CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205123Orig1s000

MEDICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
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M E M O R A N D U M

Date: August 27, 2013

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Cc: Tisha Washington, Technical Information Specialist/DDDP
Barbara Gould, Chief, Project Management Staff/DDDP

Re: DDDP Consult #1516 – NDA 205123 (simeprevir; TMC435)

Material Reviewed: portions of NDA 205123 and IND 75391

Background: TMC435 is an HCV NS3/4A protease inhibitor, proposed for treatment of chronic hepatitis C, in combination with pegylated interferon (PegIFN) and ribavirin (RBV), in adults with compensated liver disease (including cirrhosis) with or without human immunodeficiency virus (HIV) co-infection. The applicant proposes a dose regimen of TMC435 150 mg q.d. for 12 weeks in combination with PegIFN/RBV, followed by 12 or 36 weeks of PegIFN/RBV treatment.

Photosensitivity, rash events and pruritus were reported at a greater frequency in TMC435-treated subjects than in subjects treated with placebo during the first 12 weeks of treatment (i.e. the placebo-controlled period).

In the Summary of Clinical Safety, a **primary pooling** consisted of data from the Week 60 primary analyses of 3 double-blind, placebo-controlled Phase 3 trials, C208, C216, and HPC3007. Subjects were scheduled to receive 12 weeks of treatment with TMC435 150 mg or PBO q.d. plus PegIFN/RBV, followed by PegIFN/RBV for an additional 12 or 36 weeks (response-guided in the TMC435 group, and fixed 36 weeks in the PBO group). Thus, the first 12 weeks was the placebo-controlled period. In total, 781 subjects received at least 1 dose of TMC435 150 mg q.d. and 397 received at least one dose of PBO.

A **secondary pooling** included the Week 60 primary analyses of the Phase 3 trials and the final analyses of the 2 double-blind, placebo-controlled dose-finding Phase 2b trials, C205 and C206 (only subjects who received TMC435 150 mg q.d. for 12 weeks). Thus, the secondary pooling included data from studies C208, C216, and HPC3007, C205 and C206. The applicant performed the analyses of the "secondary pooling" database to enlarge the dataset of subjects treated with the recommended TMC435 dose (150 mg q.d.) and duration (12 weeks). The Phase 2b trials included arms in which subjects were dosed with regimens other than that which the applicant proposes in labeling. The applicant reported no relevant differences were observed between the secondary and the primary pooling with respect to the outcome of the comparisons between the TMC435 150 mg 12 Weeks group and the PBO group.

This consult will largely consider the "primary pooling" database.

The review division had the following specific questions/requests:

1. Does the increased frequency and severity of phototoxicity/photosensitivity cases in the TMC435 group warrant the inclusion of sun-protection recommendations for all patients in the label?
2. Please provide your overall assessment of the results of study C125 (the dedicated photosensitivity study) and discuss the apparent discrepancy between the results from C125 and the results noted in the clinical trials.
3. In your opinion, does the rash and/or phototoxicity findings from the clinical studies warrant inclusion in the Warnings/Precautions section of the label or is it sufficient to include mention of these findings in the Clinical Studies Experience section of the label?
4. In your opinion, are any of the SAEs and/or discontinuations related to rash and/or phototoxicity in the TMC435 group consistent with severe cutaneous adverse events (e.g. DRESS, SJS, etc.)?
5. There are two sulfur atoms in the molecule- is there any relationship with this structure and sulfa allergy?*
6. Is there anything about the molecular structure that would trigger an alert for potential photosensitivity?*

*Note: Questions 5 and 6 were added by e-mail from the review division May 28.

CONSULT REPLY:

1. **Does the increased frequency and severity of phototoxicity/photosensitivity cases in the TMC435 group warrant the inclusion of sun-protection recommendations for all patients in the label?**

Response: Yes. A clear signal for photosensitivity with TMC435 use has been identified in the clinical development program. That risk may be mitigated by advisement in the label of photoprotective measures. Clinical manifestations of photosensitivity may range in severity and include burning and stinging to erythema with edema, blistering, pain and constitutional symptoms (e.g. nausea, fever, chills, tachycardia).[1] Two subjects in the Phase 3 trials were

hospitalized for photosensitivity reactions that were considered to be serious adverse events (these cases are further discussed in the response to Question #4).

Recommendations for photoprotective measures were protocol-specified for all subjects in the primary pooling safety database, the Phase 3 trials C208, C216 and C3007. The same measures were also specified in the key supportive Phase 2b trials, C205 and C206. Although the protocols for the Phase 3 trials were ultimately amended to remove the photoprotective measures (based on the applicant's conclusions regarding the photoxicity study C125; study discussed in response to Question #2), the amendment became effective only after all subjects in the trials had completed TMC435 treatment. Specifically, the protocols for those trials had included the following instructions:

"Subjects should be informed that during TMC435 administration photosensitivity reactions (rash confined to sun-exposed areas) have been reported and should be counseled on the importance of sun protection during TMC435 treatment. Extreme exposure to the sun or sunbathing should be avoided, as well as the use of tanning devices (e.g., sunbed, solarium) from baseline until last intake of TMC435/placebo. Ideally, outdoor activities should be scheduled outside the hours that UV radiation is most intense or should be performed in the shade. Wide-brim hats, sunglasses, and use of sunscreens are recommended to maximize sun protection."

Additionally, it appears that photoprotective measures were to have been followed for up to one month post-dose (e.g. Section 1.4 of the protocol for C206). Despite these precautions, photosensitivity was evidenced in the trials, and with a notable imbalance in the occurrence of events in the TMC435 group compared to the placebo group; see Table 1:

Table 1 (Source: TSFAE05S1 ("Number (%) of Subjects with Adverse Events, First 12 Weeks and Entire Treatment Phase" Primary pool)

SYSTEM ORGAN CLASS AND PREFERRED TERM	FIRST 12 WEEKS				ENTIRE TREATMENT PHASE			
	PBO		TMC435 150mg		PBO		TMC435 150mg	
	N	%	N	%	N	%	N	%
Any Adverse Event								
TOTAL	376	94.7	744	95.3	382	96.2	757	96.9
Photosensitivity reaction	2	0.5	24	3.1	2	0.5	24	3.1
Sunburn	1	0.3	17	2.2	2	0.5	17	2.2

There were also single reports of Solar dermatitis and Polymorphic light eruption in TMC435-treated subjects.

Events suggesting photosensitivity were not limited to the Skin and subcutaneous disorders system organ class (SOC), e.g. "sunburn" is coded under Injury, poisoning and procedural complications (and was the most frequently reported adverse event in that SOC). Additionally, from review of the available photographs, it appears that some events of photosensitivity may have been coded as other events. For example, the cutaneous adverse event for subject C206-0292 was coded as "drug eruption," and the reaction for subject C208-0243 was coded as "rash." However, review of the photographs for these two subjects, suggests that they both suffered

severe photosensitivity reactions. Therefore, photosensitivity events may have been underreported. However, the safety database as submitted is sufficient to establish an association of TMC435 and photosensitivity events.

Cheilitis (in the Gastrointestinal disorders SOC) may represent a localized manifestation of phototoxicity.[2] However, the frequency of reports of this event may be considered similar between TMC435 and placebo treatment groups: 1.3% and 0.5%, respectively.

Dermatologists (and others) routinely dispense advice regarding ultraviolet light (UVL) avoidance and protection. There are public health campaigns designed to educate and/or to reinforce the message of UVL avoidance and precautions, often in the context of raising awareness about or preventing skin cancer, e.g. the American Academy of Dermatology (AAD) sponsors the SPOT Skin Cancer™ and the Play Sun Smart™ campaigns. See Appendix 1. The National Weather Service publishes a UV Index, "a forecast of the expected risk of overexposure to UV radiation from the sun."[3] We consider recommendations for UVL avoidance and protective measures to represent standard of care, irrespective of any factors which might heighten risk from UVL exposure, e.g. medications.

Several photosensitizers are approved for marketing in the United States and are labeled for the risk. Examples include the quinolones (ciprofloxacin, moxifloxacin, etc.), tetracyclines (minocycline, doxycline), amiodarone and voriconazole. We would consider it absolutely warranted and necessary to advise of UVL precautions in the label for TMC435 (simeprevir). We recommend the following (or similar) language for consideration in the Warning and Precautions section of the label:

Photosensitivity reactions have been observed with *tradename*, including severe sunburn reactions for which subjects were hospitalized. Photosensitivity may present as an exaggerated sunburn reaction, usually affecting areas exposed to light (typically the face, "V" area of the neck, extensor surfaces of the forearms, dorsa of the hands). Manifestations may include burning, erythema, exudation, blistering, and edema. Patients should avoid intense or prolonged exposure to direct natural (including through windowglass) or artificial sunlight (tanning beds or phototherapy) during treatment with *tradename*. If patients need to be outdoors while using *tradename*, they should wear clothes that protect skin from sun exposure, such as a long-sleeved shirt, and also a wide-brimmed hat, and sunglasses. Certain Patients should discuss other sun protection measures with their physician. *Tradename* should be discontinued if photosensitivity occurs.

Note: We did not address sunscreen use in the proposed language, as it is possible that patients might develop a false sense of security and believe that the sunscreen would protect them from risk.

2. **Please provide your overall assessment of the results of study C125 (the dedicated photosensitivity study) and discuss the apparent discrepancy between the results from C125 and the results noted in the clinical trials.**

Response: The dedicated photosensitization study is discussed below.

***Study Title*:** "A Randomized, Double-Blind, Double-Dummy, Placebo- and Positive Controlled Phase I Trial to Evaluate the Photosensitizing Potential of TMC435 in Healthy Subjects".

***Study Number*:** TMC435-TiDP16-C125 (C125):

***Study Design*:** This was a randomized, double-blind, double-dummy, placebo- and positive controlled, parallel group Phase 1 trial that compared the cutaneous photosensitizing potential of multiple oral doses of TMC435 150 mg q.d. to that observed in subjects administered multiple oral doses of placebo and ciprofloxacin, a fluoroquinolone (and photosensitizer), used as a positive control.

Study Population

Per p. 32 of the protocol, the study population was to consist of 36 healthy adult volunteers between 18 and 55 years of age with skin types I, II, and III. Per Protocol Attachment 1:

- Skin type I: Always burns easily and severely (painful burn); tans little or none and peels
- Skin type II: Usually burns easily and severely (painful burn); tans minimally or lightly, also peels
- Skin type III: Burns moderately and tans about average

After screening, subjects were randomized in a 1:1:1 ratio (12 per treatment group) to 1 of 3 treatments as below. All treatments were administered for 9 days.

- TMC435 150 mg q.d. (Treatment A),
- ciprofloxacin 500 mg b.i.d. (Treatment B) or
- placebo (Treatment C).

The Screening phase began up to 21 days before the start of the Treatment phase. Subjects who met the eligibility criteria proceeded to baseline phototesting to assess immediate photosensitivity responses and to determine the baseline minimum erythema dose (MED) value for delayed erythema. Phototesting was performed on the subject's mid-upper back skin.

Subjects who developed an immediate photosensitivity response during the baseline screening phototesting did not receive any trial medication and were considered screening failures. Subjects who received trial medication had to have had normal baseline 24h MED values.

Comment: *MED is the minimum dose of irradiation (mJ/cm^2) that produces perceptible erythema, and it has two components: immediate reactions (5-30 min after irradiation) and delayed (24-48h post irradiation).*[4]

Phototesting Methodology

The photosensitizing potential of TMC435, ciprofloxacin, and placebo was assessed by evaluating the subject's cutaneous responses to controlled light exposures. Subjects were exposed to wavebands that represented UV and visible light spectra to detect the presence of an

immediate photosensitivity response (e.g., transient edema with or without flare) and to detect delayed erythema at 24 and 48 hours post irradiation. Phototoxicity measurements were performed at the 7 wavebands that represent UVB (295±5 nm, 300±5 nm, and 305±5 nm), UVA (335±30 nm and 365±30 nm), visible light (400±30 nm and 430±30 nm) spectra and solar simulator.

See Appendix 2 for additional details of the phototesting methodology.

Skin responses were recorded and graded according to the following grading scale:

0	No evidence of any reaction
1	Faint but definite erythema filling the majority of the test site (i.e., the minimal erythema dose)
2	Definite marked erythema
3	Erythema with evidence of oedema
4	Erythema, oedema and blistering
?	Query result i.e., uncertain result; test dose to be repeated
B	Brown pigment
F	Flare
G	Petechia
U	Urticaria

Immediate photosensitivity symptom responses were additionally graded as below:

5	Nil
6	Itch
7	Burning
8	Pain
9	Prickling

Photosensitivity Endpoints

There were 2 photosensitivity endpoints:

1. Primary: the phototoxicity index for delayed erythema at each waveband and solar simulator assessed at 24 hours post-irradiation and
2. Secondary: the presence or absence of an immediate photosensitivity response (e.g., transient edema with or without flare) according to the grading of skin responses.

The **phototoxicity index for delayed erythema** was defined as the baseline MED divided by the postdose MED and was the primary endpoint for the assessment of the study medication's photosensitizing potential. Per p. 25 of the protocol, "The best parameter for assessing photosensitivity potential is the Photoxicity Index (PI) derived by division of the baseline MED by the postdose MED at a given waveband" (Note: The protocol cited no references for this statement.)

Per p. 57 of the protocol, a photosensitivity signal was to be considered clinically relevant if the mean PI for delayed erythema was ≥ 2.0. The following criteria were reported for each treatment at each waveband (i.e. percent of subjects with a PI of):

- < 1.67 (photosensitivity signal absent),

- 1.67-3.0 (mild),
- > 3.0 - 6.0 (moderate), or
- > 6.0 (severe).

Postdose MED ≥ 40% lower than the baseline MED equates to phototoxicity index ≥ 1.67. A was considered clinically relevant if the mean phototoxicity index ≥ 2.0.

Per p. 38 of protocol, immediate phototoxic reactions typically have a rapid onset and present as an exaggerated reaction with erythema and edema that occurs within minutes to hours of light exposure with dose-dependent increase in intensity. Clinical features usually peak at 24 to 48 hours after initial exposure. Clinical improvement may occur within 48 to 96 hours, and the lesions often heal with hyperpigmentation.

Pharmacokinetic Evaluations

As stated, all treatments were administered for 9 days. Full pharmacokinetic (PK) profiles of TMC435 and ciprofloxacin were determined on Day 7. Subjects were to undergo the series of phototesting on Days 8-10. Subjects were required to consume standardized breakfasts during the Treatment phase (Days 1-9). Subjects were to return to the study center 7-10 days and 30-35 days after the last intake of study medication for safety assessments and photosensitivity follow-up.

Blood samples were collected predose and up to 24 hours after the morning administration of study medication on Day 7 for the estimation of plasma concentration time profiles of TMC435 and ciprofloxacin. On Days 8 and 9, blood samples were collected predose and at 5 hours following the morning administration of study medication. The predose sample taken on Day 8 was the same sample as the 24 hour sample of Day 7.

Subjects underwent a series of irradiation doses at each of the 7 wavebands and solar simulator approximately 6 hours after the morning dose of study medication on Days 8 and 9.

Steady-state pharmacokinetic parameters maximum plasma concentration (C_{max}), t_{max}, minimum plasma concentration (C_{min}), AUC_{τ} for TMC435 and ciprofloxacin were determined. Pharmacokinetic-pharmacodynamic analyses were supposed to be performed if a phototoxic response was observed for TMC435 or ciprofloxacin. However, it does not appear that this was done for the immediate phototoxicity endpoint.

RESULTS

Demographics

Demographic Data (Modified Table 4 of study report)

Parameter	Treatment A TMC435 N = 12	Treatment B Ciprofloxacin N = 12	Treatment C Placebo N = 12	All Subjects N = 36
Age, years				
Median (range)	28.5 (19 – 48)	28.5 (18 – 52)	27.0 (19 – 50)	28.0 (18 – 52)
Sex, n (%)				
Male	11 (91.7)	10 (83.3)	12 (100.0)	33 (91.7)
Female	1 (8.3)	2 (16.7)	0	3 (8.3)
Race, n (%)				
White	12 (100.0)	12 (100.0)	12 (100.0)	36 (100.0)
Ethnic Origin, n (%)				
Hispanic or latino	1 (8.3)	0	0	1 (2.8)
Not hispanic or latino	11 (91.7)	12 (100.0)	12 (100.0)	35 (97.2)
Skin Type Classification				
Skin Type I	0	0	2 (16.7)	2 (5.6)
Skin Type II	7 (58.3)	5 (41.7)	4 (33.3)	16 (44.4)
Skin Type III	5 (41.7)	7 (58.3)	6 (50.0)	18 (50.0)

Extent of Exposure

A total of 36 subjects received at least one dose of study medication; 12 subjects each received either TMC435 150 mg q.d. (Treatment A), ciprofloxacin 500 mg b.i.d. (Treatment B), or placebo (Treatment C). All subjects received the study medication for the planned 9 days.

Primary Photosensitivity Endpoint

The primary photosensitivity endpoint was the phototoxicity index (PI) for delayed erythema at each waveband and solar simulator assessed at 24 hours post irradiation.

Mean PIs were below the pre-defined limit of 2.0 at all wavebands tested, and on the solar simulator in the TMC435 and placebo groups. The mean PI in the ciprofloxacin group reached 3.24 and 2.87 at the 335±30 nm and 365±30 nm wavebands, respectively. Mean PI values 24 hours post irradiation are provided in applicant's Figure 2 below.

