.2 Reviewer's Visit Windows

For on-treatment visits up to week 48, the reviewer used the same visit windows as the applicant. Records were considered to be on-treatment if the collection date was less than or equal to the date of last dose + 3 days. However, for the follow-up visits, the reviewer used different visit windows as shown below. The post treatment days was defined as HCV RNA collection date - date of last dose. The date of last dose was taken as the maximum of the date of the last dose of TMC/PBO, PEG and RBV.

Table 3: Follow-Up Visit Windows

Analysis Time Point	Time Interval (Post treatment days)	Comments
Follow-Up Week 4	[15, 56]	Used for SVR4
Follow-Up Week 12	[57, 140]	Used for SVR12
Follow-Up Week 24	[141,]	Used for SVR24
	[57, +∞]	Used for SVR

Note: post treatment days=date HCV RNA was collected - date of last dose.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Study C208

3.2.3.1.1 Patient Disposition

Figure 1 displays the study disposition for Study 208. There were 481 patients screened, and 395 patients were randomized. One patient was randomized but did not receive any treatment; therefore, this patient was excluded from the ITT analysis set. Of the 130 patients that were randomized and treated in the control arm (PBO), only 28 patients finished the study by the time of the database lock. Ten patients discontinued the study, and 92 patients were still in the follow-up phase. In the TMC435 arm, 264 patients were randomized and treated. Sixty-two of them finished the study. Twenty-one patients discontinued the study and 181 patients were still in the follow-up phase.

The treatment disposition is summarized in Table 4. In the PBO arm, 45 (34.6%) patients completed treatment, while in the TMC435 arm, the treatment completion rate was much higher (87.5%). In the PBO arm, 80 (61.5%) patients discontinued the treatment because they achieved the virologic endpoint, 4 (3.1%) patients discontinued due to an AE and one patient (0.8%) discontinued due to non-compliance. In the TMC435 arm, 12 (4.5%) patients discontinued because they reached a virologic endpoint, 9 (3.4%) patients discontinued due to AE, 5 (1.9%) patients discontinued due to non-compliance, 5 (1.9%) discontinued due to withdrawal of consent and 2 (0.8%) patients discontinued due to other reasons.

The treatment disposition with respect to PegIFN and RBV are summarized in Table 5 and Table 6, respectively. Compared with the PBO arm, the TMC435 arm had higher completion rates for Peg-IFN and RBV (around 86% vs. 61% for both PegIFN and RBV).

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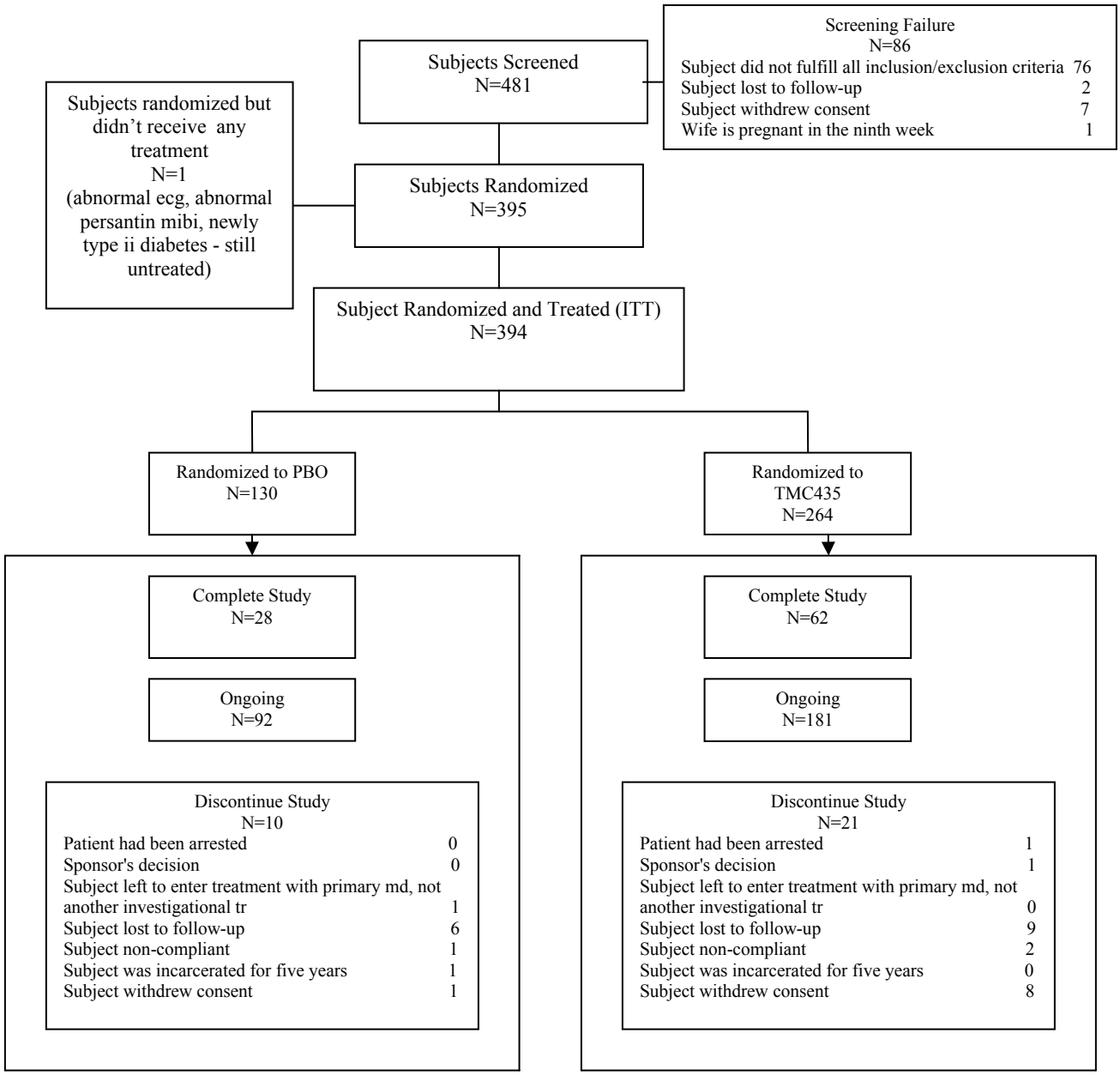
Figure 1: Study 208: Study Disposition



Source: Statistical Reviewer's analysis

Table 4: Subject Treatment Completion Status of PBO/TMC435 (ITT Analysis Set)

Treatment Disposition(PBO/TMC435)	**PBO (N=130)**	**TMC435 (N=264)**
Completed	45(34.6%)	231(87.5%)
Discontinued	85(65.4%)	33(12.5%)
Adverse event	4(3.1%)	9(3.4%)
Subject lost to follow-up	0	1(0.4%)
Subject non-compliant	1(0.8%)	5(1.9%)
Subject reached a virologic endpoint	80(61.5%)	12(4.5%)
Subject withdrew consent	0	5(1.9%)
Subject incarcerated during the study	0	1(0.4%)

Source: Statistical Reviewer's analysis.

Table 5: Subject Treatment Completion Status of PegIFN (ITT Analysis Set)

Treatment Disposition(PegINF)	**PBO (N=130)**	**TMC435 (N=264)**
Completed	79(60.8%)	230(87.1%)
Discontinued	51(39.2%)	34(12.9%)
Adverse event	12(9.2%)	8(3.0%)
Subject decision after applicant's interruption of the experimental drug	1(0.8%)	0
Subject arrested	0	1(0.4%)
Subject decision to stop medication	1(0.8%)	0
Subject lost to follow-up	1(0.8%)	3(1.1%)
Subject non-compliant	1(0.8%)	4(1.5%)
Subject reached a virologic endpoint	34(26.2%)	13(4.9%)
Subject withdrew consent	1(0.8%)	5(1.9%)

Source: Statistical Reviewer's analysis.

Table 6: Subject Treatment Completion Status of RBV
(ITT Analysis Set)

Treatment Disposition(RBV)	**PBO (N=130)**	**TMC435 (N=264)**
Completed	79(60.8%)	228(86.4%)
Discontinued	51(39.2%)	36(13.6%)
Adverse event	12(9.23%)	10(3.8%)
Subject decision after r applicant's interruption of the experimental drug	1(0.77%)	0
Subject arrested	0	1(0.4%)
Subject decision to stop medication	1(0.8%)	0
Subject lost to follow-up	1(0.8%)	3(1.1%)
Subject non-compliant	1(0.8%)	4(1.5%)
Subject reached a virologic endpoint	34(26.2%)	13(4.9%)
Subject withdrew consent	1(0.8%)	5(1.9%)

Source: Statistical Reviewer's analysis.

3.2.3.1.2 Demographic and Baseline Characteristics

Table 7 and Table 8 summarize the patient demographic and baseline characteristics. The demographic and baseline characteristics distribution was comparable between the two treatment arms. Approximately 56% of the patients were male, and 57% of the patients were more than 45 years old. The majority of the patients (89%) were white. Approximately 36% of the patients had BMI <25kg/m^2. Regarding the IL28B, 29% of the patients were genotype CC patients, 57% of the patients were genotype CT and 14% of the patients were genotype TT. About 80% of the patients had baseline HCV RNA >800000 IU/mL and 30% of the patients had metavir fibrosis score F3-F4. At baseline 63% of the patients had ALT level above grade 0. About 56% of the patients were genotype 1a patients. The majority (86%) of the patients had IP-10 <=600pg/mL at baseline.

Table 7: Study 208: Demographic (ITT Analysis Set)

	PBO 12 Wks PR 48	TMC435 150mg 12 Wks PR 24/48	Total
Analysis Set: Intent-to-treat	130	264	394
Gender			
N	130	264	394
Female	56 (43.1%)	116 (43.9%)	172 (43.7%)
Male	74 (56.9%)	148 (56.1%)	222 (56.3%)
Race			
N	130	262	392
White	122 (93.8%)	227 (86.6%)	349 (89.0%)
Black or African American	4 (3.1%)	27 (10.3%)	31 (7.9%)
American Indian or Alaska Native	0	1 (0.4%)	1 (0.3%)
Native Hawaiian or Other Pacific Islander	1 (0.8%)	1 (0.4%)	2 (0.5%)
Asian	3 (2.3%)	5 (1.9%)	8 (2.0%)
Multiple	0	1 (0.4%)	1 (0.3%)
Ethnicity			
N	130	264	394
Hispanic or Latino	14 (10.8%)	35 (13.3%)	49 (12.4%)
Not Hispanic or Latino	116 (89.2%)	229 (86.7%)	345 (87.6%)
Age (years)			
N	130	264	394
≤45	53 (40.8%)	115 (43.6%)	168 (42.6%)
>45 - ≤65	76 (58.5%)	143 (54.2%)	219 (55.6%)
>65	1 (0.8%)	6 (2.3%)	7 (1.8%)
Age (years)			
N	130	264	394
Mean (SD)	45.7 (11.04)	46.3 (10.98)	46.1 (10.99)
Median	48.0	48.0	48.0
Range	(20; 66)	(19; 68)	(19; 68)
Body weight (kg)			
N	130	264	394
Mean (SD)	82.52 (21.478)	80.13 (17.316)	80.92 (18.797)
Median	80.60	78.70	78.91
Range	(42.0; 155.0)	(47.5; 135.3)	(42.0; 155.0)
Body mass index (kg/m^2)			
N	130	264	394
<25	47 (36.2%)	96 (36.4%)	143 (36.3%)
≥25 - <30	41 (31.5%)	100 (37.9%)	141 (35.8%)
≥30	42 (32.3%)	68 (25.8%)	110 (27.9%)
Body mass index (kg/m^2)			
N	130	264	394
Mean (SD)	28.15 (6.477)	27.48 (5.703)	27.70 (5.969)
Median	26.70	26.55	26.60
Range	(17.0; 53.5)	(16.5; 45.2)	(16.5; 53.5)
IL28B Genotype[a]			
N	130	264	394
CC	37 (28.5%)	77 (29.2%)	114 (28.9%)
CT	76 (58.5%)	150 (56.8%)	226 (57.4%)
TT	17 (13.1%)	37 (14.0%)	54 (13.7%)

[a] Results obtained from the central laboratory: may not be the same as stratified.

Source: Table 14 in Clinical Study Report for study TMC435-TiDP16-C208.

Table 8: Baseline Disease Characteristics (ITT Analysis Set)

	PBO 12 Wks PR 48	TMC435 150mg 12 Wks PR 24/48	Total
Analysis Set: Intent-to-treat	130	264	394
Baseline HCV RNA level (log_{10} IU/mL)			
N	130	264	394
Mean (SD)	6.29 (0.779)	6.43 (0.600)	6.39 (0.667)
Median	6.39	6.50	6.48
Range	(1.4; 7.5)	(4.2; 7.6)	(1.4; 7.6)
Baseline HCV RNA category (IU/mL)			
N	130	264	394
<400000	19 (14.6%)	28 (10.6%)	47 (11.9%)
≥400000 - ≤800000	15 (11.5%)	18 (6.8%)	33 (8.4%)
>800000	96 (73.8%)	218 (82.6%)	314 (79.7%)
Metavir fibrosis score[a]			
N	130	260	390
Score F0-F1	50 (38.5%)	118 (45.4%)	168 (43.1%)
Score F2	40 (30.8%)	65 (25.0%)	105 (26.9%)
Score F3	23 (17.7%)	46 (17.7%)	69 (17.7%)
Score F4	17 (13.1%)	31 (11.9%)	48 (12.3%)
Baseline ALT WHO toxicity grade			
N	130	264	394
Grade 0	41 (31.5%)	106 (40.2%)	147 (37.3%)
Grade 1	55 (42.3%)	100 (37.9%)	155 (39.3%)
Grade 2	26 (20.0%)	48 (18.2%)	74 (18.8%)
Grade 3	7 (5.4%)	7 (2.7%)	14 (3.6%)
Grade 4	1 (0.8%)	3 (1.1%)	4 (1.0%)
HCV geno/subtype (NS5B)[b]			
N	130	264	394
1a	74 (56.9%)	147 (55.7%)	221 (56.1%)
1b	56 (43.1%)	117 (44.3%)	173 (43.9%)
Time since diagnosis (years)			
N	130	264	394
Mean (SD)	5.78 (6.636)	6.30 (6.681)	6.13 (6.663)
Median	2.80	3.35	3.30
Range	(0.3; 33.6)	(0.2; 35.5)	(0.2; 35.5)
IP-10 Category			
N	130	263	393
≤600 pg/mL	110 (84.6%)	226 (85.9%)	336 (85.5%)
>600 pg/mL	20 (15.4%)	37 (14.1%)	57 (14.5%)

[a] Limited to results from Metavir scoring system.
[b] HCV geno/subtype is based on the NS5B assay, and if not available on LiPA HCV II or Trugene results.

Source: Table 15 in Clinical Study Report for study TMC435-TiDP16-C208.

3.2.3.2 Study 216

3.2.3.2.1 Patient Disposition

Figure 2 displays the study disposition for Study 216. There were 474 patients screened, and 393 patients were randomized. Two patients were randomized but did not receive any treatment; therefore, they were excluded from the ITT analysis set. Of the 134 patients that were randomized and treated with PBO, 51 patients finished the study by the time of the database lock. Seventeen patients discontinued the study, and 66 patients were still in the follow-up phase. In the TMC435 arm, 257 patients were randomized and treated. One hundred and eleven of them finished the study. Twelve patients discontinued the study, and 134 patients were still in the follow-up phase.

The treatment disposition of PBO and TMC435 is summarized in Table 9. In the PBO arm, 51 (38.1%) patients completed the PBO treatment, while in the TMC435 arm, the treatment completion rate was much higher (96.1%). In the PBO arm, 82 (61.2%) patients discontinued the treatment because they reached a virologic endpoint. Only one (0.7%) patient discontinued due to AE. In the TMC435 arm, 3 (1.2%) patients discontinued because patients reached a virologic endpoint, 4 (1.6%) patients discontinued due to AE, 1 (0.4%) patient discontinued due to non-compliance and 2 (0.8%) patients discontinued due to withdrawal of consent.

The treatment disposition with respect to PegIFN and RBV are summarized in Table 10 and Table 11, respectively. Compared with the PBO arm, the TMC435 arm also has higher completion rates for PegIFN and RBV (92% vs. 60% for both PEG-IFN and RBV).

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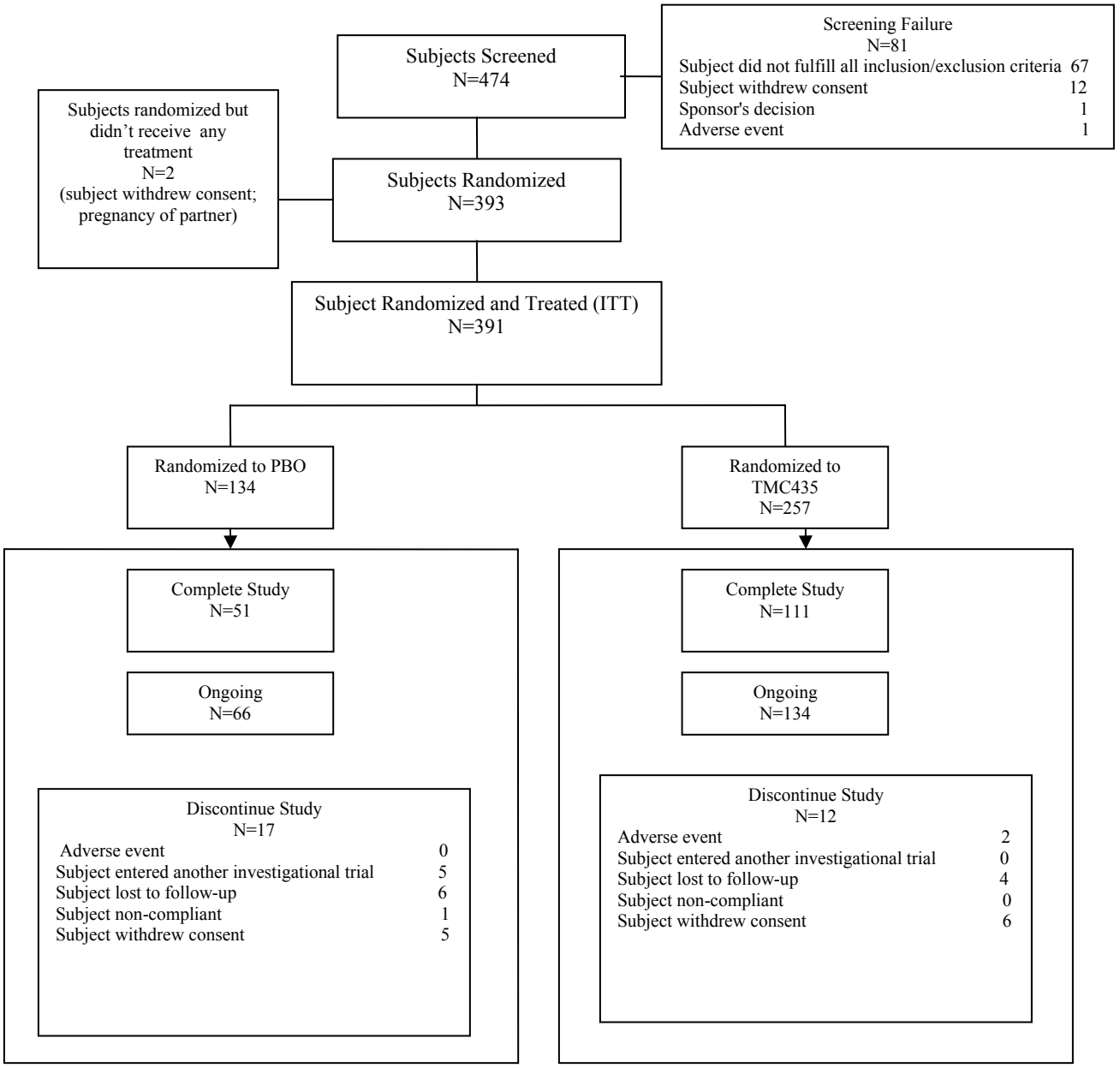
Figure 2: Study Disposition



Source: Statistical Reviewer's analysis.

Table 9: Subject Treatment Completion Status of PBO/TMC435 (ITT Analysis Set)

Treatment Disposition(PBO and TMC435)	**PBO (N=134)**	**TMC435 (N=257)**
Completed	51(38.1%)	247(96.1%)
Discontinued	83(61.9%)	10(3.9%)
Adverse event	1(0.7%)	4(1.6%)
Subject non-compliant	0	1(0.4%)
Subject reached a virologic endpoint	82(61.2%)	3(1.2%)
Subject withdrew consent	0	2(0.8%)

Source: Statistical Reviewer's analysis.

Table 10: Subject Treatment Completion Status of PegIFN (ITT Analysis Set)

Treatment Disposition(PegINF)	**PBO (N=134)**	**TMC435 (N=257)**
Completed	81(60.4%)	236(91.8%)
Discontinued	53(39.6%)	21(8.2%)
Adverse event	9(6.7%)	7(2.7%)
Subject lost to follow-up	2(1.5%)	0
Subject non-compliant	2(1.5%)	2(0.8%)
Subject reached a virologic endpoint	38(28.4%)	7(2.7%)
Subject withdrew consent	2(1.5%)	5(1.9%)

Source: Statistical Reviewer's analysis.

Table 11: Subject Treatment Completion Status of RBV (ITT Analysis Set)

Treatment Disposition(RBV)	**PBO (N=134)**	**TMC435 (N=257)**
Completed	81(60.4%)	237(92.2%)
Discontinued		
Adverse event	10(7.5%)	6(2.3%)
Subject lost to follow-up	2(1.5%)	0
Subject non-compliant	1(0.7%)	2(0.8%)
Subject reached a virologic endpoint	38(28.4%)	7(2.7%)
Subject withdrew consent	2(1.5%)	5(1.9%)

Source: Statistical Reviewer's analysis.

3.2.3.2.2 Demographic and Baseline Characteristics

Table 12 and Table 13 summarize the patient demographic and baseline characteristics for Study 216. The demographic and baseline characteristics distribution was comparable between the two treatment arms. Approximately 56% of the patients were male, and 54% of the patients were more than 45 years old. The majority of the patients (92%) were white. Approximately 43% of the patients had BMI <25kg/m^2. Regarding the IL28B, 30% of the patients were genotype CC patients, 55% of the patients were genotype CT and 16% of the patients were genotype TT. About 76% of the patients had baseline HCV RNA >800000 IU/mL and 22% of the patients had metavir fibrosis score F3-F4. At baseline, 62% of the patients had ALT level above grade 0. About 41% of the patients were genotype 1a patients. The majority (87%) of the patients had IP-10 <=600pg/mL at baseline.

Table 12: Demographic (ITT Analysis Set)

	PBO 12 Wks PR 48	TMC435 150 mg 12 Wks PR 24/48	Total
Analysis Set: Intent-to-treat	134	257	391
Gender			
N	134	257	391
Female	57 (42.5%)	117 (45.5%)	174 (44.5%)
Male	77 (57.5%)	140 (54.5%)	217 (55.5%)
Race			
N	134	257	391
White	123 (91.8%)	237 (92.2%)	360 (92.1%)
Black or African American	10 (7.5%)	16 (6.2%)	26 (6.6%)
American Indian or Alaska Native	0	1 (0.4%)	1 (0.3%)
Native Hawaiian or Other Pacific Islander	0	0	0
Asian	1 (0.7%)	2 (0.8%)	3 (0.8%)
Multiple	0	1 (0.4%)	1 (0.3%)
Ethnicity			
N	134	257	391
Hispanic or Latino	25 (18.7%)	60 (23.3%)	85 (21.7%)
Not Hispanic or Latino	109 (81.3%)	197 (76.7%)	306 (78.3%)
Age (years)			
N	134	257	391
≤45	58 (43.3%)	122 (47.5%)	180 (46.0%)
>45 - ≤65	72 (53.7%)	130 (50.6%)	202 (51.7%)
>65	4 (3.0%)	5 (1.9%)	9 (2.3%)
Age (years)			
N	134	257	391
Mean (SD)	45.7 (12.43)	45.2 (12.02)	45.4 (12.15)
Median	47.0	46.0	47.0
Range	(18; 73)	(18; 73)	(18; 73)
Body weight (kg)			
N	134	257	391
Mean (SD)	78.97 (15.907)	76.25 (16.500)	77.18 (16.330)
Median	78.85	75.00	76.20
Range	(44.5; 134.3)	(44.9; 145.8)	(44.5; 145.8)
Body Mass Index (kg/m^2)			
N	132	257	389
<25	56 (42.4%)	111 (43.2%)	167 (42.9%)
≥25 - <30	48 (36.4%)	101 (39.3%)	149 (38.3%)
≥30	28 (21.2%)	45 (17.5%)	73 (18.8%)
Body Mass Index (kg/m^2)			
N	132	257	389
Mean (SD)	26.74 (5.039)	26.37 (5.268)	26.50 (5.188)
Median	26.20	25.80	26.00
Range	(18.1; 51.6)	(17.5; 53.5)	(17.5; 53.5)
IL28B Genotype[a]			
N	134	257	391
CC	42 (31.3%)	75 (29.2%)	117 (29.9%)
CT	71 (53.0%)	142 (55.3%)	213 (54.5%)
TT	21 (15.7%)	40 (15.6%)	61 (15.6%)

[a] Results obtained from the central laboratory: may not be the same as stratified..

Source: Table 14 in Clinical Study Report for study TMC435-TiDP16-C216.

Table 13: Baseline Disease Characteristics (ITT Analysis Set)

	PBO 12 Wks PR 48	TMC435 150mg 12 Wks PR 24/48	Total
Analysis Set: Intent-to-treat	134	257	391
Baseline HCV RNA level (log_{10} IU/mL)			
N	134	257	391
Mean (SD)	6.38 (0.679)	6.38 (0.651)	6.38 (0.660)
Median	6.50	6.51	6.51
Range	(4.4; 7.5)	(4.0; 7.6)	(4.0; 7.6)
Baseline HCV RNA category (IU/mL)			
N	134	257	391
<400000	19 (14.2%)	31 (12.1%)	50 (12.8%)
≥400000 - ≤800000	17 (12.7%)	27 (10.5%)	44 (11.3%)
>800000	98 (73.1%)	199 (77.4%)	297 (76.0%)
Metavir fibrosis score[a]			
N	134	248	382
Score F0-F1	60 (44.8%)	130 (52.4%)	190 (49.7%)
Score F2	42 (31.3%)	65 (26.2%)	107 (28.0%)
Score F3	17 (12.7%)	36 (14.5%)	53 (13.9%)
Score F4	15 (11.2%)	17 (6.9%)	32 (8.4%)
Baseline ALT WHO toxicity grade			
N	134	257	391
Grade 0	55 (41.0%)	92 (35.8%)	147 (37.6%)
Grade 1	49 (36.6%)	105 (40.9%)	154 (39.4%)
Grade 2	22 (16.4%)	49 (19.1%)	71 (18.2%)
Grade 3	6 (4.5%)	10 (3.9%)	16 (4.1%)
Grade 4	2 (1.5%)	1 (0.4%)	3 (0.8%)
HCV geno/subtype (NS5B)[b]			
N	134	257	391
1	1 (0.7%)	0	1 (0.3%)
1a	54 (40.3%)	105 (40.9%)	159 (40.7%)
1b	77 (57.5%)	150 (58.4%)	227 (58.1%)
1e	1 (0.7%)	1 (0.4%)	2 (0.5%)
1g	1 (0.7%)	0	1 (0.3%)
1l	0	1 (0.4%)	1 (0.3%)
Time since diagnosis (years)			
N	134	257	391
Mean (SD)	3.76 (5.120)	5.39 (6.561)	4.83 (6.148)
Median	1.40	2.30	2.00
Range	(0.1; 21.6)	(0.1; 31.3)	(0.1; 31.3)
IP-10 Category			
N	134	257	391
≤600 pg/mL	109 (81.3%)	230 (89.5%)	339 (86.7%)
>600 pg/mL	25 (18.7%)	27 (10.5%)	52 (13.3%)

[a] Limited to results from Metavir scoring system.
[b] HCV geno/subtype is based on the NS5B assay, and if not available on LiPA HCV II or Trugene results.

Source: Table 15 in Clinical Study Report for study TMC435-TiDP16-C216.

3.2.3.3 Study 3007

3.2.3.3.1 Patient Disposition

Figure 3 displays the patient study disposition for Study 3007. There were 462 patients screened in total and 394 patients were randomized. One patient was randomized but did not receive any treatment; therefore this patient was excluded from the ITT analysis set. Of the 133 patients that were randomized and treated with PBO, fifty-seven patients finished the study by the time of the database lock. Fourteen patients discontinued the study, and 62 patients were still in the follow-up phase. In the TMC435 arm, 260 patients were randomized and treated. One hundred and twenty-seven of them finished the study. Ten patients discontinued the study, and 123 patients were still in the follow-up phase.

The treatment disposition of PBO and TMC435 is summarized in Table 14. In the PBO arm, 37 (27.8%) patients completed the PBO treatment, while in the TMC435 arm, the treatment completion rate was much higher (96.5%). In the PBO arm, 93 (69.9%) discontinued the treatment because they reached a virologic endpoint, 1 (0.8%) patient discontinued due to lost to follow-up and 2 (1.5%) patients discontinued due to withdrawal of consent. In the TMC435 arm, only 4 (1.5%) patients discontinued because patients reached a virologic endpoint, 1 (0.4%) patient discontinued due to AE, 1 (0.4%) patient discontinued due to lost to follow-up, 1 (0.4%) patient discontinued due to non-compliance and 2 (0.8%) patients discontinued due to withdrawal of consent.

The treatment disposition with respect to PegIFN and RBV is summarized in Table 15 and Table 16, respectively. Compared with the PBO arm, the TMC435 arm also has higher completion rate for PegIFN and RBV (around 94% vs. 72% for both PegIFN and RBV).

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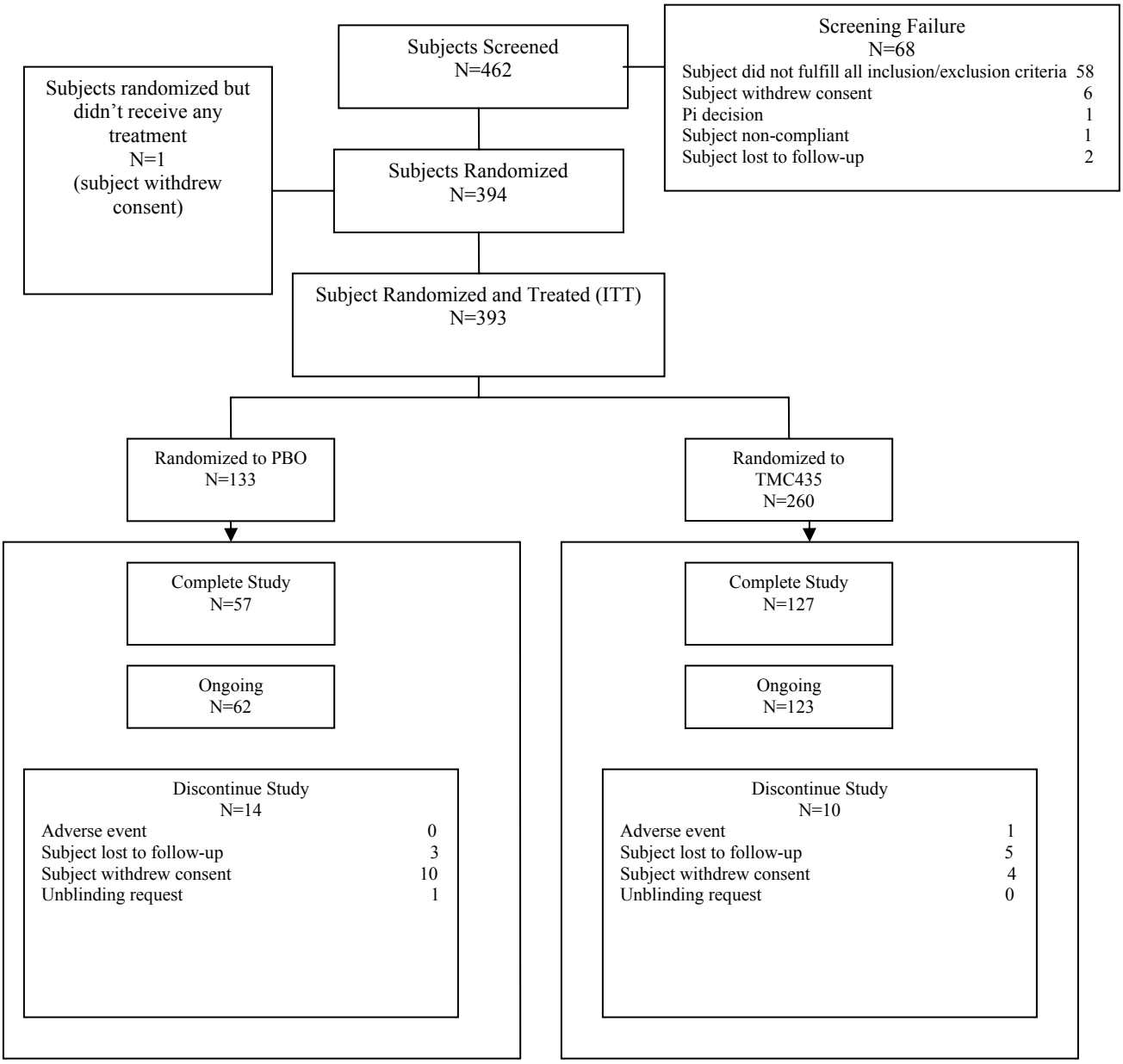
Figure 3: Study Disposition



Source: Statistical Reviewer's analysis.

Table 14: Subject Treatment Completion Status of PBO/TMC435 (ITT Analysis Set)

Treatment Disposition(PBO and TMC435)	**PBO (N=133)**	**TMC435 (N=260)**
Completed	37(27.8%)	251(96.5%)
Discontinued	96(72.2)	9(3.5%)
Adverse event	0	1(0.4%)
Subject lost to follow-up	1(0.8%)	1(0.4%)
Subject non-compliant	0	1(0.4%)
Subject reached a virologic endpoint	93(69.9%)	4(1.5%)
Subject withdrew consent	2(1.5%)	2(0.8%)

Source: Statistical Reviewer's analysis.

Table 15: Subject Treatment Completion Status of PegIFN (ITT Analysis Set)

Treatment Disposition(PegIFN)	**PBO (N=133)**	**TMC435 (N=260)**
Completed	96(72.2%)	243(93.5%)
Discontinued	37(27.8%)	17(6.5%)
Adverse event	6(4.5%)	6(2.3%)
Subject lost to follow-up	2(1.5%)	1(0.4%)
Subject non-compliant	2(1.5%)	1(0.4%)
Subject reached a virologic endpoint	13(9.8%)	5(1.9%)
Subject withdrew consent	12(9.0%)	4(1.5%)
Subject withdrew himself from study medications	1(0.8%)	0
Unblind procedure	1(0.8%)	0

Source: Statistical Reviewer's analysis.

Table 16: Subject Treatment Completion Status of RBV (ITT Analysis Set)

Treatment Disposition(RBV)	**PBO (N=133)**	**TMC435 (N=260)**
Completed	95(71.4%)	243(93.5%)
Discontinued	38(28.6%)	17(6.5%)
Adverse event	7(5.3%)	6(2.3%)
Subject lost to follow-up	2(1.5%)	1(0.4%)
Subject non-compliant	2(1.5%)	1(0.4%)
Subject reached a virologic endpoint	13(9.8%)	5(1.9%)
Subject withdrew consent	12(9.0%)	4(1.5%)
Subject withdrew himself from study medications	1(0.8%)	0
Unblind procedure	1(0.8%)	0

Source: Statistical Reviewer's analysis.

3.2.3.3.2 Demographic and Baseline Characteristics

Table 17 and Table 18 summarize the patient demographic and baseline characteristics. The demographic and baseline characteristics distribution was comparable between the two treatment arms. Approximately 66% of the patients were male and 71% of the patients were more than 45 years old. The majority of the patients (94%) were white. Approximately 31% of the patients had BMI <25kg/m^2. Regarding the IL28B, 24% of the patients were genotype CC patients, 64% of the patients were genotype CT and 12% of the patients were genotype TT. About 84% of the patients had baseline HCV RNA >800000 IU/mL and 31% of the patients had metavir fibrosis score F3-F4. At baseline 61% of the patients had ALT level above grade 0. About 42% of the patients were genotype 1a patients. Approximately 68% of the patients were previously treated with PegIFNα-2a/RBV and 27% of the patients were previously treated with PegIFNα-2b/RBV.

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Table 17: Demographic (ITT Analysis Set)

	PBO 12 Wks PR 48	TMC435 150mg 12 Wks PR 24/48	Total
Analysis Set: Intent-to-treat	133	260	393
Gender			
N	133	260	393
Female	54 (40.6%)	81 (31.2%)	135 (34.4%)
Male	79 (59.4%)	179 (68.8%)	258 (65.6%)
Race			
N	133	260	393
White	128 (96.2%)	243 (93.5%)	371 (94.4%)
Black or African American	4 (3.0%)	7 (2.7%)	11 (2.8%)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	1 (0.4%)	1 (0.3%)
Asian	1 (0.8%)	8 (3.1%)	9 (2.3%)
Multiple	0	1 (0.4%)	1 (0.3%)
Ethnicity			
N	133	260	393
Hispanic or Latino	6 (4.5%)	20 (7.7%)	26 (6.6%)
Not Hispanic or Latino	127 (95.5%)	240 (92.3%)	367 (93.4%)
Age (years)			
N	133	260	393
≤45	35 (26.3%)	78 (30.0%)	113 (28.8%)
>45 - ≤65	95 (71.4%)	172 (66.2%)	267 (67.9%)
>65	3 (2.3%)	10 (3.8%)	13 (3.3%)
Age (years)			
N	133	260	393
Mean (SD)	50.3 (10.76)	49.7 (10.27)	49.9 (10.43)
Median	52.0	52.0	52.0
Range	(21; 71)	(20; 70)	(20; 71)
Body weight (kg)			
N	133	260	393
Mean (SD)	79.51 (15.095)	81.88 (15.981)	81.08 (15.708)
Median	79.00	82.00	81.00
Range	(45.8; 126.0)	(37.0; 141.0)	(37.0; 141.0)
Body Mass Index (kg/m^2)			
N	133	260	393
<25	45 (33.8%)	78 (30.0%)	123 (31.3%)
≥25 - <30	52 (39.1%)	116 (44.6%)	168 (42.7%)
≥30	36 (27.1%)	66 (25.4%)	102 (26.0%)
Body Mass Index (kg/m^2)			
N	133	260	393
Mean (SD)	27.10 (4.569)	27.36 (4.433)	27.27 (4.475)
Median	26.80	27.20	27.00
Range	(18.5; 41.6)	(14.3; 47.7)	(14.3; 47.7)
IL28B Genotype[a]			
N	133	260	393
CC	34 (25.6%)	62 (23.8%)	96 (24.4%)
CT	83 (62.4%)	167 (64.2%)	250 (63.6%)
TT	16 (12.0%)	31 (11.9%)	47 (12.0%)

[a] Results obtained from the central laboratory: may not be the same as stratified.

Source: Table 15 in Clinical Study Report for study TMC435HPC3007.