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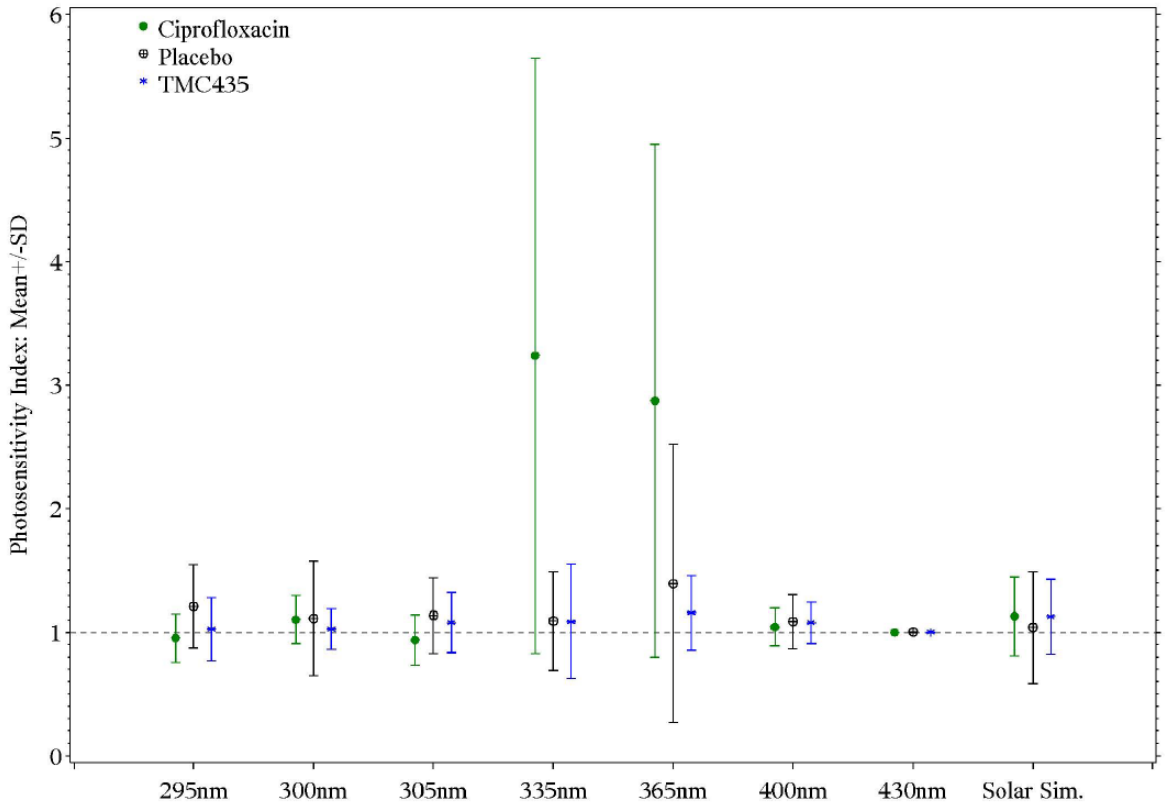
Mean ± SD Phototoxic Index Values on Day 10 (Figure 2 from study report)



In the TMC435 group, all PIs were graded as normal, except for Subject 125-0050 who had the following results, which were graded as mild photosensitivity (see Table 7 below from the study report):

- At the 335±30 nm waveband, the PI was 2.21, and
- At the 365±30 nm waveband, the PI was 1.80.

In the ciprofloxacin group, 11 subjects (91.7%) showed at least mild PI on one waveband. Three of these subjects showed photosensitvity at the 365±30 nm waveband (range: 3.85 to 4.02), and one of those subjects and an additional subject showed severe photosensitivity on the 335±30 nm and/or 365±30 nm waveband (range: 8.20 to 8.46).

In the placebo group, 4 subjects (33.3%) showed at least mild photosensitivity at some wavebands, one of these subjects (Subject 125-0069 with a concomitant active skin condition on the back reported as major protocol deviation) showed moderate PI (4.82) on the 365±30 nm waveband.

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Incidence of Delayed Photosensitivity (Phototoxic Index) Response on Day 10 (Table 7 of study report)

Wavelength Abnormality n (%)	Treatment A TMC435 N = 12	Treatment B Ciprofloxacin N = 12	Treatment C Placebo N = 12
295±5 nm			
Absent	12 (100)	12 (100)	11 (91.7)
Mild	0	0	1 (8.3)
300±5 nm			
Absent	12 (100)	12 (100)	11 (91.7)
Mild	0	0	1 (8.3)
305±5 nm			
Absent	12 (100)	12 (100)	11 (91.7)
Mild	0	0	1 (8.3)
335±30 nm			
Absent	11 (91.7)	1 (8.3)	9 (75.0)
Mild	1 (8.3)	9 (75.0)	3 (25.0)
Severe	0	2 (16.7)	0
365±30 nm			
Absent	11 (91.7)	3 (25.0)	10 (83.3)
Mild	1 (8.3)	5 (41.7)	1 (8.3)
Moderate	0	3 (25.0)	1 (8.3)
Severe	0	1 (8.3)	0
400±30 nm			
Absent	12 (100)	12 (100)	12 (100)
430±30 nm			
Absent	12 (100)	12 (100)	12 (100)
Solar Simulator			
Absent	12 (100)	11 (91.7)	11 (91.7)
Mild	0	1 (8.3)	1 (8.3)

Photosensitivity responses were classified into absent (PI < 1.67), mild (PI ≥ 1.67-3.0), moderate (PI > 3.0 - 6.0), or severe (PI > 6.0).

APPEARS THIS WAY ON ORIGINAL

Secondary Photosensitivity Endpoint
The secondary endpoint was the presence or absence of an immediate photosensitivity response according to the grading of skin responses (tables for grading of skin responses are found above). Baseline phototesting (on Day 1 and Day 2) showed no immediate photosensitivity response in any subject at any wavelength.

In the ciprofloxacin and placebo groups, no subjects had an immediate photosensitivity response after irradiation on Day 8 and/or Day 9.

In the TMC435 group, 4 subjects (33.3%) showed an immediate photosensitivity response after irradiation at the 335±30 nm or 365±30 nm waveband on Day 8 or Day 9 (see Table 8 from study report, below). Those four subjects were:

- 125-0036: on Day 8 only at the 335±30 nm waveband with reaction of erythema and edema with itching.
- 125-0050: on Day 8 at the 365±30 nm waveband with reaction of erythema and edema (with no symptoms). This subject also had delayed erythema as previously discussed.
- 125-0061: on Day 8 at the 365±30 nm waveband with reaction of erythema and edema with itching.
- 125-0081: on Day 8 only at the 335±30 nm waveband with reaction of erythema and edema with flare and itching.

All had skin type II except subject 125-0081 who had skin type III. By the Day 10 assessment (the following day), all affected sites were improved. Normal immediate response results were obtained under the protocol's allowance for retesting the same doses at "physiological irradiances" at the wavebands where the response was observed ("rechallenge"). The investigators concluded that the retesting results suggested, that "the original test result was not of clinical significance and that when subjects had reduced (physiological) irradiance testing they fell within the normal response range."

Incidence of Post-Baseline Immediate Photosensitivity Response (Table 8 of study report)

Wavelength Abnormality n (%)	Day 8			Day 9		
	Treatment A TMC435 N = 12	Treatment B Ciprofloxacin N = 12	Treatment C Placebo N = 12	Treatment A TMC435 N = 12	Treatment B Ciprofloxacin N = 12	Treatment C Placebo N = 12
295±5 nm						
Absent	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)
300±5 nm						
Absent	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)
305±5 nm						
Absent	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)
335±30 nm						
Absent	11 (91.7)	12 (100)	12 (100)	11 (91.7)	12 (100)	12 (100)
Present	1 (8.3)	0	0	1 (8.3)	0	0
365±30 nm						
Absent	10 (83.3)	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)
Present	2 (16.7)	0	0	0	0	0
400±30 nm						
Absent	12 (100)	12 (100)	12 (100)	6 (100)	6 (100)	6 (100)
430±30 nm						
Absent	12 (100)	12 (100)	12 (100)	-	-	1 (100)
Solar Simulator						
Absent	12 (100)	12 (100)	12 (100)	12 (100)	11 (100)	11 (100)

Comment: *I could find no explanation for why there were only six subjects in each treatment group for testing of the 400±30 nm waveband on Day 9.*

From review of Display PK07 (below), the four subjects who experienced immediate photosensitivity (0036, 0050, 0061, and 0081) had the four highest C_{max} values in this treatment group, and the three highest AUC_{24h} in the group (Subject 1250036 had the 5th highest AUC in the group). Thus, there appears to be a pharmacokinetic/pharmacodynamic relationship, as the events of immediate phototoxicity correlated with higher exposures of TMC435.

PK07 Supporting Data Displays: Individual PK Parameters of TMC435 (from study report)
Treatment A: 150 mg TMC435 q.d. for 9 days

		PK Parameters of TMC435											
Day	Parameter	1250032	1250036	1250045	1250047	1250049	1250050	1250061	1250063	1250064	1250075	1250081	1250082
5	C_{trough}, ng/mL	365	197	159	290	178	331	635	267	82.5	271	449	66.0
6	C_{trough}, ng/mL	447	171	163	309	216	340	848	267	65.9	305	498	89.6
7	C_{trough}, ng/mL	247	194	121	247	170	453	749	214	78.9	306	528	84.1
7	C_{min}, ng/mL	219	164	95.4	238	152	413	702	214	63.2	295	507	84.1
7	C_{max}, ng/mL	1730	1920	1210	1640	999	2770	2840	1350	991	1430	2270	992
7	t_{max}, h	5.5	6.0	5.5	5.5	5.5	6.0	5.0	4.0	5.5	6.0	6.0	5.5
7	AUC_{24h}, ng.h/mL	18320	17630	9744	15700	10720	30140	38670	16270	7518	16880	29040	9724

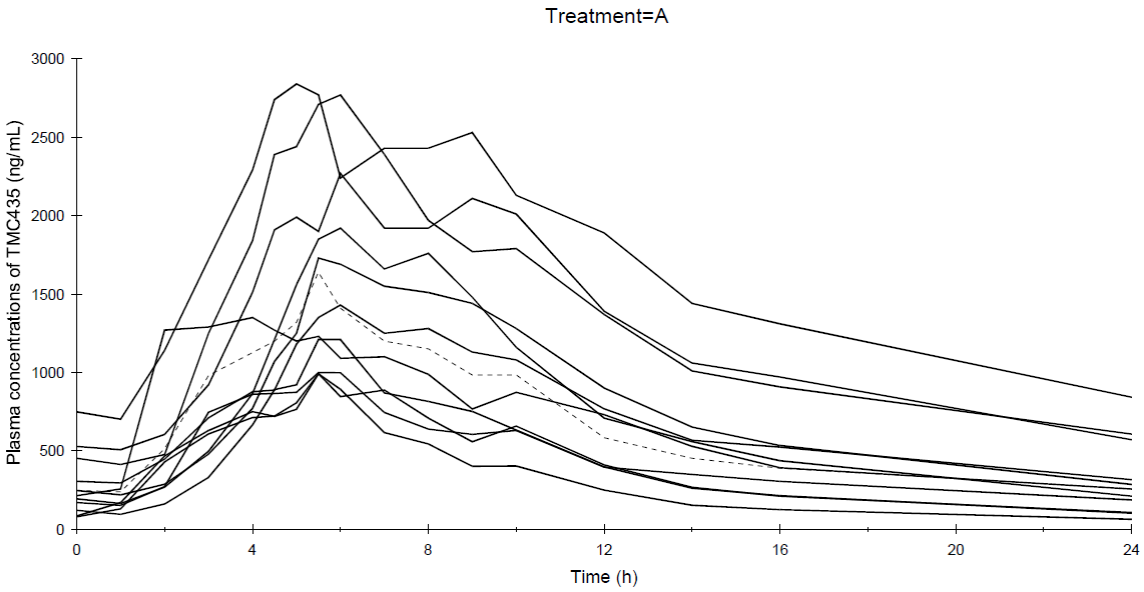
PK07 Supporting Data Displays: Individual PK Parameters of TMC435 (from study report)
Treatment A: 150 mg TMC435 q.d. for 9 day

		Descriptive Statistics							
Day	Parameter	N	Mean	SD	Min	Median	Max	%CV	Geometric Mean
5	C_{trough}, ng/mL	12	274.2	159.9	66.0	269	635	58.30	230.0
6	C_{trough}, ng/mL	12	310.0	214.1	65.9	286	848	69.08	249.2
7	C_{trough}, ng/mL	12	282.7	200.5	78.9	231	749	70.92	227.2
7	C_{min}, ng/mL	12	262.2	191.4	63.2	217	702	72.98	206.8
7	C_{max}, ng/mL	12	1679	657.0	991	1540	2840	39.14	1569
7	t_{max}, h	12	-	-	4.0	5.5	6.0	-	-
7	AUC_{24h}, ng.h/mL	12	18360	9555	7518	16580	38670	52.03	16330

Display PK04 from the study report shows the combined plasma-concentration-time curves for subjects in the TMC435 treatment group.

Supporting Data Displays: Combined Plasma Concentration-Time Curves of TMC435 (Display PK04 from the study report)

Treatment A: 150 mg TMC435 q.d. for 9 days



--- unreliable concentration at 4h, concentration excluded from descriptive statistics and PK analysis

Although the applicant acknowledged the findings of immediate photosensitivity in four subjects, they attached no significance to those findings. The applicant did not discuss the PK data for TMC435 in relation to the observations of immediate photosensitivity. They based their conclusions pertaining to immediate photosensitivity on the results of the retesting done with "physiological irradiances," and no subjects showed immediate photosensitivity on retesting.

The applicant concluded the following about study C125 included the following:

"The cutaneous photosensitizing potential of TMC435 as assessed by PI for 7 wavebands and a solar simulator covering the clinically relevant visible spectrum was similar to that observed with placebo, while ciprofloxacin showed the expected photosensitizing potential at the UVA wavebands of 335±30 nm and 365±30 nm when compared to placebo, which confirms study sensitivity. No abnormal immediate phototoxicity was detected in any of the study groups when testing at physiological irradiances using the monochromator solar simulator."

DDDP Discussion of Study C125

Immediate photosensitivity was exhibited by 33% of subjects in the TMC435 group and in no subjects in the ciprofloxacin or placebo groups. We consider these findings to be clinically significant and do not agree that they are nullified by the results from retesting or that any ultimate study conclusions should rely on the results from the retesting.

It is unclear why the investigators would discount the immediate phototoxicity responses observed with TMC435. The provided explanation was that immediate erythema may have represented an artifact of the testing method. However, the investigators do not explain why only subjects in the TMC435 group were susceptible to this "artifact." That is, the explanation that the immediate erythema was an artifact of the testing method would not explain why the reaction was observed only in the TMC435 group and only at wavelengths that correspond to absorption wavelengths of TMC435 in the UVA range.

Additionally, subjects who exhibited immediate phototoxicity during screening (i.e. prior to any study treatment) were considered to be screening failures and were not enrolled in the study. Therefore, subjects who were apparently predisposed to immediate erythema from the testing methods were excluded from the study. Thus, it is unclear how the applicant would not consider the reactions observed under study treatment to be significant, since the reactions were induced in subjects who had not exhibited the response, under the same UVL exposures, when they were not receiving TMC435 treatment.

We note also that the results of retesting do not reflect evaluation of a specified endpoint, since the study endpoint was "presence or absence of an immediate photosensitivity response" (not the outcomes from retesting of subjects with immediate photosensitivity). The exact meaning of "physiological irradiances" used in the retesting is unclear, and we are not aware that this category of UVL exposures has been defined. Phototoxicity studies, and other special safety studies of this sort, are intended to be provocative, and the testing methods that yielded the positive findings in this study appeared to be acceptable. The validity and meaningfulness of the retesting results are unclear, and the retesting methodology may represent a novel approach.

The applicant did not provide an explanation for designating delayed erythema as the reaction of primary significance. Immediate erythema seems to be considered equal to delayed erythema in representing a type of phototxicity response.[4,5,6] That is, it is not clear that delayed erythema is the more meaningful measure of phototoxicity. For example, amiodarone and chlorpromazine are reported to cause immediate phototoxicity.[7]

Subjects who had the highest TMC435 plasma levels exhibited immediate phototoxicity reactions. A similar correlation between plasma exposure and incidence of rash and pruritus has been observed (p. 118 of the Summary of Clinical Safety). TMC435 exposures (AUC) in subjects with hepatitis C are anticipated to be approximately 2-3 times higher than what they are in normal subjects (personal communication from review division on August 2, 2013). This provides additional support for the recommendation of communication of the risk of photosensitivity in the TMC435 label.

The results from study C125 add to the body of evidence that indicates that TMC435 is a photosensitizer.

3. **In your opinion, does the rash and/or phototoxicity findings from the clinical studies warrant inclusion in the Warnings/Precautions section of the label or is it sufficient to include mention of these findings in the Clinical Studies Experience section of the label?**

Response: The photosensitivity findings warrant inclusion in the Warnings and Precautions section of the label (also see response to Question #1). Photosensitivity had highly clinically significant consequences for some subjects in clinical trials for TMC435, including serious adverse reactions eventuating in hospitalization and treatment with systemic corticosteroids. There is reasonable evidence of a causal relationship between TMC435 and photosensitivity, including **a)** the frequency of reporting of adverse events associated with photosensitivity (e.g. "photosensitivity reaction" and "sunburn"), and **b)** the event rates in the TMC435 treatment group for events of this sort exceeded the rate in the placebo group. Therefore, there is a reasonable basis for a warning pertaining to photosensitivity.

Communicating the risk of photosensitivity in the label would have implications for patient management, including the recommending of measures which could mitigate the risk from this event, e.g. photoprotection. Although awareness of potential photosensitivity and photoprotective measures will not ensure against adverse reactions (as evidenced in the clinical trials), it is difficult to envisage the potential extent of adverse reactions that might be suffered by patients were the product to be introduced into the marketplace without discussion in the label of the risk of photosensitivity.

We also believe that a discussion of "rash" would be appropriate for the Warnings and Precautions section of the label, apart from the discussion of photosensitivity, including for the following reasons:

- During the placebo-controlled period (the first 12 weeks), the applicant reported the incidence of rash (any type) in the TMC435 group as exceeding the incidence in the placebo group: 23.2% vs 16.9%. This suggests a causal relationship between TMC435 and rash.
- A higher incidence of rash (any type) and pruritus correlated with increasing TMC435 plasma exposure (per p. 118 of the Summary of Clinical Safety). This suggests a causal relationship between TMC435 and rash.

- Rash was the most frequently-reported adverse event leading to discontinuation in the TMC435 group (5 subjects [0.6%]). Rash was not reported as an adverse event that to discontinuation of treatment for any subjects in the placebo group.
- The worst severity grade reported for rashes was Grade 3, and all were reported in the TMC435 group (5 subjects [0.6%]).
- There were reports of TMC435-treated subjects who experienced rash and concurrent mucosal lesions and constitutional symptoms, and a mucocutaneous syndrome such as erythema multiforme (EM) cannot be excluded based on the available information (further discussed in the response to Question #4). None of those subjects experienced serious adverse events. There is apparently one report of EM in the clinical trials database, Subject HPC3004-31-073.

The following table presents all events for which there were ≥ two reports in the TMC435 group of adverse events in the Skin and subcutaneous tissue disorders SOC (Source: ("Number (%) of Subjects with Adverse Events, First 12 Weeks and Entire Treatment Phase")-Primary Pooling:

SYSTEM ORGAN CLASS AND PREFERRED TERM	FIRST 12 WEEKS				ENTIRE TREATMENT PHASE			
	PBO		TMC435 150mg		PBO		TMC435 150mg	
	N	%	N	%	N	%	N	%
Any Adverse Event								
TOTAL	376	94.7	744	95.3	382	96.2	757	96.9
Skin and subcutaneous tissue disorders								
TOTAL	151	38.0	379	48.5	215	54.2	456	58.4
Pruritus	54	13.6	161	20.6	92	23.2	203	26.0
Rash	44	11.1	106	13.6	64	16.1	139	17.8
Dry skin	27	6.8	60	7.7	47	11.8	84	10.8
Alopecia	21	5.3	44	5.6	59	14.9	99	12.7
Erythema	11	2.8	24	3.1	15	3.8	29	3.7
Photosensitivity reaction	2	0.5	24	3.1	2	0.5	24	3.1
Hyperhidrosis	8	2.0	22	2.8	10	2.5	22	2.8
Eczema	8	2.0	18	2.3	16	4.0	25	3.2
Rash maculo-papular	3	0.8	14	1.8	3	0.8	18	2.3
Dermatitis	2	0.5	11	1.4	4	1.0	13	1.7
Rash macular	2	0.5	11	1.4	5	1.3	11	1.4
Pruritus generalized	4	1.0	9	1.2	7	1.8	9	1.2
Psoriasis	1	0.3	9	1.2	2	0.5	11	1.4
Night sweats	4	1.0	8	1.0	5	1.3	8	1.0
Rash papular	4	1.0	7	0.9	8	2.0	8	1.0
Skin exfoliation	1	0.3	5	0.6	1	0.3	6	0.8
Rash erythematous	2	0.5	4	0.5	4	1.0	7	0.9
Rash pruritic	1	0.3	4	0.5	1	0.3	7	0.9
Skin lesion			4	0.5	1	0.3	4	0.5
Urticaria	3	0.8	4	0.5	4	1.0	6	0.8
Rash generalized	1	0.3	3	0.4	1	0.3	4	0.5
Acne			2	0.3	1	0.3	3	0.4
Cold sweat			2	0.3			2	0.3
Dermatitis allergic	1	0.3	2	0.3	1	0.3	2	0.3
Dermatosis	2	0.5	2	0.3	2	0.5	2	0.3
Drug eruption			2	0.3	1	0.3	2	0.3

Heat rash	1	0.3	2	0.3	1	0.3	2	0.3
Neurodermatitis			2	0.3			2	0.3
Papule			2	0.3	1	0.3	2	0.3
Petechiae			2	0.3			2	0.3
Skin burning sensation			2	0.3			2	0.3
Vitiligo			2	0.3			2	0.3

Rash was captured under several different preferred terms, e.g. Rash maculo-papular, Rash erythematous, Rash generalized, etc. "Rash" is a non-specific term, and descriptors such as "maculo-papular" may do little to clarify the diagnosis in the absence of some clinical context. The interpretation of rash events may be further confounded because coding under this term may reflect events that might have been better coded under a different preferred term. For example, the cutaneous adverse event for subject C206-0426 was coded as "rash." However, photographs of the subject appear to reveal a single cluster of vesiculopustular lesions on an erythematous base (right thigh) and suggest a herpes simplex virus infection (all of the close-ups are out of focus). Subject C208-0243 (photosensitivity coded as rash) has been previously discussed in the response to Question #1. Nevertheless, as described above, evidence suggests that cutaneous adverse events were associated with TMC435 exposure more frequently than with placebo.

The differential in the frequency of reports of psoriasis between the TMC435 and placebo treatment groups (1.2% and 0.3%, respectively), raises a question of whether these events truly capture the condition of psoriasis or whether some of the events represent a rash (of some sort) that was coded as psoriasis.

Other possibly notable adverse events in the Skin and subcutaneous tissue disorders that were reported only in TMC435-treated subjects, but for which there were only single reports, included Exfoliative rash, Toxic skin eruption and Vasculitic rash.

Aside from photosensitivity, an association of TMC435 with a specific or particular cutaneous reaction pattern has not (yet?) been identified. Rash has also been reported with telaprevir, another inhibitor of the HCV NS3/4A protease, and the label describes that the severe rash associated with telaprevir may have a "prominent eczematous component." We noted eczematous features in some of the photographs provided for TMC435, e.g. Subject C3007-6189, but the available evidence is considered too limited to support any such description in labeling. For telaprevir, that sponsor convened a panel of experts (dermatologists and a dermatopathologist) to characterize the rash, particularly those suspicious for severe cutaneous adverse reactions. However, there was a different pattern to the occurrence and nature of cutaneous adverse events in the telaprevir development program relative to the TMC435 program.

There does not appear to be the signal from the TMC435 clinical trials database for development of severe cutaneous adverse reactions or severe rash, as was seen with telaprevir. However, we believe that the following should be considered in the interpretation of the significance of the rash observed with TMC435:

- Severe cutaneous adverse reactions have been reported with a related product (telaprevir).

- Some subjects treated with TMC435 developed a rash and were reported to have had mucosal lesions and constitutional symptoms as concurrent adverse events (further discussed in response to Question #4), and one case of erythema multiforme has apparently been reported in a clinical trial.
- Severe cutaneous adverse reactions are rare, and a signal may not be identified in the clinical development program, but only with broader use postmarketing.[8]
- Some severe cutaneous adverse reactions may start with a maculopapular (morbilliform) eruption.[8]

We recommend the following language for consideration in the Warning and Precautions section of the label:

Rash was reported in *tradename*-treated subjects at a greater rate than in the placebo group. Rash most frequently began during the first 4 weeks, but could occur at any time during *tradename* combination treatment. Rash events led to discontinuation of *tradename* alone in x% of subjects and discontinuation of *tradename* combination treatment in x% of subjects. Patients with mild to moderate rashes should be followed for progression of rash or development of mucosal lesions (e.g. oral lesions, conjunctivitits) or systemic symptoms (e.g. influenza-like symptoms). If rash progresses or becomes severe, *tradename* should be discontinued. Patients should be monitored until the rash has resolved.

4. **In your opinion, are any of the SAEs and/or discontinuations related to rash and/or phototoxicity in the TMC435 group consistent with severe cutaneous adverse events (e.g. DRESS, SJS, etc.)?**

Response: Two subjects in the TMC435 treatment group experienced serious adverse events that related to the skin, and the event for both subjects was reported by the preferred term "photosensitivity reaction." The subjects were hospitalized for the adverse event, and treatment, at least for one subject, included systemic corticosteroids. Neither of the two serious adverse events of photosensitivity reaction suggested a severe cutaneous adverse reaction, such as Stevens-Johnson syndrome (SJS)/Toxic Epidermal Necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome. The subject narratives do not describe or suggest clinical courses of critically-ill subjects.

Of the two subjects who experienced serious cutaneous adverse events, one subject had dosing interrupted for the event of photosensitivity reaction and ultimately completed study treatment. The other subject completed study treatment without interruption. Both cases are consistent with photosensitivity reactions. The two cases are discussed below:

- **C3007-6128:** A 35-year-old White male experienced a grade 1sunburn (erythema) 59 days after treatment start. He presented to the hospital with complaints of swelling of the face and pain 68 days after treatment start. He was hospitalized overnight and was discharged in good condition. Treatment included prednisone. He was reported to have a serious adverse event of photosensitivity reaction (Grade 2), which resolved approximately two weeks later. TMC435 was interrupted due to the event, but he ultimately completely the treatment.
- **C3007-6189:** A 44-year-old White male experienced a grade 1 sunburn (erythema) 5 days after start of study treatment and which resolved two days later without any treatment. Weeks later, he had sun exposure, was febrile and the following day (40 days after treatment start) developed blisters on his arms,

neck, head, ears, and nose. Two days later, he presented with "maculopapular and bullous eruptions at the photo-exposed zones on the back of the hands, the wings of the nose, ears, and vertex" and was hospitalized overnight with a Grade 3 serious adverse event (photosensitivity reaction). Treatment included antibiotics, petroleum jelly and silver sulfadiazine. No action was taken with the study medications. "Rapid scarring" of the lesions followed. Approximately one week later, "infiltrative" and bullous lesions recurred at same sites following "brief" sun exposure and despite "adequate protective clothing." He was again hospitalized. A skin biopsy "interpretation" was said to have "ruled out tardive cutaneous porphyria" (porphyria cutanea tarda) but was suggestive of "eczematous toxidermia." Immunofluorescence showed granular deposits of C3 in dermo-epidermal junction and in dermal vessels. [Note: The information for this subject was translated (b) (6) I could find no definition or translation of "toxidermia." From the context of the information provided by the applicant, "dermatitis" may be a reasonable assumption as a translation, e.g. the provided materials also discuss a "drug-induced allergic toxidermia."] He was evaluated for PCT with results that included: urine porphyrines test showed an increase of coproporphyrines, hexacarboxyporphyrines, and uroporphyrines. The subject's ferritin level was elevated. The photosensitivity was accompanied by "labial herpes" (IgG and IgM serology were positive); no other mucosal involvement was described. Ultimately, an allergist considered the eruption to be phototoxic rather than photoallergic, and blood and urine porphyrin studies were considered "negative." Measures of ANA and complement were ordered (results not found). Treatment included betamethasone (apparently as "Diprosone pomade") and hydroxyzine. He was discharged after two days. Eruption resolved. He completed all study treatment.

Comment: *This subject apparently had multiple (three) photosensitivity events. He had fever with one occurrence, and constitutional symptoms (e.g. nausea, tachycardia, chills, fever) may accompany severe sunburn reactions.*[1] *The herpes labialis eruption could have been triggered by the sun exposure.*[9] *Although his medical team apparently concluded that he did not have PCT, some of the provided test results appear to support that diagnosis, as below:*

- *recurrent bullous eruption in a photo-distribution that may have healed with scarring.*
- *urinary porphyrin profile that appears to be consistent with PCT: increased coproporphyrins, hexacarboxyporphyrins, and uroporphyrins.*[10,11,12]
- *elevated serum iron.*[13]
- *granular deposition of C3 on biopsy at the dermo-epidermal junction and in dermal vessels.*[13]

Thus, the evidence appears to support a diagnosis of PCT for this subject.

In the Phase 3 and 2b trials, it appears that 14 subjects in the TMC435 group permanently discontinued treatment due to skin-related adverse events. Of the 14, ten subjects discontinued TMC435 for "rash", and one subject each discontinued for the following (two subjects had two preferred terms listed): cutaneous vasculitis; dermatitis exfoliative and rash; drug eruption; rash erythematous and rash maculo-papular.

None of those discontinuations related to cutaneous adverse events in the TMC435 group appeared consistent with a severe cutaneous adverse reaction (e.g. SJS/TEN, DRESS). None of the subjects were considered to have experienced serious adverse events; none were hospitalized.

However, four subjects who discontinued TMC435 treatment appeared to experience a symptom constellation of rash and concurrent mucosal lesions and constitutional symptoms (and the mucosal lesions and constitutional symptoms were specifically listed by the applicant as "concurrent adverse events" in the subject narratives). In some of the cases, the constitutional

symptoms (e.g. influenza-like illness) preceded the cutaneous eruption, suggestive of a prodrome. Only one of the four subjects had photographs for review (discussed below), and none of the four subjects had biopsies. For these four subjects, a mucocutaneous syndrome such as erythema multiforme (EM) cannot be excluded, based on the available information.

The subject narratives describe the course of the adverse event(s). However, a listing of the adverse events and the dates of onset seemed to make the timing of the appearance of rash in relation to other adverse events more readily appreciated. That is what follows (as taken from the narratives from the study reports):

1. **C208-0416:** This 59-year-old White male developed rash 66 days after treatment start.
   22 Aug 2011: Pyrexia (post PegIFNα-2a injection), Chills (post injection), Arthralgia
   29 Aug 2011: Pruritus
   ?? Sep 2011 (date not provided): Ear discomfort (Bilateral pressure in ears)
   09 Sep 2011: Insomnia, Constipation, Fatigue, Mood altered (Irritable), Abdominal pain lower
   17 Oct 2011: Testicular pain
   20 Oct 2011: Depression
   27 Oct 2011: **Rash** (on abdomen, legs, arm back grade 2);
   04 Nov 2011: Aphthous stomatitis
   05 Dec 2011: Conjunctivitis**,** Alanine aminotransferase increased, Aspartate Aminotransferase, Increased, Dry skin
   21 Feb 2012: Ear congestion
   06 Oct 2012: Rash (Mild rash ankles)
   13 Oct 2012: Vision blurred

TMC435, RBV, and PegIFNα-2a were permanently discontinued due rash. The subject received the last dose of TMC435 on 02 November 2011, the last weekly dose PegIFNα-2a on 19 January 2012, and the last dose of RBV on 20 January 2012. The rash was treated with diphenhydramine hydrochloride, glaxal base, and prednisone and resolved on an unspecified date in April.

2. **C216-3022**: This 49-year-old White female developed a rash 51 days after treatment start.
   18 Mar 2011: Influenza-like illness, Fatigue, Headache
   01 May 2011: Mouth ulceration
   08 May 2011: **Rash**
   13 May 2011: Mouth ulceration (worsening), weight decreased, pruritus

TMC435 was discontinued due to rash with the last dose received on 13 May 2011. Treatment with PegIFNα-2a and RBV was discontinued due to mouth ulceration. The subject received the last dose of PegIFNα-2a on 23 May 2011, and the last dose of RBV on 24 May 2011. Concomitant medications reported for these adverse events: hydrocortisone, hydroxyzine hydrochloride, and pilocarpine hydrochloride. Rash was considered resolved on 17 June 2011 and the mouth ulceration was considered resolved on 19 June 2011.

3. **C216-3475**: This 40-year-old White male developed rash 31 days after treatment start.
   02 Aug 2011: Pyrexia

09 Aug 2011: Decreased appetite
10 Aug 2011: Asthenia
15 Aug 2011: Dizziness
24 Aug 2011: Conjunctivitis
02 Sep 2011: **Rash** maculo-papular (Grade 2)
12 Sep 2011: Aphthous stomatitis
22 Sep 2011: Rash erythematous (Grade 3; reported term: Rash and erythema in (*sic*) back of both hands)

Treatment with all three medications was discontinued due to rash adverse events. The subject received the last dose of PegIFNα-2a on 20 September 2011 and the last doses of TMC435 and RBV on 22 September 2011. Concomitant medications for these adverse events included aciclovir, cetirizine, fusidic acid, mometasone, and silicic acid. The maculopapular rash and erythematous rash were considered resolved on 30 September 2011.

Comment: *Of these four subjects, this is the only one who had photographs. The history with the photographs is consistent with erythema multiforme. Clinical features noted in the photographs included erosions on the mucosal aspect of lips with pseudomembranous deposits. Later in the course, there is hemmorhagic crusting of the lips. Hands in some frames are edematous, with patchy dusky erythema, papulovesicular lesions, and a targetoid configuration is suggested in some frames.*

4. **C206-0512:** This 65-year-old White male developed a rash on Day 7 of study treatment.
   24 Feb10: Influenza-like illness, Fatigue, Insomnia, Hypogeusia (Day 1 of study treatment)
   26 Feb 10: Keratoconjunctivitis sicca
   02 Mar 10: **Rash**, Oral herpes, Arthralgia
   16 Mar 10: Nasal dryness
   15 Apr 10: Decreased appetite
   15 Jun 10: Abdominal pain upper, Depression, Pruritus

All study treatments were permanently discontinued due to the events of hypogeusia, insomnia and rash, with the last dose of study medications on 14 July 2010. Concomitant medications included: Aciclovir, Betamethasone sodium phosphate drops, Coldargan drops, Diphenhydramine, Paracetamol, Valaciclovir.

No concomitant medication was administered for the rash. The subject was lost to follow-up.

Comment: *In the context of the timeline of events leading to rash, the influenza-like illness on Day 1 may have represented a prodrome for the oral herpes outbreak stated to have occurred on Day 7 (02 Mar 10) of treatment. If the "rash" was erythema multiforme, it could reflect the most common association for (recurrent) EM, i.e. the association with HSV.* [14,15] *However, the HSV outbreak typically precedes the rash in HSV-associated EM.*[9]

Considering the temporal relationship to the rash, it is possible that the oral lesions (e.g. "apthous stomatitis" in Subjects C208-0416 and C216-3475) represented a mucosal

manifestation of a syndrome which initially manifested in the skin, e.g. EM. With consideration of the rash, oral lesions and extracutaneous symptoms, EM is a unifying diagnostic consideration for these subjects. Of the four, the available information for subject C216-3475, which included photographs, is the most compelling for a diagnosis of EM.

If any of these cases are EM, then they would be of the major subtype, i.e. EM major (EMM), because of the mucosal involvement[15] (some authors state that two mucosal surfaces should be affected for EMM).[14] The EM minor subtype presents only with cutaneous lesions (or limited mucosal involvement).[14,15] Prodromal symptoms may precede the lesions by a week or longer. The classic presentation of the cutaneous eruption is of dusky, targetoid lesions that tend to have a symmetric, acral distribution.[9,14,15] However, lesion morphology may vary, as suggested by the name. EM is most often caused by the HSV, particularly recurrent EM.[14,15] EM may also be drug-induced, and sulfonamides have been reported as causative.[15] As with SJS/TEN, if EM is drug-induced, the offending agent must be immediately discontinued. The clinical course for EM is generally benign and resolves from one to four weeks without sequelae.[14,15] However, complications may be seen, e.g. conjunctival scarring, uveitis[14,15].

The mucosal lesions of EMM and SJS may be similar.[15] However, the pattern and nature of the cutaneous lesions may distinguish the two diseases.[14,15,16] In EMM lesions are initially acral; in SJS they initially involve the proximal limbs. In EMM target lesions are dusky, papules; in SJS, the initial lesions are dusky red to purpuric macules. Additionally, with SJS, patients are clearly seriously ill and experience rapid progression of bullae and other skin lesions, epidermal detachment, extreme pain relating to the skin and mucosa and severe extracutaneous symptoms. Biopsy may not be helpful in distinguishing between EM and SJS, although epidermal necrosis is much more prominent in SJS.[14]

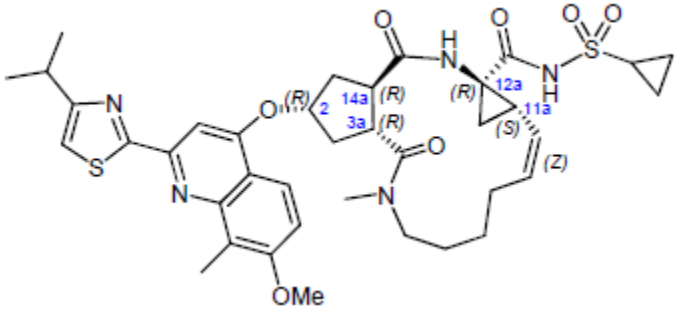
The narrative of a critically-ill subject does not describe the clinical course of any of the subjects who discontinued the Phase 3 and 2b trials due to a rash. None were considered to have experienced serious adverse events, and none were hospitalized. No information raised a suspicion of DRESS for any of the subjects who discontinued treatment due to rash.

5. **There are two sulfur atoms in the molecule- is there any relationship with this structure and sulfa allergy?**

6. **Is there anything about the molecular structure that would trigger an alert for potential photosensitivity?**

Response to Questions 5 and 6: The following is a combined response to Questions 5 and 6.

The chemical structure for TMC435 (from draft labeling) is presented below:



The product was developed under IND 75,391. The pre-IND communication to the sponsor (DARRTS date 12/13/2007) states:

"We note that TMC435530 contains a sulfonamide moiety. Presence of this moiety could potentially place patients with a known sulfa allergy at risk for an adverse event. Please consider excluding patients with a known sulfa allergy from your studies. Alternatively, you could attempt to evaluate whether the presence of the sulfonamide moiety increases risk."

Note: Per p. 19 of the Summary of Clinical Safety in the NDA, TMC435 was referred to as TMC435350 during early development. Other names are R494617 and JNJ-38733214-AAA.