Table 18: Baseline Disease Characteristics (ITT Analysis Set)

	PBO 12 Wks PR 48	TMC435 150mg 12 Wks PR 24/48	Total
Analysis Set: Intent-to-treat	133	260	393
Baseline HCV RNA level (log_{10} IU/mL)			
N	133	260	393
Mean (SD)	6.47 (0.624)	6.42 (0.555)	6.44 (0.579)
Median	6.54	6.42	6.49
Range	(3.1; 7.5)	(4.6; 7.7)	(3.1; 7.7)
Baseline HCV RNA category (IU/mL)			
N	133	260	393
<400000	9 (6.8%)	21 (8.1%)	30 (7.6%)
≥400000 - ≤800000	14 (10.5%)	20 (7.7%)	34 (8.7%)
>800000	110 (82.7%)	219 (84.2%)	329 (83.7%)
Metavir fibrosis score[a]			
N	132	250	382
Score F0-F1	47 (35.6%)	87 (34.8%)	134 (35.1%)
Score F2	51 (38.6%)	80 (32.0%)	131 (34.3%)
Score F3	15 (11.4%)	44 (17.6%)	59 (15.4%)
Score F4	19 (14.4%)	39 (15.6%)	58 (15.2%)
Baseline ALT WHO toxicity grade			
N	133	260	393
Grade 0	48 (36.1%)	104 (40.0%)	152 (38.7%)
Grade 1	52 (39.1%)	96 (36.9%)	148 (37.7%)
Grade 2	24 (18.0%)	47 (18.1%)	71 (18.1%)
Grade 3	8 (6.0%)	11 (4.2%)	19 (4.8%)
Grade 4	1 (0.8%)	2 (0.8%)	3 (0.8%)
HCV geno/subtype (NS5B)[b]			
N	133	260	393
1	0	1 (0.4%)	1 (0.3%)
1a	54 (40.6%)	110 (42.3%)	164 (41.7%)
1b	79 (59.4%)	149 (57.3%)	228 (58.0%)
Time since diagnosis (years)			
N	133	260	393
Mean (SD)	10.76 (6.409)	10.34 (6.550)	10.48 (6.498)
Median	10.40	8.65	9.30
Range	(1.9; 30.4)	(1.3; 33.1)	(1.3; 33.1)
Previous hepatitis C therapy			
N	133	260	393
PegIFNa-2a/RBV	88 (66.2%)	178 (68.5%)	266 (67.7%)
PegIFNa-2b/RBV	36 (27.1%)	70 (26.9%)	106 (27.0%)
Other	9 (6.8%)	12 (4.6%)	21 (5.3%)

[a] Limited to results from Metavir scoring system.
[b] HCV geno/subtype is based on the NS5B assay, and if not available on LiPA HCV II or Trugene results.

Source: Table 15 in Clinical Study Report for study TMC435HPC3007.

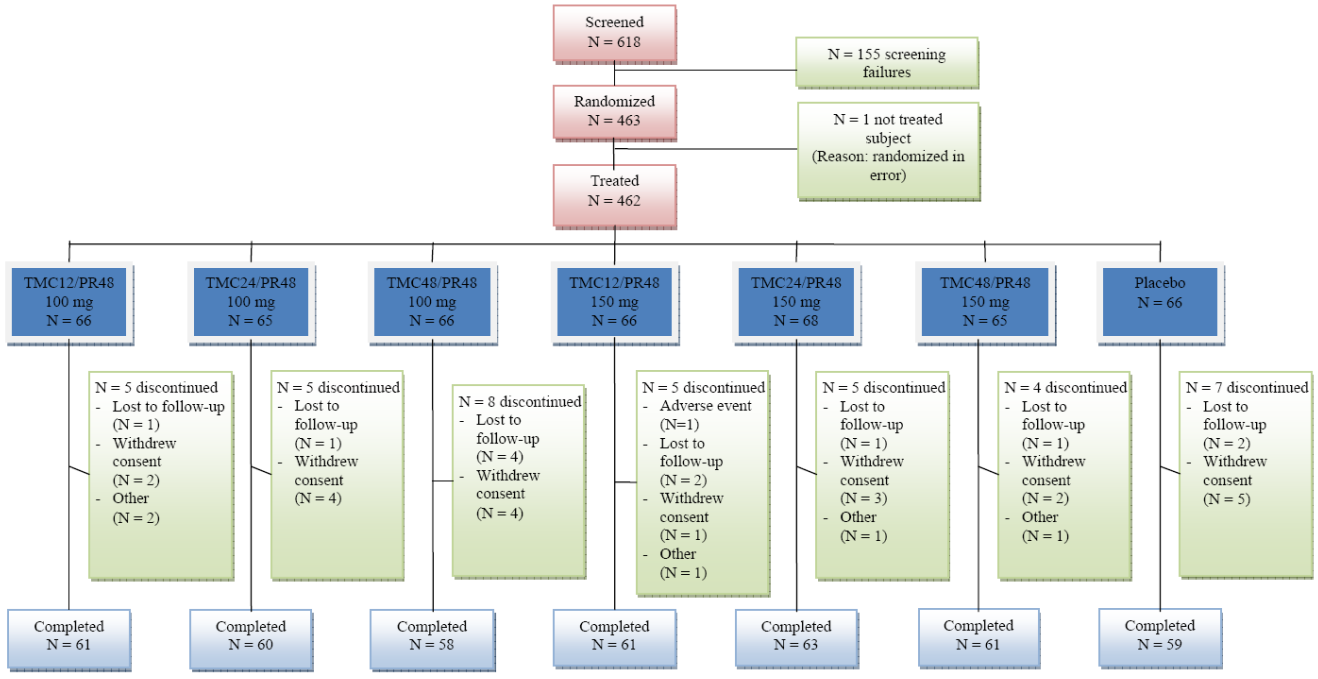
3.2.3.4 Study 206

3.2.3.4.1 Patient Disposition

Figure 4 displays the study disposition for Study 206. There were 618 patients screened and 463 patients were randomized. One patient was randomized but did not receive any treatment. Therefore this patient was excluded from the ITT analysis set. The majority of the patients in each arm completed the study. The study discontinuation rates were 6%-12%.

The treatment discontinuation of PBO and TMC434 is summarized in Table 19. For TMC435/PBO, the discontinuation rate for the TMC435 arms ranged from 21.5% to 29.2%. The placebo arm had a high discontinuation rate of 60.6%. This was primarily due to subjects who reached a virologic endpoint.

Figure 4: Study Disposition



Source: Figure 2 in the Clinical Study Report for study TiDP16-C206.

Table 19: Subject Treatment Completion Status of PBO/TMC435 (ITT Analysis Set)

Treatment Disposition (PBO and TMC435)	TMC12 PR48 100 mg N = 66	TMC24 PR48 100 mg N = 65	TMC48 PR48 100 mg N = 66	TMC12 PR48 150 mg N = 66	TMC24 PR48 150 mg N = 68	TMC48 PR48 150 mg N = 65	Placebo N = 66
Completed	49(74.2%)	46(70.8%)	47(71.2%)	50(75.8%)	52(76.5%)	51(78.5%)	26(39.4%)
Discontinued	17(25.8%)	19(29.2%)	19(28.8%)	16(24.2%)	16(23.5%)	14(21.5%)	40(60.6%)
Adverse event	6(9.1%)	4(6.2%)	5(7.6%)	4(6.1%)	7(10.3%)	6(9.2%)	2(3.0%)
Subject lost to follow-up	0	0	2(3.0%)	0	0	1(1.5%)	0
Subject non-compliant	0	2(3.1%)	1(1.5%)	0	0	0	0
Subject reached a virologic endpoint	10(15.2%)	11(16.9%)	10(15.2%)	11(16.8%)	8(11.8%)	6(9/2%)	35(53.0%)
Subject withdrew consent	0	2(3.1%)	0	1(1.5%)	1(1.5%)	0	2(3.0%)
Other	1(1.5%)	0	1(1.5%)	0	0	1(1.5%)	1(1.5%)

Source: Statistical Reviewer's analysis.

3.2.3.4.2 Demographic and Baseline Characteristics

Table 20 and Table 21 summarize the patient demographic and baseline characteristics. The demographic and baseline characteristics distribution was comparable among the treatment arms. Approximately 67% of the patients were male and the median age was 50 years old. The majority of the patients (93%) were white. The median BMI was 27.2kg/m^2. Regarding the IL28B, 18% of the patients were genotype CC patients, 65% of the patients were genotype CT and 18% of the patients were genotype TT. About 86% of the patients had baseline HCV RNA >800000 IU/mL and 37% of the patients had metavir fibrosis score F3-F4. At baseline 63% of the patients had ALT level above grade 0. About 41% of the patients were genotype 1a patients.

Table 22 summarizes the proportion of response to prior PegIFN/RBV therapy. About 25% of the patients were null responders, 35% of the patients were partial responders and 40% of the patients were relapsers.

Table 20: Demographic (ITT Analysis Set)

Demo-graphic parameter, specification n (%)	TMC12 PR48 100 mg N = 66	TMC24 PR48 100 mg N = 65	TMC48 PR48 100 mg N = 66	TMC12 PR48 150 mg N = 66	TMC24 PR48 150 mg N = 68	TMC48 PR48 150 mg N = 65	Placebo N = 66	All Subjects N = 462
Gender								
Female	22 (33.3)	21 (32.3)	21 (31.8)	21 (31.8)	25 (36.8)	17 (26.2)	24 (36.4)	151 (32.7)
Male	44 (66.7)	44 (67.7)	45 (68.2)	45 (68.2)	43 (63.2)	48 (73.8)	42 (63.6)	311 (67.3)
Race								
White	59 (89.4)	60 (92.3)	62 (93.9)	61 (92.4)	61 (89.7)	63 (96.9)	62 (93.9)	428 (92.6)
Black	5 (7.6)	2 (3.1)	3 (4.5)	3 (4.5)	5 (7.4)	2 (3.1)	1 (1.5)	21 (4.5)
Asian	1 (1.5)	3 (4.6)	1 (1.5)	1 (1.5)	0	0	2 (3.0)	8 (1.7)
Other[a]	1 (1.5)	0	0	1 (1.5)	2 (2.9)	0	1 (1.5)	5 (1.1)
Age[b], years								
Median	51.5	50.0	50.0	48.0	51.5	50.0	50.5	50.0
[Range]	[20; 68]	[20; 68]	[22; 69]	[20; 63]	[25; 68]	[21; 69]	[22; 66]	[20; 69]
Body Weight, kg								
Median	82.6	78.9	80.0	78.3	82.9	80.9	84.8	80.8
[Range]	[43; 119]	[49; 138]	[53; 128]	[50; 116]	[56; 123]	[56; 125]	[53; 112]	[43; 138]
BMI, kg/m²								
Median	27.55	26.50	26.60	26.40	27.45	27.20	27.95	27.20
[Range]	[19.5; 42.3]	[18.9; 42.9]	[18.5; 48.7]	[18.2; 43.2]	[19.7; 42.4]	[18.9; 44.1]	[18.5; 40.5]	[18.2; 48.7]

N: number of subjects with data; n: number of subjects with that observation

[a] Other includes Native Hawaiian or other Pacific Islander, and American Indian or Alaska Native.

[b] At screening

Source: Table 20 in the Clinical Study Report for Study TMC435-TiDP16-C206.

Table 21: Baseline Disease Characteristics (ITT Analysis Set)

n (%)	TMC12 PR48 100 mg N = 66	TMC24 PR48 100 mg N = 65	TMC48 PR48 100 mg N = 66	TMC12 PR48 150 mg N = 66	TMC24 PR48 150 mg N = 68	TMC48 PR48 150 mg N = 65	Placebo N = 66	All Subjects N = 462
HCV RNA (log_{10} IU/mL), N'	**66**	**65**	**66**	**66**	**68**	**65**	**66**	**462**
Median	6.49	6.68	6.64	6.62	6.60	6.55	6.61	6.60
[Range]	[4.2; 7.5]	[4.8; 7.5]	[5.2; 7.5]	[3.5; 7.5]	[5; 7.7]	[4.9; 7.5]	[5.2; 7.6]	[3.5; 7.7]
HCV RNA Category (IU/mL), N'	**66**	**65**	**66**	**66**	**68**	**65**	**66**	**462**
< 400000	3 (4.5)	3 (4.6)	7 (10.6)	4 (6.1)	4 (5.9)	5 (7.7)	4 (6.1)	30 (6.5)
[400000; 800000]	5 (7.6)	3 (4.6)	1 (1.5)	5 (7.6)	6 (8.8)	6 (9.2)	7 (10.6)	33 (7.1)
> 800000	58 (87.9)	59 (90.8)	58 (87.9)	57 (86.4)	58 (85.3)	54 (83.1)	55 (83.3)	399 (86.4)
Metavir Score, N'	**65**	**63**	**66**	**66**	**67**	**64**	**64**	**455**
F0	6 (9.2)	3 (4.8)	6 (9.1)	5 (7.6)	11 (16.4)	1 (1.6)	7 (10.9)	39 (8.6)
F1	17 (26.2)	14 (22.2)	23 (34.8)	19 (28.8)	11 (16.4)	27 (42.2)	18 (28.1)	129 (28.4)
F2	21 (32.3)	17 (27.0)	9 (13.6)	18 (27.3)	21 (31.3)	16 (25.0)	16 (25.0)	118 (25.9)
F3	14 (21.5)	16 (25.4)	14 (21.2)	11 (16.7)	11 (16.4)	7 (10.9)	13 (20.3)	86 (18.9)
F4	7 (10.8)	13 (20.6)	14 (21.2)	13 (19.7)	13 (19.4)	13 (20.3)	10 (15.6)	83 (18.2)
Baseline ALT Toxicity Grade, N'	**66**	**65**	**66**	**66**	**68**	**65**	**66**	**462**
Grade 0	30 (45.5)	16 (24.6)	21 (31.8)	26 (39.4)	25 (36.8)	22 (33.8)	29 (43.9)	169 (36.6)
Grade 1	25 (37.9)	41 (63.1)	25 (37.9)	29 (43.9)	32 (47.1)	28 (43.1)	26 (39.4)	206 (44.6)
Grade 2	9 (13.6)	7 (10.8)	16 (24.2)	10 (15.2)	9 (13.2)	15 (23.1)	8 (12.1)	74 (16.0)
Grade 3	2 (3.0)	1 (1.5)	4 (6.1)	1 (1.5)	2 (2.9)	0	3 (4.5)	13 (2.8)
HCV Geno/Subtype (NS5B), N'[a]	**66**	**63**	**65**	**66**	**65**	**64**	**66**	**455**
1a	26 (39.4)	28 (44.4)	25 (38.5)	30 (45.5)	29 (44.6)	23 (35.9)	27 (40.9)	188[b] (41.3)
1b	39 (59.1)	34 (54.0)	39 (60.0)	36 (54.5)	34 (52.3)	41 (64.1)	39 (59.1)	262 (57.6)
1d	0	1 (1.6)	0	0	1 (1.5)	0	0	2 (0.4)
1e	0	0	0	0	1 (1.5)	0	0	1 (0.2)
1i	0	0	1 (1.5)	0	0	0	0	1 (0.2)
6p[c]	1 (1.5)	0	0	0	0	0	0	1 (0.2)
Duration of HCV Infection (years), N'	**42**	**36**	**39**	**31**	**38**	**31**	**34**	**251**
Median	27.60	26.65	24.00	28.10	27.00	24.90	25.00	26.10
[Range]	[5.5; 48]	[6.1; 49.9]	[3.1; 55]	[2.5; 49]	[3.3; 56.9]	[3.9; 42.2]	[4.7; 46.2]	[2.5; 56.9]
Mode of HCV Infection, N'	**66**	**65**	**66**	**66**	**68**	**65**	**66**	**462**
Other	22 (33.3)	27 (41.5)	27 (40.9)	30 (45.5)	36 (52.9)	29 (44.6)	29 (43.9)	200 (43.3)
Blood transfusion	21 (31.8)	22 (33.8)	20 (30.3)	11 (16.7)	17 (25.0)	14 (21.5)	14 (21.2)	119 (25.8)
Intravenously injectable drug use	12 (18.2)	10 (15.4)	13 (19.7)	13 (19.7)	11 (16.2)	12 (18.5)	12 (18.2)	83 (18.0)
Multiple	9 (13.6)	3 (4.6)	2 (3.0)	7 (10.6)	3 (4.4)	8 (12.3)	7 (10.6)	39 (8.4)
Occupational exposure	1 (1.5)	1 (1.5)	2 (3.0)	1 (1.5)	0	0	2 (3.0)	7 (1.5)
Heterosexual contact	1 (1.5)	1 (1.5)	1 (1.5)	2 (3.0)	0	0	1 (1.5)	6 (1.3)
Mother to child transmission	0	1 (1.5)	0	0	1 (1.5)	1 (1.5)	1 (1.5)	4 (0.9)
Msm[d]	0	0	0	2 (3.0)	0	1 (1.5)	0	3 (0.6)
Hemophilia-associate injections	0	0	1 (1.5)	0	0	0	0	1 (0.2)

Table 21: Baseline Disease Characteristics (ITT Analysis Set)

n (%)	TMC12 PR48 100 mg N = 66	TMC24 PR48 100 mg N = 65	TMC48 PR48 100 mg N = 66	TMC12 PR48 150 mg N = 66	TMC24 PR48 150 mg N = 68	TMC48 PR48 150 mg N = 65	Placebo N = 66	All Subjects N = 462
***IL28B*, N**	**43**	**46**	**47**	**43**	**50**	**49**	**50**	**328**
CC	7 (16.3)	8 (17.4)	8 (17.0)	5 (11.6)	9 (18.0)	10 (20.4)	11 (22.0)	58 (17.7)
CT	32 (74.4)	30 (65.2)	28 (59.6)	30 (69.8)	32 (64.0)	28 (57.1)	32 (64.0)	212 (64.6)
TT	4 (9.3)	8 (17.4)	11 (23.4)	8 (18.6)	9 (18.0)	11 (22.4)	7 (14.0)	58 (17.7)

N: number of subjects from the ITT population; N': number of subjects with data; n: number of subjects with that observation

[a] Based on Virco NS5B assay. If the NS5B assay failed the results from the Trugene assay (used for stratification) were used.

[b] For 1 subject (CRF ID 202-0277), HCV genotype (NS5B) was not available in the database. Reanalysis of HCV genotype (NS5B) resulted in subtype 1a and the subject was considered as such for further analysis (Display GEN.8).

[c] At screening, HCV geno/subtype was 1 (Trugene Assay), therefore the subject (CRF ID 206-0555) was eligible for the study (Listing GEN.10).

[d] Men who have sex with men.

Source: Table 21 and Table 23 in the Clinical Study Report for Study TMC435-TiDP16-C206.

Table 22: Stratification Factors

n (%)	TMC12 PR48 100 mg N = 66	TMC24 PR48 100 mg N = 65	TMC48 PR48 100 mg N = 66	TMC12 PR48 150 mg N = 66	TMC24 PR48 150 mg N = 68	TMC48 PR48 150 mg N = 65	Placebo N = 66	All Subjects N = 462
Genotype 1 Subtype[a]								
1a	23 (34.8)	24 (36.9)	24 (36.4)	24 (36.4)	25 (36.8)	24 (36.9)	24 (36.4)	168 (36.4)
1b	37 (56.1)	36 (55.4)	36 (54.5)	36 (54.5)	36 (52.9)	36 (55.4)	37 (56.1)	254 (55.0)
Other	6 (9.1)	5 (7.7)	6 (9.1)	6 (9.1)	7 (10.3)	5 (7.7)	5 (7.6)	40 (8.7)
Response to Prior PegIFN/RBV Therapy[a]								
Null Responder	16 (24.2)	16 (24.6)	18 (27.3)	17 (25.8)	17 (25.0)	17 (26.2)	16 (24.2)	117 (25.3)
Partial Responder	23 (34.8)	23 (35.4)	22 (33.3)	23 (34.8)	24 (35.3)	22 (33.8)	23 (34.8)	160 (34.6)
Relapser	27 (40.9)	26 (40.0)	26 (39.4)	26 (39.4)	27 (39.7)	26 (40.0)	27 (40.9)	185 (40.0)

N: number of subjects with data; n: number of subjects with that observation; PR: PegIFNα-2a/RBV

[a] Genotype 1 subtype and response to prior PegIFN/RBV therapy as captured in IWRS

Source: Table 22 in the Clinical Study Report for Study TMC435-TiDP16-C206.

3.2.4 Results and Conclusions

Results and conclusions are first summarized for the naïve population evaluated in Study 208 and Study 216. Integrated data combining Studies 208 and 216 is then presented. Lastly, the results and conclusions of the experienced populations are summarized for Study 3007 (relapsers) and Study 206 (null responders, partial responders and relapsers).

3.2.4.1 Study C208

3.2.4.1.1 Primary Efficacy Endpoint

Table 23 summarizes the applicant's primary analysis. The percentage of patients that achieved SVR12 was 50% in the control arm and 79.5% in the TMC435 arm. The stratum-adjusted treatment difference was 29.3% (95% CI: 20.1%, 38.6%). This difference was statistically significant. Therefore, superiority of TMC435 over control was demonstrated in this study.

Table 24 and Table 25 summarize the reviewer's analyses based on the reviewer's definitions of SVR12 and SVR.

As shown in Table 26, one patient (TMC435-C208-0398) in the control arm had HCV RNA below detection at 12 weeks post treatment (Day 254) and 24 weeks post treatment (Day 338). This patient should have been considered as a SVR12 and SVR success. However, both of the records at Days 254 and 338 were before the SVR12 visit window according to the applicant's definition. Therefore, the patient was not counted as a success in the applicant's analysis.

Another patient (TMC435-C208-0312) in the control arm was considered as a SVR12 failure by the applicant since this patient did not meet the criteria of below detection at End of Treatment (EOT) which was not a requirement in the reviewer's analysis. In the reviewer's analysis, this patient was also considered as a SVR12 failure since the HCV RNA was greater than 25IU/mL in the Week 12 follow-up window (Day 267). However, this patient was considered as SVR success by the reviewer because the last HCV RNA records (day 435) were < 25 IU/mL.

Overall, the results of the reviewer's analyses were very similar to those of the applicant. In the reviewer's analysis, the percentage of patients who achieved SVR12 was 50.8% for the control arm and 79.5% for the TMC435 arm. The stratum-adjusted difference for SVR12 was 28.5% (95% CI: 19.4%, 37.7%). The percentage of patients who achieved SVR was 51.5% for the control arm and 79.5% for the TMC 435 arm. The stratum-adjusted difference for the SVR was 27.8% with a 95% CI of (18.6%, 37.0%).

The superiority of TMC435 to placebo was also demonstrated in the reviewer's analysis.

Table 23: Applicant's Primary Endpoint: Sustained Virologic Response 12 Weeks After the Planned End of Treatment (SVR12)

	Observed	Stratum Adjusted	Comparison versus Placebo	
	n/N (%)	% (95% CI)[c]	Difference in proportions (95% CI)[b]	p-value[a]
SVR12				
PBO 12Wks PR48	65/130 (50.0)	50.1 (42.1;58.1)		
TMC435 150 mg 12Wks PR24/48	210/264 (79.5)	79.4 (74.7;84.0)	29.3 (20.1;38.6)	<0.001

[a] based on the CMH test controlling for stratification factors.
[b] difference in proportions (active – placebo) adjusted for stratification factors and the corresponding 95% CI based on the normal approximation.
[c] proportions adjusted for stratification factors and the corresponding 95% CIs based on the normal approximation.
Stratification factors are *IL28B* and HCV geno/subtype. HCV geno/subtype is based on the NS5B assay (and if not available, LIPA II, Trugene or stratification result is used) and categorized as 1b versus 1a.

The p-value for the Breslow-Day test for homogeneity of odds ratios was 0.208.

Source: Table 25 in Clinical Study Report for study TMC435-TiDP16-C208.

Table 24: Sustained Virologic Response 12 Weeks Post Treatment (SVR12) (ITT Analysis Set)

	PBO (N=130)	**TMC435 (N=264)**
SVR12 n(%)	66(50.8%)	210(79.5%)
Stratum-adjusted Treatment Difference (TMC435- PBO) (95% CI)*	28.5% (19.4%, 37.7%)	

* The treatment difference and 95% confidence interval were adjusted for stratification factors *(IL28B: CC, CT and TT; Subgenotype 1a/other, 1b)*
Source: Statistical Reviewer's analysis.

Table 25: Sustained Virologic Response (SVR)[#] (ITT Analysis Set)

	PBO (N=130)	**TMC435 (N=264)**
SVR n(%)	67(51.5%)	210(79.5%)
Stratum-adjusted Treatment Difference (TMC435- PBO) (95% CI)*	27.8% (18.6%, 37.0%)	

SVR was defined as HCV RNA <25/IU/mL 12 weeks after the end of treatment. The 12 weeks post treatment window for the post-treatment day is [57, +∞]. If there was more than one record, the last record was taken.
* The treatment difference and 95% confidence interval were adjusted for stratification factors *(IL28B: CC, CT and TT; Subgenotype 1a/other, 1b)*
Source: Statistical Reviewer's analysis.

Table 26: HCV RNA viral loads of patients who were considered as SVR success by the reviewer but not the applicant

Patient ID	TRT	Treatment Duration (days)	Sample day	VISIT	Lab Result (IU/mL)
TMC435-C208-0312	PBO	182	-27	SCREENING	1530000
			1	BASELINE	504000
			3	DAY3	228000
			7	DAY7	135000
			14	DAY14	144000
			28	DAY28	35900
			56	WEEK8	3420
			84	WEEK12	1200
			112	WEEK16	241
			140	WEEK20	330
			168	WEEK24	168
			183	WITHDRAWAL	135
			217	FOLLOW-UP1	48
			267	FOLLOW-UP2	55
			337	FOLLOW-UP3	<25 IU/mL HCV RNA detected
			435	FOLLOW-UP4	<25 IU/mL HCV RNA detected
TMC435-C208-0398	PBO	182	-29	SCREENING	10400000
			1	BASELINE	14400000
			3	DAY3	643000
			7	DAY7	327000
			15	DAY14	18300
			28	DAY28	114
			58	WEEK8	HCV RNA not detected
			83	WEEK12	HCV RNA not detected
			111	WEEK16	HCV RNA not detected
			134	WEEK20	HCV RNA not detected
			170	WEEK24	HCV RNA not detected
			210	WITHDRAWAL	HCV RNA not detected
			238	FOLLOW-UP1	HCV RNA not detected
			254	FOLLOW-UP2	HCV RNA not detected
			338	FOLLOW-UP3	HCV RNA not detected

Source: Statistical Reviewer's analysis.

Two hundred and twenty-two patients met the response-guided treatment criteria (RGT) of HCV RNA <25 IU/ml at Week 4 (detectable or undetectable) and undetectable HCV RNA at Week 12.

For those patients that met the RGT criteria, both the SVR12 and SVR rates were 90.5% as shown in Table 27.

Table 27: SVR12 and SVR of the Patients Who Met RGT Criteria

	SVR12	SVR
n/N (%)	201/222(90.5%)	201/222(90.5%)

Source: Statistical Reviewer's analysis.

3.2.4.1.2 On-treatment Virologic Response

HCV RNA records were considered to be on-treatment if the collection date was less than or equal to the date of the last dose + 3 days. Those on-treatment records were re-aligned according to the visit window. Below, Table 28 only summarizes the available records for each visit. No data was imputed for missing values.

Compared with the control arm, higher response rates in the TMC435 arm were observed across the visits with the exception of Week 48 where only 11 TMC435 patients were included in the denominator. At Week 4, the percentage of patients with HCV RNA below detection was 11.8% in the control arm and 79.5% in the TMC435 arm. At Week 12, approximately half of the patients had HCV RNA below detection in the control arm while the below detection rate was 92.8% in the TMC435 arm. By the end of the treatment, the percentage of patients who reached HCV RNA below detection was 65.4% in the control arm and 90.5% in the TMC435 arm.

Table 28: On-treatment Virologic Response by Visits

	PBO	***TMC435***
Week 2		
HCV RNA not detected	3/ 128(2.3%)	*92/ 257(35.8%)*
HCV RNA <25 IU/mL	8/ 128(6.3%)	*197/ 257(76.7%)*
Week 4		
HCV RNA not detected	15/ 127(11.8%)	*202/ 254(79.5%)*
HCV RNA <25 IU/mL	25/ 127(19.7%)	*230/ 254(90.6%)*
Week 12		
HCV RNA not detected	62/ 125(49.6%)	*231/ 249(92.8%)*
HCV RNA <25 IU/mL	75/ 125(60.0%)	*239/ 249(96.0%)*
Week 24		
HCV RNA not detected	80/ 97(82.5%)	*219/ 234(93.6%)*
HCV RNA <25 IU/mL	83/ 97(85.6%)	*222/ 234(94.9%)*
Week 48		
HCV RNA not detected	75/ 77(97.4%)	*10/ 11(90.9%)*
HCV RNA <25 IU/mL	76/ 77(98.7%)	*11/ 11(100.0%)*
EOT		
HCV RNA not detected	85/ 130(65.4%)	*239/ 264(90.5%)*
HCV RNA <25 IU/mL	*89/ 130(68.5%)*	*246/ 264(93.2%)*

Source: Statistical Reviewer's analysis.

3.2.4.1.3 Study 208: Relapse

A relapser is defined as a patient who achieved undetected HCV RNA at EOT but did not achieve SVR. Patients with missing follow-up HCV RNA were not included in the denominator. A higher relapse rate (20.5%) was observed in the control arm compared with TMC435 arm (10.3%) as shown in table 29.

Table 29: Viral Relapse

	PBO	***TMC435***
Relapse	17/83(20.5%)	24/233(10.3%)

Source: Statistical Reviewer's analysis.

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3.2.4.2 Study 216

3.2.4.2.1 Primary Efficacy Endpoint

Table 30 below summarizes the applicant's primary analysis for Study 216. The percentage of patients who achieved SVR12 was 50% in the control arm and 81.3% in the TMC435 arm. The stratum-adjusted treatment difference was 32.2% (95% CI: 23.3%, 41.2%. This difference was statistically significant. The superiority of TMC435 compared to placebo was demonstrated in this study.

Table 31 and Table 32 summarize the reviewer's analyses based on the reviewer's definitions of SVR12 and SVR. The result of the reviewer's analysis of SVR12 was the same as applicant's results. There were 4 patients in the TMC435 arm who achieved SVR12 but later relapsed. The HCV RNA viral loads of those 4 patients are listed in Table 33. Therefore, the percentage of patients achieving SVR was 79.8% in the TMC435 arm. The stratum adjusted-difference for SVR was 30.8% with 95% CI of (21.8%, 39.8%).

Table 30: Applicant's Primary Endpoint: Sustained Virologic Response 12 Weeks After the Planned End of Treatment (SVR12)

	Observed	Stratum Adjusted	Comparison versus Placebo	
	n/N (%)	% (95% CI)[c]	Difference in proportions (95% CI)[b]	p-value[a]
SVR12				
PBO 12Wks PR48	67/134 (50.0)	49.7 (42.0;57.3)		
TMC435 150 mg 12Wks PR24/48	209/257 (81.3)	81.9 (77.2;86.6)	32.2 (23.3;41.2)	<0.001

[a] based on the CMH test controlling for type of PegIFN/RBV and stratification factors.

[b] difference in proportions (active – placebo) adjusted for type of PegIFN/RBV and stratification factors and the corresponding 95% CI based on the normal approximation.

[c] proportions adjusted for the type of PegIFN/RBV and stratification factors with corresponding 95% CIs based on the normal approximation.

Stratification factors are *IL28B* and HCV geno/subtype. HCV geno/subtype is based on the NS5B assay (if not available, LiPA II or Trugene result is used) and categorized as 1b versus any other geno/subtype (1a/other).

The p-value for the Breslow-Day test for homogeneity of odds ratios was 0.954.

Source: Table 25 in the Clinical Study Report for study TMC435-TiDP16-C216.

Table 31: Sustained Virologic Response 12 Weeks Post Treatment (SVR12) (ITT Analysis Set)

	PBO (N=134)	**TMC435 (N=257)**
SVR12 n(%)	67(50.0%)	209(81.3%)
Stratum-adjusted Treatment Difference(TMC435- PBO) (95% CI)*	32.2% (23.3%, 41.2%)	

* The treatment difference and 95% confidence interval were adjusted for stratification factors *(type of PegIFN/RBV: randomized to PegIFNα-2a, randomized to PegIFNα-2b and not randomized PegIFNα-2a ; , IL28B: CC, CT and TT; Subgenotype 1a/other, 1b)*

Source: Statistical Reviewer's analysis.

Table 32: Sustained Virologic Response (SVR)# (ITT Analysis Set)

	PBO (N=134)	**TMC435 (N=257)**
SVR n(%)	67(50.0%)	205(79.8%)
Stratum-adjusted Treatment Difference(TMC435- PBO) (95% CI)*	30.8% (21.8%, 39.8%)	

SVR was defined as HCV RNA <25/IU/mL 12 weeks after the end of treatment. The 12 weeks post treatment window for the post-treatment day is [57, +∞]. If there was more than one record, the last record was taken.

*The treatment difference and 95% confidence interval were adjusted for stratification factors *(type of PegIFN/RBV: PegIFNα-2a, PegIFNα-2b; , IL28B: CC, CT and TT; Subgenotype 1a/other, 1b)*

Source: Statistical Reviewer's analysis.

Table 33: HCV RNA viral loads of those patients who relapsed after week 12 post treatment

Patient ID	TRT	TRT Duration (days)	Sample day	VISIT	Lab Result (IU/mL)
TMC435-C216-3047	TMC435	169	-37	SCREENING	4920000
			1	BASELINE	5660000
			5	DAY3	892
			8	DAY7	345
			15	DAY14	27
			29	DAY28	HCV RNA not detected
			57	WEEK8	HCV RNA not detected
			85	WEEK12	HCV RNA not detected
			113	WEEK16	HCV RNA not detected
			141	WEEK20	HCV RNA not detected
			169	WEEK24	HCV RNA not detected
			197	WEEK28	HCV RNA not detected
			252	WEEK36	HCV RNA not detected
			337	WEEK48	405000
			351	UNSCHEDULED_VISIT3	325000
			421	WEEK60	814000
			505	WEEK72	1550000
TMC435-C216-3202	TMC435	169	-43	SCREENING	1960000
			1	BASELINE	3250000
			2	DAY3	2210
			6	DAY7	<25 IU/mL HCV RNA detected
			14	DAY14	<25 IU/mL HCV RNA detected
			29	DAY28	HCV RNA not detected
			57	WEEK8	HCV RNA not detected
			85	WEEK12	HCV RNA not detected
			113	WEEK16	HCV RNA not detected
			141	WEEK20	HCV RNA not detected
			169	WEEK24	HCV RNA not detected
			197	WEEK28	HCV RNA not detected
			253	WEEK36	HCV RNA not detected
			337	WEEK48	531
			357	UNSCHEDULED_VISIT1	559000
			428	WEEK60	137000
TMC435-C216-3398	TMC435	169	-40	SCREENING	25000000
			1	BASELINE	21100000
			3	DAY3	972
			8	DAY7	284
			15	DAY14	<25 IU/mL HCV RNA detected
			29	DAY28	HCV RNA not detected
			57	WEEK8	HCV RNA not detected

			85	WEEK12	HCV RNA not detected
			113	WEEK16	HCV RNA not detected
			141	WEEK20	HCV RNA not detected
			169	WEEK24	HCV RNA not detected
			197	WEEK28	HCV RNA not detected
			251	WEEK36	HCV RNA not detected
			337	WEEK48	HCV RNA not detected
			421	WEEK60	<25 IU/mL HCV RNA detected
			435	UNSCHEDULED_VISIT7	345
TMC435-C216-3417	TMC435	169	-41	SCREENING	10000000
			1	BASELINE	15100000
			3	DAY3	4820
			8	DAY7	277
			15	DAY14	48
			29	DAY28	HCV RNA not detected
			57	WEEK8	HCV RNA not detected
			85	WEEK12	HCV RNA not detected
			113	WEEK16	HCV RNA not detected
			141	WEEK20	HCV RNA not detected
			169	WEEK24	HCV RNA not detected
			197	WEEK28	HCV RNA not detected
			253	WEEK36	HCV RNA not detected
			330	WEEK48	HCV RNA not detected
			414	WEEK60	34

Note: All of those patients were treated for 24 weeks.
Source: Statistical Reviewer's analysis.

As shown in Table 34, 235 patients met the RGT in the TMC435 arm. The SVR12 and SVR rates of those patients were 85.5% and 83.8% respectively.

Table 34: SVR12 and SVR of the Patients Who Met RGT Criteria

	SVR12	SVR
n/N (%)	201/235(85.5%)	197/235(83.8%)

Source: Statistical Reviewer's analysis.

Two types of peginterferon were used in Study 216. Patients could receive peginterferon α-2a or peginterferon α-2b based on the region and randomization. Table 35 and Table 36 summarize the SVR12 and SVR rates separated by the type of peginterferon patients received.

The SVR rate was 53.8% for patients randomized to the control arm who received peginterferon α-2a + Copegus and 41.9% for patients randomized to the control arm who received peginterferon α-2b + Rebetol. For patients randomized to TMC435 arm, the SVR rate was 80.8% when combining TMC435 with peginterferon α-2a +Copegus and 77.5% when combining TMC435 with peginterferon α-2b + Rebetol.

Table 35: Sustained Virologic Response 12 Weeks Post Treatment (SVR12) by Received Study Drug (ITT Analysis Set)

	PBO +PEG2A+COPEGUS (N=91)	PBO +PEG2B+REBETOL (N=43)	TMC435 +PEG2A+COPEGUS (N=177)	TMC435 +PEG2B+REBETOL (N=80)
SVR12 n(%)	49(53.8%)	18(41.9%)	147(83.1%)	62(77.5%)

Source: Statistical Reviewer's analysis.

Table 36: Sustained Virologic Response(SVR[#]) by Randomized Treatment arm (ITT Analysis Set)

	PBO +PEG2A+COPEGUS (N=91)	PBO +PEG2B+REBETOL (N=43)	TMC435 +PEG2A+COPEGUS (N=177)	TMC435 +PEG2B+REBETOL (N=80)
SVR n(%)	49(53.8%)	18(41.9%)	143(80.8%)	62(77.5%)

SVR was defined as HCV RNA <25/IU/mL 12 weeks after the end of treatment. The 12 weeks post treatment window for the post-treatment day is [57, +∞]. If there were more than one record, the last record was taken.
Source: Statistical Reviewer's analysis.

3.2.4.2.2 Study 216: On-treatment Virologic Response

The on-treatment virologic response for Study 216 is summarized in Table 37. Similar to Study 208, higher response rates in the TMC435 arm were observed across the visits except for Week 48 where only 7 of the TMC435 patients were included in the denominator. At Week 4, the percentage of patients achieving HCV RNA below detection was 12.8% in the control arm and 79.2% in the TMC435 arm. At Week 12, 43.8% of the patients reached HCV RNA below detection in the control arm while the below detection rate was 96.8% in the TMC435 arm. By the end of the treatment, the percentage of patients that reached HCV RNA below detection was 67.9% in the control arm and 93.0% in the TMC435 arm.

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Table 37: On-treatment Virologic Response by Visits

	PBO	TMC435
Week 2		
HCV RNA not detected	5/ 133(3.8%)	79/ 249(31.7%)
HCV RNA <25 IU/mL	16/ 133(12.0%)	201/ 249(80.7%)
Week 4		
HCV RNA not detected	17/ 133(12.8%)	202/ 255(79.2%)
HCV RNA <25 IU/mL	29/ 133(21.8%)	244/ 255(95.7%)
Week 12		
HCV RNA not detected	57/ 130(43.8%)	241/ 249(96.8%)
HCV RNA <25 IU/mL	74/ 130(56.9%)	245/ 249(98.4%)
Week 24		
HCV RNA not detected	81/ 110(73.6%)	227/ 239(95.0%)
HCV RNA <25 IU/mL	90/ 110(81.8%)	230/ 239(96.2%)
Week 48		
HCV RNA not detected	79/ 80(98.8%)	6/ 7(85.7%)
HCV RNA <25 IU/mL	80/ 80(100.0%)	7/ 7(100.0%)
EOT		
HCV RNA not detected	91/ 134(67.9%)	239/ 257(93.0%)
HCV RNA <25 IU/mL	*96/ 134(71.6%)*	242/ 257(94.2%)

Source: Statistical Reviewer's analysis.

3.2.4.2.3 Relapse

Similar to Study 208, a higher relapse rate (23.9%) was observed in the control arm compared with the TMC435 arm (13.1%) as shown in Table 38.

Table 38: Viral Relapse

	PBO	*TMC435*
Relapse	21/88(23.9%)	31/236(13.1%)

Source: Statistical Reviewer's analysis.