Sulfa allergy describes a hypersensitivity to sulfonamide drugs (most often antimicrobials),[17] and photosensitivity has been reported with sulfonamides.[7,18,19,20] The action spectrum for sulfonamide photosensitivity is generally within the UV-B range[18,20,21], but may manifest in the UV-A range.[18,21,22]

UV-Visible spectroscopy for TMC435

The UV-Visible spectroscopy for TMC435 (then called R494617) drug substance was found on p. 15 of the CMC review of the initial submission to the IND 75,391 (reviewer Lin Qi). The UV spectrum for R494617 drug substance is shown in Figure 6 below. The absorption maxima are at 332, 288, and 238 nm.

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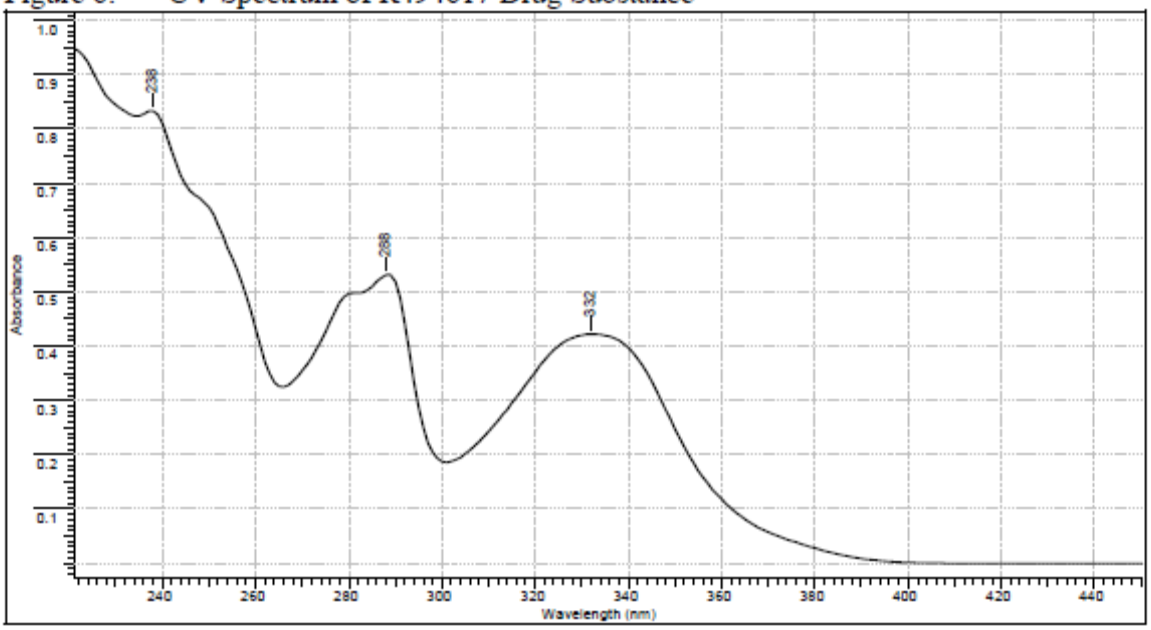
Figure 6: UV Spectrum of R494617 Drug Substance



The product absorbs in the UVB (290-320 nm) and UVA (320-400 nm) ranges. No subjects in the TMC435 group in the phototoxicity study (C125) showed photosensitivity reactions under test conditions.

Phototoxic drugs have a have a wide range of pharmacologic actions and molecular structures.[5] Adequately correlating chemical structure to photobiological action may generally be limited by the state of the science.[5,23] Additionally, the photosensitizer could be the parent drug, or an excipient, metabolite or degradation product.[24]

Discussion and Conclusions

TMC435 is a photosensitizer. Photosensitivity was clearly evidenced over the course of the clinical development program, having been observed from the first in-human study through the pivotal Phase 3 studies. The pattern of photosensitivity suggests phototoxcity, rather than photoallergy. Photoxicity classically manifests as an exaggerated sunburn, and this was the apparent presentation of affected subjects in the clinical trials with TMC435.

Phototoxicity potential was confirmed in the phototoxicity clinical study C125, and it correlated with plasma levels of TMC435. This correlation was also seen between severity of rash and systemic exposure.

Other information supported the potential for TMC435 to cause photosensitivity:

- TMC435 had phototoxic effects on BALB/c 3T3 fibroblasts exposed to UVA.
- TMC435 has absorption maxima at 332 and 288 nm.

Photoxicity reflects direct tissue injury from interaction of the photosenisitizer and UVL and presents on sun-exposed skin. Onset of the reaction may be within minutes of UVL exposure, with burning, stinging, erythema, and edema may appear within hours of irradiation. Vesiculobullous lesions may develop with severe reactions. Photoallergy is a type IV delayed hypersensitivity reaction and requires prior sensitization. It typically presents 24 to 48 hours following UVL exposure as an eczematous appearance, very similar to an allergic contact dermatitis. The reaction primarily affects sun-exposed skin, but may extend to covered areas.[25] However, some drugs may produce both types of photosensitivity,[20,25] e.g. griseofulvin, lomefoxacin, nalidixic acid**.** [25]

Phototoxicity may be considered dose-dependent on several levels. It may occur in anyone if there is sufficient tissue concentration of the offending agent, followed by exposure to the relevant wavelength of UVL at a sufficient concentration.[4,26] Individual processing of a drug, which may be genetically determined, may also influence susceptibility to photosensitivity.[7] There is a poorly-understood individual vulnerability to the degree of photosensitzation, from a given (standard) dose of medication, that is not a function of serum concentration.[27]

Photosensitivity may persist for months to years after the drug has been discontinued.[27,28]

The drug should be avoided if possible.[28,29] If not possible, then risk should be managed by patient counseling regarding UVL avoidance and protection.[28] UVL avoidance is critical.

Pertaining to antimicrobials, Vassileva et al. expressed that "not infrequently" the incidence of photosensitivity is below the level of detection in clinical development (Phase 2 and 3), and the signal becomes evident only with broader product use postmarket environment.[18] Therefore, we consider it significant that the photosensitivity signal for TMC435 was identified in the clinical development program.

Rash

From the information reviewed, no serious adverse events or discontinuations related to rash or photosensitivity appeared to suggest a severe cutaneous adverse reaction, such as Stevens-Johnson syndrome or Drug Reaction and Eosinophilia with Systemic Symptoms. However, severe cutaneous adverse reactions are rare and a signal may not be identified premarket.

Recommendations

The details of the recommendations are largely found in the body of this consult in the responses to the questions.

1. UVL avoidance and protection should be discussed and recommended in the label.
2. Photosensitivity and rash should be discussed in the Warnings and Precautions section of the label. We believe that these categories of adverse reactions and their risk mitigation strategies are sufficiently distinct to warrant separate discussion in the label.
3. The pattern, nature and severity of cutaneous adverse events should be closely monitored postmarketing.
4. The review division might consider consulting the Division of Pulmonary, Allergy, and Rheumatology Products on the question of sulfa allergy.

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APPENDIX 1: American Academy of Dermatology Recommendations for Prevention of Skin Cancer

To prevent skin cancer, the ultimate medical objective of photoprotection, the AAD recommends (http://www.aad.org/dermatology-a-to-z/health-and-beauty/general-skin-care/sun-protection/how-do-i-prevent-skin-cancer):

Sun exposure is the most preventable risk factor for all skin cancers, including melanoma.[1,2] You can have fun in the sun and decrease your risk of skin cancer. Here's how you can prevent skin cancer:

- **Seek shade when appropriate.** Remember that the sun's rays are strongest between 10 a.m. and 2 p.m. If your shadow appears to be shorter than you are, seek shade.
- **Wear protective clothing**, such as a long-sleeved shirt, pants, a wide-brimmed hat, and sunglasses, where possible.
- **Generously apply a broad-spectrum, water-resistant sunscreen** with a Sun Protection Factor (SPF) of 30 or more to all exposed skin. "Broad-spectrum" provides protection from both ultraviolet A (UVA) and ultraviolet B (UVB) rays. Reapply approximately every two hours, even on cloudy days, and after swimming or sweating.
- **Use extra caution near water, snow, and sand** because they reflect and intensify the damaging rays of the sun, which can increase your chances of sunburn.
- **Avoid tanning beds.** Ultraviolet light from the sun and tanning beds can cause skin cancer and wrinkling. If you want to look tan, consider using a self-tanning product or spray, but continue to use sunscreen with it.

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Appendix 2: Additional details of phototesting methodology

The baseline testing occurred on 3 consecutive days during the Screening phase:

- **Baseline Evaluation 1:** Subjects were tested with a series of irradiation doses at each of the 7 preselected wavebands (UVB [295±5 nm, 300±5 nm, and 305±5 nm], UVA [335±30 nm and 365±30 nm], visible light [400±30 nm and 430±30 nm]), and solar simulator. Skin photoresponses at 0, 5, 10, 15, and 30 minutes post-irradiation were assessed to detect the immediate photosensitivity response.

- **Baseline Evaluation 2**: Subjects were examined for skin photoresponses at 24 hours after the irradiations administered on Baseline Evaluation 1 to detect delayed skin erythema. Based on this assessment, the approximate baseline MED for each waveband was determined. Subjects were then exposed to a second set of irradiations at each waveband and solar simulator except 430±30 nm. In this second set, the irradiation doses were given as 20% incremental dose steps between the no-response dose and the approximate baseline MED.
- **Baseline Evaluation 3**: At 48 hours after the first set of irradiations (given on Baseline Evaluation 1; 24-hours after the second set of irradiations on Baseline Evaluation 2), subjects were examined for delayed erythema at the site(s) where irradiations were administered. Based on the skin reaction assessed at Baseline Evaluation 3 (24h MED values), the precise baseline MED for each waveband and solar simulator was determined. Subjects who received trial medication had to have had normal baseline 24h MED values.

During the Treatment phase, subjects underwent postdose photosensitivity testing on Days 8-10:

- **Day 8**: Subjects underwent a series of irradiation doses at each of the 7 wavebands and solar simulator approximately 6 hours after the morning dose of study medication. Skin photoresponses at 0, 5, 10, 15, and 30 minutes post-irradiation will be assessed to detect the immediate photosensitivity response. If an immediate photosensitivity response was observed, additional evaluations were to occur at 60 and 120 minutes post-irradiation with a second irradiation dose at a lower intensity to be given to a different patch of skin. Immediate photosensitivity responses were followed until resolution.
- **Day 9**: Subjects were examined for skin reactions from Day 8 irradiations, and based on this assessment, the approximate postdose MED for delayed erythema at each waveband was determined. Subjects underwent a second set of irradiations approximately 6 hours post dosing. In this second set, the irradiation doses were given as 20% incremental dose steps from the no-response dose to determine the approximate postdose MED. Assessments for immediate photosensitivity response were done at same time points as at Day 8.
- **Day 10**: At 48 hours after the first set of irradiations given on Day 8 (at 24 hours post Day 9 irradiations), subjects were examined for skin reactions at the irradiated site(s). Based on the skin reaction assessed at 24 hours after the second set of irradiations, the precise postdose MED for delayed erythema at each waveband and solar simulator was determined. If a subject continues to display an immediate photosensitivity response initially observed on Days 8 and 9, this subject will be examined for resolution of the immediate photosensitivity response.

Re-Testing in Case of an Immediate Photosensitivity Response

The rate of delivery of light energy (irradiance) was higher under the phototoxicity test conditions compared to physiological sunlight conditions. This allowed for testing to be accomplished within a compressed timeframe. The applicant thus believed that immediate photosensitivity responses (e.g., transient edema with or without flare) observed under test conditions could represent an artefact of the testing methods. Therefore, subjects who experienced an immediate photosensitivity response at a given waveband underwent additional phototoxicity testing using an irradiation dose said to have been close to the natural sunlight exposure. The applicant believed that this allowed for a determination of the clinical relevance of the initial immediate photosensitivity response.

On Days 8 and 9, if a subject experienced immediate photosensitivity response (at any of the wavelengths tested), the minimum oedematous dose (MOD) was to have been determined by means of additional phototesting. Once established, this dose was repeated using 1/2 of the standard irradiance level with a longer duration of light exposure to insure the same MOD at a different skin location. Additional procedures for MOD testing are discussed in Section 9.3.4 of the protocol.

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/s/

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CLINICAL REVIEW

Application Type	**NDA**
Application Number(s)	**205123**
Priority or Standard	**Priority**
Submit Date(s)	**28 March 2013**
Received Date(s)	**28 March 2013**
PDUFA Goal Date	**28 November 2013**
Division / Office	**Division of Anti-Viral Products/ Office of Antimicrobial Products**
Reviewer Name(s)	**Adam Sherwat**
Review Completion Date	**27 August 2013**
Established Name	**Simeprevir (TMC435)**
(Proposed) Trade Name	**Sovriad**
Therapeutic Class	**Protease Inhibitor**
Applicant	**Janssen Research and Development, LLC**
Formulation(s)	**Capsules**
Dosing Regimen	**150 mg taken once daily, oral route**
Indication(s)	**Treatment of Hepatitis C**
Intended Population(s)	**Adult patients (18 years and older) with genotype1 chronic hepatitis C virus infection**

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of TMC435 (simeprevir) for use in adults with chronic genotype 1 (GT1) hepatitis C virus (HCV) infection. This recommendation is based on data contained in the NDA submission 205123. In the three pivotal Phase 3 trials, C208, C216, and HPC3007, TMC435 [in combination with pegylated interferon and ribavirin (PR)] was demonstrated to be superior to placebo (in combination with PR) in achieving a sustained virologic response in both HCV treatment naïve subjects and subjects who relapsed after prior pegylated interferon-based therapy. The demonstrated safety profile of TMC435 was generally acceptable and no deficiencies preclude approval.

In the subset of subjects in the pivotal Phase 3 studies with the Q80K polymorphism at baseline, no statistically significant difference in the rate of sustained virologic response at Week 12 (SVR12) was present when comparing the TMC435 group to the control group. Given the high frequency of the Q80K polymorphism in the U.S. population and concerns regarding the generation of cross-resistance to the approved HCV protease inhibitors in TMC435 treatment failures, this Reviewer recommends screening all patients for the Q80K polymorphism prior to initiation of TMC435 with the object of excluding patients from treatment if the polymorphism is present.

Based on a review of the efficacy data from Study C206 (which included subjects categorized as prior partial responders and prior null responders to previous pegylated interferon-based therapy), this reviewer recommends that the indication for TMC435 be extended to prior partial and null responders. This recommendation assumes the acceptance of screening for the Q80K polymorphism as described above. Based on the paucity of data in prior partial and null responders with the baseline Q80K polymorphism, this Reviewer cannot recommend extending the indication to these populations in the absence of Q80K screening as recommended.

1.2 Risk Benefit Assessment

Benefits

The proposed TMC435 treatment regimen will consist of one capsule of TMC435 taken once daily in conjunction with PR. This simplified treatment regimen has the potential to improve patient adherence and to decrease medication administration errors.

In the pivotal Phase 3 trials, TMC435 administered in combination with PR was demonstrated to be superior to placebo (in combination with PR) in achieving SVR12 in

both HCV treatment-naïve subjects and subjects who experienced virologic relapse after treatment with an interferon-based regimen. This statistically significant improvement in SVR12 was demonstrated in a number of relevant subgroups (e.g. subjects stratified by IL28B genotype, by Metavir score, and by HCV viral load) but was not demonstrated in subjects with the Q80K baseline polymorphism (please refer to the "Risks" section below for additional details).

The overall safety profile of the TMC435 treatment regimen is considered generally acceptable in the context of the currently FDA approved HCV protease inhibitors. In particular, the hematologic safety profile is substantially better than that of the currently approved HCV protease inhibitors. Please refer to the "Risks" section below for a discussion of additional safety issues with respect toTMC435.

Risks

The Q80K polymorphism is a common polymorphism found in GT1a patients in the U.S. population. It was detected in 48% of the GT1a subjects in the U.S with sequencing data from pooled studies C205, C206, C208, C216, and HPC3007. In subjects in the pivotal Phase 3 studies with the Q80K polymorphism at baseline, no statistically significant difference in SVR12 rates was present when comparing the TMC435 group to the control group.

In the Sponsor's pooled virologic analysis of studies C205, C206, C208, C216, and HPC3007, emerging mutations were detected in 91% of subjects with treatment failure and sequence information available. In HCV genotype 1a infected subjects the mutation emerging most frequently was R155K alone or in combination with mutations 80, 122 and/or 168. In HCV genotype 1b infected subjects the most frequently emerging mutation was D168V. The R155 and D168V mutations confer resistance to TMC435 and cross-resistance to the currently approved HCV protease inhibitors (telaprevir and boceprevir). Although the long-term ramifications of the development of HCV protease resistance remain unclear, these mutations would significantly impact short- and mid-term HCV protease treatment options.

The major safety findings related to TMC435 are subsumed under the general categories of skin and soft tissue disorders (specifically pruritis, rash, and photosensitivity), hepatobiliary disorders (specifically hyperbilirubinemia), and cardiopulmonary disorders (specifically dyspnea).

There was a higher incidence of skin and subcutaneous tissue disorders by MedDRA Systems Organ Class (SOC) in the TMC435 group (49%) compared to the control group (38%) during the first 12 weeks of treatment. A total of 8 subjects (1%) in the TMC435 group and no subjects in the Control group experienced Grade 3 AEs during the first 12 weeks under the SOC category of 'Skin and Subcutaneous Tissue Disorders.' A total of 7 subjects (1%) discontinued TMC435 during the first 12 weeks of

treatment due to an AE under the SOC category of 'Skin and Subcutaneous Tissue Disorders' compared to 1 subject (<1%) in the Control Group. Safety analysis led to the identification of three major categories of interest: pruritis, photosensitivity, and rash.

Pruritis occurred in 22% of subjects in the TMC435 group and 15% of subjects in the control group during the first 12 weeks of treatment. However, the vast majority of pruritis AEs were of mild or moderate severity, rarely led to discontinuation of TMC435, and were not the cause of any SAEs over the first 12 weeks of treatment.

Photosensitivity was reported in 5% of the TMC435 group compared to 1% of the Control group. No discontinuations of TMC435 due to photosensitivity were reported, but two photosensitivity related SAEs (both requiring hospitalization and one requiring systemic steroids) occurred in the TMC435 group during the first 12 weeks of treatment while no SAEs occurred in the Control group.

Rash (excluding photosensitivity events) occurred in 25% of subjects in the TMC435 group and 19% of subjects in the Control group during the first 12 weeks of treatment. The majority of rash events occurred during the first 4 weeks of treatment with TMC435. Grade 3 rash AEs occurred in 1% of subjects in the TMC435 group and no subjects in the Control group. Of the seven AEs under the SOC category of 'Skin and Subcutaneous Tissue Disorders' which led to discontinuation of TMC435, six were in the category of rash.