3.2.4.3 Integrated Results from Study 208 and Study 216 (Naïve Population)

Data from Study 208 and Study 216 was integrated because the design for those two studies was similar, and both studies were conducted on treatment naïve patients.

3.2.4.3.1 Primary Efficacy Endpoint

Primary Efficacy Analysis

Table 39 and Table 40 summarize the reviewer's primary efficacy analysis by integrating data from the two studies. The percentage n of patients that achieved SVR12 was 50.4% in the control arm and 80.4 % in the TMC435 arm. The stratum- adjusted treatment difference for SVR12 was 30.1% (95% CI: 23.8%, 36.5%). The percentage of patients achieving SVR was 50.8% in the control arm and 79.7 % (415/521) in the TMC435 arm. The stratum-adjusted treatment difference for SVR was 29.0% with a 95% CI of (22.6%, 35.4%).

Table 39: Sustained Virologic Response 12 Weeks Post Treatment (SVR12) (ITT Analysis Set)

	PBO (N=264)	**TMC435 (N=521)**
SVR12 n(%)	133(50.4%)	419(80.4%)
Stratum-adjusted Treatment (TMC- PBO) difference (95% CI)*	30.1% (23.8%, 36.5%)	

* The treatment difference and 95% confidence interval were adjusted for stratification factors *(, IL28B: CC, CT and TT; Subgenotype 1a/other, 1b; Study: 208, 216)*

Source: Statistical Reviewer's analysis.

Table 40: Sustained Virologic Response (SVR)[#] (ITT Analysis Set)

	PBO (N=264)	**TMC435 (N=521)**
SVR[#] n(%)	134(50.8%)	415(79.7%)
Stratum-adjusted Treatment (TMC- PBO) difference (95% CI)*	29.0% (22.6%, 35.4%)	

SVR was defined as HCV RNA <25/IU/mL 12 weeks after the end of treatment. The 12 weeks post treatment window for the post-treatment day is [57, +∞]. If there was more than one record, the last record was taken.

*The treatment difference and 95% confidence interval were adjusted for stratification factors *(IL28B: CC, CT and TT; Subgenotype 1a/other, 1b; Study: 208, 216)*

Source: Statistical Reviewer's analysis.

Exploratory Logistic Regression Model

An exploratory logistic regression model was fit to investigate the relationship between SVR12 and baseline variables. The covariates that were tested were:

- TRT: treatment
- Study: (208 vs. 216)
- BLQ80KFL: baseline Q80K
- REGION
- SEX
- AGEGR2: age group
- BLVLGR1: baseline HCV RNA viral load group
- IL28B
- BLBMIGR2: baseline BMI group
- MTFIBGR1: Metavir score
- AHCVGCOA: sub genotype
- RACE
- IP10GR1: IP-10 group

Each variable was fit initially. Significant variables (with p-value <=0.05) were then included in one model. Non-significant variables were dropped from the model until all the variables left in the model were significant. Interactions between those significant variables were also tested.

In the final model (Table 41), treatment, baseline Q80K and their interaction were significant. Age group, IL28B, baseline HCV RNA viral load level, Metavir score, and IP-10 group were significant. The interactions between baseline HCV RNA viral load level and Metavir score, IL28B and Metavir score were also significant.

According to the model, patients who were treated with TMC435, did not have Q80K at baseline, were <=45 years old, had genotype IL28B CC, had baseline HCV RNA <=800000 IU/mL, were not cirrhotic and had IP-10 <=600 pg/mL had a higher probability of achieving SVR12.

Table 41: Logistic Regression Model for SVR12

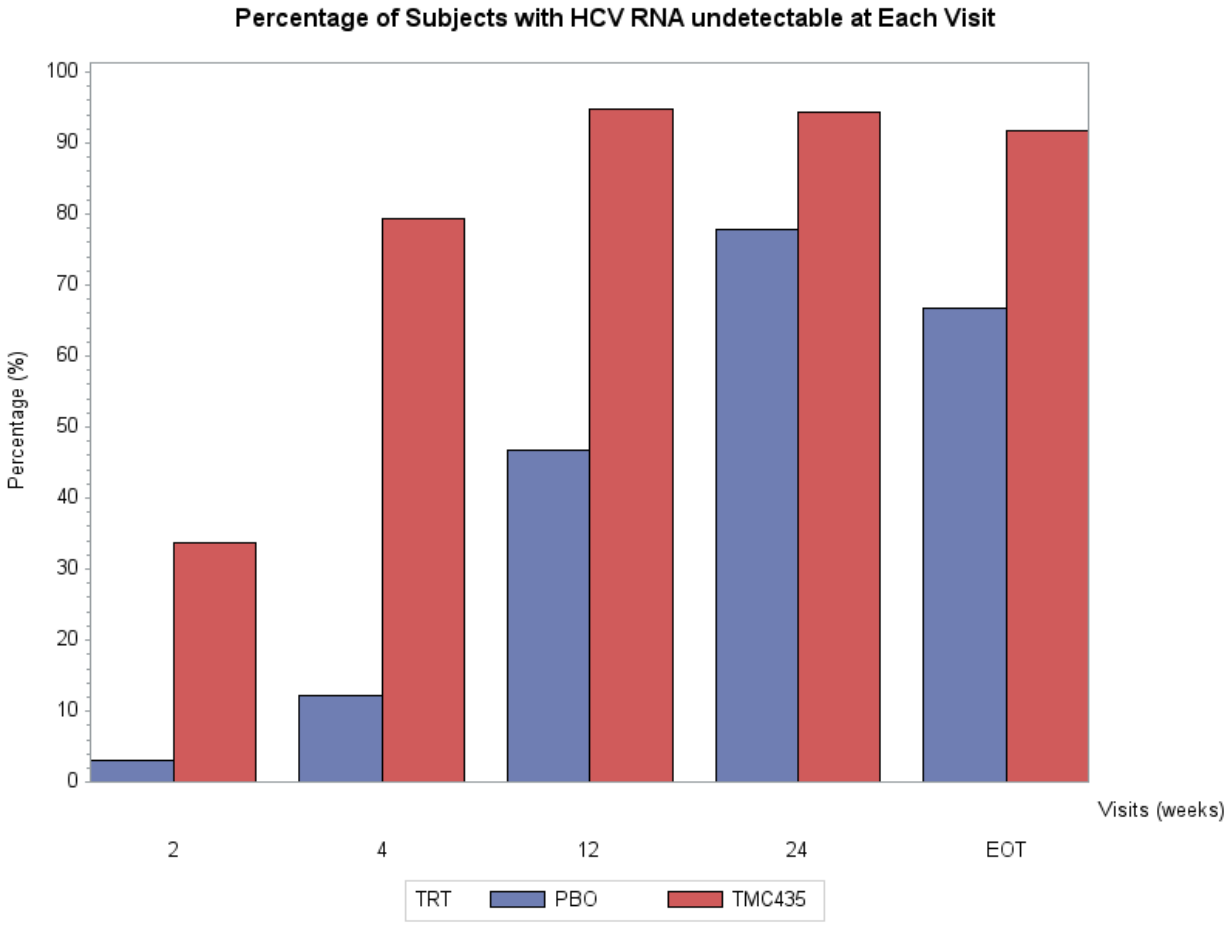
Parameter	Comment	Estimate	Standard Error	p-value
Intercept		0.5377	0.2143	0.0121
TRT	PBO vs. TMC	-0.6945	0.1344	<.0001
BLQ80KFL	No	0.2998	0.1312	0.0223
TRT*BLQ80KFL	PBO*NO	-0.5335	0.1327	<.0001
AGEGR2	>45 years vs. <=45 years	-0.3247	0.1070	0.0024
IL28B	CC vs. TT	2.0321	0.2261	<.0001
IL28B	CT vs. TT	-0.4757	0.1629	0.0035
BLVLGR1	<=800000 IU/mL vs. >800000 IU/mL	0.6934	0.1575	<.0001
MTFIBGR1	F0-F2 vs. F3-F4	0.5632	0.1704	0.0009
BLVLGR1*MTFIBGR1	<=800000 IU/mL* F0-F2	0.3086	0.1536	0.0445
IL28B*MTFIBGR1	CC*F0-F2	-0.5205	0.2135	0.0148
IL28B*MTFIBGR1	CT*F0-F2	0.1374	0.1624	0.3975
IP10GR1	<= 600 pg/mL vs. >600 pg/mL	0.5290	0.1353	<.0001

Source: Statistical Reviewer's analysis.

3.2.4.3.2 On-treatment Virologic Response

On-treatment virologic response of the integrated data is summarized in Figure 5. Overall, the TMC435 arm had higher virologic response rates than the control arm across the visits.

Figure 5: On-treatment Virologic Response by Visit



Source: Statistical Reviewer's analysis.

3.2.4.3.3 Relapse

By integrating the data from the two studies, the overall relapse rate was 22.2% in the control arm and 11.7% in the TMC435 arm as shown in Table 42 below.

Table 42: Viral Relapse

	PBO	***TMC435***
Relapse	38/171(22.2%)	55/469(11.7%)

Source: Statistical Reviewer's analysis.

3.2.4.3.4 Efficacy by Baseline Q80K

There was a statistically significant treatment by Q80K polymorphism at baseline interaction (p-value of 0.0002) with regard to SVR12 as shown in Tables 41 and 65. Detailed analyses were performed to investigate this differential effect.

Table 43 displays the summary of the efficacy endpoints by treatment arms and baseline Q80K status. In the control arm, the results of the efficacy endpoints were quite similar between the patient with and without Q80K at baseline. SVR12 rates were 48.6% for the patients without Q80K at baseline and 54.5% for the patients with Q80K at baseline. However, in the TMC435 arm, the percentage of patients who achieved SVR12 was 84.6% for the patients without Q80K at baseline and only 59.3% for the patients with Q80K at baseline. There appeared to be no improvement in SVR12 for those patients with Q80K at baseline when adding TMC435 to their treatment compared with the Q80K patients in the control arm. The results in Table 43 suggest that TMC435 suppressed the viral load while patients with Q80K were on treatment, but patients could still relapse once they were off treatment.

Table 43: Efficacy Endpoints by Baseline Q80K

	PBO		**TMC435**	
	Without Q80K at Baseline	**With Q80K at Baseline**	**Without Q80K at Baseline**	**With Q80K at Baseline**
Week 4				
HCV RNA not detected	24/214 (11.2%)	8/44 (18.2%)	345/429 (80.4%)	54/86 (62.8%)
HCV RNA <25 IU/mL	43/214 (20.1%)	10/44 (22.7%)	402/429 (93.7%)	66/86 (76.7%)
EOT (HCV RNA not detected)	140/214 (65.4%)	31/44 (70.5%)	402/429 (93.7%)	70/86 (81.4%)
SVR12	104/214 (48.6%)	24/44 (54.5%)	363/429 (84.6%)	51/86 (59.3%)
SVR	105/214 (49.1%)	24/44 (54.5%)	360/429 (83.9%)	50/86 (58.1%)
Relapse	32/136 (23.5%)	6/30 (20.0%)	39/398 (9.8%)	15/65 (23.1%)

Source: Statistical Reviewer's analysis.

To address the apparent differential treatment effect among patients with and without Q80K and the associated risks, the applicant proposed an alternative treatment algorithm (b) (4)

(b) (4)

This proposal was investigated (b) (4)

(b) (4)

(b) (4)

Given that subjects in the pivotal Phase 3 studies who were infected with HCV genotype 1a with the Q80K polymorphism at baseline were less likely to benefit from TMC435 in combination with Peg/RBV than subjects infected with other HCV polymorphic variants, there is a high prevalence of the Q80K polymorphism in genotype 1a patients in the U.S. population, and there are concerns regarding the generation of cross-resistance to the approved HCV protease inhibitors in TMC435 treatment failures (i.e., R155K), the review team is currently recommending the applicant screen all genotype 1a patients for the Q80K polymorphism prior to initiation of TMC435 with the objective of excluding patients from treatment if the polymorphism is present. The applicant's treatment algorithm can also be simplified further. The following describes one option: all patients in the treatment-naïve and relapser populations would receive a fixed 24 week course of PEG/RBV in conjunction with 12 weeks of TMC435. If the Week 4 or Week 12 HCV RNA is greater than or equal to 25 IU/mL, then discontinue all treatment. According to this simplified treatment algorithm, the estimated SVR12 would be 82.7% (assume the SVR12 rate is 0 for patients whose HCV RNA ≥25IU/mL at Week 4). The estimated SVR would be 82.1% as shown in Table 46. The applicant has accepted this proposal.

(b) (4)

Table 46: Estimated SVR12 and SVR in TMC435 Treated Naïve Patients Without Q80K at Baseline Based on the Agency's Proposal (ITT Analysis Set)

Week 4 HCV RNA Result	Proposed Treatment Duration (weeks)	Estimated Proportion of Patients %(n/N)	Estimated SVR12 %	Estimated SVR %
HCV RNA <25 IU/mL (detected or undetected)	24	93.7%(402/429)	88.3%	87.6%
HCV RNA ≥25 IU/mL or missing	24	6.3%(27/429)	0	0
Overall			**82.7%**	**82.1%**

Source: Statistical Reviewer's analysis.

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3.2.4.4 Study 3007

3.2.4.4.1 Primary Efficacy Endpoint

Table 47 below summarizes the applicant's primary analysis. The percentage of patients who achieved SVR12 was 36.8% in the control arm and 79.2% in the TMC435 arm. The stratum-adjusted treatment difference was 43.0% (95% CI: 33.8%, 52.3%). TMC435 was shown to be superior to placebo as evidenced by the statistically significant difference.

Table 48 and Table 49 summarize the reviewer's analyses based on the reviewer's definitions of SVR12 and SVR. The percentage of patients that achieved SVR12 was 36.1% in the control arm and 79.2% in the TMC435 arm. The stratum-adjusted treatment difference was 43.7% with a 95% CI of (34.6%, 52.9%). One patient (TMC435HPC3007-6194) had two HCV RNA records in the Week 12 follow-up visit window, and the records were all >25 IU/mL. This patient also had one record in the Week 24 follow-up visit window, and it was below detection level. In the reviewer's analysis, this patient was counted as a SVR12 failure but an SVR success, while in the applicant's analysis, this patient was classified as an SVR12 success.

The percentage of patients who achieved an SVR was 35.3% in the control arm and 77.3% in the TMC435 arm. The stratum-adjusted difference for SVR was 42.6% with 95% CI of (33.5%, 51.7%). There were 7 patients (2 patients in the control arm and 5 patients in the TMC435 arm) who relapsed after the Week 12 follow-up, and their HCV RNA records are listed in Table 50.

The superiority of TMC435 to placebo was also demonstrated based on the reviewer's analysis.

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Table 47: Applicant's Primary Endpoint: Sustained Virologic Response 12 Weeks After the Planned End of Treatment (SVR12)

	Observed	Stratum Adjusted	Comparison versus Placebo	
	n/N (%)	% (95% CI)[c]	Difference in proportions (95% CI)[b]	p-value[a]
SVR12				
PBO 12Wks PR48	49/133 (36.8)	36.6 (28.7;44.5)		
TMC435 150 mg 12Wks PR24/48	206/260 (79.2)	79.6 (74.8;84.4)	43.0 (33.8;52.3)	<0.001

[a] based on the CMH test controlling for stratification factors.
[b] difference in proportions (active – placebo) adjusted for stratification factors and the corresponding 95% CI based on the normal approximation.
[c] proportions adjusted for the stratification factors and the corresponding 95% CIs based on the normal approximation.

Stratification factors are *IL28B* and HCV geno/subtype. HCV geno/subtype is based on the NS5B assay (if not available, LiPA II or Trugene result is used) and categorized as 1b versus any other geno/subtype (1a/other).

The p-value for the Breslow-Day test for homogeneity of odds ratios was 0.948.

Source: Table 26 in the Clinical Study Report for study TMC435HPC3007.

Table 48: Sustained Virologic Response 12 Weeks Post Treatment (SVR12) (ITT Analysis Set)

	PBO (N=133)	**TMC435 (N=260)**
SVR12 n(%)	48(36.1%)	206(79.2%)
Stratum-adjusted Treatment Difference (TMC435 vs. PBO) (95% CI)*	43.7% (34.6%, 52.9%)	

* The treatment difference and it's 95% confidence interval were adjusted for stratification factors *(IL28B: CC, CT and TT; Subgenotype 1a/other, 1b)*
Source: Statistical Reviewer's analysis.

Table 49: Sustained Virologic Response (SVR)[#] (ITT Analysis Set)

	PBO (N=133)	**TMC435 (N=260)**
SVR n(%)	47(35.3%)	201(77.3%)
Stratum-adjusted Treatment Difference (TMC435 vs. PBO) (95% CI)*	42.6(33.5%, 51.7%)	

SVR was defined as HCV RNA <25/IU/mL 12 weeks after the end of treatment. The 12 weeks post treatment window for the post-treatment day is [57, +∞]. If there was more than one record, the last record was taken.
* The treatment difference and 95% confidence interval were adjusted for stratification factors *(IL28B: CC, CT and TT; Subgenotype 1a/other, 1b)*
Source: Statistical Reviewer's analysis.

Table 50: HCV RNA viral loads of those patients who relapsed after week 12 post treatment

Patient ID	TRT	Treatment Duration (days)	Sample day	VISIT	Lab Result (IU/mL)
TMC435HPC3007-6048	TMC435	169	-21	SCREENING	3530000
			1	BASELINE	2030000
			3	DAY3	380
			8	DAY7	<25 IU/mL HCV RNA detected
			15	DAY14	<25 IU/mL HCV RNA detected
			29	DAY28	HCV RNA not detected
			57	WEEK8	HCV RNA not detected
			85	WEEK12	HCV RNA not detected
			113	WEEK16	HCV RNA not detected
			141	WEEK20	HCV RNA not detected
			169	WEEK24	HCV RNA not detected
			197	WEEK28	HCV RNA not detected
			253	WEEK36	HCV RNA not detected
			337	WEEK48	<25 IU/mL HCV RNA detected
			361	UNSCHEDULED_VISIT1	680
			422	WEEK60	537000
			505	WEEK72	495000
TMC435HPC3007-6054	TMC435	169	-34	SCREENING	2410000
			1	BASELINE	1390000
			3	DAY3	404
			8	DAY7	36
			12	DAY14	<25 IU/mL HCV RNA detected
			29	DAY28	<25 IU/mL HCV RNA detected
			54	WEEK8	HCV RNA not detected
			85	WEEK12	HCV RNA not detected
			110	WEEK16	HCV RNA not detected
			141	WEEK20	HCV RNA not detected
			169	WEEK24	HCV RNA not detected
			194	WEEK28	HCV RNA not detected
			254	WEEK36	HCV RNA not detected
			339	WEEK48	1870000
			348	UNSCHEDULED_VISIT1	1950000
			425	WEEK60	1100000
			505	WEEK72	548000
TMC435HPC3007-6076	PBO	337	-21	SCREENING	838000
			1	BASELINE	576000
			4	DAY3	18900
			6	DAY7	23100
			15	DAY14	12600
			29	DAY28	2340
			57	WEEK8	225

			84	WEEK12	33
			112	WEEK16	<25 IU/mL HCV RNA detected
			140	WEEK20	<25 IU/mL HCV RNA detected
			174	UNSCHEDULED_VISIT4	HCV RNA not detected
			196	WEEK28	HCV RNA not detected
			251	WEEK36	HCV RNA not detected
			294	WEEK42	HCV RNA not detected
			337	WEEK48	HCV RNA not detected
			364	WEEK52	HCV RNA not detected
			426	WEEK60	HCV RNA not detected
			510	WEEK72	375000
			523	UNSCHEDULED_VISIT5	203000
TMC435HPC3007-6123	TMC435	169	-28	SCREENING	1010000
			1	BASELINE	1320000
			3	DAY3	949
			8	DAY7	<25 IU/mL HCV RNA detected
			16	DAY14	<25 IU/mL HCV RNA detected
			29	DAY28	<25 IU/mL HCV RNA detected
			57	WEEK8	HCV RNA not detected
			84	WEEK12	HCV RNA not detected
			113	WEEK16	HCV RNA not detected
			141	WEEK20	HCV RNA not detected
			169	WEEK24	HCV RNA not detected
			197	WEEK28	HCV RNA not detected
			253	WEEK36	HCV RNA not detected
			337	WEEK48	391000
			347	UNSCHEDULED_VISIT1	1600000
			421	WEEK60	21100
			505	WEEK72	469000
TMC435HPC3007-6124	PBO	336	-35	SCREENING	563000
			1	BASELINE	493000
			3	DAY3	134000
			7	DAY7	73800
			14	DAY14	30900
			28	DAY28	4260
			56	WEEK8	259
			84	WEEK12	25
			119	WEEK16	<25 IU/mL HCV RNA detected
			141	WEEK20	HCV RNA not detected
			168	WEEK24	HCV RNA not detected
			197	WEEK28	HCV RNA not detected
			249	WEEK36	HCV RNA not detected
			294	WEEK42	HCV RNA not detected
			336	WEEK48	HCV RNA not detected
			364	WEEK52	HCV RNA not detected
			421	WEEK60	HCV RNA not detected
			504	WEEK72	95900

			514	UNSCHEDULED_VISIT1	85900
TMC435HPC3007-6144	TMC435	169	-35	SCREENING	2500000
			1	BASELINE	2900000
			3	DAY3	390
			8	DAY7	<25 IU/mL HCV RNA detected
			15	DAY14	HCV RNA not detected
			29	DAY28	HCV RNA not detected
			57	WEEK8	HCV RNA not detected
			85	WEEK12	HCV RNA not detected
			113	WEEK16	HCV RNA not detected
			141	WEEK20	HCV RNA not detected
			169	WEEK24	HCV RNA not detected
			196	WEEK28	HCV RNA not detected
			253	WEEK36	HCV RNA not detected
			337	WEEK48	1060000
			351	UNSCHEDULED_VISIT2	670000
			422	WEEK60	964000
			504	WEEK72	955000
TMC435HPC3007-6332	TMC435	169	-42	SCREENING	4750000
			1	BASELINE	1430000
			4	DAY3	239
			8	DAY7	76
			15	DAY14	<25 IU/mL HCV RNA detected
			27	DAY28	HCV RNA not detected
			57	WEEK8	HCV RNA not detected
			85	WEEK12	HCV RNA not detected
			113	WEEK16	HCV RNA not detected
			140	WEEK20	HCV RNA not detected
			169	WEEK24	HCV RNA not detected
			196	WEEK28	HCV RNA not detected
			253	WEEK36	HCV RNA not detected
			337	WEEK48	288000
			361	UNSCHEDULED_VISIT1	411000
			420	WEEK60	242000

Note: Treatment duration for these patients was either 24 or 48 weeks so the corresponding SVR12 visits were at Weeks 36 and 60.
Source: Statistical Reviewer's analysis.

As shown in Table 51, 242 patients met the RGT criteria. The SVR12 and SVR rates of those patients were 82.6% and 80.6%, respectively.

Table 51: SVR12 and SVR of the Patients Who Met GRT Criteria

	SVR12	SVR
n/N (%)	200/242(82.6%)	195/242(80.6%)

Source: Statistical Reviewer's analysis.

An exploratory logistic regression model was fit to investigate the relationship between SVR12 and baseline variables. The covariates that were tested were:

- TRT: treatment
- BLQ80KFL: baseline Q80K
- REGION
- SEX
- AGEGR2: age group
- BLVLGR1: baseline HCV RNA viral load level
- IL28B
- BLBMIGR2: baseline BMI group
- MTFIBGR1: Metavir score
- AHCVGCOA: sub genotype
- RACE

Similar steps as used for the naïve population were followed.
In the final model (Table 52), treatment, baseline Q80K, region and IL28B were significant.
According to the model, patients who were treated with TMC435, did not have Q80K at baseline, from European countries and with genotype IL28B CC had a higher probability of achieving SVR12.

Table 52: Logistic Regression Model for SVR12

Parameter	Comment	Estimate	Standard Error	Wald Chi-Square	P-value
Intercept		-0.5431	0.2398	5.1291	0.0235
TRT	PBO vs. TMC	-1.1037	0.1358	66.0434	<.0001
BLQ80KFL	No vs. Yes	0.4672	0.1944	5.7788	0.0162
REGION	ASIA-PACIFIC vs. NORTH-AMERICA	-0.5467	0.2913	3.5229	0.0605
REGION	EUROPE vs. NORTH-AMERICA	0.9647	0.1990	23.4939	<.0001
IL28B	CC vs. TT	0.9443	0.2339	16.2940	<.0001
IL28B	CT vs. TT	-0.0443	0.1801	0.0605	0.8057

Source: Statistical Reviewer's analysis.

3.2.4.4.2 On-treatment Virologic Response

On-treatment virologic response is summarized in Table 53. Compared with the control arm, higher response rates in the TMC435 arm were observed across the visits. At Week 4, the percentage of patients who reached HCV RNA below detection was 3.1% in the control arm and 77.2% in the TMC435 arm. At Week 12, 27.2% of the patients had HCV RNA below detection in the control arm while the below detection rate was 97.6% in the TMC435 arm. By the end of

the treatment, the percentage of patients with HCV RNA below detection was 71.4% in the control arm and 96.9% in the TMC435 arm.

Table 53: On-treatment Virologic Response by Visits

	PBO	TMC435
Week 2		
HCV RNA not detected	1/ 130(0.8%)	73/ 258(28.3%)
HCV RNA <25 IU/mL	2/ 130(1.5%)	213/ 258(82.6%)
Week 4		
HCV RNA not detected	4/ 129(3.1%)	200/ 259(77.2%)
HCV RNA <25 IU/mL	15/ 129(11.6%)	247/ 259(95.4%)
Week 12		
HCV RNA not detected	34/ 125(27.2%)	249/ 255(97.6%)
HCV RNA <25 IU/mL	65/ 125(52.0%)	250/ 255(98.0%)
Week 24		
HCV RNA not detected	88/ 112(78.6%)	239/ 240(99.6%)
HCV RNA <25 IU/mL	106/ 112(94.6%)	240/ 240(100.0%)
Week 48		
HCV RNA not detected	84/ 95(88.4%)	9/ 9(100.0%)
HCV RNA <25 IU/mL	94/ 95(98.9%)	9/ 9(100.0%)
EOT		
HCV RNA not detected	95/ 133(71.4%)	252/ 260(96.9%)
HCV RNA <25 IU/mL	*109/ 133(82.0%)*	254/ 260(97.7%)

Source: Statistical Reviewer's analysis.

3.2.4.4.3 Relapse

A higher relapse rate (47.8%) was observed in the control arm compared with the TMC435 arm (19.3%) as shown in Table 54.

Table 54: Viral Relapse

	PBO	TMC435
Relapse	43/90(47.8%)	48/249(19.3%)

Source: Statistical Reviewer's analysis.

3.2.4.4.4 Efficacy by Baseline Q80K

Similar to the naïve population, a statistically significant treatment and Q80K polymorphism at baseline interaction (p-value=0.04) with regard to SVR12 was detected (Table 66). Detailed analyses were performed to investigate this issue.

Table 55 below displays the summary of the efficacy endpoints by treatment arms and baseline Q80K status. In the placebo arm, the SVR12 rate was 37.2% for the patients without Q80K at baseline and 30.0% for the patients with Q80K at baseline. However, in the TMC435 arm, the percentage of patients achieving SVR12 was 83.2% for the patients without Q80K at baseline and only 48.4% for the patients with Q80K at baseline.

Table 55: Efficacy Endpoints by Baseline Q80K

	PBO		***TMC435***	
	Without Q80K at Baseline	**With Q80K at Baseline**	**Without Q80K at Baseline**	**With Q80K at Baseline**
Week 4				
HCV RNA not detected	3/113(2.7%)	1/20(5.0%)	183/226(81.0%)	14/31(45.2%)
HCV RNA <25 IU/mL	14/113(12.4%)	1/20(5.0%)	218/226(96.5%)	26/31(83.9%)
EOT (HCV RNA not detected)	85/113(75.2%)	10/20(50.0%)	220/226(97.3%)	29/31(93.5%)
SVR12	42/113(37.2%)	6/20(30.0%)	188/226(83.2%)	15/31(48.4%)
SVR	41/113(36.3%)	6/20(30.0%)	183/226(81.0%)	15/31(48.4%)
Relapse	41/82(50.0%)	2/8(25.0%)	35/218(16.1%)	13/28(46.4%)

Source: Statistical Reviewer's analysis.

The applicant's proposed recommendation for the Dosage and Administration section in the label for relapsers was investigated (b) (4)

(b) (4)

The review team has recommended the applicant screen all genotype 1a patients for the Q80K polymorphism prior to initiation of TMC435 with the objective of excluding patients from treatment if the polymorphism is present. The review team also proposed a simplified treatment algorithm for the relapsers: all patients in the relapser population would receive a fixed 24 week course of PEG and RBV in conjunction with 12 weeks of TMC435. If the Week 4 or Week 12 HCV RNA is greater than or equal to 25 IU/mL then discontinue all treatment. According to this treatment algorithm, the estimated SVR12 would be 81.0% (assume the SVR12 rate is 0 for patients whose HCV RNA ≥25IU/mL at Week 4). The estimated SVR would be 78.8% as shown in Table 58. The applicant has accepted this proposal.

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Table 58: Estimated SVR12 and SVR in TMC435 Treated Relapsers Without Q80K at Baseline Based on the Agency's Proposal (ITT Analysis Set)

Week 4 HCV RNA Result	Proposed Treatment Duration (weeks)	Estimated Proportion of Patients %(n/N)	Estimated SVR12 %	Estimated SVR %
HCV RNA <25 IU/mL (detected or undetected)	24	96.5%(218/226)	83.9%(183/218)	81.7%(178/218)
HCV RNA ≥25 IU/mL or missing	24	3.5%(8/226)	0-62.5%	0-62.5%
Overall			**81.0%**	**78.8%**

Source: Statistical Reviewer's analysis.

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3.2.4.5 Study 206

The analyses and definitions of this study were similar to those of the other phase III studies. The reviewer's analyses methods were slightly different from the applicant's analysis plan. Only the control arm and other arms treated with TMC435 for 12 weeks were considered relevant and summarized in this section.

3.2.4.5.1 Primary Efficacy Endpoint

Table 59 summarizes the applicant's analysis results of the sustained virologic response. The reviewer's results were very similar to the applicant's and are summarized in Tables 60 and 61. Two patients in the TMC12 arm were counted as SVR12 successes by the reviewer but not by the applicant because of the difference in the definitions. SVR and SVR12 results were exactly the same in this study. Therefore, only SVR will be mentioned.

Due to the small sample size of each arm, the TMC12 PR48 100mg and TMC12 PR48 150mg arms were combined in order to assess the efficacy of TMC435 150mg for each type of prior responder. As shown in Table 61 for Null responders, the SVR rate was 45.5% for the TMC435 arm (combining TMC12 PR48 100mg and 150mg arms) and 18.8% for the control arm. The treatment difference was 26.7% and not statistically significant. For partial responders, the SVR rate was 70.0% for the TMC435 arm (combining TMC12 PR48 100mg and 150mg arms) and 8.7% (2/23) for the control arm. The treatment difference (61.3%) was statistically significant. For relapsers, the SVR rate was 84.9% for the TMC435 arm (combining TMC12 PR48 100mg and 150mg arms) and 37.0% for the control arm. The treatment difference was 47.9% and was also statistically significant.

Table 59: Applicant's Analysis: Sustained Virologic Response

n/N (%)	TMC12 PR48 100 mg N = 66	TMC24 PR48 100 mg N = 65	TMC48 PR48 100 mg N = 66	TMC12 PR48 150 mg N = 66	TMC24 PR48 150 mg N = 68	TMC48 PR48 150 mg N = 65	Placebo N = 66
Overall Population							
SVR4	48/66 (72.7)	45/65 (69.2)	41/66 (62.1)	46/66 (69.7)	52/68 (76.5)	52/65 (80.0)	18/66 (27.3)
SVR12	46/66 (69.7)	44/65 (67.7)	40/66 (60.6)	44/66 (66.7)	49/68 (72.1)	52/65 (80.0)	15/66 (22.7)
SVR24	46/66 (69.7)	43/65 (66.2)	40/66 (60.6)	44/66 (66.7)	49/68 (72.1)	52/65 (80.0)	15/66 (22.7)
Relapser							
SVR4	25/27 (92.6)	23/26 (88.5)	21/26 (80.8)	22/26 (84.6)	25/27 (92.6)	23/26 (88.5)	13/27 (48.1)
SVR12	24/27 (88.9)	23/26 (88.5)	20/26 (76.9)	20/26 (76.9)	24/27 (88.9)	23/26 (88.5)	10/27 (37.0)
SVR24	24/27 (88.9)	23/26 (88.5)	20/26 (76.9)	20/26 (76.9)	24/27 (88.9)	23/26 (88.5)	10/27 (37.0)
Partial Responder							
SVR4	16/23 (69.6)	13/23 (56.5)	12/22 (54.5)	15/23 (65.2)	18/24 (75.0)	19/22 (86.4)	2/23 (8.7)
SVR12	16/23 (69.6)	12/23 (52.2)	12/22 (54.5)	15/23 (65.2)	18/24 (75.0)	19/22 (86.4)	2/23 (8.7)
SVR24	16/23 (69.6)	11/23 (47.8)	12/22 (54.5)	15/23 (65.2)	18/24 (75.0)	19/22 (86.4)	2/23 (8.7)
Null Responder							
SVR4	7/16 (43.8)	9/16 (56.3)	8/18 (44.4)	9/17 (52.9)	9/17 (52.9)	10/17 (58.8)	3/16 (18.8)
SVR12	6/16 (37.5)	9/16 (56.3)	8/18 (44.4)	9/17 (52.9)	7/17 (41.2)	10/17 (58.8)	3/16 (18.8)
SVR24	6/16 (37.5)	9/16 (56.3)	8/18 (44.4)	9/17 (52.9)	7/17 (41.2)	10/17 (58.8)	3/16 (18.8)

N: number of subjects with data; n: number of subjects with SVR; SVR4: sustained virologic response 4 weeks after the planned end of treatment; SVR12: sustained virologic response 12 weeks after the planned end of treatment; SVR24: sustained virologic response 24 weeks after the planned end of treatment

Table 60: Sustained Virologic Response 12 Weeks Post Treatment (SVR12) and Sustained Virologic Response (SVR)[#]

	TMC12 PR48 100mg (N=66)	TMC12 PR48 150mg (N=66)	PR48 (N=66)
SVR12 n(%)	48(72.7%)	44(66.7%)	15(22.7%)
SVR n(%)	48(72.7%)	44(66.7%)	15(22.7%)

SVR was defined as HCV RNA <25/IU/mL 12 weeks after the end of treatment. The 12 weeks post treatment window for the post-treatment day is [57, +∞]. If there were more than one record, the last record was taken.
Source: Statistical Reviewer's analysis.

Table 61: Sustained Virologic Response 12 Weeks Post Treatment (SVR12) and Sustained Virologic Response (SVR) # by Prior Virologic Response Category

	TMC12 PR48 100mg (N=66)	TMC12 PR48 150mg (N=66)	TMC12 PR48 Total (N=132)	PR48 (N=66)	P-value*
SVR12 n/N(%)	48/66(72.7%)	44/66(66.7%)	92/132(69.7%)	15/66(22.7%)	<0.0001
Null Responder	6/16(37.5%)	9/17(52.9%)	15/33(45.5%)	3/16(18.8%)	0.11
Partial Responder	17/23(73.9%)	15/23(65.2%)	32/46(70.0%)	2/23(8.7%)	<0.0001
Relapser	25/27(92.6%)	20/26(76.9%)	45/53(84.9%)	10/27(37.0%)	<0.0001
SVR n/N(%)	48/66(72.7%)	44/66(66.7%)	92/132(69.7%)	15/66(22.7%)	<0.0001
Null Responder	6/16(37.5%)	9/17(52.9%)	15/33(45.5%)	3/16(18.8%)	0.11
Partial Responder	17/23(73.9%)	15/23(65.2%)	32/46(70.0%)	2/23(8.7%)	<0.0001
Relapser	25/27(92.6%)	20/26(76.9%)	45/53(84.9%)	10/27(37.0%)	<0.0001

SVR was defined as HCV RNA <25/IU/mL 12 weeks after the end of treatment. The 12 weeks post treatment window for the post-treatment day is [57, +∞]. If there were more than one record, the last record was taken.
* P-value is the exact p-value of the comparison between TMC12 PR48 arm and PR48 arm.
Source: Statistical Reviewer's analysis.

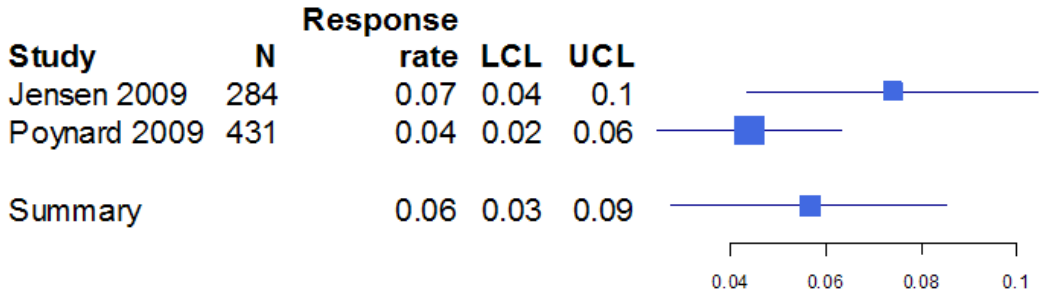
The reviewer also investigated the historical data to re-evaluate the SVR of the control arm for null responders and partial responders. Data from Boceprevir and Telaprevir labels were combined with the data from Study 206 and meta-analyses were performed to estimate the SVR rates of the Peg-IFN+RBV arm as summarized in Table 62 below. The estimate of the SVR rate for null responders was 9% with 95% CI of (0%, 21%). For the partial responders, the SVR estimate was 9% with 95% CI of (3%, 16%). Jensen (2009) and Poynard (2009) also published the SVR from their studies. However in their analyses, non-responder patients were not further divided into null responders and partial responders. They were summarized by pooling those two subgroups and defined as non-responders. The overall estimated SVR for genotype 1 non-responders was 6% with 95% CI of (3%, 9%) as shown in Figure 6.

Table 62: SVR of Historical Studies of Retreating Peginterferon Plus Ribavirin Nonresponders of Genotype 1 Patients

Source	Sponsor	Population	Treatment	SVR (n/N)	Estimate of Overall SVR and 95% CI
Jesen et al.	Roche	Patients who had received at least 12 weeks of combination therapy with Peginterferon-α2b plus Ribavirin and had detectable serum HCV RNA at every postbaseline assessment, at least 1 of which was performed after week 12	Peginterferon-α2a, 180 ug/wk plus Ribavirin for 48 weeks	7.4%* (21/284)	6% (3%, 9%)
Poynard et al.	Schering-Plough	Had detectable HCV-RNA at the end of therapy while previously was treated with Peg-IFN alfa/Ribavirin.	Peginterferon-α2b 1.5ug/kg/wk plus daily WBD Ribavirin for up to 48 weeks	4% (19/431)	
Telaprevir Label	Vertex	Null Responder	PEG+RBV for 48 weeks	5%(2/37)	9% (0%, 21%)
TMC Study 206	Janssen	Null Responder	PEG+RBV for 48 weeks	18.8%(3/16)	
Boceprevir Label	Merck	Partial Responder	PEG+RBV for 48 weeks	7%(2/29)	9% (3%, 16%)
Telaprevir Label	Vertex	Partial Responder	PEG+RBV for 48 weeks	15%(4/27)	
TMC Study 206	Janssen	Partial Responder	PEG+RBV for 48 weeks	8.7%(2/23)	

*This number is estimated based on a figure.
Source: Statistical Reviewer's analysis.

Figure 6: SVR Based on Meta analysis for Nonresponders



Source: Statistical Reviewer's analysis.

3.2.4.5.2 Other Efficacy Endpoints

Table 63 summarizes the on-treatment virologic response rates over the time. Compared with the control arm, the TMC435 arms appeared to have higher virologic response rates across most of the visits for null responders, partial responders and relapsers.

Table 63: On-treatment Virologic Response

	TMC12 PR48 100mg	**TMC12 PR48 150mg**	**PR48**
Overall			
Week 2			
HCV RNA not detected	15/ 64(23.4%)	16/ 66(24.2%)	0
HCV RNA <25 IU/mL	40/ 64(62.5%)	42/ 66(63.6%)	2/ 65(3.1%)
Week 4			
HCV RNA not detected	44/ 65(67.7%)	41/ 65(63.1%)	1/ 65(1.5%)
HCV RNA <25 IU/mL	52/ 65(80.0%)	57/ 65(87.7%)	2/ 65(3.1%)
Week 12			
HCV RNA not detected	54/ 61(88.5%)	53/ 62(85.5%)	13/ 44(29.5%)
HCV RNA <25 IU/mL	58/ 61(95.1%)	59/ 62(95.2%)	23/ 44(52.3%)
Week 24			
HCV RNA not detected	52/ 56(92.9%)	54/ 59(91.5%)	28/ 38(73.7%)
HCV RNA <25 IU/mL	54/ 56(96.4%)	57/ 59(96.6%)	33/ 38(86.8%)
Week 48			
HCV RNA not detected	46/ 47(97.9%)	46/ 48(95.8%)	22/ 24(91.7%)
HCV RNA <25 IU/mL	47/ 47(100.0%)	48/ 48(100.0%)	24/ 24(100.0%)
EOT			
HCV RNA not detected	53/ 66(80.3%)	53/ 66(80.3%)	27/ 66(40.9%)
HCV RNA <25 IU/mL	57/ 66(86.4%)	59/ 66(89.4%)	31/ 66(47.0%)
Null Responder			
Week 2			
HCV RNA not detected	1/ 16(6.3%)	0	0
HCV RNA <25 IU/mL	5/ 16(31.3%)	8/ 17(47.1%)	1/ 16(6.3%)
Week 4			
HCV RNA not detected	5/ 15(33.3%)	6/ 17(35.3%)	0
HCV RNA <25 IU/mL	7/ 15(46.7%)	12/ 17(70.6%)	0
Week 12			
HCV RNA not detected	9/ 11(81.8%)	10/ 15(66.7%)	3/ 8(37.5%)
HCV RNA <25 IU/mL	10/ 11(90.9%)	14/ 15(93.3%)	3/ 8(37.5%)
Week 24			
HCV RNA not detected	10/ 11(90.9%)	12/ 15(80.0%)	4/ 5(80.0%)
HCV RNA <25 IU/mL	11/ 11(100.0%)	14/ 15(93.3%)	4/ 5(80.0%)

Week 48			
HCV RNA not detected	8/ 9(88.9%)	10/ 11(90.9%)	3/ 3(100.0%)
HCV RNA <25 IU/mL	9/ 9(100.0%)	11/ 11(100.0%)	3/ 3(100.0%)
EOT			
HCV RNA not detected	9/ 16(56.3%)	11/ 17(64.7%)	4/ 16(25.0%)
HCV RNA <25 IU/mL	11/ 16(68.8%)	14/ 17(82.4%)	4/ 16(25.0%)
Partial Responder			
Week 2			
HCV RNA not detected	5/ 22(22.7%)	8/ 23(34.8%)	0
HCV RNA <25 IU/mL	15/ 22(68.2%)	15/ 23(65.2%)	0
Week 4			
HCV RNA not detected	15/ 23(65.2%)	15/ 23(65.2%)	0
HCV RNA <25 IU/mL	18/ 23(78.3%)	21/ 23(91.3%)	0
Week 12			
HCV RNA not detected	20/ 23(87.0%)	20/ 22(90.9%)	2/ 14(14.3%)
HCV RNA <25 IU/mL	21/ 23(91.3%)	20/ 22(90.9%)	4/ 14(28.6%)
Week 24			
HCV RNA not detected	17/ 19(89.5%)	19/ 20(95.0%)	4/ 12(33.3%)
HCV RNA <25 IU/mL	17/ 19(89.5%)	19/ 20(95.0%)	8/ 12(66.7%)
Week 48			
HCV RNA not detected	14/ 14(100.0%)	15/ 16(93.8%)	2/ 3(66.7%)
HCV RNA <25 IU/mL	14/ 14(100.0%)	16/ 16(100.0%)	3/ 3(100.0%)
EOT			
HCV RNA not detected	18/ 23(78.3%)	18/ 23(78.3%)	4/ 23(17.4%)
HCV RNA <25 IU/mL	19/ 23(82.6%)	19/ 23(82.6%)	6/ 23(26.1%)
Relapser			
Week 2			
HCV RNA not detected	9/ 26(34.6%)	8/ 26(30.8%)	0
HCV RNA <25 IU/mL	20/ 26(76.9%)	19/ 26(73.1%)	1/ 26(3.8%)
Week 4			
HCV RNA not detected	24/ 27(88.9%)	20/ 25(80.0%)	1/ 26(3.8%)
HCV RNA <25 IU/mL	27/ 27(100.0%)	24/ 25(96.0%)	2/ 26(7.7%)
Week 12			
HCV RNA not detected	25/ 27(92.6%)	23/ 25(92.0%)	8/ 22(36.4%)
HCV RNA <25 IU/mL	27/ 27(100.0%)	25/ 25(100.0%)	16/ 22(72.7%)
Week 24			
HCV RNA not detected	25/ 26(96.2%)	23/ 24(95.8%)	20/ 21(95.2%)
HCV RNA <25 IU/mL	26/ 26(100.0%)	24/ 24(100.0%)	21/ 21(100.0%)
Week 48			
HCV RNA not detected	24/ 24(100.0%)	21/ 21(100.0%)	17/ 18(94.4%)
HCV RNA <25 IU/mL	24/ 24(100.0%)	21/ 21(100.0%)	18/ 18(100.0%)

EOT			
HCV RNA not detected	26/ 27(96.3%)	24/ 26(92.3%)	19/ 27(70.4%)
HCV RNA <25 IU/mL	27/ 27(100.0%)	26/ 26(100.0%)	21/ 27(77.8%)

Source: Statistical Reviewer's analysis.

3.2.4.5.3 Relapse

The overall relapse rates as well as the relapse rates for null responders, partial responders and relapsers are summarized in Table 64. Only subjects whose HCV RNA was below detection level and had no missing post treatment records were counted in the denominator. For the overall population, TMC435 arms had lower relapse rates compared with the control arm.

Table 64: Viral Relapse Rates

	TMC12 PR48 100mg n/N(%)	**TMC12 PR48 150mg** n/N(%)	**PR48** n/N(%)
Overall	5/53(9.4%)	6/50(12.0%)	12/27(44.4%)
Null Responder	3/9(33.3%)	2/11(18.2%)	1/4(25.0%)
Partial Responder	1/18(5.6%)	1/16(6.3%)	2/4(50.0%)
Relapse	1/26(3.9%)	3/23(13.0%)	9/19(47.4%)

Source: Statistical Reviewer's analysis.

3.3 Evaluation of Safety

A safety signal was noted with respect to rash and/or photosensitivity events in the Phase 2b (205 and 206) and pivotal Phase III studies (208, 216, and 3007). This included an increased frequency and severity of adverse events, an increase in rates of serious adverse events and an increase in rates of discontinuation of TMC435 due to rash and/or photosensitivity related adverse events. The review team is currently considering including a discussion of rash and photosensitivity events in the Warnings and Precautions Section of the label, and including a recommendation that sun protection measures (consistent with those used in the pivotal trials) be initiated in all patients receiving TMC435.

For a detailed safety evaluation, please refer to the clinical review written by Dr. Adam Sherwat.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses of SVR12 were performed according to the pre-specified analysis plan. For the naïve population, subgroup analyses were performed by combining the data from Study 208 and Study 216. For the relapser population, subgroup analyses were performed based on the data from Study 3007. Subgroup analyses were not done for the null responders and partial responders due to the small sample size of those sub-populations.

4.1 Gender, Race, Age, Geographic Region

Table 65 summarizes the subgroup analyses for SVR12 for the naïve population.
Treatment differences were consistent for gender, age, and region subgroups. Due to the small proportion of Asian and African American patients, it is difficult to draw any conclusions based on the available data.

Table 65: SVR12 by Demographic and Baseline Disease Characteristics (naïve Population)

	Subgroup	PBO	TMC435	Diff (95% CI) TMC435 vs. PBO	P-value* of the Interaction
Sex					0.9061
	Female	60/113(53%)	192/233(82%)	29%(19%, 40%)	
	Male	73/151(48%)	227/288(79%)	30%(21%, 40%)	
Race					0.9926
	ASIAN	2/ 4(50%)	6/ 7(86%)	36%(-20%, 91%)	
	BLACK	5/ 14(36%)	29/ 43(67%)	32%(3%, 60%)	
	CAUCASIAN	125/245(51%)	378/464(81%)	30%(23%, 38%)	
	OTHER	1/ 1(100%)	4/ 5(80%)		
Age					0.2275
	>45 years	71/153(46%)	213/284(75%)	29%(19%, 38%)	
	<=45 years	62/111(56%)	206/237(87%)	31%(21%, 41%)	
Region					0.3005
	ASIA-PACIFIC	11/ 17(65%)	32/ 36(89%)	24%(-1%, 49%)	
	EUROPE	75/142(53%)	239/276(87%)	34%(25%, 43%)	
	NORTH-AMERICA	37/ 86(43%)	115/168(68%)	25%(13%, 38%)	
	SOUTH-AMERICA	10/ 19(53%)	33/ 41(80%)	28%(2%, 53%)	

* P-value was obtained by fitting the logistic regression model with only treatment and the baseline variable and their interaction term as the covariates.
Source: Statistical Reviewer's analysis.

Table 66 summarizes the subgroup analyses for SVR12 of the relapser population. The results were very consistent with the naïve population.

The treatment difference was consistent for gender, and region subgroups. It seems that, numerically, the older age group (>45 years) benefited more from the TMC435 treatment compared to the control. However, the treatment and age interaction was not statistically significant. Due to the small proportion of Asian and African American patients, conclusions should not be drawn regarding differences among various racial groups.

Table 66: SVR12 by Demographic and Baseline Disease Characteristics (Relapsers)

	Subgroup	PBO	TMC435	Diff (95% CI) TMC435 vs. PBO	P-value* of the Interaction
Sex					0.6179
	Female	20/ 54(37%)	67/ 81(83%)	46%(30%, 61%)	
	Male	28/ 79(35%)	139/179(78%)	42%(30%, 54%)	
Race					0.9975
	ASIAN	1/ 1(100%)	8/ 8(100%)		
	BLACK	0/ 4(0%)	5/ 7(71%)	71%(38%, 100%)	
	CAUCASIAN	47/128(37%)	192/243(79%)	42%(32%, 52%)	
	OTHER	0/ 0(0 %)	1/ 2(50%)		
Age					0.0752
	>45 years	28/ 98(29%)	142/182(78%)	49%(39%, 60%)	
	<=45 years	20/ 35(57%)	64/ 78(82%)	25%(6%, 43%)	
Region					0.4783
	ASIA-PACIFIC	1/ 10(10%)	15/ 23(65%)	55%(28%, 82%)	
	EUROPE	40/ 90(44%)	161/184(88%)	43%(32%, 54%)	
	NORTH-AMERICA	7/ 33(21%)	30/ 53(57%)	35%(16%, 55%)	

* P-value was obtained by fitting the logistic regression model with only treatment and the baseline variable and their interaction term as the covariates.
Source: Statistical Reviewer's analysis.

4.2 Other Special/Subgroup Populations

Table 67 summarizes the subgroup analyses for SVR12 by baseline disease characteristics for the naïve population. Regarding the baseline disease characteristics, the treatment difference was consistent across the subgroups except for Q80K polymorphism at baseline. There was an apparent differential effect of treatment among those with and without Q80K.

Table 67: SVR12 by Baseline Disease Characteristics (naïve Population)

	Subgroup	PBO	TMC435	Diff (95% CI) TMC435 vs. PBO	P-value* of the Interaction
BMI					0.2720
	<25 kg/m2	53/103(51%)	175/207(85%)	33%(22%, 44%)	
	>=25 kg/m2	79/159(50%)	244/314(78%)	28%(19%, 37%)	
Baseline HCV RNA					0.4961
	<=800000 IU/mL	54/ 70(77%)	96/104(92%)	15%(4%, 26%)	
	>800000 IU/mL	79/194(41%)	323/417(77%)	37%(29%, 45%)	
Sub Genotype					0.1557
	1a/other	63/131(48%)	191/254(75%)	27%(17%, 37%)	
	1b	70/133(53%)	228/267(85%)	33%(23%, 42%)	
IL28B					0.8791
	CC	64/ 79(81%)	144/152(95%)	14%(4%, 23%)	
	CT	61/147(41%)	228/292(78%)	37%(27%, 46%)	
	TT	8/ 38(21%)	47/ 77(61%)	40%(23%, 57%)	
IP-10					0.8112
	<= 600 pg/mL	122/219(56%)	381/456(84%)	28%(20%, 35%)	
	> 600 pg/mL	11/ 45(24%)	38/ 64(59%)	35%(18%, 52%)	
Metavir Score					0.8450
	F0-F2	107/192(56%)	317/378(84%)	28%(20%, 36%)	
	F3-F4	26/ 72(36%)	89/130(68%)	32%(19%, 46%)	
Q80K					0.0002
	No	104/214(49%)	363/429(85%)	36%(29%, 44%)	
	Yes	24/ 44(55%)	51/ 86(59%)	5%(-13%, 23%)	

* P-value was obtained by fitting the logistic regression model with only treatment and the baseline variable and their interaction term as the covariates.
Source: Statistical Reviewer's analysis.

Table 68 summarizes the subgroup analyses SVR12 by baseline disease characteristics of the relapser population. The results were very consistent with the naïve population. The treatment difference was consistent across the subgroups except for Q80K polymorphism at baseline. There appeared to be a differential effect of treatment among those with and without Q80K.

Table 68: SVR12 by Demographic and Baseline Disease Characteristics (Relapsers)

	Subgroup	PBO	TMC435	Diff (95% CI) TMC435 vs. PBO	P-value* of the Interaction
BMI					0.6363
	<25 kg/m2	18/ 45(40%)	66/ 78(85%)	45%(28%, 61%)	
	>=25 kg/m2	30/ 88(34%)	140/182(77%)	43%(31%, 54%)	
Baseline HCV RNA					0.4155
	<=800000 IU/mL	12/ 23(52%)	34/ 41(83%)	31%(7%, 54%)	
	>800000 IU/mL	36/110(33%)	172/219(79%)	46%(35%, 56%)	
Sub Genotype					0.7206
	1a/other	14/ 54(26%)	78/111(70%)	44%(30%, 59%)	
	1b	34/ 79(43%)	128/149(86%)	43%(31%, 55%)	
IL28B					0.9835
	CC	17/ 34(50%)	55/ 62(89%)	39%(20%, 57%)	
	CT	28/ 83(34%)	131/167(78%)	45%(33%, 57%)	
	TT	3/ 16(19%)	20/ 31(65%)	46%(20%, 71%)	
Metavir Score					0.4001
	F0-F2	40/ 98(41%)	137/167(82%)	41%(30%, 53%)	
	F3-F4	7/ 34(21%)	61/ 83(73%)	53%(36%, 69%)	
Q80K					0.0424
	No	42/113(37%)	188/226(83%)	46%(36%, 56%)	
	Yes	6/ 20(30%)	15/ 31(48%)	18%(-8%, 45%)	

* P-value was obtained by fitting the logistic regression model with only treatment and the baseline variable and their interaction term as the covariates.
Source: Statistical Reviewer's analysis.

To further evaluate the baseline Q80K polymorphism effect on SVR12, subgroup analyses were performed by study. The SVR12 difference in patients with and without Q80K when treated with TMC435 was less in Study 216 when compared with Study 208. However the number of patients with Q80K at baseline was smaller in Study 216 than in Study 208. The reviewer also performed the similar analysis for Study 206. However, the small sample size makes it difficult to draw any conclusions based on the available data.

Table 69: SVR12 by Baseline Q80K Polymorphism

Population	Study	Treatment Arms	Baseline Q80K	SVR12
Naïve	**208**	PBO	No	48/99(48%)
			Yes	17/30(57%)
		TMC435	No	176/201(88%)
			Yes	32/61(52%)
	216	PBO	No	56/115(49%)
			Yes	7/14(50%)
		TMC435	No	187/228(82%)
			Yes	19/25(76%)
Relapsers	**3007**	PBO	No	42/113(37%)
			Yes	6/20(30%)
		TMC435	No	188/226(83%)
			Yes	15/31(48%)
Null Responders, Partial Responders and Relapsers	**206**	PBO	No	14/61(23%)
			Yes	1/5(20%)
		TMC435*	No	83/116(71%)
			Yes	9/16(56%)

*: Combination of TMC12 PR48 100mg and TMC12 PR48 150mg arms.
Source: Statistical Reviewer's analysis.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Although Simeprevir has demonstrated treatment benefit overall in treatment-naïve patients, relapsers, and partial responders, little benefit was shown in patients with Q80K polymorphism at baseline. A statistically significant treatment by Q80K polymorphism at baseline interaction was observed with regard to SVR12 in the treatment-naïve patients. In the control arm, the efficacy endpoints were quite similar between the patient with and without Q80K at baseline; the SVR12 rate was 49% for patients without Q80K at baseline and 55% (for patients with Q80K at baseline. However, in the Simeprevir arm, the percentage of patients that achieved SVR12 was 85%) for patients without Q80K at baseline and only 59% (51/86) for patients with Q80K at baseline. There appeared to be no improvement in SVR12 for those patients with Q80K at baseline when adding TMC435 to their treatment compared with the Q80K patients in the control arm.

A similar trend was also shown in the relapser population. Again statistically significant treatment and Q80K polymorphism at baseline interaction with regard to SVR12 was detected. In the control arm, SVR12 rate was 37% for the patients without Q80K at baseline and 30% for the patients with Q80K at baseline. However, in the Simeprevir arm, the proportion of patients who achieved SVR12 was 83% for patients without Q80K at baseline and only 48% for patients with Q80K at baseline.

In order to address the issue with Q80K, the applicant proposed an alternative treatment algorith (b) (4)

5.2 Collective Evidence

The statistical reviewer evaluated the efficacy results from Studies 208 and 216, two pivotal phase III, randomized, double-blind, placebo-controlled studies in the treatment-naïve genotype 1 hepatitis C-infected population. Study 3007, another phase III, randomized, double-blind, placebo-controlled study, was also reviewed. Study 3007 was conducted in genotype 1 hepatitis C-infected patients who relapsed after previous interferon-based therapy. Efficacy results from Study 206, a phase IIb study, were also reviewed to investigate the efficacy of Simeprevir in prior null responders and partial responders.

The superiority of Simeprevir to control with regard to SVR12 was demonstrated in the treatment-naïve population, relapsers, and partial responders. A numerical benefit was also observed in the null responders. However, the benefit of TMC435 over control in the overall population was not demonstrated in patients with Q80K polymorphism at baseline.

5.3 Conclusions and Recommendations

The efficacy of Simeprevir as measured by the proportion of patients achieving SVR12 was demonstrated in the treatment-naïve, relapser population, and partial responders.

Given that subjects in the confirmatory studies who were infected with HCV genotype 1a with the Q80K polymorphism at baseline were less likely to benefit from TMC435 in combination with pegylated interferon and ribavirin than subjects infected with other HCV polymorphic variants, there is a the high prevalence of the Q80K polymorphism in genotype 1a patients in the U.S. population, and there are concerns regarding the generation of cross-resistance to the approved HCV protease inhibitors in TMC435 treatment failures (i.e., R155K), the review team recommends the applicant screen all genotype 1a patients for the Q80K polymorphism prior to initiation of TMC435 with the objective of excluding patients from treatment if the polymorphism is present. The following simplified treatment algorithm could be used:

- All patients in the naïve and relapser populations should receive a fixed 24 week course of pegylated interferon and ribavirin in conjunction with 12 weeks of TMC435.
- All patients in the partial- and null-responder populations should receive a fixed 48 week course of pegylated interferon and ribavirin in conjunction with 12 weeks of TMC435.

The following stopping rules should also be implemented.

Table 70: Treatment Stopping Rules in Any Patient with Inadequate On-Treatment Virologic Response

HCV RNA	Action
Treatment Week 4: greater than or equal to 25 IU/mL	Discontinue TMC435, peginterferon alfa and ribavirin
Treatment Week 12: greater than or equal to 25 IU/mL	Discontinue peginterferon alfa and ribavirin (treatment with TMC435 is complete at Week 12)
Treatment Week 24: greater than or equal to 25 IU/mL	Discontinue peginterferon alfa and ribavirin

5.4 Labeling Recommendations (as applicable)

The review team has the following labeling recommendations:

1. Maintain the currently proposed indication (including naïve, relapser, partial and null responder populations).

2. Include the following statement in the indication and usage section:

   TRADENAME efficacy in combination with peginterferon alfa and ribavirin is substantially reduced in patients infected with HCV genotype 1a with an NS3 Q80K polymorphism at baseline compared to patients infected with hepatitis C virus (HCV) genotype 1a without the Q80K polymorphism *[see Microbiology 12.4 and Clinical Studies (14)]*. Screening patients with HCV genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism at baseline is strongly recommended. Alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism.

3. Include detailed information on the impact of the baseline Q80K polymorphism on treatment outcome (i.e. SVR12) in the Clinical Studies section of the prescribing information.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YANMING YIN
11/07/2013

FRASER B SMITH
11/07/2013

DIONNE L PRICE
11/07/2013
concur with overall conclusions

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 205123
Drug Name:	Simeprevir 150mg capsules
Indication(s):	treatment of chronic hepatitis C genotype-1 infection, in combination with peginterferon-alpha and ribavirin, in adult patients with compensated liver disease, including cirrhosis, who are treatment-naive or who have failed previous interferon and ribavirin therapy
Applicant:	Janssen Research & Development
Date(s):	Received Date: March 28, 2013 Filing Date: May 27, 2013 MidCycle Date: July 9, 2013 PDUFA Due Date: November 27, 2013
Review Priority:	Priority
Biometrics Division:	DBIV
Statistical Reviewer:	Yanming Yin, Ph.D.
Concurring Reviewers:	Fraser Smith, Ph.D.
Medical Division:	DAVP
Clinical Team:	Mary Singer, M.D.; Medical Team Leader Adam Sherwat, M.D.; Medical Reviewer
Project Manager:	Victoria Tyson

Keywords:

Chronic Hepatitis C (CHC), Genotype 1 infection, simeprevir, TMC435, peginterferon alfa (PEG), ribavirin (RBV), Q80K.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

On March 28, 2013, Janssen submitted the NDA 205123 to seek the agency's approval of Simeprevir (TMC435) 150 mg capsule taken once daily in combination with peginterferon alpha and ribavirin. The desired indication is treatment of chronic hepatitis C (CHC) genotype 1 infection, in adult paients with compensated liver disease (including cirrhosis) who are treatment-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without rivavirin.

The statistical reviewer evaluated the efficacy results from Study 208 and Study 216, two pivotal phase III, randomized, double-blind, placebo-controlled studies in treatment-naïve genotype 1 hepatitis C-infected population. Another phase III, randomized, double-blind, placebo-controlled study (Study 3007) was also reviewed. Study 3007 enrolled genotype 1 hepatitis C-infected patients who had relapsed after previous interferon-based therapy. Efficacy results from Study 206, a phase IIb study, were also reviewed to investigate the efficacy of Simeprevir in prior null responders and partial responders.

In Study 208, the percentage of patients achieving sustained virologic response 12 weeks after the end of treatment (SVR12) was 51% (66/130) in the control arm and 80% (210/264) in the Simeprevir (TMC435) arm. The treatment difference for SVR12 was 29% with 95% confidence interval (CI) of (19%, 38%). The superiority of Simeprevir to the control was demonstrated in Study 208.

In Study 216, the percentage of patients achieving SVR12 was 50% (67/134) in the control arm and 81% (209/257) in the Simeprevir (TMC435) arm. The treatment difference for SVR12 was 32% (95% CI: 23%, 41%). The superiority of Simeprevir to the control was demonstrated in Study 216.

By integrating the data from Study 208 and Study 216 for the treatment-naïve population, the percentage of patients achieving SVR12 was 50% (133/264) in the control arm and 80% (419/521) in the Simeprevir (TMC435) arm. The treatment difference for SVR12 was 30% (95% CI: 24%, 37%).

In Study 3007, the proportion of patients that achieved SVR12 was 36% (48/133) in the control arm and 79% (206/260) in the Simeprevir arm. The treatment difference was 44% (95% CI: 35%, 53%). The superiority of Simeprevir to control was again demonstrated in the relapser population with regard to SVR12.

Based on the data from Study 206, the SVR12 rate for null responders was 46% (15/33) in patients treated with Simeprevir for 12 weeks and 19% (3/16) for the control arm. The treatment difference was 27% and was not statistically significant (p-value 0.11). For partial responders, the SVR rate was 70% (32/46) in patients treated with Simeprevir for 12 weeks and 9% (2/23) for the control arm. The treatment difference (61%) was statistically significant (p-value <0.0001). For relapsers, the SVR rate was 85% (45/53) in patients treated with Simeprevir for 12

weeks and 37% (10/27) for the control arm. The treatment difference was 48% and was also significant (p-value <0.0001).

Although Simeprevir has demonstrated treatment benefit in treatment-naïve patients, relapsers, and partial responders, little benefit was shown in patients with the Q80K polymorphism at baseline. Q80K is considered to be a clinically important prognostic factor. This lack of benefit was noted in an in vitro study early in the development. A statistically significant treatment by Q80K polymorphism at baseline interaction (p-value of 0.0002) was observed with regard to SVR12 in the treatment-naïve patients. In the control arm, the efficacy endpoints were quite similar between the patients with and without Q80K at baseline. The SVR12 rate was 49% (104/214) for patients without Q80K at baseline and 55% (24/44) for patients with Q80K at baseline. However in the Simeprevir arm, the proportion of patients that achieved SVR12 was 85% (363/429) for patients without Q80K at baseline and only 59% (51/86) for patients with Q80K at baseline. There appeared to be no improvement in SVR12 for those patients with Q80K at baseline when adding TMC435 to their treatment regime compared with the Q80K patients in the control arm. A similar trend was also shown in the relapser population. Again, a statistically significant treatment by Q80K polymorphism at baseline interaction (p-value=0.04) with regard to SVR12 was detected. In the control arm, SVR12 rate was 37% (42/113) for the patients without Q80K at baseline and 30% (6/20) for the patients with Q80K at baseline. However in the Simeprevir arm, the proportion of patients achieving SVR12 was 83% (188/226) for patients without Q80K at baseline and only 48% (15/31) for patients with Q80K at baseline.

In order to address the concerns and mitigate risk, the applicant proposed an alternative treatment algorithm (b) (4)

(b) (4)

Given that subjects in the pivotal Phase IIIstudies who were infected with HCV genotype 1a and had the Q80K polymorphism at baseline were less likely to benefit from TMC435 in combination with pegylated interferon and ribavirin than subjects infected with other HCV polymorphic variants, there is a high prevalence of the Q80K polymorphism in genotype 1a patients in the U.S. population, and there are concerns regarding the generation of cross-resistance to the approved HCV protease inhibitors in TMC435 treatment failures (i.e., R155K), the review team recommends that the applicant screen all patients for the Q80K polymorphism prior to initiation of TMC435 with the objective of excluding patients from treatment if the

polymorphism is present. The applicant's proposed treatment algorithm can also be simplified. One of the options is:

- All patients in the naïve and relapser populations would receive a fixed 24 week course of pegylated interferon and ribavirin in conjunction with 12 weeks of TMC435.
- All patients in the partial- and null-responder populations would receive a fixed 48 week course of pegylated interferon and ribavirin in conjunction with 12 weeks of TMC435.

Based on this proposal, the reviewer's estimated SVR12 would be above 83% for the naïve population and above 81% for the relapsers. Other options are still under discussion currently.

An Advisory Committee meeting is scheduled in October, 2013. Topics of discussion have yet to be decided.

2 INTRODUCTION

2.1 Overview

TMC435 is an inhibitor of the HCV NS3/4A protease and was developed for the treatment of chronic HCV infection. According to the applicant, an in vitro study demonstrated the anti-HCV effect of TMC435 in genotype 1 and genotype 4 patients. It also showed the anti-HCV effect of TMC435 was reduced by amino acid substitution Q80K. The anti-HCV activity was low in genotype 2 and 3 patients.

Different doses and treatment durations were tested in phase I and phase II studies. Based on the results of phase II studies, the proposed dose regimen of TMC435 150 mg once daily (q.d.) for a duration of 12 weeks in combination with peginterferon and ribavirin (PegIFN/ RBV) followed by another 12 or 36 weeks PegIFN/ RBV alone (response-guided duration for treatment with PegIFN/RBV for subjects who are treatment-naïve or relapsed after prior IFN-based therapy) was recommended for phase III studies.

Before the NDA submission, the statistical reviewer evaluated the statistical analysis plan for the pooling of the efficacy data, and comments were sent to the applicant. The reviewer indicated that the applicant had to follow the original method that was pre-specified in the protocols and analysis plans. The applicant was informed that the newly proposed (b) (4) procedure could not be used to make a labeling claim. Janssen acknowledged the agency's feedback and stated that SVR12 would be the primary efficacy endpoint. All other endpoints would be ordered to support submission to other health authorities and for publication of key results. The agency stated that the additional endpoints could be submitted, but they would not be considered for labeling purposes.
The applicant submitted the results of their clinical studies to support the indication for treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin,

in adult patients with compensated liver disease who are treatment-naïve or who have failed previous interferon therapy(pegylated or non-pegylated) with or without ribavirin.

The statistical review focused on the below listed studies. Complete study report for Study 206 was submitted. For the Phase III studies (208, 216 and 3007), 60 weeks interim results were submitted.

Table 1: List of all studies included in analysis

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects Total (ITT population)	Study Population
208	Phase 3	24/48 weeks	24 weeks	394 (ratio: 1:2)	HCV Genotype1 naïve patients
216	Phase 3	24/48 weeks	24 weeks	391 (ratio: 1:2)	HCV Genotype1 naïve patients
HPC3007	Phase 3	24/48 weeks	24 weeks	393 (ratio: 1:2)	HCV Genotype1 experienced patients (relapser)
206	Phase 2	24/48 weeks	24 weeks	462 (ratio: 1:1:1:1:1:1:1)	HCV Genotype1 experienced patients

2.2 Data Sources

The NDA is located at:
\\CDSESUB1\EVSPROD\NDA205123\0000
Both SDTM and ADAM datasets were submitted. Some of the SAS programs were also submitted.

The SDTM datasets for Study 208 are located in the following directory:
\\CDSESUB1\EVSPROD\ NDA205123\0000\m5\datasets\tmc435-tidp16-c208\tabulations\sdtm
The ADAM datasets of Study 208 are under the the following directory:
\\CDSESUB1\EVSPROD\ NDA205123\0000\m5\datasets\tmc435-tidp16 c208\analysis\adam\datasets

The SDTM datasets of Study 216 are located in the following directory:
\\CDSESUB1\EVSPROD\ NDA205123\0000\m5\datasets\tmc435-tidp16-c216\tabulations\sdtm
The ADAM datasets of Study 216 are under the directory of:
\\CDSESUB1\EVSPROD\ NDA205123\0000\m5\datasets\tmc435-tidp16-c216\analysis\adam\datasets

The SDTM datasets of Study 3007 are under the directory of:
\\CDSESUB1\EVSPROD\ NDA205123\0000\m5\datasets\tmc435hpc3007\tabulations\sdtm
The ADAM datasets of Study 3007 are under the directory of:
\\CDSESUB1\EVSPROD\ NDA205123\0000\m5\datasets\ tmc435hpc3007\analysis\adam\datasets

The SDTM datasets of Study 206 are under the directory of:
\\CDSESUB1\EVSPROD\ NDA205123\0000\m5\datasets\tmc435-tidp16-c206\tabulations\sdtm
The ADAM datasets of Study 206 are under the directory of:
\\CDSESUB1\EVSPROD\ NDA205123\0000\m5\datasets\tmc435-tidp16 c206\analysis\adam\datasets

The statistical reviewer's analyses were primarily based on the raw (SDTM) datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The applicant submitted data of good quality. However, the derivation of the efficacy variables were not described in detail in the **define** files. The review's analyses were based on the raw datasets and the methods described in Section 3.2.2.2. Statistical analysis plans were also submitted.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The study design, objective and primary endpoints are described in the sections below for each study. The phase III studies were designed appropriately to meet the primary objective.

3.2.1.1 Study 208

Study 208 was a Phase III, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of TMC435 as part of a treatment regimen including peginterferon alpha-2a and ribavirin (PegIFNα-2a/RBV) in treatment-naïve, genotype 1 hepatitis C-infected subjects. The primary objective of this study was to demonstrate the superiority of TMC435 compared to placebo as part of a treatment regimen including PegIFNα-2a/RBV with respect to the proportion of subjects with sustained virologic response (SVR) 12 weeks after the planned end of treatment.

Subjects with documented chronic genotype 1 HCV infection, who were treatment-naïve and had a screening plasma HCV ribonucleic acid (RNA) level of > 10,000 IU/mL, were randomly assigned in a 2:1 ratio to receive TMC435 or placebo, stratified by HCV genotype 1 subtype and *IL28B* genotype.

In the first 24 weeks, subjects received 12 weeks TMC435 150 mg or placebo q.d. with PegIFNα-2a/RBV, followed by 12 weeks of PegIFNα-2a/RBV alone. As part of a response-guided treatment duration, HCV therapy was stopped at Week 24 in subjects in the TMC435 treatment group when they achieved HCV RNA levels < 25 IU/mL (detectable or undetectable) at Week 4 and < 25 IU/mL undetectable HCV RNA levels at Week 12. All other subjects continued PegIFNα-2a/RBV until Week 48. In the control group, all subjects continued PegIFNα-2a/RBV alone until Week 48.

The complete virologic stopping criteria used in Study 206 and all the phase III studies were:
Stop TMC435/placebo and continue with PegIFN and RBV if HCV RNA is >1000 IU/mL at Week 4.
Stop PegIFN and RBV if HCV RNA reduction is less than 2 log10 at Week 12 compared to baseline; confirmed detectable at Week 24 and confirmed detectable at Week 36.

The primary efficacy endpoint was the proportion of subjects in each treatment group achieving sustained virologic response 12 weeks after the planned end of therapy (SVR12).

3.2.1.2 Study 216

Study 216 was a Phase III, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of TMC435 versus placebo as part of a treatment regimen including peginterferon α-2a (Pegasys®) and ribavirin (Copegus®) or peginterferon α-2b (PegIntron®) and ribavirin (Rebetol®) in treatment-naïve,genotype 1, hepatitis C-infected subjects. The primary objective of this study was to demonstrate the superiority of TMC435 as part of a treatment regimen including PegIFNα-2a/RBV or PegIFNα-2b/RBV, with respect to the proportion of treatment-naïve genotype 1 HCV-infected subjects with sustained virologic response 12 weeks after the planned end of treatment.
Subjects with documented chronic genotype 1 HCV infection, who were treatment-naïve and had a screening plasma HCV RNA level of > 10,000 IU/mL, were randomly assigned in a 2:1 ratio to receive TMC435 or placebo, stratified by HCV genotype 1 subtype and *IL28B* genotype.

In the first 24 weeks, subjects received 12 weeks TMC435 150 mg or placebo q.d. along with PegIFNα- 2a/2b and RBV, followed by 12 weeks of PegIFN/RBV alone. As part of a response-guided treatment duration, HCV therapy was stopped at Week 24 in subjects in the TMC435 treatment group when they achieved HCV RNA levels < 25 IU/mL (detectable or undetectable) at Week 4 and < 25 IU/mL undetectable HCV RNA levels at Week 12. All other subjects continued PegIFN/RBV alone until Week 48. In the control group, all subjects continued PegIFN/RBV alone until Week 48.

The use of PegIFNα-2b was limited to a selected number of countries. A maximum of 30% of the overall study population was randomized to a PegIFNα-2b containing regimen. In these countries, subjects were randomized in a 1:1 ratio to PegIFNα-2a/RBV or PegIFNα-2b/RBV.

The primary efficacy endpoint was the proportion of subjects in each treatment group achieving SVR12.

3.2.1.3 Study 3007

Study 3007 was a Phase III, randomized, double-blind, placebo controlled study to investigate the efficacy, safety and tolerability of TMC435 as part of a treatment regimen including PegIFNα-2a/RBV in hepatitis C, genotype 1 infected subjects who relapsed after previous interferon-based therapy. The primary objective of this study was to demonstrate the superiority of TMC435 as part of a treatment regimen including PegIFNα-2a/RBV, with respect to the proportion of subjects with sustained virologic response 12 weeks after the planned end of treatment.

Subjects with documented chronic genotype 1 HCV infection, who relapsed after previous

Peg-IFN-based therapy and had a screening plasma HCV ribonucleic acid (RNA) level of > 10,000 IU/mL, were randomized in a 2:1 ratio to receive TMC435 or placebo, stratified by HCV genotype 1 subtype and *IL28B* genotype.

In the first 24 weeks, subjects received 12 weeks TMC435 150 mg or placebo q.d. along with PegIFNα-2a/RBV, followed by 12 weeks of PegIFNα-2a/RBV alone. As part of a response-guided treatment duration, HCV therapy was stopped at Week 24 in subjects in the TMC435 treatment group when they achieved HCV RNA levels < 25 IU/mL (detectable or undetectable) at Week 4 and < 25 IU/mL undetectable HCV RNA levels at Week 12. All other subjects continued PegIFNα-2a/RBV until Week 48. In the control group, all subjects would continue PegIFNα-2a/ RBV alone until Week 48.

The primary efficacy endpoint was the proportion of subjects in each treatment group achieving SVR12.

3.2.1.4 Study 206

Study 206 was a Phase IIb, randomized, 7-arm, double-blind, placebo-controlled trial to investigate the efficacy, tolerability, safety and pharmacokinetics of TMC435 as part of a treatment regimen including PegIFNα-2a and ribavirin in HCV genotype 1 infected subjects who failed to respond or relapsed following at least 1 course of PegIFNα-2a/b and RBV therapy. The primary objective of the trial was to evaluate the treatment effect of 6 different regimens of TMC435 in combination with PegIFNα-2a/RBV on the proportion of subjects with < 25 IU/mL undetectable HCV RNA 24 weeks after the planned end of treatment (SVR24) compared to the control group receiving PegIFNα-2a/RBV in combination with TMC435-matched placebo.

Subjects were randomized in a 1:1:1:1:1:1:1 ratio to 1 of 7 different treatment arms as described below

- Treatment arms 1 and 2 consisted of 12 weeks triple therapy with 100 mg and 150 mg TMC435 q.d., respectively, along with PegIFNα-2a/RBV followed by 36 weeks of PegIFNα-2a/RBV with TMC435-matched placebo and 24 weeks of post-therapy follow up.
- Treatment arms 3 and 4 consisted of 24 weeks triple therapy with 100 mg and 150 mg

TMC435 q.d., respectively, with PegIFNα-2a/RBV followed by 24 weeks of PegIFNα-2a/RBV with TMC435 matched placebo and 24 weeks of post-therapy follow-up.

- Treatment arms 5 and 6 consisted of 48 weeks triple therapy with 100 mg and 150 mg TMC435 q.d., respectively, with PegIFNα-2a/RBV and 24 weeks of post-therapy follow-up.
- Treatment arm 7 (control arm) consisted of 48 weeks of TMC435-matched placebo plus PegIFNα-2a/RBV and 24 weeks of post-therapy follow up.

Two stratification factors were used in the randomization process: genotype 1 subtype and prior PegIFNα-2a/b and RBV response (i.e. relapsers, partial responders, and null responders).

The primary efficacy endpoint was the proportion of subjects in each treatment group achieving SVR24 defined as having undetectable HCV RNA at the EOT and 24 weeks after the planned EOT, i.e., Week 72.