A greater frequency of AEs associated with increased bilirubin (including grade 3 and 4 AEs) occurred in the TMC435 group compared to the Control group. However, little correlation was noted between the development of hyperbilirubinemia and clinical events necessitating discontinuation of study drug or serious adverse events related to study drug use. Consistent with the AE profile, a marked increase in frequency of graded bilirubin elevations in the TMC435 group (49%) compared to the Control group (26%) was noted. This difference was primarily driven by grade 1 and 2 laboratory abnormalities. Elevations in bilirubin occurred early after treatment initiation, peaking by Week 2. By four weeks following completion of TMC435 treatment (i.e. Week 16), levels were shown to return to near baseline values. No association between the bilirubin elevations anticipated with TMC435 use and clinically relevant hepatototoxicty was appreciated. This Reviewer's safety analyses were generally supportive of the Sponsor's view that the increased bilirubin associated with TMC435 use is primarily due to the inhibition of hepatic transporters.

The most notable finding with respect to the cardiopulmonary assessment was an increased frequency of dyspnea in the TMC435 group compared to the Control group. The majority of these events occurred in the first 4 weeks of treatment with TMC435. All of these AEs were of mild or moderate severity. There were no grade 3 or 4 AEs, SAEs, or discontinuations due to dyspnea during the first 12 weeks of treatment in the TMC435 group. The vast majority of dyspnea cases resolved within the follow-up

period. An analysis to ascertain whether the reported dyspnea events were associated with the presence of anemia was performed and was unrevealing. The reason for the finding of increased rates of dyspnea in the TMC435 group remains unclear.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no recommendations for Postmarket Risk Evaluation and Mitigation Strategies related to this NDA submission.

1.4 Recommendations for Postmarket Requirements and Commitments

This reviewer would recommend that Study HPC3001 (*A Phase III, randomized, double-blind trial to evaluate the efficacy, safety and tolerability of TMC435 vs. telaprevir, both in combination with PegIFNα-2a and ribavirin, in chronic hepatitis C genotype-1 infected subjects who were null or partial responders to prior PegIFNα and ribavirin therapy*) be categorized as a postmarket commitment. This would allow for the confirmation of efficacy of TMC435 in conjunction with PR in the partial and null responder patient populations.

With respect to the Pediatric Research Equity Act requirements, the Sponsor has requested a partial waiver of pediatric studies for pediatric subjects less than 3 years of age and a deferral for studies in subjects ≥ 3 to < 18 years of age pending availability of an interferon-free direct acting antiviral treatment regimen. Please refer to Section 7.6.3 for details.

2 Introduction and Regulatory Background

2.1 Product Information

Generic Name: Simeprevir

Trade Name: Sovriad (proposed)

Chemical Class: New molecular entities

Pharmacological Class: HCV NS3 protease inhibitor

Proposed Indication: TMC435 is indicated for the 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-naïve or who have failed previous interferon and RBV therapy.

Dosage: TMC435 will be administered at 150 mg once daily (q.d.) for a duration of 12 weeks.

Dosage Form: Oral capsule

Age Group: Adults

TMC435 is a specific inhibitor of the hepatitis C virus (HCV) NS3/4A serine protease. HCV protease inhibitors block the NS3/4A protease-dependent cleavage of the HCV polyprotein, thereby inhibiting viral replication in infected host cells.

2.2 Tables of Currently Available Treatments for Proposed Indications

The current standard of care treatment for chronic hepatitis C GT1 is combination therapy with peginterferon alfa-2a or alfa-2b plus ribavirin plus either boceprevir or telaprevir. The currently approved drugs for the treatment of HCV infection are listed in Table 1.

Table 1: Currently Approved Drugs for the Treatment of Chronic Hepatitis C

Drug Class	Generic Name	Trade Name
Pegylated interferons	Peginterferon alfa-2a	Pegasys®
	Peginterferon alfa-2b	PegIntron®
Interferons	Interferon alfa-2a	Roferon-A®*
	Interferon alfa-2b	Intron-A®
Consensus Interferon	Interferon alfacon-1	Infergen®
Nucleoside Analogue	Ribavirin	Rebetol®, Copegus®
Protease Inhibitors	Boceprevir	Victrelis®
	Telaprevir	Incivek™

* Voluntarily withdrawn from U.S. market 10/1/2007; not due to safety or efficacy concerns

2.3 Availability of Proposed Active Ingredient in the United States

Simeprevir is not currently available in the Untied States.

2.4 Important Safety Issues With Consideration to Related Drugs

Initially approved in the US in 2011, boceprevir (Victrelis®) and telaprevir (Incivek™) are the only HCV protease inhibitors currently available for use. The following is a summary

of the known safety issues related to these drugs drawn from the licensing trials and from postmarket experience:

Boceprevir:

In clinical trials, the most commonly reported adverse reactions (more than 35% of subjects regardless of investigator's causality assessment) in adult subjects were fatigue, anemia, nausea, headache, and dysgeusia when boceprevir was used in combination with PegIntron and Rebetol.

Notable AEs and Laboratory Abnormalities from Clinical Trials Experience:

Anemia: In clinical trials with Victrelis, the proportion of subjects who experienced hemoglobin values less than 10 g per dL and less than 8.5 g per dL was higher in subjects treated with the combination of Victrelis with PegIntron®/Rebetol® than in those treated with PegIntron/Rebetol alone. With the interventions used for anemia management in the clinical trials, the average additional decrease of hemoglobin was approximately 1 g per dL. Certain adverse reactions consistent with symptoms of anemia, such as dyspnea, exertional dyspnea, dizziness and syncope were reported more frequently in subjects who received the combination of Victrelis with PegIntron/ Rebetol than in those treated with PegIntron/Rebetol alone. In clinical trials with Victrelis, dose modifications (generally of PegIntron/Rebetol) due to anemia occurred twice as often in subjects treated with the combination of Victrelis with PegIntron/ Rebetol (26%) compared to PegIntron/Rebetol (13%). The proportion of subjects who discontinued study drug due to anemia was 1% in subjects treated with the combination of Victrelis with PegIntron/Rebetol and 1% in subjects who received PegIntron/Rebetol. The proportion of subjects who received an erythropoiesis stimulating agent was 43% in the Victrelis containing arms compared to 24% in the PegIntron/Rebetol arms. The proportion of subjects who received a transfusion for the management of anemia was 3% of subjects in the Victrelis -containing arms compared to less than 1% in subjects who received PegIntron/Rebetol alone.

Neutropenia: In Phase 2 and 3 clinical trials, 7% of subjects receiving the combination of Victrelis with PegIntron/Rebetol had neutrophil counts of less than 0.5×10^9 per L compared to 4% of subjects receiving PegIntron/Rebetol alone. Three subjects experienced severe or life-threatening infections associated with neutropenia, and two subjects experienced life-threatening neutropenia while receiving the combination of Victrelis with PegIntron/Rebetol.

Thrombocytopenia: Three percent of subjects receiving the combination of Victrelis with PegIntron/Rebetol had platelet counts of less than 50×10^9 per L compared to 1% of subjects receiving PegIntron/Rebetol alone.

Serious acute hypersensitivity reactions (e.g., urticaria, angioedema) have been observed during combination therapy with Victrelis, peginterferon alfa and ribavirin.

Dysgeusia (alteration of taste) was an adverse event reported at an increased frequency in subjects receiving Victrelis in combination with peginterferon alfa and ribavirin compared with subjects receiving peginterferon alfa and ribavirin alone.

Adverse events such as dry mouth, nausea, vomiting and diarrhea were also reported at an increased frequency in subjects receiving Victrelis in combination with peginterferon alfa and ribavirin.

The following ADRs were identified during post-approval use: mouth ulceration, stomatitis, angioedema, urticaria, drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, exfoliative rash, exfoliative dermatitis, Stevens-Johnson syndrome, toxic skin eruption, and toxicoderma.

Telaprevir:

The most common adverse drug reactions to Incivek (incidence at least 5% higher with Incivek than in controls) were rash, pruritus, anemia, nausea, hemorrhoids, diarrhea, anorectal discomfort, dysgeusia, fatigue, vomiting, and anal pruritus. The most frequent adverse drug reactions leading to discontinuation of Incivek were rash, anemia, fatigue, pruritus, nausea, and vomiting.

Notable AEs and Laboratory Abnormalities from Clinical Trials Experience:

Serious Skin Reactions/Rash: In clinical trials, serious skin reactions, including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Stevens Johnson Syndrome (SJS) were reported in less than 1% of subjects who received Incivek combination treatment compared to none who received peginterferon alfa and ribavirin alone. These serious skin reactions required hospitalization, and all subjects recovered. The presenting signs of DRESS may include rash, fever, facial edema, and evidence of internal organ involvement (e.g., hepatitis, nephritis). Eosinophilia may or may not be present. The presenting signs of SJS may include fever, target lesions, and mucosal erosions or ulcerations (e.g., conjunctivae, lips).

Rash events (all grades) developed in 56% of subjects who received Incivek combination treatment and in 34% of subjects who received peginterferon alfa and ribavirin. Rash most frequently began during the first 4 weeks, but could occur at any time during Incivek combination treatment. Rash events led to discontinuation of Incivek alone in 6% of subjects and discontinuation of Incivek combination treatment in 1% of subjects. Severe rash (e.g., a generalized rash or rash with vesicles or bullae or ulcerations other than SJS) was reported in 4% of subjects who received Incivek

combination treatment compared to less than 1% who received peginterferon alfa and ribavirin alone. The severe rash may have a prominent eczematous component.

Anemia: Anemia has been reported with peginterferon alfa and ribavirin therapy. The addition of Incivek to peginterferon alfa and ribavirin is associated with an additional decrease in hemoglobin concentrations. A decrease in hemoglobin levels occurred during the first 4 weeks of treatment, with lowest values reached at the end of Incivek dosing. Hemoglobin values gradually returned to levels observed with peginterferon alfa and ribavirin after Incivek dosing was completed. Hemoglobin values less than or equal to 10 g per dL were observed in 36% of subjects who received Incivek combination treatment compared to 17% of subjects who received peginterferon alfa and ribavirin. In clinical trials, the median time to onset of hemoglobin less than or equal to 10 g per dL was faster among subjects treated with Incivek combination treatment compared to those who received peginterferon alfa and ribavirin: 56 days (range 8-365 days) versus 63 days (range 13-341 days), respectively. Hemoglobin values less than 8.5 g per dL were observed in 14% of subjects who received Incivek combination treatment compared to 5% of subjects receiving peginterferon alfa and ribavirin.

In subjects receiving Incivek combination treatment, 32% underwent a ribavirin dose modification (reduction, interruption or discontinuation) due to anemia, 6% received a blood transfusion, 4% discontinued Incivek, and 1% discontinued Incivek combination treatment. In subjects treated with peginterferon alfa and ribavirin alone, 12% underwent ribavirin dose modification due to anemia, 1% received a blood transfusion, and fewer than 1% discontinued treatment. Anemia requiring ribavirin dose reduction, blood transfusion, and/or erythropoiesis stimulating agent (ESA) has been reported to occur as soon as 10 days following initiation of Incivek combination treatment.

Anorectal Signs and Symptoms: In the controlled clinical trials, 29% of subjects treated with Incivek combination treatment experienced anorectal adverse events, compared to 7% of those treated with peginterferon alfa and ribavirin alone. The majority of these events (e.g., hemorrhoids, anorectal discomfort, anal pruritus, and rectal burning) were mild to moderate in severity; less than 1% led to treatment discontinuation and all resolved during or after completion of Incivek dosing.

Lymphopenia: More subjects treated with Incivek had decreases in lymphocyte counts to 499/mm3 or less (15% compared to 5%).

Thrombocytopenia: Treatment with peginterferon alfa is associated with decreases in mean platelet counts. More patients treated with Incivek combination treatment had decreases in mean platelet values of all grades: 47% compared to 36% treated with peginterferon alfa and ribavirin alone. Three percent of Incivek combination treatment subjects had decreases to 49,999/mm3 or less compared to 1% of those treated with peginterferon alfa and ribavirin-treated alone.

Elevated Bilirubin: Forty one percent of subjects treated with Incivek compared to 28% of peginterferon alfa and ribavirin-treated subjects had all grade elevations in bilirubin levels; 4% and 2% of subjects, respectively, had greater than or equal to 2.6 x ULN elevations. Bilirubin levels increased most steeply during the first 1 to 2 weeks of Incivek dosing, stabilized and between Weeks 12 and 16 were at baseline levels.

Elevated Uric Acid: During the Incivek combination treatment period, 73% of subjects had elevated uric acid levels compared to 29% for those treated with peginterferon alfa and ribavirin alone. Shifts to greater than or equal to 12.1 mg per dL from baseline in uric acid levels were also more frequent among subjects treated with Incivek (7%) compared to peginterferon alfa and ribavirin (1%). Less than 1% of subjects had clinical events of gout/gouty arthritis; none were serious and none resulted in treatment discontinuation.

The following ADRs were identified during post-approval use: Toxic Epidermal Necrolysis (TEN) and Erythema Multiforme (EM).

The following information was conveyed post-approval as a boxed warning: Fatal and non-fatal serious skin reactions, including Stevens Johnson Syndrome (SJS), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and Toxic Epidermal Necrolysis (TEN), have been reported in patients treated with Incivek combination treatment. Fatal cases have been reported in patients with progressive rash and systemic symptoms who continued to receive Incivek combination treatment after a serious skin reaction was identified.

Pegylated Interferon and Ribavirin:

The Sponsor's proposed indication for simeprevir use is in combination with pegylated interferon and ribavirin. Therefore, the safety profile of these drugs is discussed briefly in this section.

Almost all patients treated with pegylated interferons and ribavirin experience one or more adverse events during the course of therapy. The most commonly reported adverse events are influenza-like side effects such as fatigue, headache, myalgia, fever and rigors. Other common adverse events include anorexia, nausea, vomiting, diarrhea, arthralgias, injection site reactions, alopecia, and pruritus. Neuropsychiatric side effects include depression, anxiety, insomnia, emotional lability, mood disorders, frank psychosis, suicidal ideation, completed suicide, and homicide. The currently approved alpha-interferon product labels carry Warnings and Precautions regarding potential toxicities in a substantial number of organ systems as shown in Table 2. All the approved interferon products carry a Pregnancy Category rating of C.

Table 2: Class Effects of Alpha-Interferons in Combination with Ribavirin

Adverse Events (Warnings and Precautions)	
Neuropsychiatric	Suicide, suicidal/homicidal ideation, depression, relapse of drug addiction, drug overdose
Infections	Serious and severe infections (bacterial, viral, or fungal)
Bone marrow toxicity	Neutropenia, anemia, thrombocytopenia
Cardiovascular disorders	Hypotension, hypertension, supraventricular arrhythmias, chest pain, myocardial infarction
Cerebrovascular disorders	Ischemic and hemorrhagic cerebrovascular events
Hepatic failure and hepatitis exacerbations	Risk of hepatic decompensation in patients with cirrhosis
Hypersensitivity	Severe acute reactions, serious skin reactions (Stevens Johnson Syndrome, exfoliative dermatitis)
Endocrine disorders	Hypo- or hyperthyroidism, hypo- or hyperglycemia, diabetes mellitus
Autoimmune disorders	Myositis, hepatitis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, psoriasis, rheumatoid arthritis, systemic lupus erythematosis, interstitial nephritis, thyroiditis
Pulmonary disorders	Dyspnea,pulmonary infiltrates, interstitial pneumonitis, bronchiolitis obliterans, pneumonia, pulmonary hypertension, sarcoidosis
Colitis	Ulcerative colitis, hemorrhagic/ischemic colitis
Ophthalmologic disorders	Macular edema, retinal artery/vein thrombosis, retinal hemorrhages and cotton wool spots, optic neuritis, papilledema, serous retinal detachment
Pancreatitis	Fatal and nonfatal pancreatitis

Source: US Package Inserts: Pegasys® and PegIntron®

The most common and concerning adverse events related to ribavirin are hemolytic anemia and rash. Ribavirin is genotoxic and teratogenic and is classified as Pregnancy Category X.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The initial Investigational New Drug (IND) Application for TMC435 was submitted on 30 April 2008.

An End-of-Phase 1 meeting was conducted with the Division of Antiviral Products (DAVP) on 13 January 2009 to seek input on the proposed Phase 2b development program for TMC435 in HCV GT1 infected subjects. A Phase 2b study in treatment-naïve HCV GT1 infected subjects (C205) and a Phase 2b study in treatment-experienced HCV GT1 infected subjects (C206) were subsequently initiated.

An End-of-Phase 2 (EOP2) meeting was conducted with the Division on 18 October 2010 to seek input on the proposed Phase III development program for TMC435 in

treatment-naïve HCV GT1 infected subjects and subjects with viral relapse following previous (Peg)IFN-based therapy. DAVP provided input related to the design of the proposed Phase 3 pivotal studies, the adequacy of the nonclinical, virology, clinical pharmacology and Phase 1/2a/2b packages to support the proposed Phase 3 program, and the adequacy of the proposed Phase 3 program to support a NDA for approval. Subsequent to this meeting, two Phase 3 studies in treatment-naïve HCV GT1 infected subjects (C208 and C216) and a Phase 3 study in HCV GT1 infected subjects with viral relapse following previous (Peg)IFN based therapy (HPC3007) were initiated.

A second EOP2 meeting was conducted with the Division on 15 September 2011 to seek input on the proposed Phase 3 study HPC3001 for TMC435 in HCV GT1-infected subjects who are partial or null-responders to previous PegIFN/RBV therapy. This Phase 3 study was subsequently initiated January 2012 and is currently ongoing.

A Pre-NDA meeting was conducted with the Division on 30 January 2013. The Sponsor provided, as part of the meeting package, preliminary safety and efficacy data from the Phase 3 Studies C208, C216, and HPC3007. The impact of the Q80K mutation on SVR12 rates in these studies in patients infected with HCV genotype 1a was discussed. The Sponsor proposed to mitigate the risk to HCV 1a Q80K-infected subjects (b) (4) (b) (4) (b) (4). DAVP also provided input on the Sponsor's proposal to seek an indication for the null and partial responder population based on data from their Phase 2b study C206 and their viral kinetic model. The Division also provided clarification on issues related to data generated from the HIV/HCV co-infection study (C212) and studies assessing HCV genotype 4 infection (C202 and HPC3011). Issues related to data submission, labeling, the Sponsor's Pediatric Development Plan, and the Safety Update Report were also discussed.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Site audits by Division of Scientific Investigations (DSI) were conducted for this NDA. Two domestic sites and two international sites (both located in Poland) were selected for inspection. The data from three of the four sites were deemed acceptable in support of this NDA application. The inspection of the fourth site is currently ongoing. Please refer to Antoine El-Hage's DSI review for additional details.

3.2 Compliance with Good Clinical Practices

The Applicant certified that their clinical trials were conducted in accordance with ICH Good Clinical Practice guidelines. The trial protocols and amendments were reviewed and approved by Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs). Written informed consent was obtained from all subjects prior to any trial-related procedures. Inspections of selected clinical sites by DSI are currently ongoing (refer to section 3.1 for additional detail). With respect to the pivotal phase 3 studies, major protocol deviations were observed in 3.6% of subjects in Study C208, 6.4% of subjects in Study C216, and 5.1% of subjects in Study HPC3007. There was no substantive difference in the rate of major protocol deviations between the treatment and control arms for these studies.