3.2.2 Statistical Methodologies

3.2.2.1 Applicant's Statistical Methodologies

3.2.2.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint and the null hypothesis of three phase III studies were stated by the applicant as follows:

> The primary efficacy endpoint is the proportion of subjects in each treatment group achieving sustained virologic response 12 weeks after the planned end of therapy (SVR12).
>
> The null hypothesis that will be tested to address the primary objective of this trial is that there is no statistically significant difference between the active treatment arm and the control group for the primary efficacy endpoint (SVR12).

The difference in SVR12 rates was calculated using Cochran–Mantel–Haenszel (CMH) method to control stratification factors.

The applicant used the following algorithm to derive SVR12:

SVR12 is defined as follows:

- 1=Success (both of the below conditions were met):
  - at the actual end of treatment (see section 2.1)
    - HCV RNA < 25 IU/ml undetectable or
    - HCV RNA < 25 IU/ml detectable/≥ 25 IU/mL quantifiable, and at the previous measurement < 25 IU/mL undetectable, and the next measurement (either retest or next visit) is available and HCV RNA < 25 IU/mL undetectable for this next visit
  - at the timepoint of SVR
    - < 25 IU/mL undetectable or
    - < 25 IU/mL detectable and
      - the sample obtained at a confirmation visit* OR
      - the sample is the last available HCV RNA measurement OR
      - the next available measurement has HCV RNA < 25 IU/mL (undetectable or detectable)
    - ≥ 25 IU/mL quantifiable and
      - the sample not obtained at a confirmation visit* AND
      - not the last available measurement in the study AND
      - a next measurement is available and HCV RNA < 25 IU/mL (undetectable or detectable) for this next measurement
- 0= failure: otherwise

*Confirmation visit: an unscheduled visit following a measurement with HCV RNA levels which became <25 IU/mL detectable or ≥25 IU/mL after previous undetectability

Timepoint of SVR:

- 12 weeks after the planned EOT (i.e. the last available measurement in the SVR12 analysis window)
- or, if not available, the first available measurement at least 12 weeks after the planned EOT (i.e. the first available measurement after the SVR12 analysis window)
- or, if not available (i.e. no measurement at least 12 weeks after the planned EOT), the subject is considered a failure

3.2.2.1.2 Analysis Set

The applicant defined the *Intent-to-treat (ITT) population* as all randomized subjects who took at least 1 dose of investigational medication (TMC435 or placebo). The applicant also stated that all analyses would be done on the ITT population.

Major protocol deviations were identified prior to database lock. If there were more than 10% of subjects with a major protocol deviation, a per protocol analysis was performed on the primary endpoint excluding these subjects.

3.2.2.1.3 Visit Windows

The Applicant realigned all visits according to the visit windows below. If two visits fell within the same interval, the last measurement within the interval was used for the descriptive statistics/tabulations per time point and graphics in order to have only one evaluation per subject per analysis time point. If there were two measurements on the same day, then the measurement with the highest sequence number was used.

Table 2: On-treatment Visit Windows of the Phase III studies

Trial phase	Target day	Analysis time point (numeric version)	Analysis time point	Time interval (days)[a]
Screening	-∞	-1	Screening	<0
72 weeks study period[c]	1	0	Baseline[b]	<=1
	3	0.3	Day 3	[2,5]
	7	1	Week 1	[6,11]
	14	2	Week 2	[12,21]
	28	4	Week 4	[22,42]
	56	8	Week 8	[43,70]
	84	12	Week 12	[71,98]
	112	16	Week 16	[99,126]
	140	20	Week 20	[127,154]
	168	24	Week 24	[155,182]
	196	28	Week 28	[183,224]
	252	36	Week 36	[225,273]
	294	42	Week 42	[274,315]
	336	48	Week 48	[316,350]
	364	52	Week 52	[351,392]
	420	60	Week 60	[393,476]
	504	72	Week 72	[477,+∞]
	last visit while on study therapy or 3 days after the day of last dose	999	EOT	

[a] the first double-blind medication day is day 1.
[b] If the reldy of the baseline value closest to the target day is less than 0, only the record closest to the target day will be retained in the ADAM dataset, otherwise only the record(s) with reldy 1 will be kept.
[c] The same analysis time points can be used for the other phases (TMC435/PBO + PR, Entire Treatment, PR only, Follow-up). Distinction between the time points of different phases, should be based on the combination of phase and analysis time point.

Plasma HCV RNA values were determined using the Roche COBAS Taqman HCV/HPS v2.0 assay with a linear range from 25-300,000,000 IU/mL, a limit of quantification of 25 IU/mL.

For the purpose of the analysis, HCV RNA results of '<25 IU/mL HCV RNA detected' were set to 24 IU/mL and 'HCV RNA not detected' was set to 9 IU/mL before log transformation.
The visit windows of Study 206 were slightly different from the visit windows of the phase III studies due to more frequent visits.

3.2.2.2 Reviewer's Statistical Methodologies

The statistical reviewer performed all efficacy analyses on the ITT analysis set.
All HCV RNA records including withdrawal visits and unscheduled visits were treated as regular visits and included in the analysis.

3.2.2.2.1 Reviewer's Primary Efficacy Endpoint

The primary efficacy endpoint, SVR12, was modified by the reviewer slightly and was defined as the proportion of subjects in each treatment group achieving sustained virologic response (HCV RNA < 25IU/mL) 12 weeks after the end of therapy. Instead of using the planned end of therapy, the actual date of the end of therapy was used. Missing SVR12 was substituted by SVR24 if available. If both SVR12 and SVR24 were missing, SVR12 was imputed as failure.

The reviewer also defined another important efficacy endpoint, SVR, which was the proportion of subjects in each treatment group achieving sustained virologic response (HCV RNA < 25IU/mL) at least 12 weeks after the end of therapy. If there was more than one record in the follow-up visit window [57, +∞], the last record was taken. This was a more conservative definition to capture the latest available HCV RNA record. Patients that relapsed after Week 12 follow-up were considered as SVR failures by this definition. For patients with missing SVR, SVR was imputed as failure.

For Study 206, the analyses performed were similar to those of the Phase III studies in order to be consistent.

3.2.2.2.2 Reviewer's Visit Windows

For on-treatment visits up to week 48, the reviewer used the same visit windows as the applicant. Records were considered to be on-treatment if the collection date was less than or equal to the date of last dose + 3 days. However, for the follow-up visits, the reviewer used different visit windows as shown below. The post treatment days was defined as HCV RNA collection date - date of last dose. The date of last dose was taken as the maximum of the date of the last dose of TMC/PBO, PEG and RBV.

Table 3: Follow-Up Visit Windows

Analysis Time Point	Time Interval (Post treatment days)	Comments
Follow-Up Week 4	[15, 56]	Used for SVR4
Follow-Up Week 12	[57, 140]	Used for SVR12
Follow-Up Week 24	[141,]	Used for SVR24
	[57, +∞]	Used for SVR

Note: post treatment days=date HCV RNA was collected - date of last dose.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Study C208

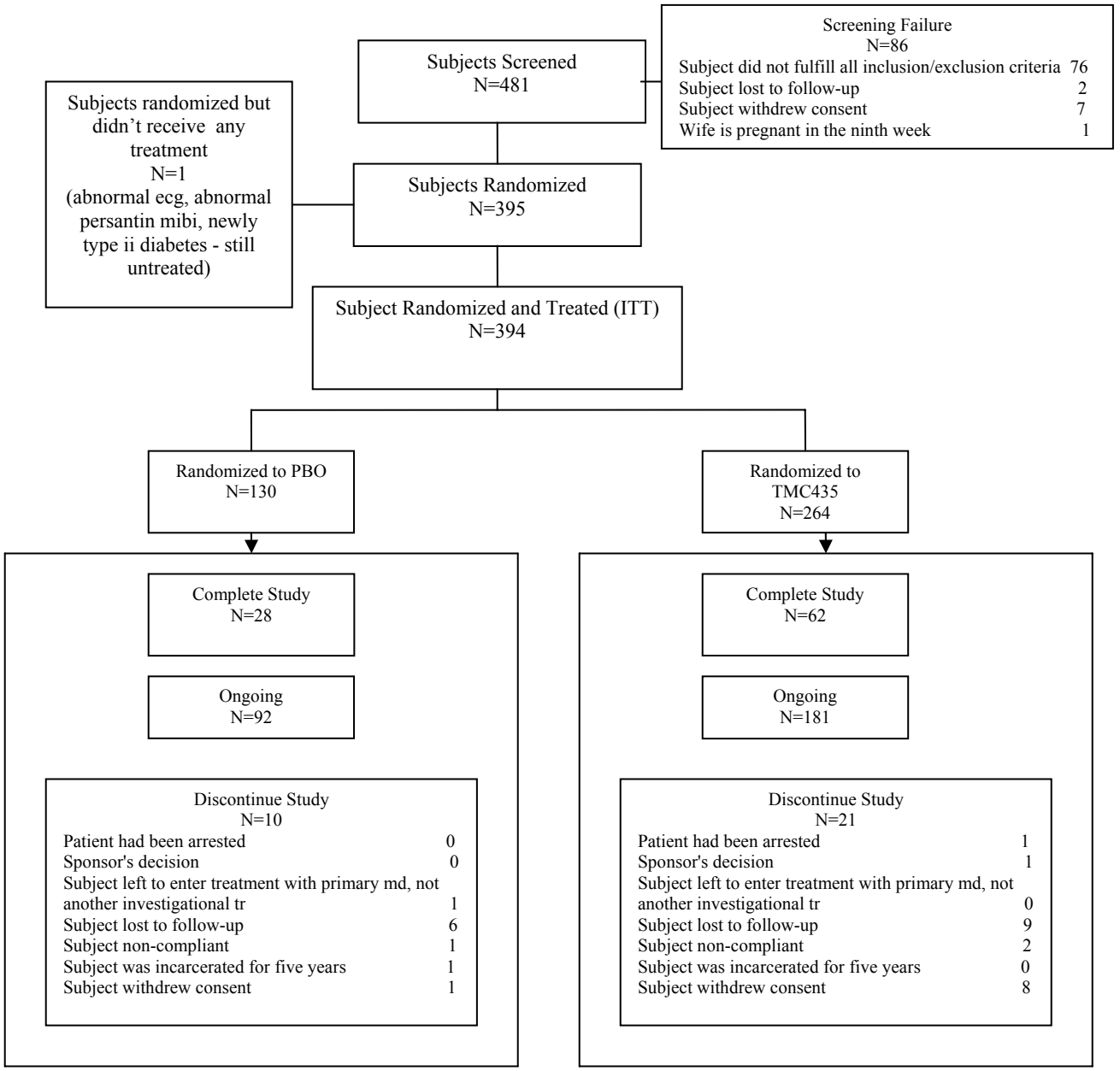
3.2.3.1.1 Patient Disposition

Figure 1 displays the study disposition for Study 208. There were 481 patients screened, and 395 patients were randomized. One patient was randomized but did not receive any treatment; therefore, this patient was excluded from the ITT analysis set. Of the 130 patients that were randomized and treated in the control arm (PBO), only 28 patients finished the study by the time of the database lock. Ten patients discontinued the study, and 92 patients were still in the follow-up phase. In the TMC435 arm, 264 patients were randomized and treated. Sixty-two of them finished the study. Twenty-one patients discontinued the study and 181 patients were still in the follow-up phase.

The treatment disposition is summarized in Table 4. In the PBO arm, 45 (34.6%) patients completed treatment, while in the TMC435 arm, the treatment completion rate was much higher (87.5%). In the PBO arm, 80 (61.5%) patients discontinued the treatment because they achieved the virologic endpoint, 4 (3.1%) patients discontinued due to an AE and one patient (0.8%) discontinued due to non-compliance. In the TMC435 arm, 12 (4.5%) patients discontinued because they reached a virologic endpoint, 9 (3.4%) patients discontinued due to AE, 5 (1.9%) patients discontinued due to non-compliance, 5 (1.9%) discontinued due to withdrawal of consent and 2 (0.8%) patients discontinued due to other reasons.

The treatment disposition with respect to PegIFN and RBV are summarized in Table 5 and Table 6, respectively. Compared with the PBO arm, the TMC435 arm had higher completion rates for Peg-IFN and RBV (around 86% vs. 61% for both PegIFN and RBV).

Figure 1: Study 208: Study Disposition



Source: Statistical Reviewer's analysis

Table 4: Subject Treatment Completion Status of PBO/TMC435 (ITT Analysis Set)

Treatment Disposition(PBO/TMC435)	**PBO (N=130)**	**TMC435 (N=264)**
Completed	45(34.6%)	231(87.5%)
Discontinued	85(65.4%)	33(12.5%)
Adverse event	4(3.1%)	9(3.4%)
Subject lost to follow-up	0	1(0.4%)
Subject non-compliant	1(0.8%)	5(1.9%)
Subject reached a virologic endpoint	80(61.5%)	12(4.5%)
Subject withdrew consent	0	5(1.9%)
Subject incarcerated during the study	0	1(0.4%)

Source: Statistical Reviewer's analysis.

Table 5: Subject Treatment Completion Status of PegIFN (ITT Analysis Set)

Treatment Disposition(PegINF)	**PBO (N=130)**	**TMC435 (N=264)**
Completed	79(60.8%)	230(87.1%)
Discontinued	51(39.2%)	34(12.9%)
Adverse event	12(9.2%)	8(3.0%)
Subject decision after applicant's interruption of the experimental drug	1(0.8%)	0
Subject arrested	0	1(0.4%)
Subject decision to stop medication	1(0.8%)	0
Subject lost to follow-up	1(0.8%)	3(1.1%)
Subject non-compliant	1(0.8%)	4(1.5%)
Subject reached a virologic endpoint	34(26.2%)	13(4.9%)
Subject withdrew consent	1(0.8%)	5(1.9%)

Source: Statistical Reviewer's analysis.

Table 6: Subject Treatment Completion Status of RBV
(ITT Analysis Set)

Treatment Disposition(RBV)	**PBO (N=130)**	**TMC435 (N=264)**
Completed	79(60.8%)	228(86.4%)
Discontinued	51(39.2%)	36(13.6%)
Adverse event	12(9.23%)	10(3.8%)
Subjectt decision after r applicant's interruption of the experimental drug	1(0.77%)	0
Subject arrested	0	1(0.4%)
Subject decision to stop medication	1(0.8%)	0
Subject lost to follow-up	1(0.8%)	3(1.1%)
Subject non-compliant	1(0.8%)	4(1.5%)
Subject reached a virologic endpoint	34(26.2%)	13(4.9%)
Subject withdrew consent	1(0.8%)	5(1.9%)

Source: Statistical Reviewer's analysis.

3.2.3.1.2 Demographic and Baseline Characteristics

Table 7 and Table 8 summarize the patient demographic and baseline characteristics. The demographic and baseline characteristics distribution was comparable between the two treatment arms. Approximately 56% of the patients were male, and 57% of the patients were more than 45 years old. The majority of the patients (89%) were white. Approximately 36% of the patients had BMI <25kg/m^2. Regarding the IL28B, 29% of the patients were genotype CC patients, 57% of the patients were genotype CT and 14% of the patients were genotype TT. About 80% of the patients had baseline HCV RNA >800000 IU/mL and 30% of the patients had metavir fibrosis score F3-F4. At baseline 63% of the patients had ALT level above grade 0. About 56% of the patients were genotype 1a patients. The majority (86%) of the patients had IP-10 <=600pg/mL at baseline.

Table 7: Study 208: Demographic (ITT Analysis Set)

	PBO 12 Wks PR 48	TMC435 150mg 12 Wks PR 24/48	Total
Analysis Set: Intent-to-treat	130	264	394
Gender			
N	130	264	394
Female	56 (43.1%)	116 (43.9%)	172 (43.7%)
Male	74 (56.9%)	148 (56.1%)	222 (56.3%)
Race			
N	130	262	392
White	122 (93.8%)	227 (86.6%)	349 (89.0%)
Black or African American	4 (3.1%)	27 (10.3%)	31 (7.9%)
American Indian or Alaska Native	0	1 (0.4%)	1 (0.3%)
Native Hawaiian or Other Pacific Islander	1 (0.8%)	1 (0.4%)	2 (0.5%)
Asian	3 (2.3%)	5 (1.9%)	8 (2.0%)
Multiple	0	1 (0.4%)	1 (0.3%)
Ethnicity			
N	130	264	394
Hispanic or Latino	14 (10.8%)	35 (13.3%)	49 (12.4%)
Not Hispanic or Latino	116 (89.2%)	229 (86.7%)	345 (87.6%)
Age (years)			
N	130	264	394
≤45	53 (40.8%)	115 (43.6%)	168 (42.6%)
>45 - ≤65	76 (58.5%)	143 (54.2%)	219 (55.6%)
>65	1 (0.8%)	6 (2.3%)	7 (1.8%)
Age (years)			
N	130	264	394
Mean (SD)	45.7 (11.04)	46.3 (10.98)	46.1 (10.99)
Median	48.0	48.0	48.0
Range	(20; 66)	(19; 68)	(19; 68)
Body weight (kg)			
N	130	264	394
Mean (SD)	82.52 (21.478)	80.13 (17.316)	80.92 (18.797)
Median	80.60	78.70	78.91
Range	(42.0; 155.0)	(47.5; 135.3)	(42.0; 155.0)
Body mass index (kg/m^2)			
N	130	264	394
<25	47 (36.2%)	96 (36.4%)	143 (36.3%)
≥25 - <30	41 (31.5%)	100 (37.9%)	141 (35.8%)
≥30	42 (32.3%)	68 (25.8%)	110 (27.9%)
Body mass index (kg/m^2)			
N	130	264	394
Mean (SD)	28.15 (6.477)	27.48 (5.703)	27.70 (5.969)
Median	26.70	26.55	26.60
Range	(17.0; 53.5)	(16.5; 45.2)	(16.5; 53.5)
IL28B Genotype[a]			
N	130	264	394
CC	37 (28.5%)	77 (29.2%)	114 (28.9%)
CT	76 (58.5%)	150 (56.8%)	226 (57.4%)
TT	17 (13.1%)	37 (14.0%)	54 (13.7%)

[a] Results obtained from the central laboratory: may not be the same as stratified.

Source: Table 14 in Clinical Study Report for study TMC435-TiDP16-C208.

Table 8: Baseline Disease Characteristics (ITT Analysis Set)

	PBO 12 Wks PR 48	TMC435 150mg 12 Wks PR 24/48	Total
Analysis Set: Intent-to-treat	130	264	394
Baseline HCV RNA level (log_{10} IU/mL)			
N	130	264	394
Mean (SD)	6.29 (0.779)	6.43 (0.600)	6.39 (0.667)
Median	6.39	6.50	6.48
Range	(1.4; 7.5)	(4.2; 7.6)	(1.4; 7.6)
Baseline HCV RNA category (IU/mL)			
N	130	264	394
<400000	19 (14.6%)	28 (10.6%)	47 (11.9%)
≥400000 - ≤800000	15 (11.5%)	18 (6.8%)	33 (8.4%)
>800000	96 (73.8%)	218 (82.6%)	314 (79.7%)
Metavir fibrosis score[a]			
N	130	260	390
Score F0-F1	50 (38.5%)	118 (45.4%)	168 (43.1%)
Score F2	40 (30.8%)	65 (25.0%)	105 (26.9%)
Score F3	23 (17.7%)	46 (17.7%)	69 (17.7%)
Score F4	17 (13.1%)	31 (11.9%)	48 (12.3%)
Baseline ALT WHO toxicity grade			
N	130	264	394
Grade 0	41 (31.5%)	106 (40.2%)	147 (37.3%)
Grade 1	55 (42.3%)	100 (37.9%)	155 (39.3%)
Grade 2	26 (20.0%)	48 (18.2%)	74 (18.8%)
Grade 3	7 (5.4%)	7 (2.7%)	14 (3.6%)
Grade 4	1 (0.8%)	3 (1.1%)	4 (1.0%)
HCV geno/subtype (NS5B)[b]			
N	130	264	394
1a	74 (56.9%)	147 (55.7%)	221 (56.1%)
1b	56 (43.1%)	117 (44.3%)	173 (43.9%)
Time since diagnosis (years)			
N	130	264	394
Mean (SD)	5.78 (6.636)	6.30 (6.681)	6.13 (6.663)
Median	2.80	3.35	3.30
Range	(0.3; 33.6)	(0.2; 35.5)	(0.2; 35.5)
IP-10 Category			
N	130	263	393
≤600 pg/mL	110 (84.6%)	226 (85.9%)	336 (85.5%)
>600 pg/mL	20 (15.4%)	37 (14.1%)	57 (14.5%)

[a] Limited to results from Metavir scoring system.
[b] HCV geno/subtype is based on the NS5B assay, and if not available on LiPA HCV II or Trugene results.

Source: Table 15 in Clinical Study Report for study TMC435-TiDP16-C208.

3.2.3.2 Study 216

3.2.3.2.1 Patient Disposition

Figure 2 displays the study disposition for Study 216. There were 474 patients screened, and 393 patients were randomized. Two patients were randomized but did not receive any treatment; therefore, they were excluded from the ITT analysis set. Of the 134 patients that were randomized and treated with PBO, 51 patients finished the study by the time of the database lock. Seventeen patients discontinued the study, and 66 patients were still in the follow-up phase. In the TMC435 arm, 257 patients were randomized and treated. One hundred and eleven of them finished the study. Twelve patients discontinued the study, and 134 patients were still in the follow-up phase.

The treatment disposition of PBO and TMC435 is summarized in Table 9. In the PBO arm, 51 (38.1%) patients completed the PBO treatment, while in the TMC435 arm, the treatment completion rate was much higher (96.1%). In the PBO arm, 82 (61.2%) patients discontinued the treatment because they reached a virologic endpoint. Only one (0.7%) patient discontinued due to AE. In the TMC435 arm, 3 (1.2%) patients discontinued because patients reached a virologic endpoint, 4 (1.6%) patients discontinued due to AE, 1 (0.4%) patient discontinued due to non-compliance and 2 (0.8%) patients discontinued due to withdrawal of consent.

The treatment disposition with respect to PegIFN and RBV are summarized in Table 10 and Table 11, respectively. Compared with the PBO arm, the TMC435 arm also has higher completion rates for PegIFN and RBV (92% vs. 60% for both PEG-IFN and RBV).

Figure 2: Study Disposition

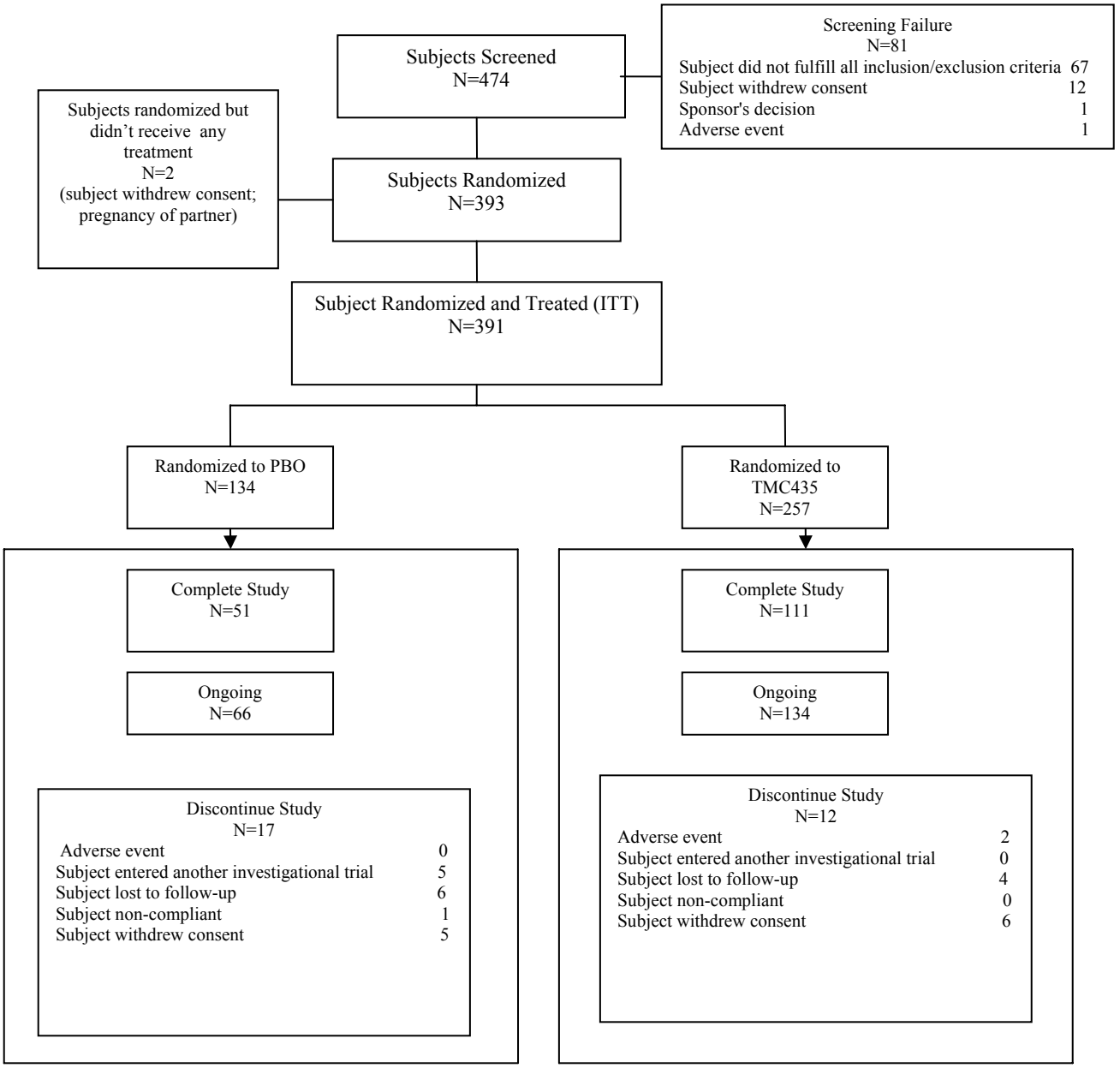


Table 9: Subject Treatment Completion Status of PBO/TMC435 (ITT Analysis Set)

Treatment Disposition(PBO and TMC435)	**PBO (N=134)**	**TMC435 (N=257)**
Completed	51(38.1%)	247(96.1%)
Discontinued	83(61.9%)	10(3.9%)
Adverse event	1(0.7%)	4(1.6%)
Subject non-compliant	0	1(0.4%)
Subject reached a virologic endpoint	82(61.2%)	3(1.2%)
Subject withdrew consent	0	2(0.8%)

Source: Statistical Reviewer's analysis.

Table 10: Subject Treatment Completion Status of PegIFN (ITT Analysis Set)

Treatment Disposition(PegINF)	**PBO (N=134)**	**TMC435 (N=257)**
Completed	81(60.4%)	236(91.8%)
Discontinued	53(39.6%)	21(8.2%)
Adverse event	9(6.7%)	7(2.7%)
Subject lost to follow-up	2(1.5%)	0
Subject non-compliant	2(1.5%)	2(0.8%)
Subject reached a virologic endpoint	38(28.4%)	7(2.7%)
Subject withdrew consent	2(1.5%)	5(1.9%)

Source: Statistical Reviewer's analysis.

Table 11: Subject Treatment Completion Status of RBV (ITT Analysis Set)

Treatment Disposition(RBV)	**PBO (N=134)**	**TMC435 (N=257)**
Completed	81(60.4%)	237(92.2%)
Discontinued		
Adverse event	10(7.5%)	6(2.3%)
Subject lost to follow-up	2(1.5%)	0
Subject non-compliant	1(0.7%)	2(0.8%)
Subject reached a virologic endpoint	38(28.4%)	7(2.7%)
Subject withdrew consent	2(1.5%)	5(1.9%)

Source: Statistical Reviewer's analysis.

3.2.3.2.2 Demographic and Baseline Characteristics

Table 12 and Table 13 summarize the patient demographic and baseline characteristics for Study 216. The demographic and baseline characteristics distribution was comparable between the two treatment arms. Approximately 56% of the patients were male, and 54% of the patients were more than 45 years old. The majority of the patients (92%) were white. Approximately 43% of the patients had BMI <25kg/m^2. Regarding the IL28B, 30% of the patients were genotype CC patients, 55% of the patients were genotype CT and 16% of the patients were genotype TT. About 76% of the patients had baseline HCV RNA >800000 IU/mL and 22% of the patients had metavir fibrosis score F3-F4. At baseline, 62% of the patients had ALT level above grade 0. About 41% of the patients were genotype 1a patients. The majority (87%) of the patients had IP-10 <=600pg/mL at baseline.

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Table 12: Demographic (ITT Analysis Set)

	PBO 12 Wks PR 48	TMC435 150 mg 12 Wks PR 24/48	Total
Analysis Set: Intent-to-treat	134	257	391
Gender			
N	134	257	391
Female	57 (42.5%)	117 (45.5%)	174 (44.5%)
Male	77 (57.5%)	140 (54.5%)	217 (55.5%)
Race			
N	134	257	391
White	123 (91.8%)	237 (92.2%)	360 (92.1%)
Black or African American	10 (7.5%)	16 (6.2%)	26 (6.6%)
American Indian or Alaska Native	0	1 (0.4%)	1 (0.3%)
Native Hawaiian or Other Pacific Islander	0	0	0
Asian	1 (0.7%)	2 (0.8%)	3 (0.8%)
Multiple	0	1 (0.4%)	1 (0.3%)
Ethnicity			
N	134	257	391
Hispanic or Latino	25 (18.7%)	60 (23.3%)	85 (21.7%)
Not Hispanic or Latino	109 (81.3%)	197 (76.7%)	306 (78.3%)
Age (years)			
N	134	257	391
≤45	58 (43.3%)	122 (47.5%)	180 (46.0%)
>45 - ≤65	72 (53.7%)	130 (50.6%)	202 (51.7%)
>65	4 (3.0%)	5 (1.9%)	9 (2.3%)
Age (years)			
N	134	257	391
Mean (SD)	45.7 (12.43)	45.2 (12.02)	45.4 (12.15)
Median	47.0	46.0	47.0
Range	(18; 73)	(18; 73)	(18; 73)
Body weight (kg)			
N	134	257	391
Mean (SD)	78.97 (15.907)	76.25 (16.500)	77.18 (16.330)
Median	78.85	75.00	76.20
Range	(44.5; 134.3)	(44.9; 145.8)	(44.5; 145.8)
Body Mass Index (kg/m^2)			
N	132	257	389
<25	56 (42.4%)	111 (43.2%)	167 (42.9%)
≥25 - <30	48 (36.4%)	101 (39.3%)	149 (38.3%)
≥30	28 (21.2%)	45 (17.5%)	73 (18.8%)
Body Mass Index (kg/m^2)			
N	132	257	389
Mean (SD)	26.74 (5.039)	26.37 (5.268)	26.50 (5.188)
Median	26.20	25.80	26.00
Range	(18.1; 51.6)	(17.5; 53.5)	(17.5; 53.5)
IL28B Genotype[a]			
N	134	257	391
CC	42 (31.3%)	75 (29.2%)	117 (29.9%)
CT	71 (53.0%)	142 (55.3%)	213 (54.5%)
TT	21 (15.7%)	40 (15.6%)	61 (15.6%)

[a] Results obtained from the central laboratory: may not be the same as stratified..

Source: Table 14 in Clinical Study Report for study TMC435-TiDP16-C216.

Table 13: Baseline Disease Characteristics (ITT Analysis Set)

	PBO 12 Wks PR 48	TMC435 150mg 12 Wks PR 24/48	Total
Analysis Set: Intent-to-treat	134	257	391
Baseline HCV RNA level (log_{10} IU/mL)			
N	134	257	391
Mean (SD)	6.38 (0.679)	6.38 (0.651)	6.38 (0.660)
Median	6.50	6.51	6.51
Range	(4.4; 7.5)	(4.0; 7.6)	(4.0; 7.6)
Baseline HCV RNA category (IU/mL)			
N	134	257	391
<400000	19 (14.2%)	31 (12.1%)	50 (12.8%)
≥400000 - ≤800000	17 (12.7%)	27 (10.5%)	44 (11.3%)
>800000	98 (73.1%)	199 (77.4%)	297 (76.0%)
Metavir fibrosis score[a]			
N	134	248	382
Score F0-F1	60 (44.8%)	130 (52.4%)	190 (49.7%)
Score F2	42 (31.3%)	65 (26.2%)	107 (28.0%)
Score F3	17 (12.7%)	36 (14.5%)	53 (13.9%)
Score F4	15 (11.2%)	17 (6.9%)	32 (8.4%)
Baseline ALT WHO toxicity grade			
N	134	257	391
Grade 0	55 (41.0%)	92 (35.8%)	147 (37.6%)
Grade 1	49 (36.6%)	105 (40.9%)	154 (39.4%)
Grade 2	22 (16.4%)	49 (19.1%)	71 (18.2%)
Grade 3	6 (4.5%)	10 (3.9%)	16 (4.1%)
Grade 4	2 (1.5%)	1 (0.4%)	3 (0.8%)
HCV geno/subtype (NS5B)[b]			
N	134	257	391
1	1 (0.7%)	0	1 (0.3%)
1a	54 (40.3%)	105 (40.9%)	159 (40.7%)
1b	77 (57.5%)	150 (58.4%)	227 (58.1%)
1e	1 (0.7%)	1 (0.4%)	2 (0.5%)
1g	1 (0.7%)	0	1 (0.3%)
1l	0	1 (0.4%)	1 (0.3%)
Time since diagnosis (years)			
N	134	257	391
Mean (SD)	3.76 (5.120)	5.39 (6.561)	4.83 (6.148)
Median	1.40	2.30	2.00
Range	(0.1; 21.6)	(0.1; 31.3)	(0.1; 31.3)
IP-10 Category			
N	134	257	391
≤600 pg/mL	109 (81.3%)	230 (89.5%)	339 (86.7%)
>600 pg/mL	25 (18.7%)	27 (10.5%)	52 (13.3%)

[a] Limited to results from Metavir scoring system.
[b] HCV geno/subtype is based on the NS5B assay, and if not available on LiPA HCV II or Trugene results.

Source: Table 15 in Clinical Study Report for study TMC435-TiDP16-C216.

3.2.3.3 Study 3007

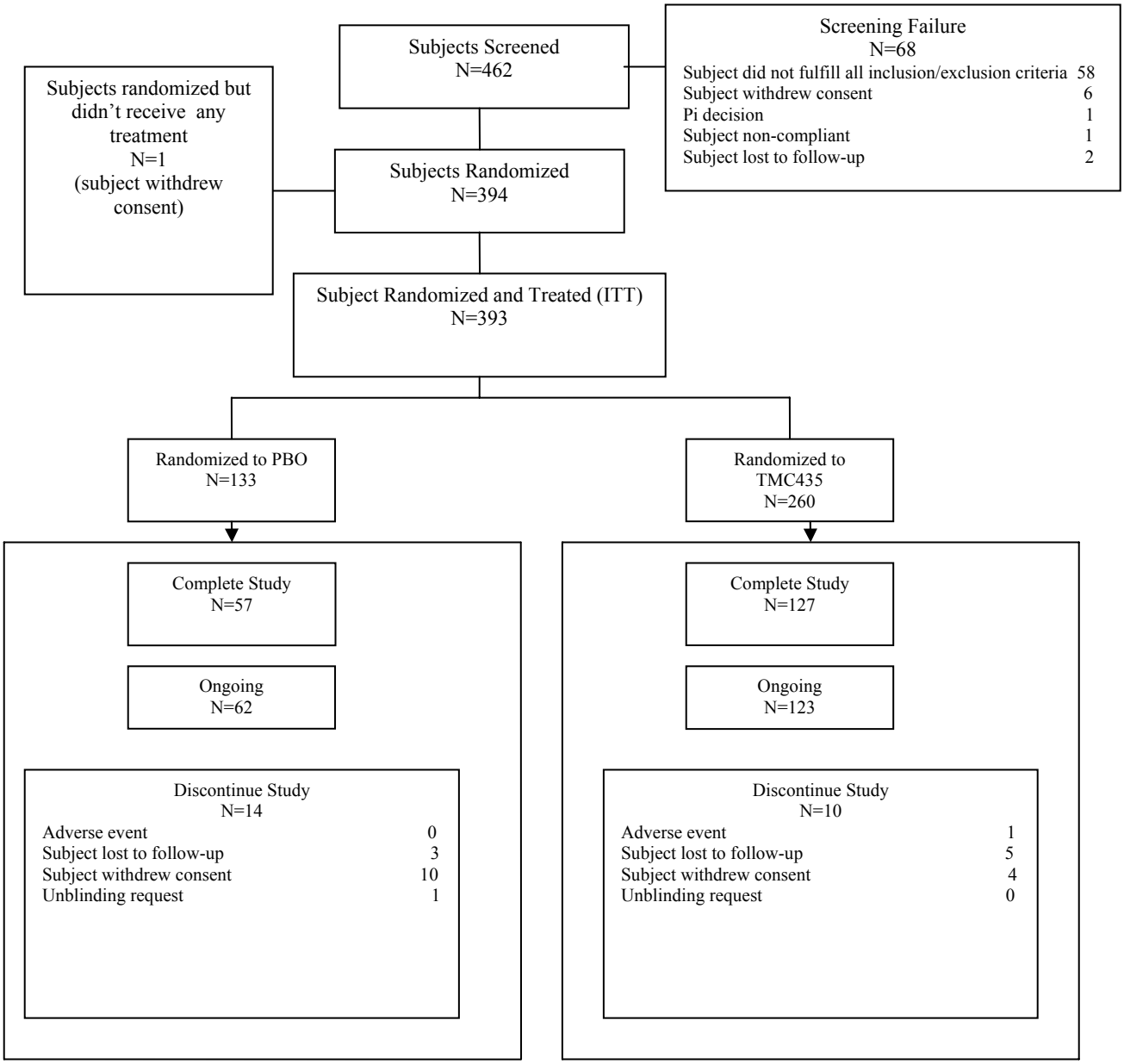
3.2.3.3.1 Patient Disposition

Figure 3 displays the patient study disposition for Study 3007. There were 462 patients screened in total and 394 patients were randomized. One patient was randomized but did not receive any treatment; therefore this patient was excluded from the ITT analysis set. Of the 133 patients that were randomized and treated with PBO, fifty-seven patients finished the study by the time of the database lock. Fourteen patients discontinued the study, and 62 patients were still in the follow-up phase. In the TMC435 arm, 260 patients were randomized and treated. One hundred and twenty-seven of them finished the study. Ten patients discontinued the study, and 123 patients were still in the follow-up phase.

The treatment disposition of PBO and TMC435 is summarized in Table 14. In the PBO arm, 37 (27.8%) patients completed the PBO treatment, while in the TMC435 arm, the treatment completion rate was much higher (96.5%). In the PBO arm, 93 (69.9%) discontinued the treatment because they reached a virologic endpoint, 1 (0.8%) patient discontinued due to lost to follow-up and 2 (1.5%) patients discontinued due to withdrawal of consent. In the TMC435 arm, only 4 (1.5%) patients discontinued because patients reached a virologic endpoint, 1 (0.4%) patient discontinued due to AE, 1 (0.4%) patient discontinued due to lost to follow-up, 1 (0.4%) patient discontinued due to non-compliance and 2 (0.8%) patients discontinued due to withdrawal of consent.

The treatment disposition with respect to PegIFN and RBV is summarized in Table 15 and Table 16, respectively. Compared with the PBO arm, the TMC435 arm also has higher completion rate for PegIFN and RBV (around 94% vs. 72% for both PegIFN and RBV).

Figure 3: Study Disposition



Source: Statistical Reviewer's analysis.

Table 14: Subject Treatment Completion Status of PBO/TMC435 (ITT Analysis Set)

Treatment Disposition(PBO and TMC435)	**PBO (N=133)**	**TMC435 (N=260)**
Completed	37(27.8%)	251(96.5%)
Discontinued	96(72.2)	9(3.5%)
Adverse event	0	1(0.4%)
Subject lost to follow-up	1(0.8%)	1(0.4%)
Subject non-compliant	0	1(0.4%)
Subject reached a virologic endpoint	93(69.9%)	4(1.5%)
Subject withdrew consent	2(1.5%)	2(0.8%)

Source: Statistical Reviewer's analysis.

Table 15: Subject Treatment Completion Status of PegIFN (ITT Analysis Set)

Treatment Disposition(PegIFN)	**PBO (N=133)**	**TMC435 (N=260)**
Completed	96(72.2%)	243(93.5%)
Discontinued	37(27.8%)	17(6.5%)
Adverse event	6(4.5%)	6(2.3%)
Subject lost to follow-up	2(1.5%)	1(0.4%)
Subject non-compliant	2(1.5%)	1(0.4%)
Subject reached a virologic endpoint	13(9.8%)	5(1.9%)
Subject withdrew consent	12(9.0%)	4(1.5%)
Subject withdrew himself from study medications	1(0.8%)	0
Unblind procedure	1(0.8%)	0

Source: Statistical Reviewer's analysis.

Table 16: Subject Treatment Completion Status of RBV (ITT Analysis Set)

Treatment Disposition(RBV)	**PBO (N=133)**	**TMC435 (N=260)**
Completed	95(71.4%)	243(93.5%)
Discontinued	38(28.6%)	17(6.5%)
Adverse event	7(5.3%)	6(2.3%)
Subject lost to follow-up	2(1.5%)	1(0.4%)
Subject non-compliant	2(1.5%)	1(0.4%)
Subject reached a virologic endpoint	13(9.8%)	5(1.9%)
Subject withdrew consent	12(9.0%)	4(1.5%)
Subject withdrew himself from study medications	1(0.8%)	0
Unblind procedure	1(0.8%)	0

Source: Statistical Reviewer's analysis.

3.2.3.3.2 Demographic and Baseline Characteristics

Table 17 and Table 18 summarize the patient demographic and baseline characteristics. The demographic and baseline characteristics distribution was comparable between the two treatment arms. Approximately 66% of the patients were male and 71% of the patients were more than 45 years old. The majority of the patients (94%) were white. Approximately 31% of the patients had BMI <25kg/m^2. Regarding the IL28B, 24% of the patients were genotype CC patients, 64% of the patients were genotype CT and 12% of the patients were genotype TT. About 84% of the patients had baseline HCV RNA >800000 IU/mL and 31% of the patients had metavir fibrosis score F3-F4. At baseline 61% of the patients had ALT level above grade 0. About 42% of the patients were genotype 1a patients. Approximately 68% of the patients were previously treated with PegIFNα-2a/RBV and 27% of the patients were previously treated with PegIFNα-2b/RBV.

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Table 17: Demographic (ITT Analysis Set)

	PBO 12 Wks PR 48	TMC435 150mg 12 Wks PR 24/48	Total
Analysis Set: Intent-to-treat	133	260	393
Gender			
N	133	260	393
Female	54 (40.6%)	81 (31.2%)	135 (34.4%)
Male	79 (59.4%)	179 (68.8%)	258 (65.6%)
Race			
N	133	260	393
White	128 (96.2%)	243 (93.5%)	371 (94.4%)
Black or African American	4 (3.0%)	7 (2.7%)	11 (2.8%)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	1 (0.4%)	1 (0.3%)
Asian	1 (0.8%)	8 (3.1%)	9 (2.3%)
Multiple	0	1 (0.4%)	1 (0.3%)
Ethnicity			
N	133	260	393
Hispanic or Latino	6 (4.5%)	20 (7.7%)	26 (6.6%)
Not Hispanic or Latino	127 (95.5%)	240 (92.3%)	367 (93.4%)
Age (years)			
N	133	260	393
≤45	35 (26.3%)	78 (30.0%)	113 (28.8%)
>45 - ≤65	95 (71.4%)	172 (66.2%)	267 (67.9%)
>65	3 (2.3%)	10 (3.8%)	13 (3.3%)
Age (years)			
N	133	260	393
Mean (SD)	50.3 (10.76)	49.7 (10.27)	49.9 (10.43)
Median	52.0	52.0	52.0
Range	(21; 71)	(20; 70)	(20; 71)
Body weight (kg)			
N	133	260	393
Mean (SD)	79.51 (15.095)	81.88 (15.981)	81.08 (15.708)
Median	79.00	82.00	81.00
Range	(45.8; 126.0)	(37.0; 141.0)	(37.0; 141.0)
Body Mass Index (kg/m^2)			
N	133	260	393
<25	45 (33.8%)	78 (30.0%)	123 (31.3%)
≥25 - <30	52 (39.1%)	116 (44.6%)	168 (42.7%)
≥30	36 (27.1%)	66 (25.4%)	102 (26.0%)
Body Mass Index (kg/m^2)			
N	133	260	393
Mean (SD)	27.10 (4.569)	27.36 (4.433)	27.27 (4.475)
Median	26.80	27.20	27.00
Range	(18.5; 41.6)	(14.3; 47.7)	(14.3; 47.7)
IL28B Genotype[a]			
N	133	260	393
CC	34 (25.6%)	62 (23.8%)	96 (24.4%)
CT	83 (62.4%)	167 (64.2%)	250 (63.6%)
TT	16 (12.0%)	31 (11.9%)	47 (12.0%)

[a] Results obtained from the central laboratory: may not be the same as stratified.

Source: Table 15 in Clinical Study Report for study TMC435HPC3007.

Table 18: Baseline Disease Characteristics (ITT Analysis Set)

	PBO 12 Wks PR 48	TMC435 150mg 12 Wks PR 24/48	Total
Analysis Set: Intent-to-treat	133	260	393
Baseline HCV RNA level (log_{10} IU/mL)			
N	133	260	393
Mean (SD)	6.47 (0.624)	6.42 (0.555)	6.44 (0.579)
Median	6.54	6.42	6.49
Range	(3.1; 7.5)	(4.6; 7.7)	(3.1; 7.7)
Baseline HCV RNA category (IU/mL)			
N	133	260	393
<400000	9 (6.8%)	21 (8.1%)	30 (7.6%)
≥400000 - ≤800000	14 (10.5%)	20 (7.7%)	34 (8.7%)
>800000	110 (82.7%)	219 (84.2%)	329 (83.7%)
Metavir fibrosis score[a]			
N	132	250	382
Score F0-F1	47 (35.6%)	87 (34.8%)	134 (35.1%)
Score F2	51 (38.6%)	80 (32.0%)	131 (34.3%)
Score F3	15 (11.4%)	44 (17.6%)	59 (15.4%)
Score F4	19 (14.4%)	39 (15.6%)	58 (15.2%)
Baseline ALT WHO toxicity grade			
N	133	260	393
Grade 0	48 (36.1%)	104 (40.0%)	152 (38.7%)
Grade 1	52 (39.1%)	96 (36.9%)	148 (37.7%)
Grade 2	24 (18.0%)	47 (18.1%)	71 (18.1%)
Grade 3	8 (6.0%)	11 (4.2%)	19 (4.8%)
Grade 4	1 (0.8%)	2 (0.8%)	3 (0.8%)
HCV geno/subtype (NS5B)[b]			
N	133	260	393
1	0	1 (0.4%)	1 (0.3%)
1a	54 (40.6%)	110 (42.3%)	164 (41.7%)
1b	79 (59.4%)	149 (57.3%)	228 (58.0%)
Time since diagnosis (years)			
N	133	260	393
Mean (SD)	10.76 (6.409)	10.34 (6.550)	10.48 (6.498)
Median	10.40	8.65	9.30
Range	(1.9; 30.4)	(1.3; 33.1)	(1.3; 33.1)
Previous hepatitis C therapy			
N	133	260	393
PegIFNa-2a/RBV	88 (66.2%)	178 (68.5%)	266 (67.7%)
PegIFNa-2b/RBV	36 (27.1%)	70 (26.9%)	106 (27.0%)
Other	9 (6.8%)	12 (4.6%)	21 (5.3%)

[a] Limited to results from Metavir scoring system.
[b] HCV geno/subtype is based on the NS5B assay, and if not available on LiPA HCV II or Trugene results.

Source: Table 15 in Clinical Study Report for study TMC435HPC3007.

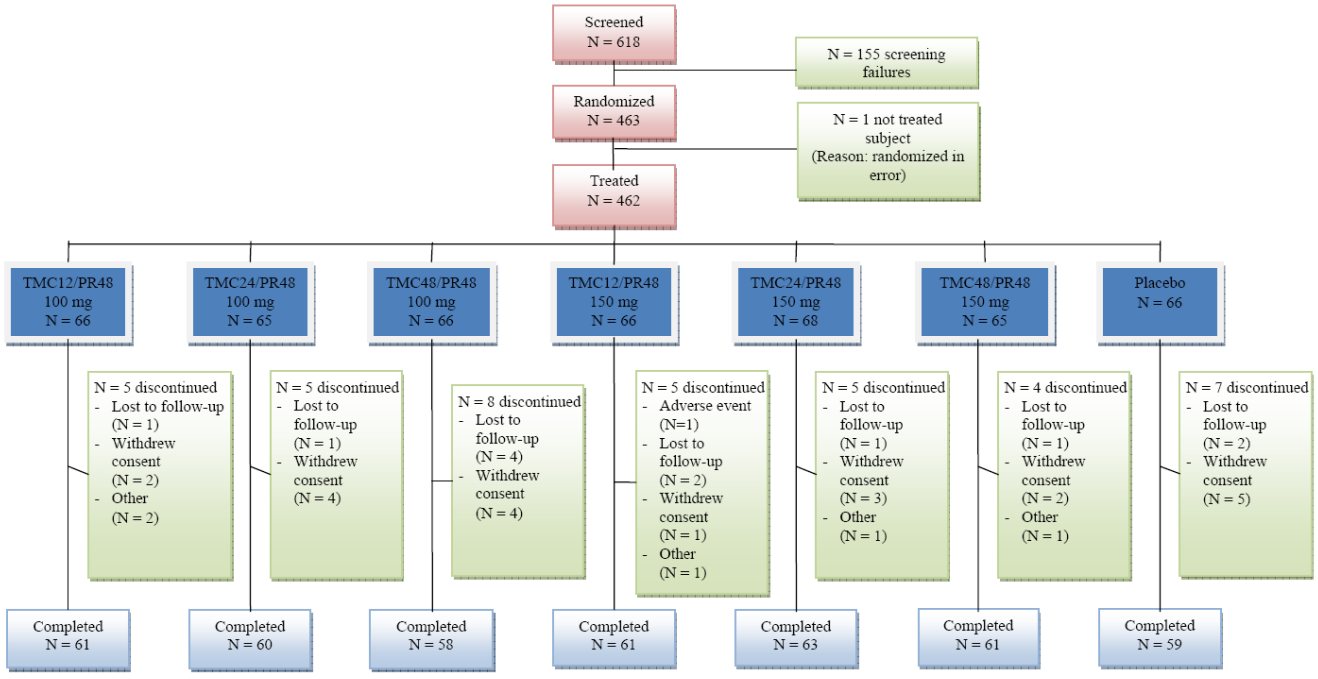
3.2.3.4 Study 206

3.2.3.4.1 Patient Disposition

Figure 4 displays the study disposition for Study 206. There were 618 patients screened and 463 patients were randomized. One patient was randomized but did not receive any treatment. Therefore this patient was excluded from the ITT analysis set. The majority of the patients in each arm completed the study. The study discontinuation rates were 6%-12%.

The treatment discontinuation of PBO and TMC434 is summarized in Table 19. For TMC435/PBO, the discontinuation rate for the TMC435 arms ranged from 21.5% to 29.2%. The placebo arm had a high discontinuation rate of 60.6%. This was primarily due to subjects who reached a virologic endpoint.

Figure 4: Study Disposition



Source: Figure 2 in the Clinical Study Report for study TiDP16-C206.

Table 19: Subject Treatment Completion Status of PBO/TMC435 (ITT Analysis Set)

Treatment Disposition (PBO and TMC435)	TMC12 PR48 100 mg N = 66	TMC24 PR48 100 mg N = 65	TMC48 PR48 100 mg N = 66	TMC12 PR48 150 mg N = 66	TMC24 PR48 150 mg N = 68	TMC48 PR48 150 mg N = 65	Placebo N = 66
Completed	49(74.2%)	46(70.8%)	47(71.2%)	50(75.8%)	52(76.5%)	51(78.5%)	26(39.4%)
Discontinued	17(25.8%)	19(29.2%)	19(28.8%)	16(24.2%)	16(23.5%)	14(21.5%)	40(60.6%)
Adverse event	6(9.1%)	4(6.2%)	5(7.6%)	4(6.1%)	7(10.3%)	6(9.2%)	2(3.0%)
Subject lost to follow-up	0	0	2(3.0%)	0	0	1(1.5%)	0
Subject non-compliant	0	2(3.1%)	1(1.5%)	0	0	0	0
Subject reached a virologic endpoint	10(15.2%)	11(16.9%)	10(15.2%)	11(16.8%)	8(11.8%)	6(9/2%)	35(53.0%)
Subject withdrew consent	0	2(3.1%)	0	1(1.5%)	1(1.5%)	0	2(3.0%)
Other	1(1.5%)	0	1(1.5%)	0	0	1(1.5%)	1(1.5%)

Source: Statistical Reviewer's analysis.

3.2.3.4.2 Demographic and Baseline Characteristics

Table 20 and Table 21 summarize the patient demographic and baseline characteristics. The demographic and baseline characteristics distribution was comparable among the treatment arms. Approximately 67% of the patients were male and the median age was 50 years old. The majority of the patients (93%) were white. The median BMI was 27.2kg/m^2. Regarding the IL28B, 18% of the patients were genotype CC patients, 65% of the patients were genotype CT and 18% of the patients were genotype TT. About 86% of the patients had baseline HCV RNA >800000 IU/mL and 37% of the patients had metavir fibrosis score F3-F4. At baseline 63% of the patients had ALT level above grade 0. About 41% of the patients were genotype 1a patients.

Table 22 summarizes the proportion of response to prior PegIFN/RBV therapy. About 25% of the patients were null responders, 35% of the patients were partial responders and 40% of the patients were relapsers.

Table 20: Demographic (ITT Analysis Set)

Demo-graphic parameter, specification n (%)	TMC12 PR48 100 mg N = 66	TMC24 PR48 100 mg N = 65	TMC48 PR48 100 mg N = 66	TMC12 PR48 150 mg N = 66	TMC24 PR48 150 mg N = 68	TMC48 PR48 150 mg N = 65	Placebo N = 66	All Subjects N = 462
Gender								
Female	22 (33.3)	21 (32.3)	21 (31.8)	21 (31.8)	25 (36.8)	17 (26.2)	24 (36.4)	151 (32.7)
Male	44 (66.7)	44 (67.7)	45 (68.2)	45 (68.2)	43 (63.2)	48 (73.8)	42 (63.6)	311 (67.3)
Race								
White	59 (89.4)	60 (92.3)	62 (93.9)	61 (92.4)	61 (89.7)	63 (96.9)	62 (93.9)	428 (92.6)
Black	5 (7.6)	2 (3.1)	3 (4.5)	3 (4.5)	5 (7.4)	2 (3.1)	1 (1.5)	21 (4.5)
Asian	1 (1.5)	3 (4.6)	1 (1.5)	1 (1.5)	0	0	2 (3.0)	8 (1.7)
Other[a]	1 (1.5)	0	0	1 (1.5)	2 (2.9)	0	1 (1.5)	5 (1.1)
Age[b], years								
Median	51.5	50.0	50.0	48.0	51.5	50.0	50.5	50.0
[Range]	[20; 68]	[20; 68]	[22; 69]	[20; 63]	[25; 68]	[21; 69]	[22; 66]	[20; 69]
Body Weight, kg								
Median	82.6	78.9	80.0	78.3	82.9	80.9	84.8	80.8
[Range]	[43; 119]	[49; 138]	[53; 128]	[50; 116]	[56; 123]	[56; 125]	[53; 112]	[43; 138]
BMI, kg/m²								
Median	27.55	26.50	26.60	26.40	27.45	27.20	27.95	27.20
[Range]	[19.5; 42.3]	[18.9; 42.9]	[18.5; 48.7]	[18.2; 43.2]	[19.7; 42.4]	[18.9; 44.1]	[18.5; 40.5]	[18.2; 48.7]

N: number of subjects with data; n: number of subjects with that observation

[a] Other includes Native Hawaiian or other Pacific Islander, and American Indian or Alaska Native.

[b] At screening

Source: Table 20 in the Clinical Study Report for Study TMC435-TiDP16-C206.

Table 21: Baseline Disease Characteristics (ITT Analysis Set)

n (%)	TMC12 PR48 100 mg N = 66	TMC24 PR48 100 mg N = 65	TMC48 PR48 100 mg N = 66	TMC12 PR48 150 mg N = 66	TMC24 PR48 150 mg N = 68	TMC48 PR48 150 mg N = 65	Placebo N = 66	All Subjects N = 462
HCV RNA (log_{10} IU/mL), N'	**66**	**65**	**66**	**66**	**68**	**65**	**66**	**462**
Median	6.49	6.68	6.64	6.62	6.60	6.55	6.61	6.60
[Range]	[4.2; 7.5]	[4.8; 7.5]	[5.2; 7.5]	[3.5; 7.5]	[5; 7.7]	[4.9; 7.5]	[5.2; 7.6]	[3.5; 7.7]
HCV RNA Category (IU/mL), N'	**66**	**65**	**66**	**66**	**68**	**65**	**66**	**462**
< 400000	3 (4.5)	3 (4.6)	7 (10.6)	4 (6.1)	4 (5.9)	5 (7.7)	4 (6.1)	30 (6.5)
[400000; 800000]	5 (7.6)	3 (4.6)	1 (1.5)	5 (7.6)	6 (8.8)	6 (9.2)	7 (10.6)	33 (7.1)
> 800000	58 (87.9)	59 (90.8)	58 (87.9)	57 (86.4)	58 (85.3)	54 (83.1)	55 (83.3)	399 (86.4)
Metavir Score, N'	**65**	**63**	**66**	**66**	**67**	**64**	**64**	**455**
F0	6 (9.2)	3 (4.8)	6 (9.1)	5 (7.6)	11 (16.4)	1 (1.6)	7 (10.9)	39 (8.6)
F1	17 (26.2)	14 (22.2)	23 (34.8)	19 (28.8)	11 (16.4)	27 (42.2)	18 (28.1)	129 (28.4)
F2	21 (32.3)	17 (27.0)	9 (13.6)	18 (27.3)	21 (31.3)	16 (25.0)	16 (25.0)	118 (25.9)
F3	14 (21.5)	16 (25.4)	14 (21.2)	11 (16.7)	11 (16.4)	7 (10.9)	13 (20.3)	86 (18.9)
F4	7 (10.8)	13 (20.6)	14 (21.2)	13 (19.7)	13 (19.4)	13 (20.3)	10 (15.6)	83 (18.2)
Baseline ALT Toxicity Grade, N'	**66**	**65**	**66**	**66**	**68**	**65**	**66**	**462**
Grade 0	30 (45.5)	16 (24.6)	21 (31.8)	26 (39.4)	25 (36.8)	22 (33.8)	29 (43.9)	169 (36.6)
Grade 1	25 (37.9)	41 (63.1)	25 (37.9)	29 (43.9)	32 (47.1)	28 (43.1)	26 (39.4)	206 (44.6)
Grade 2	9 (13.6)	7 (10.8)	16 (24.2)	10 (15.2)	9 (13.2)	15 (23.1)	8 (12.1)	74 (16.0)
Grade 3	2 (3.0)	1 (1.5)	4 (6.1)	1 (1.5)	2 (2.9)	0	3 (4.5)	13 (2.8)
HCV Geno/Subtype (NS5B), N'[a]	**66**	**63**	**65**	**66**	**65**	**64**	**66**	**455**
1a	26 (39.4)	28 (44.4)	25 (38.5)	30 (45.5)	29 (44.6)	23 (35.9)	27 (40.9)	188[b] (41.3)
1b	39 (59.1)	34 (54.0)	39 (60.0)	36 (54.5)	34 (52.3)	41 (64.1)	39 (59.1)	262 (57.6)
1d	0	1 (1.6)	0	0	1 (1.5)	0	0	2 (0.4)
1e	0	0	0	0	1 (1.5)	0	0	1 (0.2)
1i	0	0	1 (1.5)	0	0	0	0	1 (0.2)
6p[c]	1 (1.5)	0	0	0	0	0	0	1 (0.2)
Duration of HCV Infection (years), N'	**42**	**36**	**39**	**31**	**38**	**31**	**34**	**251**
Median	27.60	26.65	24.00	28.10	27.00	24.90	25.00	26.10
[Range]	[5.5; 48]	[6.1; 49.9]	[3.1; 55]	[2.5; 49]	[3.3; 56.9]	[3.9; 42.2]	[4.7; 46.2]	[2.5; 56.9]
Mode of HCV Infection, N'	**66**	**65**	**66**	**66**	**68**	**65**	**66**	**462**
Other	22 (33.3)	27 (41.5)	27 (40.9)	30 (45.5)	36 (52.9)	29 (44.6)	29 (43.9)	200 (43.3)
Blood transfusion	21 (31.8)	22 (33.8)	20 (30.3)	11 (16.7)	17 (25.0)	14 (21.5)	14 (21.2)	119 (25.8)
Intravenously injectable drug use	12 (18.2)	10 (15.4)	13 (19.7)	13 (19.7)	11 (16.2)	12 (18.5)	12 (18.2)	83 (18.0)
Multiple	9 (13.6)	3 (4.6)	2 (3.0)	7 (10.6)	3 (4.4)	8 (12.3)	7 (10.6)	39 (8.4)
Occupational exposure	1 (1.5)	1 (1.5)	2 (3.0)	1 (1.5)	0	0	2 (3.0)	7 (1.5)
Heterosexual contact	1 (1.5)	1 (1.5)	1 (1.5)	2 (3.0)	0	0	1 (1.5)	6 (1.3)
Mother to child transmission	0	1 (1.5)	0	0	1 (1.5)	1 (1.5)	1 (1.5)	4 (0.9)
Msm[d]	0	0	0	2 (3.0)	0	1 (1.5)	0	3 (0.6)
Hemophilia-associate injections	0	0	1 (1.5)	0	0	0	0	1 (0.2)

Table 21: Baseline Disease Characteristics (ITT Analysis Set)

n (%)	TMC12 PR48 100 mg N = 66	TMC24 PR48 100 mg N = 65	TMC48 PR48 100 mg N = 66	TMC12 PR48 150 mg N = 66	TMC24 PR48 150 mg N = 68	TMC48 PR48 150 mg N = 65	Placebo N = 66	All Subjects N = 462
***IL28B*, N**	**43**	**46**	**47**	**43**	**50**	**49**	**50**	**328**
CC	7 (16.3)	8 (17.4)	8 (17.0)	5 (11.6)	9 (18.0)	10 (20.4)	11 (22.0)	58 (17.7)
CT	32 (74.4)	30 (65.2)	28 (59.6)	30 (69.8)	32 (64.0)	28 (57.1)	32 (64.0)	212 (64.6)
TT	4 (9.3)	8 (17.4)	11 (23.4)	8 (18.6)	9 (18.0)	11 (22.4)	7 (14.0)	58 (17.7)

N: number of subjects from the ITT population; N': number of subjects with data; n: number of subjects with that observation

[a] Based on Virco NS5B assay. If the NS5B assay failed the results from the Trugene assay (used for stratification) were used.

[b] For 1 subject (CRF ID 202-0277), HCV genotype (NS5B) was not available in the database. Reanalysis of HCV genotype (NS5B) resulted in subtype 1a and the subject was considered as such for further analysis (Display GEN.8).

[c] At screening, HCV geno/subtype was 1 (Trugene Assay), therefore the subject (CRF ID 206-0555) was eligible for the study (Listing GEN.10).

[d] Men who have sex with men.

Source: Table 21 and Table 23 in the Clinical Study Report for Study TMC435-TiDP16-C206.

Table 22: Stratification Factors

n (%)	TMC12 PR48 100 mg N = 66	TMC24 PR48 100 mg N = 65	TMC48 PR48 100 mg N = 66	TMC12 PR48 150 mg N = 66	TMC24 PR48 150 mg N = 68	TMC48 PR48 150 mg N = 65	Placebo N = 66	All Subjects N = 462
Genotype 1 Subtype[a]								
1a	23 (34.8)	24 (36.9)	24 (36.4)	24 (36.4)	25 (36.8)	24 (36.9)	24 (36.4)	168 (36.4)
1b	37 (56.1)	36 (55.4)	36 (54.5)	36 (54.5)	36 (52.9)	36 (55.4)	37 (56.1)	254 (55.0)
Other	6 (9.1)	5 (7.7)	6 (9.1)	6 (9.1)	7 (10.3)	5 (7.7)	5 (7.6)	40 (8.7)
Response to Prior PegIFN/RBV Therapy[a]								
Null Responder	16 (24.2)	16 (24.6)	18 (27.3)	17 (25.8)	17 (25.0)	17 (26.2)	16 (24.2)	117 (25.3)
Partial Responder	23 (34.8)	23 (35.4)	22 (33.3)	23 (34.8)	24 (35.3)	22 (33.8)	23 (34.8)	160 (34.6)
Relapser	27 (40.9)	26 (40.0)	26 (39.4)	26 (39.4)	27 (39.7)	26 (40.0)	27 (40.9)	185 (40.0)

N: number of subjects with data; n: number of subjects with that observation; PR: PegIFNα-2a/RBV

[a] Genotype 1 subtype and response to prior PegIFN/RBV therapy as captured in IWRS

Source: Table 22 in the Clinical Study Report for Study TMC435-TiDP16-C206.

3.2.4 Results and Conclusions

Results and conclusions are first summarized for the naïve population evaluated in Study 208 and Study 216. Integrated data combining Studies 208 and 216 is then presented. Lastly, the results and conclusions of the experienced populations are summarized for Study 3007 (relapsers) and Study 206 (null responders, partial responders and relapers).

3.2.4.1 Study C208

3.2.4.1.1 Primary Efficacy Endpoint

Table 23 summarizes the applicant's primary analysis. The percentage of patients that achieved SVR12 was 50% in the control arm and 79.5% in the TMC435 arm. The stratum-adjusted treatment difference was 29.3% (95% CI: 20.1%, 38.6%). This difference was statistically significant. Therefore, superiority of TMC435 over control was demonstrated in this study.

Table 24 and Table 25 summarize the reviewer's analyses based on the reviewer's definitions of SVR12 and SVR.

As shown in Table 26, one patient (TMC435-C208-0398) in the control arm had HCV RNA below detection at 12 weeks post treatment (Day 254) and 24 weeks post treatment (Day 338). This patient should have been considered as a SVR12 and SVR success. However, both of the records at Days 254 and 338 were before the SVR12 visit window according to the applicant's definition. Therefore, the patient was not counted as a success in the applicant's analysis.

Another patient (TMC435-C208-0312) in the control arm was considered as a SVR12 failure by the applicant since this patient did not meet the criteria of below detection at End of Treatment (EOT) which was not a requirement in the reviewer's analysis. In the reviewer's analysis, this patient was also considered as a SVR12 failure since the HCV RNA was greater than 25IU/mL in the Week 12 follow-up window (Day 267). However, this patient was considered as SVR success by the reviewer because the last HCV RNA records (day 435) were < 25 IU/mL.

Overall, the results of the reviewer's analyses were very similar to those of the applicant. In the reviewer's analysis, the percentage of patients who achieved SVR12 was 50.8% for the control arm and 79.5% for the TMC435 arm. The stratum-adjusted difference for SVR12 was 28.5% (95% CI: 19.4%, 37.7%). The percentage of patients who achieved SVR was 51.5% for the control arm and 79.5% for the TMC 435 arm. The stratum-adjusted difference for the SVR was 27.8% with a 95% CI of (18.6%, 37.0%).

The superiority of TMC435 to placebo was also demonstrated in the reviewer's analysis.

Table 23: Applicant's Primary Endpoint: Sustained Virologic Response 12 Weeks After the Planned End of Treatment (SVR12)

	Observed	Stratum Adjusted	Comparison versus Placebo	
	n/N (%)	% (95% CI)[c]	Difference in proportions (95% CI)[b]	p-value[a]
SVR12				
PBO 12Wks PR48	65/130 (50.0)	50.1 (42.1;58.1)		
TMC435 150 mg 12Wks PR24/48	210/264 (79.5)	79.4 (74.7;84.0)	29.3 (20.1;38.6)	<0.001

[a] based on the CMH test controlling for stratification factors.
[b] difference in proportions (active – placebo) adjusted for stratification factors and the corresponding 95% CI based on the normal approximation.
[c] proportions adjusted for stratification factors and the corresponding 95% CIs based on the normal approximation. Stratification factors are *IL28B* and HCV geno/subtype. HCV geno/subtype is based on the NS5B assay (and if not available, LIPA II, Trugene or stratification result is used) and categorized as 1b versus 1a.

The p-value for the Breslow-Day test for homogeneity of odds ratios was 0.208.

Source: Table 25 in Clinical Study Report for study TMC435-TiDP16-C208.

Table 24: Sustained Virologic Response 12 Weeks Post Treatment (SVR12) (ITT Analysis Set)

	PBO (N=130)	**TMC435 (N=264)**
SVR12 n(%)	66(50.8%)	210(79.5%)
Stratum-adjusted Treatment Difference (TMC435- PBO) (95% CI)*	28.5% (19.4%, 37.7%)	

* The treatment difference and 95% confidence interval were adjusted for stratification factors *(IL28B: CC, CT and TT; Subgenotype 1a/other, 1b)*
Source: Statistical Reviewer's analysis.

Table 25: Sustained Virologic Response (SVR)# (ITT Analysis Set)

	PBO (N=130)	**TMC435 (N=264)**
SVR n(%)	67(51.5%)	210(79.5%)
Stratum-adjusted Treatment Difference (TMC435- PBO) (95% CI)*	27.8% (18.6%, 37.0%)	

SVR was defined as HCV RNA <25/IU/mL 12 weeks after the end of treatment. The 12 weeks post treatment window for the post-treatment day is [57, +∞]. If there was more than one record, the last record was taken.
* The treatment difference and 95% confidence interval were adjusted for stratification factors *(IL28B: CC, CT and TT; Subgenotype 1a/other, 1b)*
Source: Statistical Reviewer's analysis.

Table 26: HCV RNA viral loads of patients who were considered as SVR success by the reviewer but not the applicant

Patient ID	TRT	Treatment Duration (days)	Sample day	VISIT	Lab Result (IU/mL)
TMC435-C208-0312	PBO	182	-27	SCREENING	1530000
			1	BASELINE	504000
			3	DAY3	228000
			7	DAY7	135000
			14	DAY14	144000
			28	DAY28	35900
			56	WEEK8	3420
			84	WEEK12	1200
			112	WEEK16	241
			140	WEEK20	330
			168	WEEK24	168
			183	WITHDRAWAL	135
			217	FOLLOW-UP1	48
			267	FOLLOW-UP2	55
			337	FOLLOW-UP3	<25 IU/mL HCV RNA detected
			435	FOLLOW-UP4	<25 IU/mL HCV RNA detected
TMC435-C208-0398	PBO	182	-29	SCREENING	10400000
			1	BASELINE	14400000
			3	DAY3	643000
			7	DAY7	327000
			15	DAY14	18300
			28	DAY28	114
			58	WEEK8	HCV RNA not detected
			83	WEEK12	HCV RNA not detected
			111	WEEK16	HCV RNA not detected
			134	WEEK20	HCV RNA not detected
			170	WEEK24	HCV RNA not detected
			210	WITHDRAWAL	HCV RNA not detected
			238	FOLLOW-UP1	HCV RNA not detected
			254	FOLLOW-UP2	HCV RNA not detected
			338	FOLLOW-UP3	HCV RNA not detected

Source: Statistical Reviewer's analysis.

Two hundred and twenty-two patients met the response-guided treatment criteria (RGT) of HCV RNA <25 IU/ml at Week 4 (detectable or undetectable) and undetectable HCV RNA at Week 12.

For those patients that met the RGT criteria, both the SVR12 and SVR rates were 90.5% as shown in Table 27.

Table 27: SVR12 and SVR of the Patients Who Met RGT Criteria

	SVR12	SVR
n/N (%)	201/222(90.5%)	201/222(90.5%)

Source: Statistical Reviewer's analysis.

3.2.4.1.2 On-treatment Virologic Response

HCV RNA records were considered to be on-treatment if the collection date was less than or equal to the date of the last dose + 3 days. Those on-treatment records were re-aligned according to the visit window. Below, Table 28 only summarizes the available records for each visit. No data was imputed for missing values.

Compared with the control arm, higher response rates in the TMC435 arm were observed across the visits with the exception of Week 48 where only 11 TMC435 patients were included in the denominator. At Week 4, the percentage of patients with HCV RNA below detection was 11.8% in the control arm and 79.5% in the TMC435 arm. At Week 12, approximately half of the patients had HCV RNA below detection in the control arm while the below detection rate was 92.8% in the TMC435 arm. By the end of the treatment, the percentage of patients who reached HCV RNA below detection was 65.4% in the control arm and 90.5% in the TMC435 arm.

Table 28: On-treatment Virologic Response by Visits

	PBO	***TMC435***
Week 2		
HCV RNA not detected	3/ 128(2.3%)	*92/ 257(35.8%)*
HCV RNA <25 IU/mL	8/ 128(6.3%)	*197/ 257(76.7%)*
Week 4		
HCV RNA not detected	15/ 127(11.8%)	*202/ 254(79.5%)*
HCV RNA <25 IU/mL	25/ 127(19.7%)	*230/ 254(90.6%)*
Week 12		
HCV RNA not detected	62/ 125(49.6%)	*231/ 249(92.8%)*
HCV RNA <25 IU/mL	75/ 125(60.0%)	*239/ 249(96.0%)*
Week 24		
HCV RNA not detected	80/ 97(82.5%)	*219/ 234(93.6%)*
HCV RNA <25 IU/mL	83/ 97(85.6%)	*222/ 234(94.9%)*
Week 48		
HCV RNA not detected	75/ 77(97.4%)	*10/ 11(90.9%)*
HCV RNA <25 IU/mL	76/ 77(98.7%)	*11/ 11(100.0%)*
EOT		
HCV RNA not detected	85/ 130(65.4%)	*239/ 264(90.5%)*
HCV RNA <25 IU/mL	*89/ 130(68.5%)*	*246/ 264(93.2%)*

Source: Statistical Reviewer's analysis.

3.2.4.1.3 Study 208: Relapse

A relapser is defined as a patient who achieved undetected HCV RNA at EOT but did not achieve SVR. Patients with missing follow-up HCV RNA were not included in the denominator. A higher relapse rate (20.5%) was observed in the control arm compared with TMC435 arm (10.3%) as shown in table 29.

Table 29: Viral Relapse

	PBO	***TMC435***
Relapse	*17/83(20.5%)*	*24/233(10.3%)*

Source: Statistical Reviewer's analysis.

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3.2.4.2 Study 216

3.2.4.2.1 Primary Efficacy Endpoint

Table 30 below summarizes the applicant's primary analysis for Study 216. The percentage of patients who achieved SVR12 was 50% in the control arm and 81.3% in the TMC435 arm. The stratum-adjusted treatment difference was 32.2% (95% CI: 23.3%, 41.2%. This difference was statistically significant. The superiority of TMC435 compared to placebo was demonstrated in this study.

Table 31 and Table 32 summarize the reviewer's analyses based on the reviewer's definitions of SVR12 and SVR. The result of the reviewer's analysis of SVR12 was the same as applicant's results. There were 4 patients in the TMC435 arm who achieved SVR12 but later relapsed. The HCV RNA viral loads of those 4 patients are listed in Table 33. Therefore, the percentage of patients achieving SVR was 79.8% in the TMC435 arm. The stratum adjusted-difference for SVR was 30.8% with 95% CI of (21.8%, 39.8%).

Table 30: Applicant's Primary Endpoint: Sustained Virologic Response 12 Weeks After the Planned End of Treatment (SVR12)

	Observed	Stratum Adjusted	Comparison versus Placebo	
	n/N (%)	% (95% CI)[c]	Difference in proportions (95% CI)[b]	p-value[a]
SVR12				
PBO 12Wks PR48	67/134 (50.0)	49.7 (42.0;57.3)		
TMC435 150 mg 12Wks PR24/48	209/257 (81.3)	81.9 (77.2;86.6)	32.2 (23.3;41.2)	<0.001

[a] based on the CMH test controlling for type of PegIFN/RBV and stratification factors.

[b] difference in proportions (active – placebo) adjusted for type of PegIFN/RBV and stratification factors and the corresponding 95% CI based on the normal approximation.

[c] proportions adjusted for the type of PegIFN/RBV and stratification factors with corresponding 95% CIs based on the normal approximation.

Stratification factors are *IL28B* and HCV geno/subtype. HCV geno/subtype is based on the NS5B assay (if not available, LiPA II or Trugene result is used) and categorized as 1b versus any other geno/subtype (1a/other).

The p-value for the Breslow-Day test for homogeneity of odds ratios was 0.954.

Source: Table 25 in the Clinical Study Report for study TMC435-TiDP16-C216.

Table 31: Sustained Virologic Response 12 Weeks Post Treatment (SVR12) (ITT Analysis Set)

	PBO (N=134)	**TMC435 (N=257)**
SVR12 n(%)	67(50.0%)	209(81.3%)
Stratum-adjusted Treatment Difference(TMC435- PBO) (95% CI)*	32.2% (23.3%, 41.2%)	

* The treatment difference and 95% confidence interval were adjusted for stratification factors *(type of PegIFN/RBV: randomized to PegIFNα-2a, randomized to PegIFNα-2b and not randomized PegIFNα-2a ; , IL28B: CC, CT and TT; Subgenotype 1a/other, 1b)*

Source: Statistical Reviewer's analysis.

Table 32: Sustained Virologic Response (SVR)# (ITT Analysis Set)

	PBO (N=134)	**TMC435 (N=257)**
SVR n(%)	67(50.0%)	205(79.8%)
Stratum-adjusted Treatment Difference(TMC435- PBO) (95% CI)*	30.8% (21.8%, 39.8%)	

SVR was defined as HCV RNA <25/IU/mL 12 weeks after the end of treatment. The 12 weeks post treatment window for the post-treatment day is [57, +∞]. If there was more than one record, the last record was taken.

*The treatment difference and 95% confidence interval were adjusted for stratification factors *(type of PegIFN/RBV: PegIFNα-2a, PegIFNα-2b; , IL28B: CC, CT and TT; Subgenotype 1a/other, 1b)*

Source: Statistical Reviewer's analysis.

Table 33: HCV RNA viral loads of those patients who relapsed after week 12 post treatment

Patient ID	TRT	TRT Duration (days)	Sample day	VISIT	Lab Result (IU/mL)
TMC435-C216-3047	TMC435	169	-37	SCREENING	4920000
			1	BASELINE	5660000
			5	DAY3	892
			8	DAY7	345
			15	DAY14	27
			29	DAY28	HCV RNA not detected
			57	WEEK8	HCV RNA not detected
			85	WEEK12	HCV RNA not detected
			113	WEEK16	HCV RNA not detected
			141	WEEK20	HCV RNA not detected
			169	WEEK24	HCV RNA not detected
			197	WEEK28	HCV RNA not detected
			252	WEEK36	HCV RNA not detected
			337	WEEK48	405000
			351	UNSCHEDULED_VISIT3	325000
			421	WEEK60	814000
			505	WEEK72	1550000
TMC435-C216-3202	TMC435	169	-43	SCREENING	1960000
			1	BASELINE	3250000
			2	DAY3	2210
			6	DAY7	<25 IU/mL HCV RNA detected
			14	DAY14	<25 IU/mL HCV RNA detected
			29	DAY28	HCV RNA not detected
			57	WEEK8	HCV RNA not detected
			85	WEEK12	HCV RNA not detected
			113	WEEK16	HCV RNA not detected
			141	WEEK20	HCV RNA not detected
			169	WEEK24	HCV RNA not detected
			197	WEEK28	HCV RNA not detected
			253	WEEK36	HCV RNA not detected
			337	WEEK48	531
			357	UNSCHEDULED_VISIT1	559000
			428	WEEK60	137000
TMC435-C216-3398	TMC435	169	-40	SCREENING	25000000
			1	BASELINE	21100000
			3	DAY3	972
			8	DAY7	284
			15	DAY14	<25 IU/mL HCV RNA detected
			29	DAY28	HCV RNA not detected
			57	WEEK8	HCV RNA not detected

			85	WEEK12	HCV RNA not detected
			113	WEEK16	HCV RNA not detected
			141	WEEK20	HCV RNA not detected
			169	WEEK24	HCV RNA not detected
			197	WEEK28	HCV RNA not detected
			251	WEEK36	HCV RNA not detected
			337	WEEK48	HCV RNA not detected
			421	WEEK60	<25 IU/mL HCV RNA detected
			435	UNSCHEDULED_VISIT7	345
TMC435-C216-3417	TMC435	169	-41	SCREENING	10000000
			1	BASELINE	15100000
			3	DAY3	4820
			8	DAY7	277
			15	DAY14	48
			29	DAY28	HCV RNA not detected
			57	WEEK8	HCV RNA not detected
			85	WEEK12	HCV RNA not detected
			113	WEEK16	HCV RNA not detected
			141	WEEK20	HCV RNA not detected
			169	WEEK24	HCV RNA not detected
			197	WEEK28	HCV RNA not detected
			253	WEEK36	HCV RNA not detected
			330	WEEK48	HCV RNA not detected
			414	WEEK60	34

Note: All of those patients were treated for 24 weeks.
Source: Statistical Reviewer's analysis.