3.3 Financial Disclosures

The Applicant submitted financial data regarding significant payments and equity in accordance with 21 CFR Part 54 for all investigators in the Phase 2b studies C205 and C206 and in the Pivotal Phase 3 studies C208, C216, and HPC3007. The Applicant provided certification (Form 3454) which indicated that the vast majority of investigators (>90%) who participated in these studies had no financial arrangements with the Applicant. In addition, the Applicant provided the signed financial disclosure form (Form 3455) detailing all investigators reporting "significant payments of other sorts" in excess of $25,000. These payments primarily consisted of honorarium, consulting fees and research grants. A total of three investigators in the two Phase 2b studies, and a total of eight investigators in the three Phase 3 studies participated in financial arrangements that required disclosure. Based on the low proportion of investigators with a financial interest and the double-blind, randomized, placebo-controlled design of these trials, the likelihood that trial results were substantively biased based on financial interest is low.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The active drug substance is referred to as TMC435. It is a white to off-white powder with the chemical name (2R,3aR,10Z,11aS,12aR,14aR)-N- (cyclopropylsulfonyl)-2-[[2-(4-isopropyl-1,3- thiazol-2-yl)-7-methoxy-8-methyl-4- quinolinyl]oxy]-5-methyl-4,14-dioxo- 2,3,3a,4,5,6,7,8,9,11a,12,13,14,14atetradecahydrocyclopenta[c]cyclopropa[g][1,6]d iazacyclotetradecine-12a(1H)-carboxamide.

The clinical formulations used during Phase 3 clinical studies were oral capsules containing the Na salt of TMC435. These capsules contain (b) (4) sodium lauryl sulphate, magnesium stearate, colloidal anhydrous

silica, croscarmellose sodium and lactose monohydrate as additional excipients in hard gelatin capsules.

Please refer to the CMC Review for further details on manufacturing processes, process controls, formulation specifications, and the adequacy of data provided to assure drug stability, strength, purity and quality. The inspections of the production facilities are currently ongoing

4.2 Clinical Microbiology

Pre-Clinical Studies:

In vitro antiviral activity of TMC435 against HCV genotype 1a and 1b replicons was demonstrated in pre-clinical studies. A number of specific mutations in the NS3 domain were identified which led to a loss of activity against HCV. These included mutations at NS3 positions 80, 155, 156, and/or 168. Please refer to the Virology Review for additional details on the pre-clinical virology assessments.

Virology results from Clinical Studies

As previously discussed, the presence of a Q80K baseline polymorphism had a substantial impact on SVR12 rates in the TMC435 groups in the Phase 3 trials (C208, C216, and HPC3007). Please refer to Section 6.1.7 for details.

The Sponsor performed a pooled virologic analysis of studies C205, C206, C208, C216, and HPC3007. In 91% of subjects with treatment failure and sequence information available, emerging mutations were detected at one or more of the NS3 positions 80, 122, 155, and/or 168 at time of failure. Differences in type of emerging mutations were observed between genotype 1a and 1b infected subjects. In HCV genotype 1a-infected subjects (with and without Q80K) the mutation emerging most frequently was R155K alone or in combination with mutations 80, 122 and/or 168. In HCV genotype 1b-infected subjects the most frequently emerging mutation was D168V. The R155K and D168V mutations are known to confer resistance to the protease inhibitors currently approved for use in the U.S., telaprevir and boceprevir.

The Sponsor also assessed for the persistence of emerging mutations reported at the time of virologic failure. In 90 of 180 subjects with emerging mutations at the time of failure, emerging mutations were no longer observed at the end of the studies after a median follow-up of 28 weeks (range 0-70 weeks). Instead, either wild type or the same amino acid sequence as the baseline sequence was observed at this time point. However, the clinical relevance of these findings (i.e. the lack of later detectability of the emerging mutations) remains unclear.

Please refer to the Virology Review by Dr. Damon Deming for further details.

4.3 Preclinical Pharmacology/Toxicology

A complete pharmacology/toxicology package was submitted by the Sponsor which included pivotal studies in the mouse, rat, and dog. No carcinogenicity studies were required as the Sponsor's proposed treatment duration of TMC435 is only 12 weeks. TMC435 was not found to be genotoxic in a series of tests including the Ames test, mouse lymphoma test and mouse bone marrow micronucleus test.

The primary findings identified by the Pharmacology/Toxicology Reviewer are summarized below.

Safety Pharmacology: Respiratory findings including noisy breathing and rales which did not appear to be related to TMC435 but instead appeared to be related to oral gavage administration of study drug. Central nervous system findings included diminished alertness in rats. Cardiac findings included acute myocardial necrosis in the dog at high dose multiples (AUC ~ 26X and Cmax ~ 32X the anticipated clinical exposure). This finding was not observed in other species nor was it observed in longer duration toxicology studies in the dog with oral administration at lower exposures.

Nonclinical PK/ADME: Reduced exposure was noted with repeat doses. This may lead to potential false negative results in the longer duration repeat-dose toxicology studies. This finding was not observed in the clinical trials to date.

Standard Toxicology: Hepatobiliary and gastrointestinal findings were noted.

> Hepatobiliary histopathologic findings included hepatocellular necrosis, peri-portal inflammation, and brown pigmented/ hemosiderin in Kupffer cells. Clinical chemistry findings included increased transaminases, bilirubin, alkaline phosphatase, and gamma-glutamyltransferase. No safety margins were present for either the rat or the dog for these findings.
>
> Gastrointestinal findings included vacuolization of apical enterocytes of the duodenum and jejunum with an increase in fat droplets, however this was not considered an adverse finding. Inhibition of gastric emptying in rat was also noted.

Reproductive Toxicology—Mouse Embryofetal Studies:

> In the pilot mouse study, maximal doses of 2000 mg/kg were administered. Findings in this study included exencephaly and protruding tongues in 6/50 mice at 1000 mg/kg and 4/64 at 2000 mg/kg (2 different litters/group). In addition, fetal weight was noted to be decreased at doses of 2000 mg/kg.

In the pivotal mouse study, maximal doses of 1000 mg/kg were administered. Findings included two maternal deaths at 1000 mg/kg, high post-implantation loss, decreased fetal weight, and increase in skeletal variations. Teratogenic findings were not reported. The NOAEL for this study was 500 mg/kg which is ~4X greater than the 150 mg clinical AUC.

Reproductive Toxicology--Peri-, Post-Natal Rat Studies:

In maternal animals, a significant decrease in body weight was reported.

In offspring (F1) in the high dose cohort (1000 mg/kg) the following findings were reported: small-build, significant decrease in body weight, delayed righting reflex, delayed sexual maturation, and delayed motor activity (rearing and ambulatory) compared to controls.

A kinked tail deformity of unclear significance was also reported. Seen in isolation this is not a clear teratogenic signal.

The NOAEL for this study was 150 mg/kg based on F1 growth and developmental delays. This provides limited to no safety margin.

Special Studies: TMC435 was found to be a mild eye irritant, but was not irritating to the skin and is not likely to cause skin sensitization. TMC435 was phototoxic after UVA exposure in vitro.

Please refer to the Pharmacology/Toxicology Review by Dr. Janice Lansita for additional details. Please refer to Section 9.2 for a discussion of the potential impact of the reproductive toxicology findings on the Sponsor's proposed product labeling.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

TMC435 is a specific inhibitor of the HCV NS3/4A serine protease.

4.4.2 Pharmacodynamics

In vitro, TMC435 is a moderate inhibitor of CYP2A6, CYP2C8 and CYP2D6 (IC_{50} > 32 µg/mL) and a weak inhibitor of CYP2C19 and CYP3A (IC_{50} > 64 µg/mL). In vivo, TMC435 has no clinically relevant effect on the activity of CYP2C9, CYP2C19 and CYP2D6. TMC435 is a mild inhibitor of intestinal CYP3A4 activity, while it does not affect hepatic CYP3A4 activity. TMC435 mildly inhibits CYP1A2. Strong inhibitors of CYP3A4 may increase the plasma exposure of TMC435, and strong inducers of CYP3A4 may reduce plasma exposure of TMC435.

4.4.3 Pharmacokinetics

Absorption: In healthy subjects in Study C103 (mass balance study), all subjects had quantifiable TMC435 concentrations 0.5 hours after administration and the average peak concentration was reached at 6 hours.

Distribution: TMC435 is highly protein bound in humans with in vitro plasma protein binding greater than 99.8%.

Metabolism: The primary enzyme involved in the biotransformation of TMC435 is CYP3A4 (and CYP3A5, 3A7), and to a lesser extent CYP2C enzymes. Other enzymes involved include CYP2B6 and CYP2E1. In a mass balance study in healthy subjects, TMC435 metabolite concentrations in plasma were low relative to circulating parent TMC435, with no indication for significant metabolite accumulation. Only one minor metabolite peak (representing M21) was observed in plasma and accounted for 8% of the mean plasma-$AUC_{0\text{-}24h}$ of unchanged drug.

Elimination: The majority of the radioactivity was excreted in feces (91% of the dose), while the radioactivity measured in urine was very low (0.038% of the dose), suggesting that renal clearance plays an insignificant role in the elimination of TMC435. The major metabolites in human feces extract samples were M21 and M22.

Food Effect: Administration of TMC435 with food to healthy subjects increased the relative bioavailability (AUC) by 61% and 69% after a high fat, high caloric (928 kcal) and normal caloric (533 kcal) breakfast, respectively, and delayed the absorption by 1 hour and 1.5 hours, respectively. Based on these PK parameters, it will be recommended that TMC435 be taken with food.

Assessment of Dose Proportionality and Drug Exposure in Healthy and HCV-Infected Subjects:

In healthy subjects, the exposure for single or repeated doses exceeding 100 mg increases more than dose-proportional. Similar to data in healthy subjects, a more than dose-proportional increase in exposure was observed in both treatment-naïve and treatment-experienced subjects with TMC435 at doses between 75 and 200 mg q.d. Of note, two to three fold higher exposures of TMC435 occur in subjects with HCV compared to HCV uninfected healthy subjects.

In Phase 2b studies C205 and C206, there were no differences in exposure (AUC) between subjects by Metavir score. In treatment-naïve subjects with CHC infection, steady-state pharmacokinetics of TMC435 were comparable following monotherapy or when given in combination with PegIFN/RBV. Exposure to RBV was not affected by TMC435 co-administration.

Drug Exposure in Asian Subjects:

In healthy Japanese subjects living in the United States, exposure was 1.6-fold higher at 100 mg q.d. and 1.25-fold higher at 200 mg q.d. compared to healthy Caucasians. In the Phase II clinical studies, exposure in Japanese subjects treated with 100 mg q.d. was similar to exposure in Caucasian subjects treated with 150 mg q.d.

A cross-study comparison of Chinese subjects (living in Hong Kong), Japanese subjects, and Caucasian subjects indicated that plasma exposures in healthy Chinese subjects were within the same range as in Japanese healthy subjects at 100 and 200 mg q.d. For the 100 mg dose level, mean C_{max} and AUC_{∞} (single dose) were 1.4- to 1.8-fold higher and mean C_{max} and AUC_{24h} (steady-state) were 1.9- to 2.3-fold higher in Japanese and Chinese subjects compared to Caucasians. For the 200 mg dose level the ethnic differences were not apparent.

In the pivotal phase 3 studies (C208, C216, and HPC3007), the mean AUC_{24} was 3.4 fold higher in Asian subjects receiving a TMC435 dose of 150 mg daily compared to the pooled subjects as a whole. Analyses assessing the correlation of TMC435 exposure (based on subjects' AUC_{24} values) with adverse event frequency in the pooled Phase 3 trials demonstrated an increased frequency of anemia, dyspnea, increased bilirubin, pruritis, rash and photosensitivity events with increasing drug exposures.

Based on PK parameters in Asian subjects and the exposure-adverse event analyses, the clinical pharmacology team has recommended that the TMC435 treatment dose in Asian patients (including those living in the U.S.) be lowered from 150 mg daily to 100 mg daily. It is also notable that the TMC435 Phase 3 development program in Japan has been entirely limited to the 100 mg treatment dose.

Drug Exposure in Moderate Hepatic Insufficiency:

In subjects with moderate hepatic impairment, C_{max} and AUC_{24h} values for TMC435 at Day 7 were, respectively, 1.71 and 2.44 fold higher as compared to matched control subjects with normal hepatic function (refer to Section 7.4.5 for additional details). Based on PK parameters in this population and the exposure-adverse event analyses discussed above, the clinical pharmacology team has recommended that the TMC435 treatment dose in patients with moderate hepatic insufficiency be lowered from 150 mg daily to 100 mg daily.

Please refer to the Clinical Pharmacology Review by Dr. Leslie Chinn for additional details.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The three pivotal phase 3 trials (that formed the primary basis of the Clinical Review) and the two supportive phase 2b clinical trials are summarized in Table 3 and discussed at length in Section 5.3. In addition, a large number of phase 1 clinical pharmacology studies have been submitted by the Applicant. Please refer to the Clinical Pharmacology Review for further details on these studies. The uncontrolled studies that were targeted for a focused safety review are summarized in Table 4 and discussed at length in Section 7.4.5.

Table 3: Supportive Phase 2b and Pivotal Phase 3 Clinical Trials

Trial Name	Study Design	Population	TMC435 Dose and Duration	Number Enrolled	Primary Efficacy Endpoint
TMC435-TiDP16-C205	Phase 2b, Randomized, double-blinded, active-control (PR)	Genotype 1 Treatment-Naïve	75 or 150 mg q.d. administered as TMC12/PR24 or TMC24/PR24	386	SVR at Week 72
TMC435-TiDP16-C206	Phase 2b, Randomized, double-blinded, active-control (PR)	Genotype 1 Relapsers, Null-Responders, & Partial Responders	100 or 150 mg q.d. administered as TMC12/PR48, TMC24/PR48 or TMC48/PR48	462	SVR24
TMC435-TiDP16-C208	Phase 3, Randomized, double-blinded, active-control (PR)	Genotype 1 Treatment-Naïve	150 mg q.d. administered as TMC12/PR24 or TMC12/PR48[a]	394	SVR12
TMC435-TiDP16-C216	Phase 3, Randomized, double-blinded, active-control (PR)	Genotype 1 Treatment-Naïve	150 mg q.d. administered as TMC12/PR24 or TMC12/PR48[a]	393	SVR12
TMC435HPC3007	Phase 3, Randomized, double-blinded, active-control (PR)	Genotype 1 Relapsers	150 mg q.d. administered as TMC12/PR24 or TMC12/PR48[a]	393	SVR12

a = based on response guided therapy

Table 4: Uncontrolled Studies Targeted for Safety Review

Trial Name	Population	Trial Objective	TMC435 Dose and Duration	Number of Subjects
TMC435-TiDP16-C117	Healthy Subjects	QT Evaluation	150 or 350 mg administered as MD for 7 days	60
TMC435-TiDP16-C126	Healthy and Renally Impaired Subjects	Renal Impairment Study	150 mg q.d. administered as MD for 7 days	16
TMC435-TiDP16-C113	Healthy and Hepatically Impaired Subjects	Hepatic Insufficiency Study	150 mg q.d. administered as MD for 7 days	24
TMC435-TiDP16-C125	Healthy Subjects	Photosensitivity Study	150 mg q.d. administered as MD for 9 days	49
TMC435-TiDP16-C212	HCV-HIV Co-Infected Subjects	Safety and Efficacy	150 mg q.d. for 12 weeks plus PR x 24-48 weeks	106

MD = multiple dose

5.2 Review Strategy

The clinical review for this NDA was based primarily on data from three Phase 3 trials: C208, C216, and HPC3007 (described in detail in Section 5.3). The safety analysis was conducted by integrating safety data from these three trials. In addition, data from two Phase 2 trials (C205 and C206) were reviewed for key safety analyses.

5.3 Discussion of Individual Studies/Clinical Trials

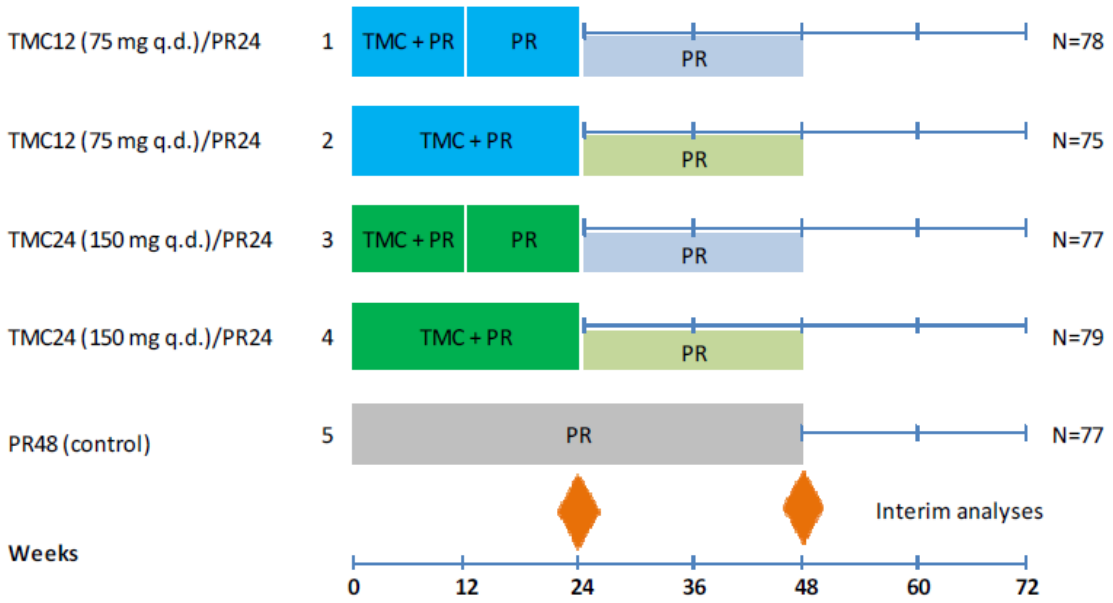
C205: A completed randomized, double-blind, 5-arm, placebo-controlled study to investigate the efficacy, tolerability, safety and pharmacokinetics of TMC435 (75 and 150 mg q.d.) in combination with PegIFNα-2a and RBV in treatment-naïve CHC genotype-1 infected subjects.

The study was conducted in Europe, Australia/New Zealand, and North America. A total of 386 subjects were enrolled.

Subjects were randomized in a 1:1:1:1:1 fashion over 4 TMC435 dose groups and 1 placebo group. In treatment groups 1 and 2, subjects received 12 weeks of triple therapy with 75 or 150 mg TMC435 q.d. plus PegIFNα-2a and RBV, followed by 12

weeks of treatment with PegIFNα-2a and RBV and TMC435-matched placebo (hereafter identified as the TMC12PR24 75 mg and 150 mg groups). In treatment groups 3 and 4, subjects received 24 weeks of triple therapy with 75 or 150 mg TMC435 q.d. plus PegIFNα-2a and RBV (hereafter identified as the TMC24PR24 75 mg and 150 mg groups). In treatment group 5, subjects received PegIFNα-2a and RBV for 48 weeks and TMC435-matched placebo for the first 24 weeks (control group).