As shown in Table 34, 235 patients met the RGT in the TMC435 arm. The SVR12 and SVR rates of those patients were 85.5% and 83.8% respectively.

Table 34: SVR12 and SVR of the Patients Who Met RGT Criteria

	SVR12	SVR
n/N (%)	201/235(85.5%)	197/235(83.8%)

Source: Statistical Reviewer's analysis.

Two types of peginterferon were used in Study 216. Patients could receive peginterferon α-2a or peginterferon α-2b based on the region and randomization. Table 35 and Table 36 summarize the SVR12 and SVR rates separated by the type of peginterferon patients received.

The SVR rate was 53.8% for patients randomized to the control arm who received peginterferon α-2a + Copegus and 41.9% for patients randomized to the control arm who received peginterferon α-2b + Rebetol. For patients randomized to TMC435 arm, the SVR rate was 80.8% when combining TMC435 with peginterferon α-2a +Copegus and 77.5% when combining TMC435 with peginterferon α-2b + Rebetol.

Table 35: Sustained Virologic Response 12 Weeks Post Treatment (SVR12) by Received Study Drug (ITT Analysis Set)

	PBO +PEG2A+COPEGUS (N=91)	PBO +PEG2B+REBETOL (N=43)	TMC435 +PEG2A+COPEGUS (N=177)	TMC435 +PEG2B+REBETOL (N=80)
SVR12 n(%)	49(53.8%)	18(41.9%)	147(83.1%)	62(77.5%)

Source: Statistical Reviewer's analysis.

Table 36: Sustained Virologic Response(SVR[#]) by Randomized Treatment arm (ITT Analysis Set)

	PBO +PEG2A+COPEGUS (N=91)	PBO +PEG2B+REBETOL (N=43)	TMC435 +PEG2A+COPEGUS (N=177)	TMC435 +PEG2B+REBETOL (N=80)
SVR n(%)	49(53.8%)	18(41.9%)	143(80.8%)	62(77.5%)

SVR was defined as HCV RNA <25/IU/mL 12 weeks after the end of treatment. The 12 weeks post treatment window for the post-treatment day is [57, +∞]. If there were more than one record, the last record was taken.
Source: Statistical Reviewer's analysis.

3.2.4.2.2 Study 216: On-treatment Virologic Response

The on-treatment virologic response for Study 216 is summarized in Table 37. Similar to Study 208, higher response rates in the TMC435 arm were observed across the visits except for Week 48 where only 7 of the TMC435 patients were included in the denominator. At Week 4, the percentage of patients achieving HCV RNA below detection was 12.8% in the control arm and 79.2% in the TMC435 arm. At Week 12, 43.8% of the patients reached HCV RNA below detection in the control arm while the below detection rate was 96.8% in the TMC435 arm. By the end of the treatment, the percentage of patients that reached HCV RNA below detection was 67.9% in the control arm and 93.0% in the TMC435 arm.

Table 37: On-treatment Virologic Response by Visits

	PBO	TMC435
Week 2		
HCV RNA not detected	5/ 133(3.8%)	79/ 249(31.7%)
HCV RNA <25 IU/mL	16/ 133(12.0%)	201/ 249(80.7%)
Week 4		
HCV RNA not detected	17/ 133(12.8%)	202/ 255(79.2%)
HCV RNA <25 IU/mL	29/ 133(21.8%)	244/ 255(95.7%)
Week 12		
HCV RNA not detected	57/ 130(43.8%)	241/ 249(96.8%)
HCV RNA <25 IU/mL	74/ 130(56.9%)	245/ 249(98.4%)
Week 24		
HCV RNA not detected	81/ 110(73.6%)	227/ 239(95.0%)
HCV RNA <25 IU/mL	90/ 110(81.8%)	230/ 239(96.2%)
Week 48		
HCV RNA not detected	79/ 80(98.8%)	6/ 7(85.7%)
HCV RNA <25 IU/mL	80/ 80(100.0%)	7/ 7(100.0%)
EOT		
HCV RNA not detected	91/ 134(67.9%)	239/ 257(93.0%)
HCV RNA <25 IU/mL	*96/ 134(71.6%)*	242/ 257(94.2%)

Source: Statistical Reviewer's analysis.

3.2.4.2.3 Relapse

Similar to Study 208, a higher relapse rate (23.9%) was observed in the control arm compared with the TMC435 arm (13.1%) as shown in Table 38.

Table 38: Viral Relapse

	PBO	*TMC435*
Relapse	*21/88(23.9%)*	*31/236(13.1%)*

Source: Statistical Reviewer's analysis.

3.2.4.3 Integrated Results from Study 208 and Study 216 (Naïve Population)

Data from Study 208 and Study 216 was integrated because the design for those two studies was similar, and both studies were conducted on treatment naïve patients.

3.2.4.3.1 Primary Efficacy Endpoint

Primary Efficacy Analysis

Table 39 and Table 40 summarize the reviewer's primary efficacy analysis by integrating data from the two studies. The percentage n of patients that achieved SVR12 was 50.4% in the control arm and 80.4 % in the TMC435 arm. The stratum- adjusted treatment difference for SVR12 was 30.1% (95% CI: 23.8%, 36.5%). The percentage of patients achieving SVR was 50.8% in the control arm and 79.7 % (415/521) in the TMC435 arm. The stratum-adjusted treatment difference for SVR was 29.0% with a 95% CI of (22.6%, 35.4%).

Table 39: Sustained Virologic Response 12 Weeks Post Treatment (SVR12) (ITT Analysis Set)

	PBO (N=264)	**TMC435 (N=521)**
SVR12 n(%)	133(50.4%)	419(80.4%)
Stratum-adjusted Treatment (TMC- PBO) difference (95% CI)*	30.1%(23.8%, 36.5%)	

* The treatment difference and 95% confidence interval were adjusted for stratification factors *(, IL28B: CC, CT and TT; Subgenotype 1a/other, 1b; Study: 208, 216)*

Source: Statistical Reviewer's analysis.

Table 40: Sustained Virologic Response (SVR)[#] (ITT Analysis Set)

	PBO (N=264)	**TMC435 (N=521)**
SVR[#] n(%)	134(50.8%)	415(79.7%)
Stratum-adjusted Treatment (TMC- PBO) difference (95% CI)*	29.0%(22.6%, 35.4%)	

SVR was defined as HCV RNA <25/IU/mL 12 weeks after the end of treatment. The 12 weeks post treatment window for the post-treatment day is [57, +∞]. If there was more than one record, the last record was taken.

*The treatment difference and 95% confidence interval were adjusted for stratification factors *(IL28B: CC, CT and TT; Subgenotype 1a/other, 1b; Study: 208, 216)*

Source: Statistical Reviewer's analysis.

Exploratory Logistic Regression Model

An exploratory logistic regression model was fit to investigate the relationship between SVR12 and baseline variables. The covariates that were tested were:

- TRT: treatment
- Study: (208 vs. 216)
- BLQ80KFL: baseline Q80K
- REGION
- SEX
- AGEGR2: age group
- BLVLGR1: baseline HCV RNA viral load group
- IL28B
- BLBMIGR2: baseline BMI group
- MTFIBGR1: Metavir score
- AHCVGCOA: sub genotype
- RACE
- IP10GR1: IP-10 group

Each variable was fit initially. Significant variables (with p-value <=0.05) were then included in one model. Non-significant variables were dropped from the model until all the variables left in the model were significant. Interactions between those significant variables were also tested.

In the final model (Table 41), treatment, baseline Q80K and their interaction were significant. Age group, IL28B, baseline HCV RNA viral load level, Metavir score, and IP-10 group were significant. The interactions between baseline HCV RNA viral load level and Metavir score, IL28B and Metavir score were also significant.

According to the model, patients who were treated with TMC435, did not have Q80K at baseline, were <=45 years old, had genotype IL28B CC, had baseline HCV RNA <=800000 IU/mL, were not cirrhotic and had IP-10 <=600 pg/mL had a higher probability of achieving SVR12.

Table 41: Logistic Regression Model for SVR12

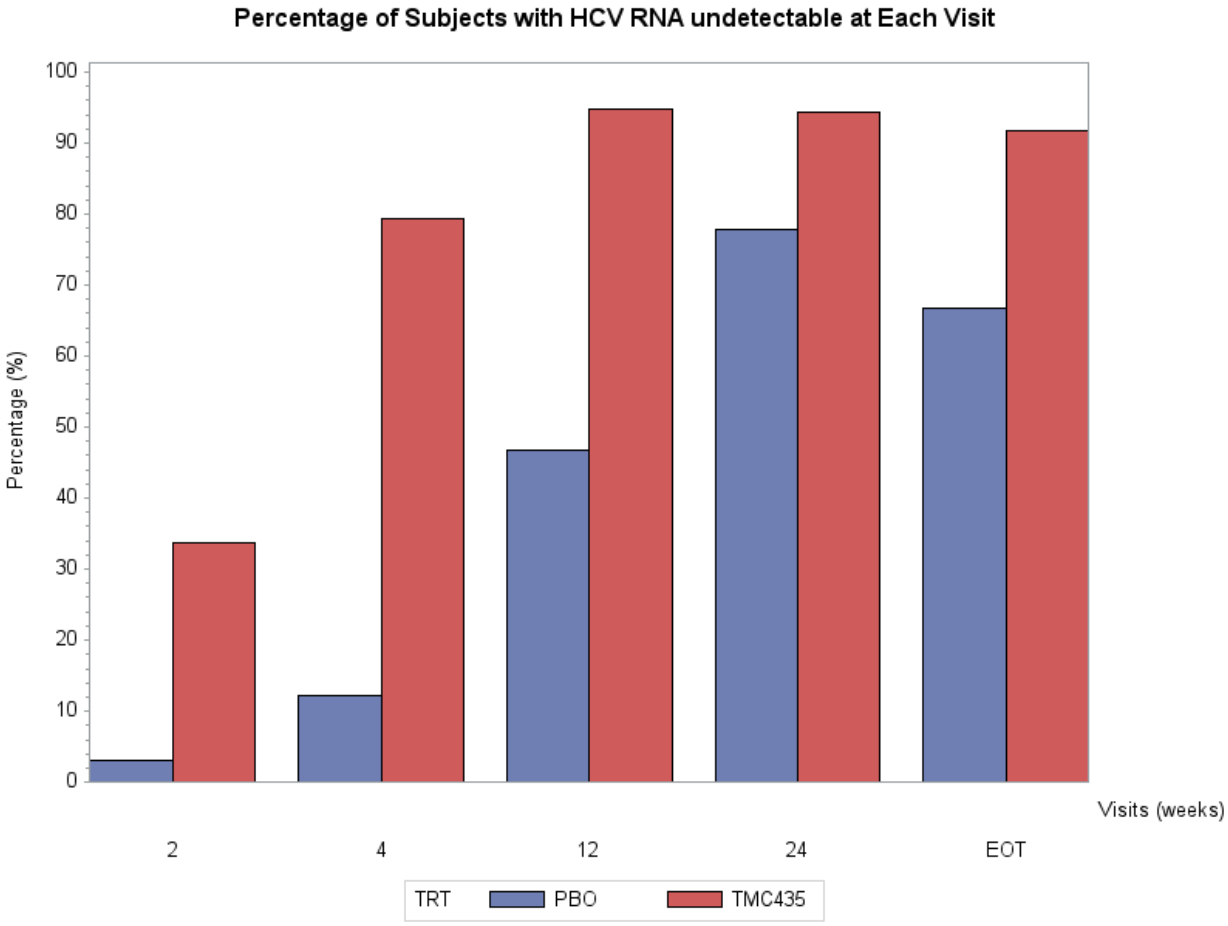
Parameter	Comment	Estimate	Standard Error	p-value
Intercept		0.5377	0.2143	0.0121
TRT	PBO vs. TMC	-0.6945	0.1344	<.0001
BLQ80KFL	No	0.2998	0.1312	0.0223
TRT*BLQ80KFL	PBO*NO	-0.5335	0.1327	<.0001
AGEGR2	>45 years vs. <=45 years	-0.3247	0.1070	0.0024
IL28B	CC vs. TT	2.0321	0.2261	<.0001
IL28B	CT vs. TT	-0.4757	0.1629	0.0035
BLVLGR1	<=800000 IU/mL vs. >800000 IU/mL	0.6934	0.1575	<.0001
MTFIBGR1	F0-F2 vs. F3-F4	0.5632	0.1704	0.0009
BLVLGR1*MTFIBGR1	<=800000 IU/mL* F0-F2	0.3086	0.1536	0.0445
IL28B*MTFIBGR1	CC*F0-F2	-0.5205	0.2135	0.0148
IL28B*MTFIBGR1	CT*F0-F2	0.1374	0.1624	0.3975
IP10GR1	<= 600 pg/mL vs. >600 pg/mL	0.5290	0.1353	<.0001

Source: Statistical Reviewer's analysis.

3.2.4.3.2 On-treatment Virologic Response

On-treatment virologic response of the integrated data is summarized in Figure 5. Overall, the TMC435 arm had higher virologic response rates than the control arm across the visits.

Figure 5: On-treatment Virologic Response by Visit



Source: Statistical Reviewer's analysis.

3.2.4.3.3 Relapse

By integrating the data from the two studies, the overall relapse rate was 22.2% in the control arm and 11.7% in the TMC435 arm as shown in Table 42 below.

Table 42: Viral Relapse

	PBO	***TMC435***
Relapse	*38/171(22.2%)*	*55/469(11.7%)*

Source: Statistical Reviewer's analysis.

3.2.4.3.4 Efficacy by Baseline Q80K

There was a statistically significant treatment by Q80K polymorphism at baseline interaction (p-value of 0.0002) with regard to SVR12 as shown in Tables 41 and 65. Detailed analyses were performed to investigate this differential effect.

Table 43 displays the summary of the efficacy endpoints by treatment arms and baseline Q80K status. In the control arm, the results of the efficacy endpoints were quite similar between the patient with and without Q80K at baseline. SVR12 rates were 48.6% for the patients without Q80K at baseline and 54.5% for the patients with Q80K at baseline. However, in the TMC435 arm, the percentage of patients who achieved SVR12 was 84.6% for the patients without Q80K at baseline and only 59.3% for the patients with Q80K at baseline. There appeared to be no improvement in SVR12 for those patients with Q80K at baseline when adding TMC435 to their treatment compared with the Q80K patients in the control arm. The results in Table 43 suggest that TMC435 suppressed the viral load while patients with Q80K were on treatment, but patients could still relapse once they were off treatment.

Table 43: Efficacy Endpoints by Baseline Q80K

	PBO		**TMC435**	
	Without Q80K at Baseline	**With Q80K at Baseline**	**Without Q80K at Baseline**	***With Q80K at Baseline***
Week 4				
HCV RNA not detected	24/214 (11.2%)	8/44 (18.2%)	345/429 (80.4%)	54/86 (62.8%)
HCV RNA <25 IU/mL	43/214 (20.1%)	10/44 (22.7%)	402/429 (93.7%)	66/86 (76.7%)
EOT (HCV RNA not detected)	140/214 (65.4%)	31/44 (70.5%)	402/429 (93.7%)	70/86 (81.4%)
SVR12	104/214 (48.6%)	24/44 (54.5%)	363/429 (84.6%)	51/86 (59.3%)
SVR	105/214 (49.1%)	24/44 (54.5%)	360/429 (83.9%)	50/86 (58.1%)
Relapse	32/136 (23.5%)	6/30 (20.0%)	39/398 (9.8%)	15/65 (23.1%)

Source: Statistical Reviewer's analysis.

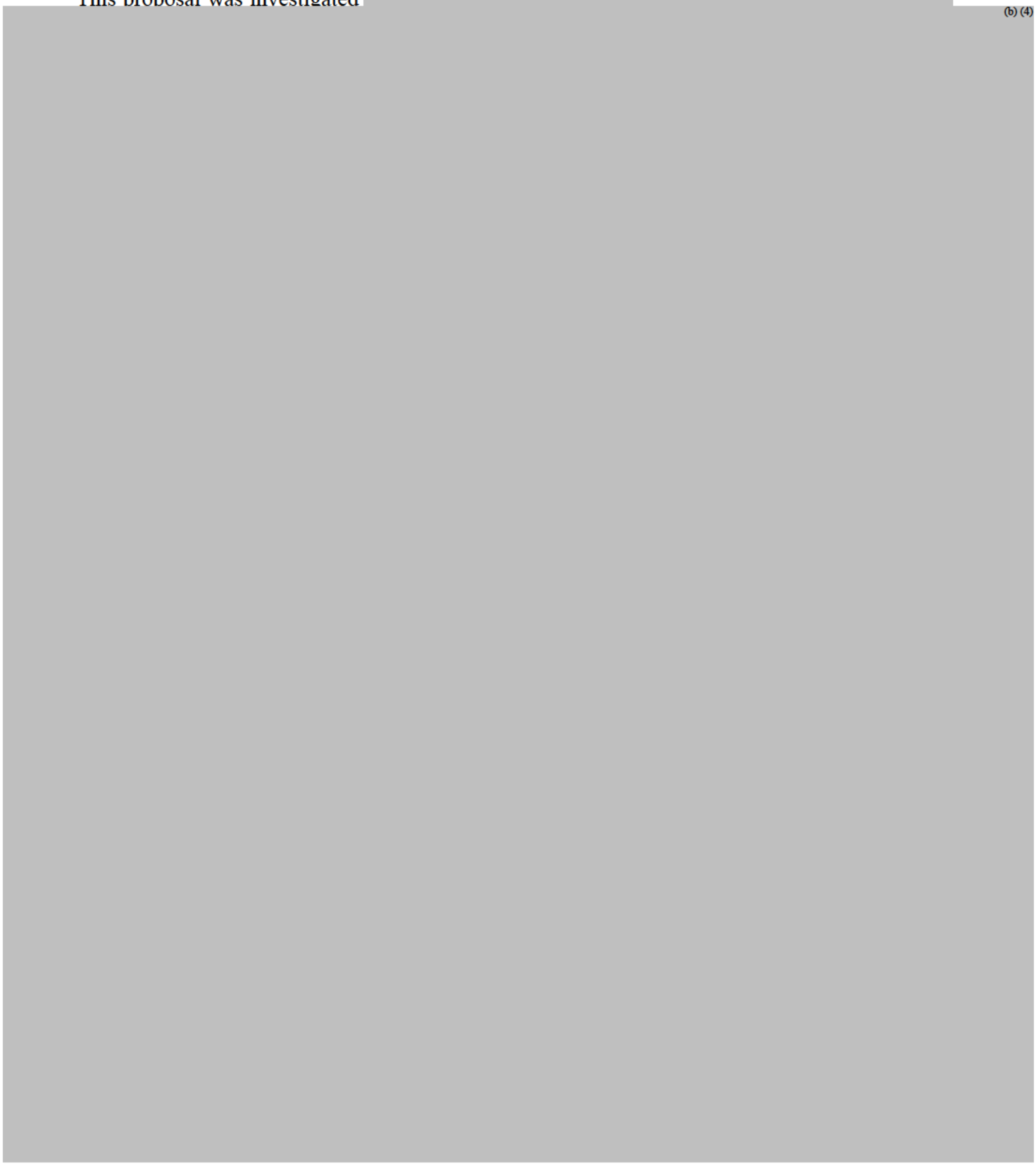
To address the apparent differential treatment effect among patients with and without Q80K and the associated risks, the applicant proposed an alternative treatment algorithm (b) (4)

(b) (4)

[redacted]

This proposal was investigated (b) (4)

(b) (4)



Given that subjects in the pivotal Phase 3 studies who were infected with HCV genotype 1a with the Q80K polymorphism at baseline were less likely to benefit from TMC435 in combination with Peg/RBV than subjects infected with other HCV polymorphic variants, there is a high prevalence of the Q80K polymorphism in genotype 1a patients in the U.S. population, and there are concerns regarding the generation of cross-resistance to the approved HCV protease inhibitors in TMC435 treatment failures (i.e., R155K), the review team is currently recommending the applicant screen all patients for the Q80K polymorphism prior to initiation of TMC435 with the objective of excluding patients from treatment if the polymorphism is present. The applicant's treatment algorithm can also be simplified further. The following describes one option: all patients in the treatment-naïve and relapser populations would receive a fixed 24 week course of PEG/RBV in conjunction with 12 weeks of TMC435. According to this simplified treatment algorithm, the estimated SVR12 would be between 82.7% (assume the SVR12 rate is 0 for patients whose HCV RNA ≥25IU/mL at week 4) to 84.6% (assume the SVR12 rate is 29.6% for patients whose HCV RNA ≥25IU/mL at week 4 based on the 48 weeks treatment data in Table 43). The estimated SVR would be between 82.1% and 83.9% as shown in Table 46. Other options are currently still under discussion.

Table 46: Estimated SVR12 and SVR in TMC435 Treated Naïve Patients Without Q80K at Baseline Based on the Agency's Proposal (ITT Analysis Set)

Week 4 HCV RNA Result	Proposed Treatment Duration (weeks)	Estimated Proportion of Patients %(n/N)	Estimated SVR12 %	Estimated SVR %
HCV RNA <25 IU/mL (detected or undetected)	24	93.7%(402/429)	88.3%	87.6%
HCV RNA ≥25 IU/mL or missing	24	6.3%(27/429)	0-29.6%	0-29.6%
Overall			**82.7% - 84.6%**	**82.1% - 83.9%**

Source: Statistical Reviewer's analysis.

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3.2.4.4 Study 3007

3.2.4.4.1 Primary Efficacy Endpoint

Table 47 below summarizes the applicant's primary analysis. The percentage of patients who achieved SVR12 was 36.8% in the control arm and 79.2% in the TMC435 arm. The stratum-adjusted treatment difference was 43.0% (95% CI: 33.8%, 52.3%). TMC435 was shown to be superior to placebo as evidenced by the statistically significant difference.

Table 48 and Table 49 summarize the reviewer's analyses based on the reviewer's definitions of SVR12 and SVR. The percentagen of patients that achieved SVR12 was 36.1% in the control arm and 79.2% in the TMC435 arm. The stratum-adjusted treatment difference was 43.7% with a 95% CI of (34.6%, 52.9%). One patient (TMC435HPC3007-6194) had two HCV RNA records in the Week 12 follow-up visit window, and the records were all >25 IU/mL. This patient also had one record in the Week 24 follow-up visit window, and it was below detection level. In the reviewer's analysis, this patient was counted as a SVR12 failure but an SVR success, while in the applicant's analysis, this patient was classified as an SVR12 success.

The percentage of patients who achieved an SVR was 35.3% in the control arm and 77.3% in the TMC435 arm. The stratum-adjusted difference for SVR was 42.6% with 95% CI of (33.5%, 51.7%). There were 7 patients (2 patients in the control arm and 5 patients in the TMC435 arm) who relapsed after the Week 12 follow-up, and their HCV RNA records are listed in Table 50.

The superiority of TMC435 to placebo was also demonstrated based on the reviewer's analysis.

Table 47: Applicant's Primary Endpoint: Sustained Virologic Response 12 Weeks After the Planned End of Treatment (SVR12)

	Observed	Stratum Adjusted	Comparison versus Placebo	
	n/N (%)	% (95% CI)[c]	Difference in proportions (95% CI)[b]	p-value[a]
SVR12				
PBO 12Wks PR48	49/133 (36.8)	36.6 (28.7;44.5)		
TMC435 150 mg 12Wks PR24/48	206/260 (79.2)	79.6 (74.8;84.4)	43.0 (33.8;52.3)	<0.001

[a] based on the CMH test controlling for stratification factors.
[b] difference in proportions (active – placebo) adjusted for stratification factors and the corresponding 95% CI based on the normal approximation.
[c] proportions adjusted for the stratification factors and the corresponding 95% CIs based on the normal approximation.

Stratification factors are *IL28B* and HCV geno/subtype. HCV geno/subtype is based on the NS5B assay (if not available, LiPA II or Trugene result is used) and categorized as 1b versus any other geno/subtype (1a/other).

The p-value for the Breslow-Day test for homogeneity of odds ratios was 0.948.

Source: Table 26 in the Clinical Study Report for study TMC435HPC3007.

Table 48: Sustained Virologic Response 12 Weeks Post Treatment (SVR12) (ITT Analysis Set)

	PBO (N=133)	**TMC435 (N=260)**
SVR12 n(%)	48(36.1%)	206(79.2%)
Stratum-adjusted Treatment Difference (TMC435 vs. PBO) (95% CI)*	43.7% (34.6%, 52.9%)	

* The treatment difference and it's 95% confidence interval were adjusted for stratification factors *(IL28B: CC, CT and TT; Subgenotype 1a/other, 1b)*
Source: Statistical Reviewer's analysis.

Table 49: Sustained Virologic Response (SVR)[#] (ITT Analysis Set)

	PBO (N=133)	**TMC435 (N=260)**
SVR n(%)	47(35.3%)	201(77.3%)
Stratum-adjusted Treatment Difference (TMC435 vs. PBO) (95% CI)*	42.6(33.5%, 51.7%)	

SVR was defined as HCV RNA <25/IU/mL 12 weeks after the end of treatment. The 12 weeks post treatment window for the post-treatment day is [57, +∞]. If there was more than one record, the last record was taken.
* The treatment difference and 95% confidence interval were adjusted for stratification factors *(IL28B: CC, CT and TT; Subgenotype 1a/other, 1b)*
Source: Statistical Reviewer's analysis.

Table 50: HCV RNA viral loads of those patients who relapsed after week 12 post treatment

Patient ID	TRT	Treatment Duration (days)	Sample day	VISIT	Lab Result (IU/mL)
TMC435HPC3007-6048	TMC435	169	-21	SCREENING	3530000
			1	BASELINE	2030000
			3	DAY3	380
			8	DAY7	<25 IU/mL HCV RNA detected
			15	DAY14	<25 IU/mL HCV RNA detected
			29	DAY28	HCV RNA not detected
			57	WEEK8	HCV RNA not detected
			85	WEEK12	HCV RNA not detected
			113	WEEK16	HCV RNA not detected
			141	WEEK20	HCV RNA not detected
			169	WEEK24	HCV RNA not detected
			197	WEEK28	HCV RNA not detected
			253	WEEK36	HCV RNA not detected
			337	WEEK48	<25 IU/mL HCV RNA detected
			361	UNSCHEDULED_VISIT1	680
			422	WEEK60	537000
			505	WEEK72	495000
TMC435HPC3007-6054	TMC435	169	-34	SCREENING	2410000
			1	BASELINE	1390000
			3	DAY3	404
			8	DAY7	36
			12	DAY14	<25 IU/mL HCV RNA detected
			29	DAY28	<25 IU/mL HCV RNA detected
			54	WEEK8	HCV RNA not detected
			85	WEEK12	HCV RNA not detected
			110	WEEK16	HCV RNA not detected
			141	WEEK20	HCV RNA not detected
			169	WEEK24	HCV RNA not detected
			194	WEEK28	HCV RNA not detected
			254	WEEK36	HCV RNA not detected
			339	WEEK48	1870000
			348	UNSCHEDULED_VISIT1	1950000
			425	WEEK60	1100000
			505	WEEK72	548000
TMC435HPC3007-6076	PBO	337	-21	SCREENING	838000
			1	BASELINE	576000
			4	DAY3	18900
			6	DAY7	23100
			15	DAY14	12600
			29	DAY28	2340
			57	WEEK8	225

			84	WEEK12	33
			112	WEEK16	<25 IU/mL HCV RNA detected
			140	WEEK20	<25 IU/mL HCV RNA detected
			174	UNSCHEDULED_VISIT4	HCV RNA not detected
			196	WEEK28	HCV RNA not detected
			251	WEEK36	HCV RNA not detected
			294	WEEK42	HCV RNA not detected
			337	WEEK48	HCV RNA not detected
			364	WEEK52	HCV RNA not detected
			426	WEEK60	HCV RNA not detected
			510	WEEK72	375000
			523	UNSCHEDULED_VISIT5	203000
TMC435HPC3007-6123	TMC435	169	-28	SCREENING	1010000
			1	BASELINE	1320000
			3	DAY3	949
			8	DAY7	<25 IU/mL HCV RNA detected
			16	DAY14	<25 IU/mL HCV RNA detected
			29	DAY28	<25 IU/mL HCV RNA detected
			57	WEEK8	HCV RNA not detected
			84	WEEK12	HCV RNA not detected
			113	WEEK16	HCV RNA not detected
			141	WEEK20	HCV RNA not detected
			169	WEEK24	HCV RNA not detected
			197	WEEK28	HCV RNA not detected
			253	WEEK36	HCV RNA not detected
			337	WEEK48	391000
			347	UNSCHEDULED_VISIT1	1600000
			421	WEEK60	21100
			505	WEEK72	469000
TMC435HPC3007-6124	PBO	336	-35	SCREENING	563000
			1	BASELINE	493000
			3	DAY3	134000
			7	DAY7	73800
			14	DAY14	30900
			28	DAY28	4260
			56	WEEK8	259
			84	WEEK12	25
			119	WEEK16	<25 IU/mL HCV RNA detected
			141	WEEK20	HCV RNA not detected
			168	WEEK24	HCV RNA not detected
			197	WEEK28	HCV RNA not detected
			249	WEEK36	HCV RNA not detected
			294	WEEK42	HCV RNA not detected
			336	WEEK48	HCV RNA not detected
			364	WEEK52	HCV RNA not detected
			421	WEEK60	HCV RNA not detected
			504	WEEK72	95900

			514	UNSCHEDULED_VISIT1	85900
TMC435HPC3007-6144	TMC435	169	-35	SCREENING	2500000
			1	BASELINE	2900000
			3	DAY3	390
			8	DAY7	<25 IU/mL HCV RNA detected
			15	DAY14	HCV RNA not detected
			29	DAY28	HCV RNA not detected
			57	WEEK8	HCV RNA not detected
			85	WEEK12	HCV RNA not detected
			113	WEEK16	HCV RNA not detected
			141	WEEK20	HCV RNA not detected
			169	WEEK24	HCV RNA not detected
			196	WEEK28	HCV RNA not detected
			253	WEEK36	HCV RNA not detected
			337	WEEK48	1060000
			351	UNSCHEDULED_VISIT2	670000
			422	WEEK60	964000
			504	WEEK72	955000
TMC435HPC3007-6332	TMC435	169	-42	SCREENING	4750000
			1	BASELINE	1430000
			4	DAY3	239
			8	DAY7	76
			15	DAY14	<25 IU/mL HCV RNA detected
			27	DAY28	HCV RNA not detected
			57	WEEK8	HCV RNA not detected
			85	WEEK12	HCV RNA not detected
			113	WEEK16	HCV RNA not detected
			140	WEEK20	HCV RNA not detected
			169	WEEK24	HCV RNA not detected
			196	WEEK28	HCV RNA not detected
			253	WEEK36	HCV RNA not detected
			337	WEEK48	288000
			361	UNSCHEDULED_VISIT1	411000
			420	WEEK60	242000

Note: Treatment duration for these patients was either 24 or 48 weeks so the corresponding SVR12 visits were at Weeks 36 and 60.
Source: Statistical Reviewer's analysis.

As shown in Table 51, 242 patients met the RGT criteria. The SVR12 and SVR rates of those patients were 82.6% and 80.6%, respectively.

Table 51: SVR12 and SVR of the Patients Who Met GRT Criteria

	SVR12	SVR
n/N (%)	200/242(82.6%)	195/242(80.6%)

Source: Statistical Reviewer's analysis.

An exploratory logistic regression model was fit to investigate the relationship between SVR12 and baseline variables. The covariates that were tested were:

- TRT: treatment
- BLQ80KFL: baseline Q80K
- REGION
- SEX
- AGEGR2: age group
- BLVLGR1: baseline HCV RNA viral load level
- IL28B
- BLBMIGR2: baseline BMI group
- MTFIBGR1: Metavir score
- AHCVGCOA: sub genotype
- RACE

Similar steps as used for the naïve population were followed.
In the final model (Table 52), treatment, baseline Q80K, region and IL28B were significant.
According to the model, patients who were treated with TMC435, did not have Q80K at baseline, from European countries and with genotype IL28B CC had a higher probability of achieving SVR12.

Table 52: Logistic Regression Model for SVR12

Parameter	Comment	Estimate	Standard Error	Wald Chi-Square	P-value
Intercept		-0.5431	0.2398	5.1291	0.0235
TRT	PBO vs. TMC	-1.1037	0.1358	66.0434	<.0001
BLQ80KFL	No vs. Yes	0.4672	0.1944	5.7788	0.0162
REGION	ASIA-PACIFIC vs. NORTH-AMERICA	-0.5467	0.2913	3.5229	0.0605
REGION	EUROPE vs. NORTH-AMERICA	0.9647	0.1990	23.4939	<.0001
IL28B	CC vs. TT	0.9443	0.2339	16.2940	<.0001
IL28B	CT vs. TT	-0.0443	0.1801	0.0605	0.8057

Source: Statistical Reviewer's analysis.

3.2.4.4.2 On-treatment Virologic Response

On-treatment virologic response is summarized in Table 53. Compared with the control arm, higher response rates in the TMC435 arm were observed across the visits. At Week 4, the percentage of patients who reached HCV RNA below detection was 3.1% in the control arm and 77.2% in the TMC435 arm. At Week 12, 27.2% of the patients had HCV RNA below detection in the control arm while the below detection rate was 97.6% in the TMC435 arm. By the end of

the treatment, the percentage of patients with HCV RNA below detection was 71.4% in the control arm and 96.9% in the TMC435 arm.

Table 53: On-treatment Virologic Response by Visits

	PBO	***TMC435***
Week 2		
HCV RNA not detected	1/ 130(0.8%)	*73/ 258(28.3%)*
HCV RNA <25 IU/mL	2/ 130(1.5%)	*213/ 258(82.6%)*
Week 4		
HCV RNA not detected	4/ 129(3.1%)	*200/ 259(77.2%)*
HCV RNA <25 IU/mL	15/ 129(11.6%)	*247/ 259(95.4%)*
Week 12		
HCV RNA not detected	34/ 125(27.2%)	*249/ 255(97.6%)*
HCV RNA <25 IU/mL	65/ 125(52.0%)	*250/ 255(98.0%)*
Week 24		
HCV RNA not detected	88/ 112(78.6%)	*239/ 240(99.6%)*
HCV RNA <25 IU/mL	106/ 112(94.6%)	*240/ 240(100.0%)*
Week 48		
HCV RNA not detected	84/ 95(88.4%)	*9/ 9(100.0%)*
HCV RNA <25 IU/mL	94/ 95(98.9%)	*9/ 9(100.0%)*
EOT		
HCV RNA not detected	95/ 133(71.4%)	*252/ 260(96.9%)*
HCV RNA <25 IU/mL	*109/ 133(82.0%)*	*254/ 260(97.7%)*

Source: Statistical Reviewer's analysis.

3.2.4.4.3 Relapse

A higher relapse rate (47.8%) was observed in the control arm compared with the TMC435 arm (19.3%) as shown in Table 54.

Table 54: Viral Relapse

	PBO	***TMC435***
Relapse	*43/90(47.8%)*	*48/249(19.3%)*

Source: Statistical Reviewer's analysis.

3.2.4.4.4 Efficacy by Baseline Q80K

Similar to the naïve population, a statistically significant treatment and Q80K polymorphism at baseline interaction (p-value=0.04) with regard to SVR12 was detected (Table 66). Detailed analyses were performed to investigate this issue.

Table 55 below displays the summary of the efficacy endpoints by treatment arms and baseline Q80K status. In the placebo arm, the SVR12 rate was 37.2% for the patients without Q80K at baseline and 30.0% for the patients with Q80K at baseline. However, in the TMC435 arm, the percentage of patients achieving SVR12 was 83.2% for the patients without Q80K at baseline and only 48.4% for the patients with Q80K at baseline.

Table 55: Efficacy Endpoints by Baseline Q80K

	PBO		***TMC435***	
	Without Q80K at Baseline	**With Q80K at Baseline**	**Without Q80K at Baseline**	***With Q80K at Baseline***
Week 4				
HCV RNA not detected	3/113(2.7%)	1/20(5.0%)	183/226(81.0%)	*14/31(45.2%)*
HCV RNA <25 IU/mL	14/113(12.4%)	1/20(5.0%)	218/226(96.5%)	*26/31(83.9%)*
EOT (HCV RNA not detected)	85/113(75.2%)	10/20(50.0%)	220/226(97.3%)	*29/31(93.5%)*
SVR12	42/113(37.2%)	6/20(30.0%)	188/226(83.2%)	*15/31(48.4%)*
SVR	41/113(36.3%)	6/20(30.0%)	183/226(81.0%)	*15/31(48.4%)*
Relapse	*41/82(50.0%)*	*2/8(25.0%)*	*35/218(16.1%)*	*13/28(46.4%)*

Source: Statistical Reviewer's analysis.

The applicant's proposed recommendation for the Dosage and Administration section in the label for relapsers was investigated (b) (4)

[redacted]

The review team has recommended the applicant screen all patients for the Q80K polymorphism prior to initiation of TMC435 with the objective of excluding patients from treatment if the polymorphism is present. In response, the applicant proposed has proposed a treatment algorithm that can also be simplified. The following is one of the options: all patients in the relapser population would receive a fixed 24 week course of PEG and RBV in conjunction with 12 weeks of TMC435. According to this treatment algorithm, the estimated SVR12 would be between 81.0% (assume the SVR12 rate is 0 for patients whose HCV RNA ≥25IU/mL at Week 4) and 83.2% (assume the SVR12 rate is 62.5% for patients whose HCV RNA ≥25IU/mL at Week 4 based on the 48 weeks treatment data in Table 56). The estimated SVR would be between 78.8% to 81.0% as shown in Table 58. Other options are currently under discussion.

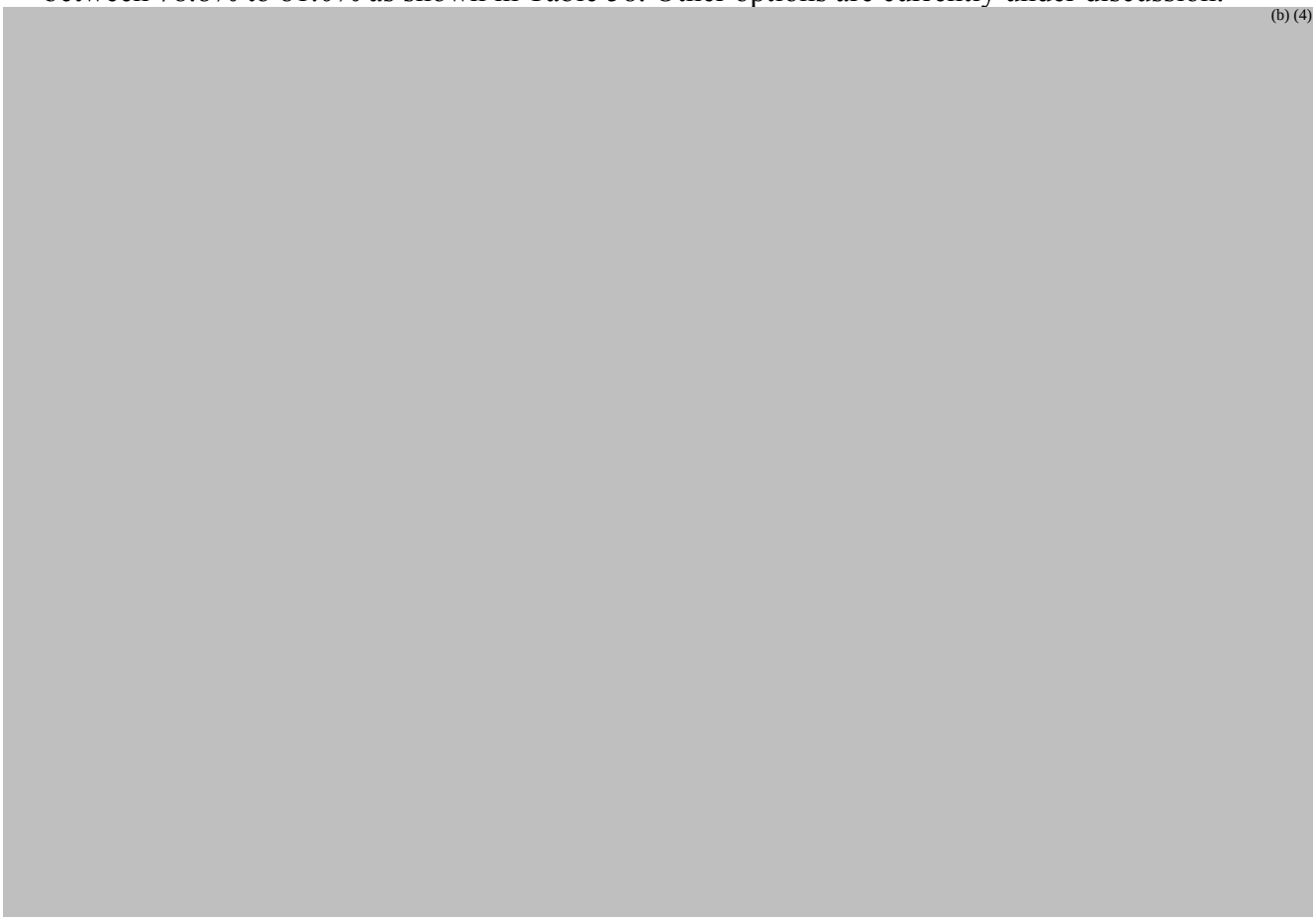

Table 58: Estimated SVR12 and SVR in TMC435 Treated Relapsers Without Q80K at Baseline Based on the Agency's Proposal (ITT Analysis Set)

Week 4 HCV RNA Result	Proposed Treatment Duration (weeks)	Estimated Proportion of Patients %(n/N)	Estimated SVR12 %	Estimated SVR %
HCV RNA <25 IU/mL (detected or undetected)	24	96.5%(218/226)	83.9%(183/218)	81.7%(178/218)
HCV RNA ≥25 IU/mL or missing	24	3.5%(8/226)	0-62.5%	0-62.5%
Overall			**81.0% -83.2%**	**78.8% - 81.0%**

Source: Statistical Reviewer's analysis.

3.2.4.5 Study 206

The analyses and definitions of this study were similar to those of the other phase III studies. The reviewer's analyses methods were slightly different from the applicant's analysis plan. Only the control arm and other arms treated with TMC435 for 12 weeks were considered relevant and summarized in this section.

3.2.4.5.1 Primary Efficacy Endpoint

Table 59 summarizes the applicant's analysis results of the sustained virologic response. The reviewer's results were very similar to the applicant's and are summarized in Tables 60 and 61. Two patients in the TMC12 arm were counted as SVR12 successes by the reviewer but not by the applicant because of the difference in the definitions. SVR and SVR12 results were exactly the same in this study. Therefore, only SVR will be mentioned.

Due to the small sample size of each arm, the TMC12 PR48 100mg and TMC12 PR48 150mg arms were combined in order to assess the efficacy of TMC435 150mg for each type of prior responder. As shown in Table 61 for Null responders, the SVR rate was 45.5% for the TMC435 arm (combining TMC12 PR48 100mg and 150mg arms) and 18.8% for the control arm. The treatment difference was 26.7% and not statistically significant. For partial responders, the SVR rate was 70.0% for the TMC435 arm (combining TMC12 PR48 100mg and 150mg arms) and 8.7% (2/23) for the control arm. The treatment difference (61.3%) was statistically significant. For relapsers, the SVR rate was 84.9% for the TMC435 arm (combining TMC12 PR48 100mg and 150mg arms) and 37.0% for the control arm. The treatment difference was 47.9% and was also statistically significant.

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Table 59: Applicant's Analysis: Sustained Virologic Response

n/N (%)	TMC12 PR48 100 mg N = 66	TMC24 PR48 100 mg N = 65	TMC48 PR48 100 mg N = 66	TMC12 PR48 150 mg N = 66	TMC24 PR48 150 mg N = 68	TMC48 PR48 150 mg N = 65	Placebo N = 66
Overall Population							
SVR4	48/66 (72.7)	45/65 (69.2)	41/66 (62.1)	46/66 (69.7)	52/68 (76.5)	52/65 (80.0)	18/66 (27.3)
SVR12	46/66 (69.7)	44/65 (67.7)	40/66 (60.6)	44/66 (66.7)	49/68 (72.1)	52/65 (80.0)	15/66 (22.7)
SVR24	46/66 (69.7)	43/65 (66.2)	40/66 (60.6)	44/66 (66.7)	49/68 (72.1)	52/65 (80.0)	15/66 (22.7)
Relapser							
SVR4	25/27 (92.6)	23/26 (88.5)	21/26 (80.8)	22/26 (84.6)	25/27 (92.6)	23/26 (88.5)	13/27 (48.1)
SVR12	24/27 (88.9)	23/26 (88.5)	20/26 (76.9)	20/26 (76.9)	24/27 (88.9)	23/26 (88.5)	10/27 (37.0)
SVR24	24/27 (88.9)	23/26 (88.5)	20/26 (76.9)	20/26 (76.9)	24/27 (88.9)	23/26 (88.5)	10/27 (37.0)
Partial Responder							
SVR4	16/23 (69.6)	13/23 (56.5)	12/22 (54.5)	15/23 (65.2)	18/24 (75.0)	19/22 (86.4)	2/23 (8.7)
SVR12	16/23 (69.6)	12/23 (52.2)	12/22 (54.5)	15/23 (65.2)	18/24 (75.0)	19/22 (86.4)	2/23 (8.7)
SVR24	16/23 (69.6)	11/23 (47.8)	12/22 (54.5)	15/23 (65.2)	18/24 (75.0)	19/22 (86.4)	2/23 (8.7)
Null Responder							
SVR4	7/16 (43.8)	9/16 (56.3)	8/18 (44.4)	9/17 (52.9)	9/17 (52.9)	10/17 (58.8)	3/16 (18.8)
SVR12	6/16 (37.5)	9/16 (56.3)	8/18 (44.4)	9/17 (52.9)	7/17 (41.2)	10/17 (58.8)	3/16 (18.8)
SVR24	6/16 (37.5)	9/16 (56.3)	8/18 (44.4)	9/17 (52.9)	7/17 (41.2)	10/17 (58.8)	3/16 (18.8)

N: number of subjects with data; n: number of subjects with SVR; SVR4: sustained virologic response 4 weeks after the planned end of treatment; SVR12: sustained virologic response 12 weeks after the planned end of treatment; SVR24: sustained virologic response 24 weeks after the planned end of treatment

Table 60: Sustained Virologic Response 12 Weeks Post Treatment (SVR12) and Sustained Virologic Response (SVR)[#]

	TMC12 PR48 100mg (N=66)	TMC12 PR48 150mg (N=66)	PR48 (N=66)
SVR12 n(%)	48(72.7%)	44(66.7%)	15(22.7%)
SVR n(%)	48(72.7%)	44(66.7%)	15(22.7%)

SVR was defined as HCV RNA <25/IU/mL 12 weeks after the end of treatment. The 12 weeks post treatment window for the post-treatment day is [57, +∞]. If there were more than one record, the last record was taken.
Source: Statistical Reviewer's analysis.

Table 61: Sustained Virologic Response 12 Weeks Post Treatment (SVR12) and Sustained Virologic Response (SVR) # by Prior Virologic Response Category

	TMC12 PR48 100mg (N=66)	TMC12 PR48 150mg (N=66)	TMC12 PR48 Total (N=132)	PR48 (N=66)	P-value*
SVR12 n/N(%)	48/66(72.7%)	44/66(66.7%)	92/132(69.7%)	15/66(22.7%)	<0.0001
Null Responder	6/16(37.5%)	9/17(52.9%)	15/33(45.5%)	3/16(18.8%)	0.11
Partial Responder	17/23(73.9%)	15/23(65.2%)	32/46(70.0%)	2/23(8.7%)	<0.0001
Relapser	25/27(92.6%)	20/26(76.9%)	45/53(84.9%)	10/27(37.0%)	<0.0001
SVR n/N(%)	48/66(72.7%)	44/66(66.7%)	92/132(69.7%)	15/66(22.7%)	<0.0001
Null Responder	6/16(37.5%)	9/17(52.9%)	15/33(45.5%)	3/16(18.8%)	0.11
Partial Responder	17/23(73.9%)	15/23(65.2%)	32/46(70.0%)	2/23(8.7%)	<0.0001
Relapser	25/27(92.6%)	20/26(76.9%)	45/53(84.9%)	10/27(37.0%)	<0.0001

SVR was defined as HCV RNA <25/IU/mL 12 weeks after the end of treatment. The 12 weeks post treatment window for the post-treatment day is [57, +∞]. If there were more than one record, the last record was taken.
* P-value is the exact p-value of the comparison between TMC12 PR48 arm and PR48 arm.
Source: Statistical Reviewer's analysis.

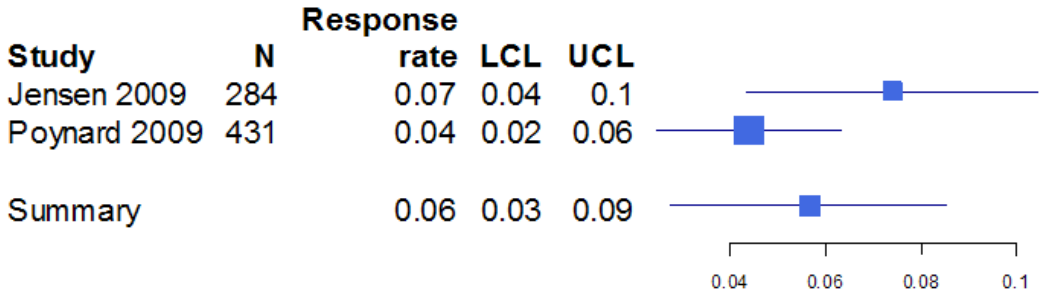
The reviewer also investigated the historical data to re-evaluate the SVR of the control arm for null responders and partial responders. Data from Boceprevir and Telaprevir labels were combined with the data from Study 206 and meta analyses were performed to estimate the SVR rates of the Peg-IFN+RBV arm as summarized in Table 62 below. The estimate of the SVR rate for null responders was 9% with 95% CI of (0%, 21%). For the partial responders, the SVR estimate was 9% with 95% CI of (3%, 16%). Jensen (2009) and Poynard (2009) also published the SVR from their studies. However in their analyses, non-responder patients were not further divided into null responders and partial responders. They were summarized by pooling those two subgroups and defined as non-responders. The overall estimated SVR for genotype 1 non-responders was 6% with 95% CI of (3%, 9%) as shown in Figure 6.

Table 62: SVR of Historical Studies of Retreating Peginterferon Plus Ribavirin Nonresponders of Genotype 1 Patients

Source	Sponsor	Population	Treatment	SVR (n/N)	Estimate of Overall SVR and 95% CI
Jesen et al.	Roche	Patients who had received at least 12 weeks of combination therapy with Pegiterferon-α2b plus Ribavirin and had detectable serum HCV RNA at every postbaseline assessment, at least 1 of which was performed after week 12	Pegiterferon-α2a, 180 ug/wk plus Ribavirin for 48 weeks	7.4%* (21/284)	6% (3%, 9%)
Poynard et al.	Schering-Plough	Had detectable HCV-RNA at the end of therapy while previously was treated with Peg-IFN alfa/Ribavirin.	Pegiterferon-α2b 1.5ug/kg/wk plus daily WBD Ribavirin for up to 48 weeks	4% (19/431)	
Telaprevir Label	Vertex	Null Responder	PEG+RBV for 48 weeks	5%(2/37)	9% (0%, 21%)
TMC Study 206	Janssen	Null Responder	PEG+RBV for 48 weeks	18.8%(3/16)	
Boceprevir Label	Merck	Partial Responder	PEG+RBV for 48 weeks	7%(2/29)	9% (3%, 16%)
Telaprevir Label	Vertex	Partial Responder	PEG+RBV for 48 weeks	15%(4/27)	
TMC Study 206	Janssen	Partial Responder	PEG+RBV for 48 weeks	8.7%(2/23)	

*This number is estimated based on a figure.
Source: Statistical Reviewer's analysis.

Figure 6: SVR Based on Meta analysis for Nonresponders



Source: Statistical Reviewer's analysis.

3.2.4.5.2 Other Efficacy Endpoints

Table 63 summarizes the on-treatment virologic response rates over the time. Compared with the control arm, the TMC435 arms appeared to have higher virologic response rates across most of the visits for null responders, partial responders and relapsers.

Table 63: On-treatment Virologic Response

	TMC12 PR48 100mg	**TMC12 PR48 150mg**	**PR48**
Overall			
Week 2			
HCV RNA not detected	15/ 64(23.4%)	16/ 66(24.2%)	0
HCV RNA <25 IU/mL	40/ 64(62.5%)	42/ 66(63.6%)	2/ 65(3.1%)
Week 4			
HCV RNA not detected	44/ 65(67.7%)	41/ 65(63.1%)	1/ 65(1.5%)
HCV RNA <25 IU/mL	52/ 65(80.0%)	57/ 65(87.7%)	2/ 65(3.1%)
Week 12			
HCV RNA not detected	54/ 61(88.5%)	53/ 62(85.5%)	13/ 44(29.5%)
HCV RNA <25 IU/mL	58/ 61(95.1%)	59/ 62(95.2%)	23/ 44(52.3%)
Week 24			
HCV RNA not detected	52/ 56(92.9%)	54/ 59(91.5%)	28/ 38(73.7%)
HCV RNA <25 IU/mL	54/ 56(96.4%)	57/ 59(96.6%)	33/ 38(86.8%)
Week 48			
HCV RNA not detected	46/ 47(97.9%)	46/ 48(95.8%)	22/ 24(91.7%)
HCV RNA <25 IU/mL	47/ 47(100.0%)	48/ 48(100.0%)	24/ 24(100.0%)
EOT			
HCV RNA not detected	53/ 66(80.3%)	53/ 66(80.3%)	27/ 66(40.9%)
HCV RNA <25 IU/mL	57/ 66(86.4%)	59/ 66(89.4%)	31/ 66(47.0%)
Null Responder			
Week 2			
HCV RNA not detected	1/ 16(6.3%)	0	0
HCV RNA <25 IU/mL	5/ 16(31.3%)	8/ 17(47.1%)	1/ 16(6.3%)
Week 4			
HCV RNA not detected	5/ 15(33.3%)	6/ 17(35.3%)	0
HCV RNA <25 IU/mL	7/ 15(46.7%)	12/ 17(70.6%)	0
Week 12			
HCV RNA not detected	9/ 11(81.8%)	10/ 15(66.7%)	3/ 8(37.5%)
HCV RNA <25 IU/mL	10/ 11(90.9%)	14/ 15(93.3%)	3/ 8(37.5%)
Week 24			
HCV RNA not detected	10/ 11(90.9%)	12/ 15(80.0%)	4/ 5(80.0%)
HCV RNA <25 IU/mL	11/ 11(100.0%)	14/ 15(93.3%)	4/ 5(80.0%)

Week 48			
HCV RNA not detected	8/ 9(88.9%)	10/ 11(90.9%)	3/ 3(100.0%)
HCV RNA <25 IU/mL	9/ 9(100.0%)	11/ 11(100.0%)	3/ 3(100.0%)
EOT			
HCV RNA not detected	9/ 16(56.3%)	11/ 17(64.7%)	4/ 16(25.0%)
HCV RNA <25 IU/mL	11/ 16(68.8%)	14/ 17(82.4%)	4/ 16(25.0%)
Partial Responder			
Week 2			
HCV RNA not detected	5/ 22(22.7%)	8/ 23(34.8%)	0
HCV RNA <25 IU/mL	15/ 22(68.2%)	15/ 23(65.2%)	0
Week 4			
HCV RNA not detected	15/ 23(65.2%)	15/ 23(65.2%)	0
HCV RNA <25 IU/mL	18/ 23(78.3%)	21/ 23(91.3%)	0
Week 12			
HCV RNA not detected	20/ 23(87.0%)	20/ 22(90.9%)	2/ 14(14.3%)
HCV RNA <25 IU/mL	21/ 23(91.3%)	20/ 22(90.9%)	4/ 14(28.6%)
Week 24			
HCV RNA not detected	17/ 19(89.5%)	19/ 20(95.0%)	4/ 12(33.3%)
HCV RNA <25 IU/mL	17/ 19(89.5%)	19/ 20(95.0%)	8/ 12(66.7%)
Week 48			
HCV RNA not detected	14/ 14(100.0%)	15/ 16(93.8%)	2/ 3(66.7%)
HCV RNA <25 IU/mL	14/ 14(100.0%)	16/ 16(100.0%)	3/ 3(100.0%)
EOT			
HCV RNA not detected	18/ 23(78.3%)	18/ 23(78.3%)	4/ 23(17.4%)
HCV RNA <25 IU/mL	19/ 23(82.6%)	19/ 23(82.6%)	6/ 23(26.1%)
Relapser			
Week 2			
HCV RNA not detected	9/ 26(34.6%)	8/ 26(30.8%)	0
HCV RNA <25 IU/mL	20/ 26(76.9%)	19/ 26(73.1%)	1/ 26(3.8%)
Week 4			
HCV RNA not detected	24/ 27(88.9%)	20/ 25(80.0%)	1/ 26(3.8%)
HCV RNA <25 IU/mL	27/ 27(100.0%)	24/ 25(96.0%)	2/ 26(7.7%)
Week 12			
HCV RNA not detected	25/ 27(92.6%)	23/ 25(92.0%)	8/ 22(36.4%)
HCV RNA <25 IU/mL	27/ 27(100.0%)	25/ 25(100.0%)	16/ 22(72.7%)
Week 24			
HCV RNA not detected	25/ 26(96.2%)	23/ 24(95.8%)	20/ 21(95.2%)
HCV RNA <25 IU/mL	26/ 26(100.0%)	24/ 24(100.0%)	21/ 21(100.0%)
Week 48			
HCV RNA not detected	24/ 24(100.0%)	21/ 21(100.0%)	17/ 18(94.4%)
HCV RNA <25 IU/mL	24/ 24(100.0%)	21/ 21(100.0%)	18/ 18(100.0%)

EOT			
HCV RNA not detected	26/ 27(96.3%)	24/ 26(92.3%)	19/ 27(70.4%)
HCV RNA <25 IU/mL	27/ 27(100.0%)	26/ 26(100.0%)	21/ 27(77.8%)

Source: Statistical Reviewer's analysis.

3.2.4.5.3 Relapse

The overall relapse rate as well as the relapse rates for null responders, partial responders and relapsers are summarized in Table 64. Only subjects whose HCV RNA was below detection level and had no missing post treatment records were counted in the denominator. For the overall population, TMC435 arms had lower relapse rates compared with the control arm.

Table 64: Viral Relapse Rates

	TMC12 PR48 100mg n/N(%)	**TMC12 PR48 150mg** n/N(%)	**PR48** n/N(%)
Overall	5/53(9.4%)	6/50(12.0%)	12/27(44.4%)
Null Responder	3/9(33.3%)	2/11(18.2%)	1/4(25.0%)
Partial Responder	1/18(5.6%)	1/16(6.3%)	2/4(50.0%)
Relapse	1/26(3.9%)	3/23(13.0%)	9/19(47.4%)

Source: Statistical Reviewer's analysis.

3.3 Evaluation of Safety

A safety signal was noted with respect to rash and/or photosensitivity events in the Phase 2b (205 and 206) and pivotal Phase III studies (208, 216, and 3007). This included an increased frequency and severity of adverse events, an increase in rates of serious adverse events and an increase in rates of discontinuation of TMC435 due to rash and/or photosensitivity related adverse events. The review team is currently considering including a discussion of rash and photosensitivity events in the Warnings and Precautions Section of the label, and including a recommendation that sun protection measures (consistent with those used in the pivotal trials) be initiated in all patients receiving TMC435.

For a detailed safety evaluation, please refer to the clinical review written by Dr. Adam Sherwat.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses of SVR12 were performed according to the pre-specified analysis plan. For the naïve population, subgroup analyses were performed by combining the data from Study 208 and Study 216. For the relapser population, subgroup analyses were performed based on the data from Study 3007. Subgroup analyses were not done for the null responders and partial responders due to the small sample size of those sub-populations.

4.1 Gender, Race, Age, Geographic Region and Other Demographic and Baseline Characteristics

Table 65 summarizes the subgroup analyses for SVR12 for the naïve population.
Treatment differences were consistent for gender, age, BMI and region subgroups. Due to the small proportion of Asian and African American patients, it is difficult to draw any conclusions based on the available data.
Regarding the baseline disease characteristics, the treatment difference was consistent across the subgroups except for Q80K polymorphism at baseline. There was an apparent differential effect of treatment among those with and without Q80K.

Table 65: SVR12 by Demographic and Baseline Disease Characteristics (naïve Population)

	Subgroup	PBO	TMC435	Diff (95% CI) TMC435 vs. PBO	P-value* of the Interaction
Sex					*0.9061*
	Female	60/113(53%)	192/233(82%)	29%(19%, 40%)	
	Male	73/151(48%)	227/288(79%)	30%(21%, 40%)	
Race					*0.9926*
	ASIAN	2/ 4(50%)	6/ 7(86%)	36%(-20%, 91%)	
	BLACK	5/ 14(36%)	29/ 43(67%)	32%(3%, 60%)	
	CAUCASIAN	125/245(51%)	378/464(81%)	30%(23%, 38%)	
	OTHER	1/ 1(100%)	4/ 5(80%)		
Age					*0.2275*
	>45 years	71/153(46%)	213/284(75%)	29%(19%, 38%)	
	<=45 years	62/111(56%)	206/237(87%)	31%(21%, 41%)	
BMI					*0.2720*
	<25 kg/m2	53/103(51%)	175/207(85%)	33%(22%, 44%)	
	>=25 kg/m2	79/159(50%)	244/314(78%)	28%(19%, 37%)	
Region					*0.3005*
	ASIA-PACIFIC	11/ 17(65%)	32/ 36(89%)	24%(-1%, 49%)	
	EUROPE	75/142(53%)	239/276(87%)	34%(25%, 43%)	
	NORTH-AMERICA	37/ 86(43%)	115/168(68%)	25%(13%, 38%)	
	SOUTH-AMERICA	10/ 19(53%)	33/ 41(80%)	28%(2%, 53%)	
Baseline HCV RNA					*0.4961*
	<=800000 IU/mL	54/ 70(77%)	96/104(92%)	15%(4%, 26%)	
	>800000 IU/mL	79/194(41%)	323/417(77%)	37%(29%, 45%)	
Sub					*0.1557*

Genotype					
	1a/other	63/131(48%)	191/254(75%)	27%(17%, 37%)	
	1b	70/133(53%)	228/267(85%)	33%(23%, 42%)	
IL28B					*0.8791*
	CC	64/ 79(81%)	144/152(95%)	14%(4%, 23%)	
	CT	61/147(41%)	228/292(78%)	37%(27%, 46%)	
	TT	8/ 38(21%)	47/ 77(61%)	40%(23%, 57%)	
IP-10					*0.8112*
	<= 600 pg/mL	122/219(56%)	381/456(84%)	28%(20%, 35%)	
	> 600 pg/mL	11/ 45(24%)	38/ 64(59%)	35%(18%, 52%)	
Metavir Score					*0.8450*
	F0-F2	107/192(56%)	317/378(84%)	28%(20%, 36%)	
	F3-F4	26/ 72(36%)	89/130(68%)	32%(19%, 46%)	
Q80K					*0.0002*
	No	104/214(49%)	363/429(85%)	36%(29%, 44%)	
	Yes	*24/ 44(55%)*	*51/ 86(59%)*	*5%(-13%, 23%)*	

* P-value was obtained by fitting the logistic regression model with only treatment and the baseline variable and their interaction term as the covariates.
Source: Statistical Reviewer's analysis.

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Table 66 summarizes the subgroup analyses for SVR12 of the relapser population. The results were very consistent with the naïve population.

The treatment difference was consistent for gender, BMI and region subgroups. It seems that, numerically, the older age group (>45 years) benefited more from the TMC435 treatment compared to the control. However, the treatment and age interaction was not statistically significant. Due to the small proportion of Asian and African American patients, conclusions should not be drawn regarding differences among various racial groups.
Regarding the baseline disease characteristics, the treatment difference was consistent across the subgroups except for Q80K polymorphism at baseline. There appeared to be a differential effect of treatment among those with and without Q80K.

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Table 66: SVR12 by Demographic and Baseline Disease Characteristics (Relapsers)

	Subgroup	PBO	TMC435	Diff (95% CI) TMC435 vs. PBO	P-value* of the Interaction
Sex					0.6179
	Female	20/ 54(37%)	67/ 81(83%)	46%(30%, 61%)	
	Male	28/ 79(35%)	139/179(78%)	42%(30%, 54%)	
Race					0.9975
	ASIAN	1/ 1(100%)	8/ 8(100%)		
	BLACK	0/ 4(0%)	5/ 7(71%)	71%(38%, 100%)	
	CAUCASIAN	47/128(37%)	192/243(79%)	42%(32%, 52%)	
	OTHER	0/ 0(0 %)	1/ 2(50%)		
Age					0.0752
	>45 years	28/ 98(29%)	142/182(78%)	49%(39%, 60%)	
	<=45 years	20/ 35(57%)	64/ 78(82%)	25%(6%, 43%)	
BMI					0.6363
	<25 kg/m2	18/ 45(40%)	66/ 78(85%)	45%(28%, 61%)	
	>=25 kg/m2	30/ 88(34%)	140/182(77%)	43%(31%, 54%)	
Region					0.4783
	ASIA-PACIFIC	1/ 10(10%)	15/ 23(65%)	55%(28%, 82%)	
	EUROPE	40/ 90(44%)	161/184(88%)	43%(32%, 54%)	
	NORTH-AMERICA	7/ 33(21%)	30/ 53(57%)	35%(16%, 55%)	
Baseline HCV RNA					0.4155
	<=800000 IU/mL	12/ 23(52%)	34/ 41(83%)	31%(7%, 54%)	
	>800000 IU/mL	36/110(33%)	172/219(79%)	46%(35%, 56%)	
Sub Genotype					0.7206
	1a/other	14/ 54(26%)	78/111(70%)	44%(30%, 59%)	
	1b	34/ 79(43%)	128/149(86%)	43%(31%, 55%)	
IL28B					0.9835
	CC	17/ 34(50%)	55/ 62(89%)	39%(20%, 57%)	
	CT	28/ 83(34%)	131/167(78%)	45%(33%, 57%)	
	TT	3/ 16(19%)	20/ 31(65%)	46%(20%, 71%)	
Metavir Score					0.4001
	F0-F2	40/ 98(41%)	137/167(82%)	41%(30%, 53%)	
	F3-F4	7/ 34(21%)	61/ 83(73%)	53%(36%, 69%)	
Q80K					0.0424
	N	42/113(37%)	188/226(83%)	46%(36%, 56%)	
	Y	6/ 20(30%)	15/ 31(48%)	18%(-8%, 45%)	

* P-value was obtained by fitting the logistic regression model with only treatment and the baseline variable and their interaction term as the covariates.
Source: Statistical Reviewer's analysis.

4.2 Other Special/Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Although Simeprevir has demonstrated treatment benefit overall in treatment-naïve patients, relapsers, and partial responders, little benefit was shown in patients with Q80K polymorphism at baseline. A statistically significant treatment by Q80K polymorphism at baseline interaction was observed with regard to SVR12 in the treatment-naïve patients. In the control arm, the efficacy endpoints were quite similar between the patient with and without Q80K at baseline; the SVR12 rate was 49% for patients without Q80K at baseline and 55% (for patients with Q80K at baseline. However, in the Simeprevir arm, the percentage of patients that achieved SVR12 was 85%) for patients without Q80K at baseline and only 59% (51/86) for patients with Q80K at baseline. There appeared to be no improvement in SVR12 for those patients with Q80K at baseline when adding TMC435 to their treatment compared with the Q80K patients in the control arm.

A similar trend was also shown in the relapser population. Again statistically significant treatment and Q80K polymorphism at baseline interaction with regard to SVR12 was detected. In the control arm, SVR12 rate was 37% for the patients without Q80K at baseline and 30% for the patients with Q80K at baseline. However, in the Simeprevir arm, the proportion of patients who achieved SVR12 was 83% for patients without Q80K at baseline and only 48% for patients with Q80K at baseline.

In order to address the issue with Q80K, the applicant proposed an alternative treatment algorithm [redacted] (b) (4)

5.2 Collective Evidence

The statistical reviewer evaluated the efficacy results from Studies 208 and 216, two pivotal phase III, randomized, double-blind, placebo-controlled studies in the treatment-naïve genotype 1 hepatitis C-infected population. Study 3007, another phase III, randomized, double-blind, placebo-controlled study, was also reviewed. Study 3007 was conducted in genotype 1 hepatitis C-infected patients who relapsed after previous interferon-based therapy. Efficacy results from Study 206, a phase IIb study, were also reviewed to investigate the efficacy of Simeprevir in prior null responders and partial responders.

The superiority of Simeprevir to control with regard to SVR12 was demonstrated in the treatment-naïve population, relapsers, and partial responders. A numerical benefit was also observed in the null responders. However, the benefit of TMC435 over control in the overall population was not demonstrated in patients with Q80K polymorphism at baseline.

5.3 Conclusions and Recommendations

The efficacy of Simeprevir as measured by the proportion of patients achieving SVR12 was demonstrated in the treatment-naïve, relapser population, and partial responders.

Given that subjects in the confirmatory studies who were infected with HCV genotype 1a with the Q80K polymorphism at baseline were less likely to benefit from TMC435 in combination with pegylated interferon and ribavirin than subjects infected with other HCV polymorphic variants, there is a the high prevalence of the Q80K polymorphism in genotype 1a patients in the U.S. population, and there are concerns regarding the generation of cross-resistance to the approved HCV protease inhibitors in TMC435 treatment failures (i.e., R155K), the review team recommends the applicant screen all patients for the Q80K polymorphism prior to initiation of TMC435 with the objective of excluding patients from treatment if the polymorphism is present. The following simplified treatment algorithm could be used:

- All patients in the naïve and relapser populations should receive a fixed 24 week course of pegylated interferon and ribavirin in conjunction with 12 weeks of TMC435.
- All patients in the partial- and null-responder populations should receive a fixed 48 week course of pegylated interferon and ribavirin in conjunction with 12 weeks of TMC435.

5.4 Labeling Recommendations (as applicable)

The review team has the following labeling recommendations:

1. Maintain the currently proposed indication (including naïve, relapser, partial and null responder populations).

2. Include the following statements as points to consider under the stated indication:

a. Simeprevir efficacy in combination with peginterferon alpha and ribavirin is substantially reduced in patients with hepatitis C genotype 1a with a Q80K polymorphism at baseline.
b. Screening for baseline Q80K polymorphism in patients with HCV genotype 1a is recommended in all patients.
c. Alternative therapy should be considered for all patients with the Q80K polymorphism at baseline.

3. Include detailed information on the impact of the baseline Q80K polymorphism on treatment outcome (i.e. SVR12) in the Clinical Studies section of the prescribing information.

4. Revise, and where possible, simplify the currently proposed treatment algorithm. Based on the recommended guidance to be provided under the indication (see #2 above), the treatment algorithm should be tailored to patients who are either infected with HCV G1a non-Q80K or HCV G1b.

A revised treatment algorithm is under discussion.

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/s/

YANMING YIN
08/28/2013

FRASER B SMITH
08/28/2013

DIONNE L PRICE
08/28/2013
concur with overall conclusion

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 205123 **Applicant: Janssen** **Stamp Date: 3/28/2013**

Drug Name: TMC435(simeprevir) **NDA/BLA Type: NDA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			Text of ISS and ISE are covered in SCS and SCE. ISS and ISE outputs were submitted in module 5.3.5.3. Complete study reports are available.
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			Subgroup analyses were performed for primary efficacy endpoint.
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? _____Yes__

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the	X			

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STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

protocols/statistical analysis plans.				
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	**X**			
Appropriate references for novel statistical methodology (if present) are included.			NA	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	**X**			

Brief summary of controlled clinical trials
The following table contains information on the relevant trials contained in the submission.

Study number	Design	Treatment arms/Sample size	Primary endpoint/Analysis	Sponsor's findings
tmc435-tidp16-c208**(QUEST-1)**	A Phase III, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability of TMC435 vs. placebo as part of a treatment regimen including peginterferon a-2a and ribavirin in treatment-naïve, genotype 1 hepatitis C-infected subjects.	**Arm 1:** TMC435 150mg +PR (n = 264) **Arm 2:** PR (n = 130)	The primary efficacy endpoint was the proportion of subjects in each treatment arm achieving SVR 12 weeks after the planned end of treatment (SVR12), defined as having HCV RNA <25 IU/mL undetectable at the end of treatment and HCV RNA <25 IU/mL 12 weeks after the planned end of treatment In the primary analysis, the difference in SVR12 rate between the TMC435/PR and PBO/PR arms was calculated using a CMH test, controlling	The proportion of subjects with SVR12 was 79.5% in the TMC435/PR arm versus 50.0% in the PBO/PR arm, resulting in a significant p-value for the CMH test controlling for the stratification factors (p <0.001; adjusted difference [95% CI] between treatment arms was 29.3% [20.1%; 38.6%]).

			for the stratification factors HCV geno/subtype (1a or 1b) and *IL28B* genotype (CC, CT, or TT).	
TMC435-TiDP16-C216 (QUEST-2)	**A Phase III, randomized, double blind, placebo controlled study to investigate the efficacy, safety and tolerability of TMC435 versus placebo as part of a treatment regimen including peginterferon α-2a (Pegasys®) and ribavirin (Copegus®) or peginterferon α-2b (PegIntron®) and ribavirin (Rebetol®) in treatment-naïve, genotype 1, hepatitis C-infected subjects**	**Arm 1:** TMC435 150mg +PR (n = 257) **Arm 2:** PR (n = 134)	The primary endpoint was the proportion of subjects in each treatment arm achieving SVR 12 weeks after the planned end of treatment (SVR12), defined as having HCV RNA <25 IU/mL undetectable at the end of treatment and HCV RNA <25 IU/mL 12 weeks after the planned end of treatment. In the primary analysis, the difference in SVR12 rate between the TMC435/PR and PBO/PR arms was calculated using a CMH test, controlling for type of PegIFN/RBV (randomized to PegIFNα-2a, randomized to PegIFNα-2b, or PegIFNα-2a [not randomized]) and the stratification factors HCV geno/subtype (1a/other or 1b) and *IL28B* genotype (CC, CT, or TT).	The proportion of subjects with SVR12 was 81.3% in the TMC435/PR arm versus 50.0% in the PBO/PR arm, resulting in a significant p value for the CMH test controlling for the type of PegIFN/RBV and the stratification factors (p = <0.001; adjusted difference [95% CI] between treatment arms was 32.2% [23.3%; 41.2%]).
TMC435HPC3007 (PROMISE)	**A Phase III, randomized, double blind, placebo controlled study to investigate the efficacy, safety and tolerability of TMC435 vs. placebo**	**Arm 1:** TMC435 150mg +PR (n = 260) **Arm 2:** PR (n = 133)	The primary endpoint was the proportion of subjects in each treatment arm achieving SVR 12 weeks after the planned end of treatment (SVR12), defined as having HCV RNA <25 IU/mL undetectable at	The proportion of subjects with SVR12 was 79.2% in the TMC435/PR arm versus 36.8% in the PBO/PR arm, resulting in a significant p value for the CMH test controlling for the

	as part of a treatment regimen including peginterferon α-2a and ribavirin in hepatitis C, genotype 1 infected subjects who relapsed after previous interferon based therapy		the end of treatment and HCV RNA <25 IU/mL 12 weeks after the planned end of treatment. In the primary analysis, the difference in SVR12 rate between the TMC435/PR and PBO/PR arms was calculated using a CMH test, controlling for the stratification factors HCV geno/subtype (1a/other or 1b) and *IL28B* genotype (CC, CT, or TT).	stratification factors (p <0.001; adjusted difference [95% CI] between treatment arms was 43.0% [33.8%; 52.3%]).
TMC435-TiDP16-C206	A Phase IIb, randomized, double blind, placebo-controlled trial to investigate the efficacy, tolerability, safety and pharmacokinetics of TMC435 as part of a treatment regimen including PegIFNα-2a and ribavirin in HCV genotype 1 infected subjects who failed to respond or relapsed following at least 1 course of PegIFNα-2a/b and RBV therapy	1. 12 weeks triple therapy with 100 mg TMC435 q.d. plus PegIFNα-2a/RBV followed by 36 weeks of PegIFNα-2a/RBV (n=66) 2. 12 weeks triple therapy with 150 mg TMC435 q.d. plus PegIFNα-2a/RBV followed by 36 weeks of PegIFNα-2a/RBV (n=66) 3. 24 weeks triple therapy with 100 mg TMC435 q.d. plus PegIFNα-2a/RBV, followed by 24 weeks of PegIFNα-2a/RBV	The primary efficacy parameter was the SVR24 rate demonstrated by achieving undetectable HCV RNA 24 weeks after the planned end of treatment (Week 72). The 95% confidence intervals (CIs) were calculated around the observed response rates in each treatment group. The TMC435 treatment groups were compared to the control group using a logistic regression model including the factors baseline HCV RNA, which was included as continuous parameter, and the factors genotype 1 subtype, previous PegIFNα-2a/b and RBV response, dose and duration and their interaction.	In the overall population, the majority of TMC435-treated subjects achieved SVR24 (primary endpoint) and a larger proportion of subjects with SVR24 were observed across the TMC435 treatment groups (range 60.6% to 80.0%) compared to the placebo group (22.7%). In the overall population, comparable sustained virologic response (SVR) rates were observed between the different TMC435 doses (100 and 150-mg q.d.) and different TMC435 duration groups (i.e., 12, 24 or 48 weeks). In each of the 3 subpopulations (null responders, partial responders and relapsers), a higher proportion of subjects in all TMC435 treatment groups

		(n=65) 4. 24 weeks triple therapy with 150 mg TMC435 q.d. plus PegIFNα-2a/RBV, followed by 24 weeks of PegIFNα-2a/RBV (n=68) 5. 48 weeks triple therapy with 100 mg TMC435 q.d. plus PegIFNα-2a/ RBV (n=66) 6. 48 weeks triple therapy with 150 mg TMC435 q.d. plus PegIFNα-2a/RBV (n=65) 7. 48 weeks of TMC435-matched placebo plus PegIFNα-2a/RBV, (control arm) (n=66)		achieved SVR24 compared to placebo.

Yanming Yin **4/17/2013**

Reviewing Statistician Date

Fraser Smith **4/17/2013**

Supervisor/Team Leader Date

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STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

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/s/

YANMING YIN
04/23/2013

FRASER B SMITH
04/23/2013