As part of a response-guided treatment duration, HCV therapy was stopped at Week 24 in the TMC435 treatment groups when subjects achieved HCV RNA levels < 25 IU/mL (detectable or undetectable) at Week 4 and < 25 IU/mL undetectable HCV RNA levels at Weeks 12, 16 and 20. All other subjects continued PegIFNα-2a and RBV until Week 48. In treatment group 5, all subjects were treated with PegIFNα-2a and RBV treatment for 48 weeks with TMC435-matched placebo for the first 24 weeks. The trial design for C205 is shown in Figure 1.



Response-guided treatment duration in the TMC435 treatment group: subjects who did not achieve HCV RNA < 25 IU/mL (detectable or undetectable) at Week 4 and undetectable HCV RNA (< 25 IU/mL undetectable) at Weeks 12, 16 and 20 continued PR until Week 48.

(P): PegIFN = peginterferon alfa-2a, 180 µg/week
(R): Ribavirin 1000 or 1200 mg/day (b.i.d. regimen), depending on body weight (< 75 or ≥ 75 kg)
(TMC): TMC435

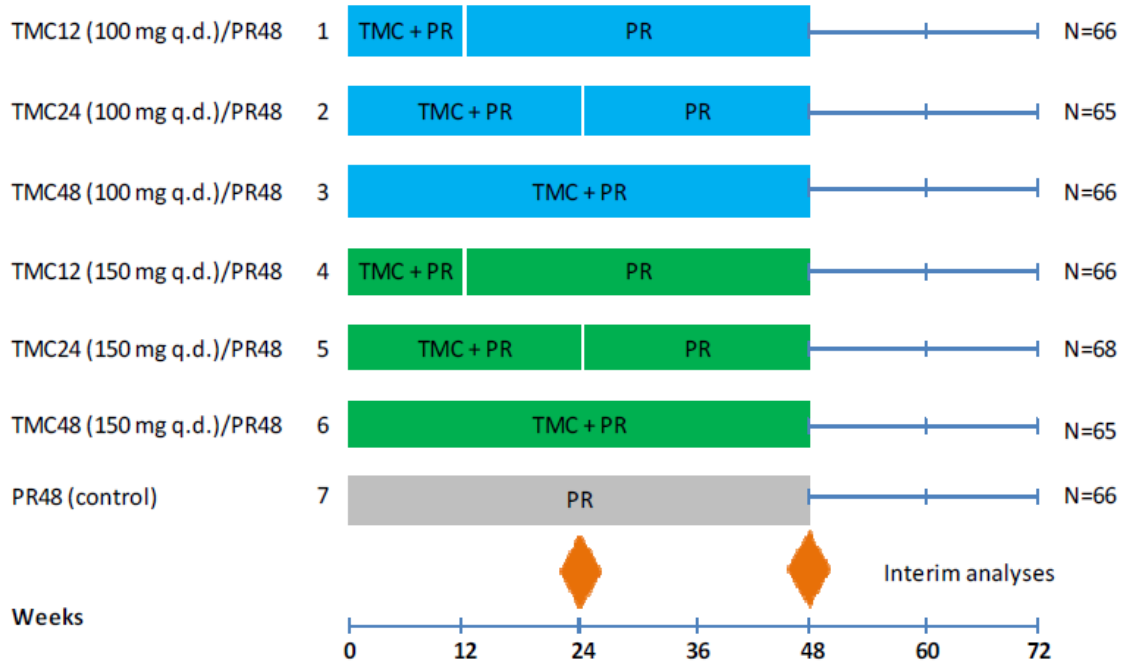
Figure 1: Study Schema for Study C205
Source: Clinical Study Report for Study C205

The primary efficacy parameter for the study was the sustained virologic response (SVR) at Week 72.

C206: A completed, randomized, double-blind, 7-arm, placebo-controlled study to compare the efficacy, tolerability and safety of different regimens of TMC435 (100 and 150 mg q.d.) plus PegIFNα-2a and RBV versus PegIFNα-2a and RBV alone in CHC genotype-1 infected subjects who failed to respond during or relapsed following at least 1 course of PegIFN and RBV therapy.

The study was conducted in Europe, Australia/New Zealand, and North America. A total of 462 subjects were enrolled.

Subjects in study C206 were randomized in a 1:1:1:1:1:1:1 fashion over 6 TMC435 dose groups and 1 placebo group. In treatment groups 1 and 4, subjects received 12 weeks of triple therapy with 100 or 150 mg TMC435 q.d. plus PegIFNα-2a and RBV, followed by 36 weeks of treatment with PegIFNα-2a and RBV and TMC435-matched placebo (hereafter identified as the TMC12PR48 100 mg and TMC12PR48 150 mg groups). In treatment groups 2 and 5, subjects received 24 weeks of triple therapy with 100 or 150 mg TMC435 q.d. plus PegIFNα-2a and RBV (TMC24PR48 100 mg and TMC24PR48 150 mg groups). In treatment groups 3 and 6, subjects received 48 weeks of triple therapy with 100 or 150 mg TMC435 q.d. plus PegIFNα-2a and RBV (TMC48PR48 100 mg and TMC48PR48 150 mg groups). In treatment group 7, subjects received PegIFNα-2a, RBV and TMC435-matched placebo for 48 weeks (control group). The trial design for C206 is shown in Figure 2.



(P): PegIFN = peginterferon alfa-2a 180 µg/week
(R): Ribavirin 1000 or 1200 mg/day (b.i.d. regimen), depending on body weight (< 75 or ≥ 75 kg)
(TMC): TMC435

Figure 2: Study Schema for Study C206
Source: Clinical Study Report for Study C206

The primary efficacy endpoint was the SVR24 response rate demonstrated by achieving undetectable HCV RNA 24 weeks after the planned end of treatment.

C208: An ongoing multicenter, phase 3, randomized, double-blind controlled trial with 2 parallel treatment arms: TMC435 150 mg or placebo as part of a treatment regimen including pegylated interferon α-2a and ribavirin (PR), in treatment-naive, genotype 1 HCV-infected patients, with compensated liver disease including cirrhosis.

A total of 394 patients were randomized from 13 countries. Fourteen percent of subjects were drawn from the Asia-pacific region, 42% from Europe and 44% from North America (with 30% from the United States).

The primary objective was to demonstrate the superiority of TMC435 versus placebo as part of a treatment regimen including PR. The primary efficacy endpoint was sustained virologic response 12 weeks after the planned end of treatment (SVR12). The primary analysis set for efficacy was the intent-to-treat population which includes all subjects who were randomized and received at least one dose of study medication. The study was designed to detect a difference of at least 20% in SVR12 between treatment arms at the 2-sided 5% significance level with >90% power.

Subjects were randomized with a 2:1 allocation ratio (TMC435: placebo) with stratification factors for HCV geno/subtype (1a, 1b, other) and IL28B (CC, CT, TT).

Subjects with any liver disease of non-HCV etiology or with HBV or HIV co-infection were excluded.

As outlined in the figure below, all trial patients received 12 weeks of treatment with TMC435 at 150 mg per day or placebo. All patients in the control arm received 48 weeks of treatment with PR. All patients in the TMC arm received either 24 or 48 weeks of PR based on the following predefined response guided PR treatment duration algorithm: HCV therapy was stopped at Week 24 in subjects in the TMC435 treatment group if they both 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 in the TMC435 treatment group continued PR until Week 48. The trial design for C208 is shown in Figure 3.

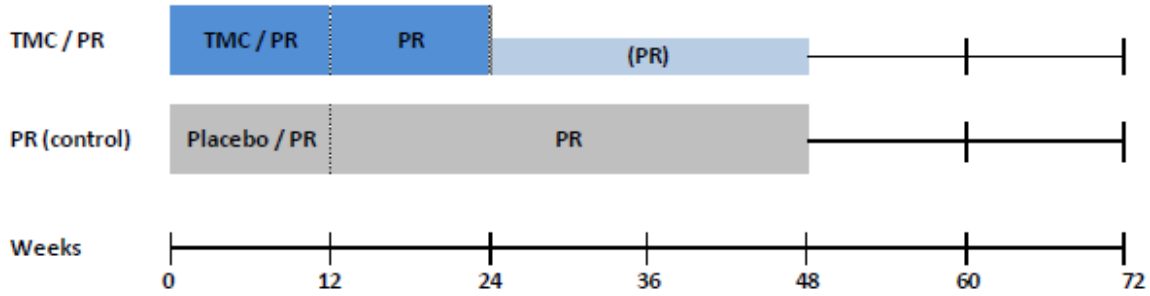


Figure 3: Study Schema for Study C208
(P): PegIFNα-2a 180 µg/week
(R): Ribavirin 1000 or 1200 mg/day, depending on body weight (< 75 or ≥ 75 kg)
(TMC): TMC435 150 mg once daily
Source: Clinical Study Report for Study C208

All patients will be followed for up to 72-weeks after the start of treatment.

C216: An ongoing multicenter, phase 3, randomized, double-blind controlled trial with 2 parallel treatment arms: TMC435 150 mg or placebo as part of a treatment regimen including pegylated interferon α-2a and ribavirin or pegylated interferon α-2b and ribavirin, in treatment-naive, genotype 1 HCV-infected patients, with compensated liver disease including cirrhosis.

A total of 391 patients were randomized from 14 countries. Sixty-five percent of subjects were drawn from Europe, 15% from South America and 20% from North America (all from United States).

The study design (including the primary objective and endpoint, stratification factors, inclusion/exclusion criteria, and study schema) was virtually identical to that of C208 with the following notable exception: The use of PegIFNα-2b was studied in a limited number of selected European countries. In these countries, subjects were randomized in a 1:1 ratio to PegIFNα-2a/RBV or PegIFNα-2b/RBV with the intent to randomize no greater than 30% of the overall study population to a PegIFNα-2b containing regimen. A total of 77 patients were randomized to receive PegIFNα-2a/RBV + TMC435 and 80 patients were randomized to receive PegIFNα-2b/RBV +TMC435. The doses of study medications were as follows: For Pegasys® 180 μg/week and for PegIntron® pre-filled pens per weight band; For Copegus® 1000 or 1200 mg/day, depending on body weight and for Rebetol® 800-1400 mg/day; depending on body weight; TMC435 150 mg once daily.

HPC3007: An ongoing multicenter, Phase 3, randomized, double-blind controlled trial with 2 parallel treatment arms: TMC435 150 mg or placebo as part of a treatment regimen including pegylated interferon α-2a and ribavirin, in Hepatitis C, genotype 1 infected patients who relapsed after previous interferon-based therapy, with compensated liver disease including cirrhosis.

A total of 393 patients were randomized from 14 countries. Eight percent of subjects were drawn from the Asia-pacific region, 70% from Europe and 22% from North America (with 18% from the United States).

The study design of this trial was virtually identical to that of C208 discussed above with the exception of the patient population which included only patients who received at least 24 weeks of a pegylated interferon-based therapy and relapsed within 1 year after the last medication intake.

6 Review of Efficacy

Efficacy Summary

The Applicant's proposed indication for the treatment of chronic HCV infection is based primarily on the SVR12 results from the Phase 3 pivotal trials (C208, C216, and HPC3007). As trials C208 and C216 were both performed in a HCV treatment-naïve population and employed a nearly identical study design, efficacy results were pooled for analysis. The pooled SVR12 results from the treatment-naïve studies demonstrated an SVR12 rate of 80% in the TMC435 group and 50% in the control group. Trial HPC3007 was performed in patients who had relapsed after previous interferon-based HCV treatment. In HPC3007, the SVR12 rate in the TMC435 arm was 79% compared to 37% in the control arm. SVR24 rates were comparable to SVR12 rates in each of the pivotal trials.

Subpopulation analyses revealed statistically significant benefit of TMC435 over control regardless of sex, age, race, HCV geno/subtype (1a versus 1b), IL28B genotype, baseline HCV RNA or Metavir score. However, in subjects with the Q80K polymorphism at baseline, no statistically significant difference in SVR12 rates was present when comparing the TMC435 group to the control group. Given the high frequency of the Q80K polymorphism in the U.S. population, this Reviewer recommends screening for the Q80K polymorphism prior to initiation of TMC435 and excluding patients from treatment if the polymorphism is present.

In lieu of screening out patients with the Q80K polymorphism prior to initiation of TMC435, the Sponsor proposed (b) (4) . This approach, however, was not employed in the pivotal Phase 3 studies. (b) (4)

(b) (4)

The Sponsor has also requested that the indication include treatment of HCV in partial and null responders. This request is primarily supported by data from study C206 (a Phase 2b study in relapsers, partial and null responders). Based on results of this study (including pooled post hoc analyses), in this Reviewer's opinion, it is reasonable to extend the indication of TMC435 for the treatment of partial and null responders. However, given the limited data on outcomes in partial and null responder patients with the Q80K baseline polymorphism, it is not recommended that this subgroup of patients receive treatment with TMC435. In addition, this Reviewer recommends that the submission of final data from the ongoing Phase 3 study in partial and null responders (HPC3001) be deemed a post-marketing commitment (refer to Section 1.4 for additional details).

6.1 Indication

The Applicant has requested an indication for 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-naïve or who have failed previous interferon therapy (pegylated or non-pegylated) with or without ribavirin.

6.1.1 Methods

The Applicant's proposed indication is based primarily on data from the Phase 3 pivotal trials (C208, C216, and HPC3007) and Phase 2b trial (C206). Trials C208 and C216 were provided to support the treatment-naïve indication. Trial HPC3007 was provided to support the indication for use in patients who relapsed after previous interferon- based HCV treatment. The Phase 2b trial, C206, was provided to support the indication for use in the HCV partial and null responder populations.

All data and data tables in this section were generated by the primary clinical reviewer using JReview in conjunction with the Applicant's ISE or individual study datasets unless otherwise specified.

6.1.2 Demographics

Background: Demographic and baseline characteristics that have been shown to predict a lower SVR rate with standard of care treatment include a high viral load at baseline, advanced disease on histology (bridging fibrosis and cirrhosis), obesity, older age, and African American race[1]. A genetic polymorphism near the IL28B gene is a strong predictor of SVR in patients receiving therapy with pegylated interferon and ribavirin. Numerous studies have demonstrated that patients who carry the variant alleles (C/T and T/T genotypes) have lower SVR rates than individuals with the C/C genotype.

The demographic data (including the predictive characteristics discussed above) are presented in several distinct formats in this section as various pooling of subjects was performed for specific safety and efficacy analyses.

Individual Phase 3 Trials: Tables 5 and 6 summarize the relevant demographic data from each of the pivotal phase 3 trials. Demographic characteristics were generally well balanced between the TMC435 arms and Control arms for each of the Phase 3 trials. The majority of subjects in all arms of the phase 3 trials were of Caucasian race (range 86-96%) and non-Hispanic/Latino ethnicity (range 77-95%). Trial C208 had the highest representation of North American subjects at 44%, while rates in C216 (20%) and HPC3007 (22%) were substantially lower. Cirrhotic subjects (Metavir Fibrosis score of F4) comprised from 7 to 15% of subjects across study arms. IL28b CC status ranged from 24-31% across study arms. Both HCV genotype/subtype 1a and 1b subjects were well represented in the Phase 3 studies (range for 1a across arms: 40-57%; range for 1b across arms: 43-59%).

The following differences (> 5%) were noted between the TMC435 and control groups in the individual studies, as shown in Tables 5 and 6:

C208: A greater percentage of black subjects and subjects with baseline HCV RNA > 800,000 IU/mL were enrolled in the TMC435 arm. A higher percentage of subjects with a baseline BMI ≥ 30 kg/m2 were enrolled in the Control arm.

C216: No differences > 5% noted.

HPC3007: A greater percentage of men and a higher percentage of subjects with combined F3/F4 Metavir scores were enrolled in the TMC435 arm.

Table 5: General Demographics of Subjects in the Individual Phase 3 Trials

	C208 N=394		C216 N=391		HPC3007 N=393	
	TMC435 N=264	PBO N=130	TMC 435 N=257	PBO N=134	TMC435 N=260	PBO N=133
Gender n (%)						
Male	148 (56%)	74 (57%)	140 (54%)	77 (57%)	179 (69%)	79 (59%)
Female	116 (44%)	56 (43%)	117 (46%)	57 (43%)	81 (31%)	54 (41%)
Race n (%)						
Caucasian	227 (86%)	122 (94%)	237 (92%)	123 (92%)	243 (93%)	128 (96%)
Black	27 (10%)	4 (3%)	16 (6%)	10 (7%)	7 (3%)	4 (3%)
Asian	5 (2%)	3 (2%)	2 (1%)	1 (1%)	8 (3%)	1 (1%)
Other	3 (1%)	1 (1%)	2 (1%)	0 (0%)	2 (1%)	0 (0%)
Ethnicity n (%)						
Hispanic or Latino	35 (13%)	14 (11%)	60 (23%)	25 (19%)	20 (8%)	6 (5%)
Not Hispanic or Latino	229 (87%)	116 (89%)	197 (77%)	109 (81%)	240 (92%)	127 (95%)
Age (years)						
Median (min, max)	48 (19,68)	48 (20,66)	46 (18,73)	47 (18,73)	52 (20,70)	52 (21,71)
Baseline BMI						
(missing)	0 (0%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)	0 (0%)
<25 kg/m2	96 (36%)	47 (36%)	111 (43%)	56 (42%)	78 (30%)	45 (34%)
>=25 - <30 kg/m2	100 (38%)	41 (32%)	101 (39%)	48 (36%)	116 (45%)	52 (39%)
>=30 kg/m2	68 (26%)	42 (32%)	45 (18%)	28 (21%)	66 (25%)	36 (27%)
Geographical Region n (%)						
North America	114 (43%)	61 (47%)	54 (21%)	25 (19%)	53 (20%)	33 (25%)
Europe	114 (43%)	52 (40%)	162 (63%)	90 (67%)	184 (71%)	90 (68%)
South America	0 (0%)	0 (0%)	41 (16%)	19 (14%)	0 (0%)	0 (0%)
Asia-Pacific	36 (14%)	17 (13%)	0 (0%)	0 (0%)	23 (9%)	10 (8%)

Table 6: Additional Demographics in the Individual Phase 3 Trials—Characteristics of the Subject and Virus

	C208 N=394		C216 N=391		HPC3007 N=393	
	TMC 435 N=264	PBO N=130	TMC 435 N=257	PBO N=134	TMC 435 N=260	PBO N=133
IL-28B Genotype						
CC	77 (29%)	37 (28%)	75 (29%)	42 (31%)	62 (24%)	34 (26%)
CT	150 (57%)	76 (58%)	142 (55%)	71 (53%)	167 (64%)	83 (62%)
TT	37 (14%)	17 (13%)	40 (16%)	21 (16%)	31 (12%)	16 (12%)
HCV Genotype/ Subtype						
1a	147 (56%)	74 (57%)	105 (41%)	54 (40%)	110 (42%)	54 (41%)
1b	117 (44%)	56 (43%)	150 (58%)	77 (57%)	149 (57%)	79 (59%)
Metavir Fibrosis Score						
F0-F1	118 (45%)	50 (38%)	130 (51%)	60 (45%)	87 (33%)	47 (35%)
F2	65 (25%)	40 (31%)	65 (25%)	42 (31%)	80 (31%)	51 (38%)
F3	46 (17%)	23 (18%)	36 (14%)	17 (13%)	44 (17%)	15 (11%)
F4	31 (12%)	17 (13%)	17 (7%)	15 (11%)	39 (15%)	19 (14%)
Baseline HCV RNA Log_{10} IU/mL						
Mean	6.4	6.3	6.4	6.4	6.4	6.5
SD	0.6	0.8	0.7	0.7	0.6	0.6
Baseline HCV RNA (IU/mL)						
<400,000	28 (11%)	19 (15%)	31 (12%)	19 (14%)	21 (8%)	9 (7%)
>=400,000 - <=800,000	18 (7%)	15 (12%)	27 (11%)	17 (13%)	20 (8%)	14 (11%)
>800,000	218 (83%)	96 (74%)	199 (77%)	98 (73%)	219 (84%)	110 (83%)

Tables 7 and 8 below summarize the demographic data from the treatment-naïve efficacy pool (studies C208 and C216) and the primary safety pool (studies C208, C216, and HPC3007).

Treatment-Naïve Efficacy Pool (C208 and C216):

The Naïve Efficacy Pool included 785 subjects in the intent to treat (ITT) population. The TMC435 group included 521 subjects while the Control group included 264 subjects. Baseline characteristics, including gender, race, ethnicity, age, and geographical region of origin were comparable between groups. There was a greater percentage of subjects in the Control group with a BMI ≥ 30 kg/m2 and a greater percentage of subjects in the TMC435 group with baseline HCV RNA > 800,000 IU/mL.

Primary Safety Pool (C208, C216, and HPC3007):

The Primary Safety Pool included 1,178 subjects in the ITT population. The TMC435 group included 781 subjects while the Control group included 397 subjects. Baseline characteristics, including gender, race, ethnicity, age, and geographical region of origin were comparable between groups. There was a greater percentage of subjects in the Control group with a BMI ≥ 30 kg/m2 and a greater percentage of subjects in the TMC435 group with baseline HCV RNA > 800,000 IU/mL.

Table 7: General Demographics of Subjects in the Treatment-Naïve Efficacy Pool (C208 and C216) and the Primary Safety Pool (C208, C216, and HPC3007)

	C208 & C216 N=785		C208, C216, & HPC3007 N=1178	
	Pooled TMC435 N=521	Pooled PBO N=264	Pooled TMC435 N=781	Pooled PBO N=397
Gender n (%)				
Male	288 (55%)	151 (57%)	467 (60%)	230 (58%)
Female	233 (45%)	113 (43%)	314 (40%)	167 (42%)
Race n (%)				
Caucasian	464 (89%)	245 (93%)	707 (91%)	373 (94%)
Black	43 (8%)	14 (5%)	50 (6%)	18 (5%)
Asian	7 (1%)	4 (2%)	15 (2%)	5 (1%)
Other	5 (<1%)	1 (<1%)	7 (1%)	1 (<1%)
Ethnicity n (%)				
Hispanic or Latino	95 (18%)	39 (15%)	115 (15%)	45 (11%)
Not Hispanic or Latino	426 (82%)	225 (85%)	666 (85%)	352 (89%)
Age (years)				
Median (min, max)	47 (18,73)	47 (18,73)	49 (18,73)	49 (18,73)
Baseline BMI				
(missing)	0 (0%)	2 (<1%)	0 (0%)	2 (1%)
<25 kg/m2	207 (40%)	103 (39%)	285 (36%)	148 (37%)
>=25 - <30 kg/m2	201 (39%)	89 (34%)	317 (41%)	141 (36%)
>=30 kg/m2	113 (22%)	70 (27%)	179 (23%)	106 (27%)
Geographical Region n (%)				
North America	168 (32%)	86 (33%)	221 (28%)	119 (30%)
Europe	276 (53%)	142 (54%)	460 (59%)	232 (58%)
South America	41 (8%)	19 (7%)	41 (5%)	19 (5%)
Asia-Pacific	36 (7%)	17 (6%)	59 (8%)	27 (7%)

Table 8: Additional Demographics in the Treatment-Naïve Efficacy Pool (C208 and C216) and the Primary Safety Pool (C208, C216, and HPC3007)—Characteristics of the Subject and Virus

	C208 & C216 N=785		C208, C216, & HPC3007 N=1178	
	Pooled TMC435 N=521	Pooled PBO N=264	Pooled TMC435 N=781	Pooled PBO N=397
IL-28B Genotype				
CC	152 (29%)	79 (30%)	214 (27%)	113 (28%)
CT	292 (56%)	147 (56%)	459 (59%)	230 (58%)
TT	77 (15%)	38 (14%)	108 (14%)	54 (14%)
HCV Genotype/ Subtype				
1a	252 (48%)	128 (48%)	362 (46%)	182 (46%)
1b	267 (51%)	133 (50%)	416 (53%)	212 (53%)
Metavir Fibrosis Score				
F0-F1	248 (48%)	110 (42%)	335 (43%)	157 (40%)
F2	130 (25%)	82 (31%)	210 (27%)	133 (34%)
F3	82 (16%)	40 (15%)	126 (16%)	55 (14%)
F4	48 (9%)	32 (12%)	87 (11%)	51 (13%)
Baseline HCV RNA Log_{10} IU/mL				
Mean	6.4	6.3	6.4	6.4
SD	0.6	0.7	0.6	0.7
Baseline HCV RNA (IU/mL)				
<400,000	59 (11%)	38 (14%)	80 (10%)	47 (12%)
>=400,000 - <=800,000	45 (9%)	32 (12%)	65 (8%)	46 (12%)
>800,000	417 (80%)	194 (73%)	636 (81%)	304 (77%)

There was a slight imbalance between the TMC435 and Control groups with a greater percentage of subjects with an F2 metavir fibrosis score in the Control Groups. However, the percentage of subjects with combined F0-F2 metavir fibrosis scores was well balanced between the TMC435 and Control Groups.

6.1.3 Subject Disposition

Tables 9, 10, and 11 describe subject disposition in Studies C208, C216, and HPC3007 respectively. All subjects, including those categorized as “ongoing” in the tables that follow, have completed the period of planned study drug administration and at least 12 weeks of additional follow-up after completion of planned treatment.

Table 9: Subject Disposition in Study C208

	C208 N=394	
	TMC435 N=264	PBO N=130
Standardized Disposition Term		
SUBJECT ONGOING AT CUT-OFF DATE OF INTERIM LOCK	181 (69%)	92 (71%)
COMPLETED	62 (23%)	28 (22%)
DISCONTINUED	21 (8%)	10 (8%)
LOST TO FOLLOW-UP	9 (3%)	6 (5%)
SUBJECT NON-COMPLIANT	2 (1%)	1 (1%)
WITHDRAWAL BY SUBJECT	8 (3%)	1 (1%)
SPONSOR'S DECISION	1 (<1%)	0 (0%)
OTHER	1 (<1%)	2 (2%)

Table 10: Subject Disposition in Study C216

	C216 N=391	
	TMC435 N=257	PBO N=134
Standardized Disposition Term		
SUBJECT ONGOING AT CUT-OFF DATE OF INTERIM LOCK	134 (52%)	66 (49%)
COMPLETED	111 (43%)	51 (38%)
DISCONTINUED	12 (5%)	17 (13%)
ADVERSE EVENT	2 (1%)	0 (0%)
LOST TO FOLLOW-UP	4 (2%)	6 (4%)
SUBJECT ENTERED ANOTHER INVESTIGATIONAL TRIAL	0 (0%)	5 (4%)
SUBJECT NON-COMPLIANT	0 (0%)	1 (1%)
WITHDRAWAL BY SUBJECT	6 (2%)	5 (4%)

Table 11: Subject Disposition in Study HPC3007

	HPC3007 N=393	
	TMC435 N=260	PBO N=133
Standardized Disposition Term		
SUBJECT ONGOING AT CUT-OFF DATE OF INTERIM LOCK	123 (47%)	62 (47%)
COMPLETED	127 (49%)	57 (43%)
DISCONTINUED	10 (4%)	13 (10%)
ADVERSE EVENT	1 (<1%)	0 (0%)
LOST TO FOLLOW-UP	5 (2%)	3 (2%)
WITHDRAWAL BY SUBJECT	4 (2%)	10 (8%)

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint for each of the pivotal Phase 3 trials was SVR12. Table 12 describes the primary endpoint analysis for the pooled phase 3 treatment-naïve trials (C208 and C216) and the phase 3 trial in subjects who relapsed after interferon-based HCV treatment (HPC3007).

Table 12: Primary Efficacy Analysis in the Pooled Treatment-Naive Trials (C208 and C216) and Treatment Experienced (Relapser) Trial (HPC3007)

Studies (Number of Subjects)	C208 & C216 (N=785)		HPC3007 (N=393)	
Treatment Outcome	Pooled TMC435 N=521	Pooled PBO N=264	TMC435 N=260	PBO N=133
Overall SVR12[a]	419 (80%)	132 (50%)	206 (79%)	49 (37%)
Outcome for Patients Without SVR12				
Missing SVR12	13 (2%)	6 (2%)	5 (2%)	5 (4%)
On-treatment failure[b]	42 (8%)	87 (33%)	8 (3%)	36 (27%)
Viral Relapse	51 (10%)[c]	39 (15%)[c]	46 (18%)[d]	45 (34%)[d]

a. SVR12 is defined as the proportion of subjects with undetectable HCV RNA (< 25 IU/mL undetectable) at the end of treatment and HCV RNA < 25 IU/mL detectable or undetectable 12 weeks after the planned end of treatment.
b. On treatment failure was defined as the proportion of patients with confirmed detectable HCV RNA at EOT (including but not limited to patients who met the protocol specified treatment stopping rules and/or experienced viral breakthrough).
c. If viral relapse rate is calculated with a denominator of patients with undetectable HCV RNA at actual EOT (i.e. a denominator of 470 for the TMC435 group and a denominator of 172 for the Control group, rather than using the total N as denominator, as shown) then the percentage of subjects with viral relapse is 11% in the TMC435 group and 23% in the Control group.
d. If viral relapse rate is calculated with a denominator of patients with undetectable HCV RNA at actual EOT (i.e. a denominator of 249 for the TMC435 group and a denominator of 93 for the Control group, rather than using the total N as denominator, as shown) then the percentage of subjects with viral relapse is 19% in the TMC435 group and 48% in the Control group.

6.1.5 Analysis of Secondary Endpoints(s)

SVR24 was included as a secondary endpoint in each of the phase 3 pivotal trials and SVR24 results correlated well with the primary SVR12 endpoint. However, SVR24 data was incomplete at the time of the Week 60 data cutoff as discussed below.

Pooled Treatment-Naïve Studies C208 & C216: At the time of data cut-off for the Week 60 primary analysis, SVR24 data was available for 500 of the 521 subjects in the TMC435 pooled group and 91 of the 264 subjects in the pooled Control group. A total of 411 of 500 subjects receiving TMC435 or 82% of subjects achieved SVR24; while 46 of the 91 Control subjects or 51% of Control subjects achieved SVR24.

HPC3007 (Relapsers): At the time of data cut-off for the Week 60 primary analysis, SVR24 data was available for 254 of the 260 subjects in the TMC435 arm and 64 of the

133 subjects in the Control arm. A total of 199 of 254 subjects receiving TMC435 or 78% of subjects achieved SVR24; while 20 of the 64 Control subjects or 31% of Control subjects achieved SVR24.

SVR72 was also considered a secondary endpoint and data were also incomplete at the time of the Week 60 data cutoff.

Pooled Naïve Studies C208 & C216: At the time of data cut-off for the Week 60 primary analysis, SVR72 data was available for 191 of the 521 subjects in the TMC435 pooled group and 91 of the 264 subjects in the pooled Control group. A total of 143 of 191 subjects receiving TMC435 or 75% of subjects achieved SVR72; while 46 of the 91 Control subjects or 51% of Control subjects achieved SVR72.

HPC3007 (Relapsers): At the time of data cut-off for the Week 60 primary analysis, SVR72 data was available for 131 of the 260 subjects in the TMC435 arm and 64 of the 133 subjects in the Control arm. A total of 99 of 131 subjects receiving TMC435 or 76% of subjects achieved SVR72; while 20 of the 64 Control subjects or 31% of Control subjects achieved SVR72.

6.1.6 Other Endpoints

Additional secondary efficacy endpoints included the proportion of subjects with on-treatment failure and the proportion of subjects with viral relapse. These data were presented in Table 12 in Section 6.1.4.

Please refer to the Statistical Review and Virology Review for additional details with respect to secondary endpoint analyses.

6.1.7 Subpopulations

Table 13 presents SVR12 data by subgroups from the pooled studies in treatment-naïve subjects (C208 and C216) as well as the study in patients who relapsed after prior interferon-based therapy (HPC3007). Subjects in the TMC435 group with genotype 1a (without the Q80K baseline polymorphism) and genotype1b HCV demonstrated similar SVR12 rates. As previously mentioned, a number of demographic and baseline characteristics have been shown to predict a lower SVR rate with standard of care treatment. These include a high viral load at baseline, advanced disease on histology (bridging fibrosis and cirrhosis), older age, African American race, and absence of the IL28B CC genetic polymorphism. Each of these factors impacted efficacy results in both the TMC435 and Control groups in the pivotal phase 3 studies, as anticipated.

Most striking in the subgroup analysis was the substantial impact of the Q80K baseline polymorphism on the efficacy of TMC435. In subjects with the Q80K polymorphism at baseline, no statistically significant difference in SVR12 rates was observed when

comparing the TMC435 group to the control group. In all other subgroups analyzed, SVR12 rates were statistically significantly higher in the TMC435 group compared with the control group (please refer to the Statistical Review for additional details).

Table 13: SVR12 Subgroup Analysis for Treatment-Naive Pooled Studies (C208 and C216) and Relapser Study (HPC3007)

	C208 & C216 (Pooled) (N=785)		HPC3007 (N=393)	
	TMC435 N=521	PBO N=264	TMC435 N=260	PBO N=133
	N (%) of subjects achieving SVR12		N (%) of subjects achieving SVR12	
GT1a				
without Q80K	138/165 (84%)	36/86 (43%)	188/226 (83%)	43/113 (38%)
with Q80K	49/84 (58%)	23/44 (52%)	15/31 (48%)	6/20 (30%)
GT1b (as stratified)				
	231/272 (85%)	72/134 (54%)	129/150 (86%)	34/77 (44%)
IL-28B Genotype				
CC	141/149 (95%)	63/79 (80%)	55/62 (89%)	17/32 (53%)
CT	230/294 (78%)	61/147 (42%)	131/167 (78%)	29/85 (34%)
TT	48/78 (62%)	8/38 (21%)	20/31 (65%)	3/16 (19%)
Race				
Caucasian	378/364 (81%)	124/245 (51%)	192/243 (79%)	48/128 (38%)
Black	29/43 (67%)	5/14 (36%)	5/7 (71%)	0/4 (0%)
Sex				
Male	227/288 (79%)	72/151 (48%)	139/179 (78%)	28/79 (35%)
Female	192/233 (82%)	60/113 (53%)	67/81 (83%)	21/54 (39%)
Age				
Age ≤ 45	206/237 (87%)	61/111 (55%)	64/78 (82%)	20/35 (57%)
Age > 45	213/284 (75%)	71/153 (46%)	142/182 (78%)	29/98 (30%)
Metavir Fibrosis Score				
F0-F2	317/378 (84%)	106/192 (55%)	137/167 (82%)	40/98 (41%)
F3	60/82 (73%)	15/40 (38%)	32/44 (73%)	3/15 (20%)
F4	29/48 (60%)	11/32 (34%)	29/39 (74%)	5/19 (26%)
Baseline HCV RNA (IU/mL)				
<=800,000	96/104 (92%)	54/70 (77%)	34/41 (83%)	13/23 (57%)
>800,000	323/417 (77%)	78/194 (40%)	172/219 (79%)	36/110 (33%)

The Q80K polymorphism is a common polymorphism found in GT1a patients in the U.S. population. The Sponsor performed an analysis pooling all subjects from Studies C205, C206, C208, C216, and HPC3007 and found that of the 298 GT1a subjects in the U.S with sequencing data, 48% had the Q80K polymorphism at baseline. None of the 113 GT1b subjects in the U.S. with sequencing data had the Q80K polymorphism at baseline.

Given the high frequency of the Q80K polymorphism in the U.S. population, this Reviewer recommends screening for the Q80K polymorphism prior to initiation of TMC435 and excluding patients from treatment if the polymorphism is present.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Studies C205 and C206 were the key dose-finding studies (refer to Section 5.3 for details on their study designs).

In Study C205, a trend for higher SVR24 rates was noted when study arms which received 150 mg of TMC435 were pooled and compared to pooled study arms which received 75 mg of TMC435. No clear benefit of administration of TMC435 beyond 12 weeks was apparent.

In Study C206, a trend for higher SVR12 and SVR24 rates in partial and null responders was noted when study arms which received 150 mg of TMC435 were pooled and compared to pooled study arms which received 100 mg of TMC435. In the 150 mg dose groups there appeared to be a trend favoring longer duration of treatment with TMC435 (with respect to SVR 12 and SVR24), but a similar trend in the 100 mg dose groups was not apparent. However, the small number of subjects in the individual study arms limits the interpretability of these data.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

HPC3002 is an ongoing, multicenter, prospective, 3-year observational follow-up study in subjects who received a TMC435-containing regimen for the treatment of HCV infection in Phase 2b or Phase 3 studies.

An interim analysis was performed which includes data obtained up to the data cut-off date of 15 September 2012. As of this cut-off date, 195 subjects were enrolled: 166 TMC435-treated subjects who achieved SVR in the parent study (SVR subjects) and 29 subjects who failed TMC435-containing therapy in the parent study (i.e. subjects who did not achieve SVR). Only 3 subjects (1.5%) had discontinued HPC3002 participation at the time of the interim analysis.

All subjects in the SVR-achiever cohort previously participated in Phase 2b study C205 in treatment-naïve subjects (30 subjects) or in Phase 2b study C206 in treatment-experienced subjects (136 subjects). The demographics of the subjects in HPC3002 were similar to the overall population of the parent studies. All 166 subjects in HPC3002 maintained undetectable HCV RNA until the last available measurement at the time of database lock. Median follow-up time in HPC3002 was 15.7 months (range: 14 to 20 months).

In 16 of 23 evaluable subjects (70%) with sequence data available in the TMC435 treatment-failure cohort, the emergent resistance mutations were no longer detectable at the last HPC3002 visit (median follow-up time: 88 weeks [range: 47 to 147]). In 1 subject (out of these 23 subjects), the mutations present at time of failure

(Q80R+R168E) were no longer detectable at the end of the parent study, and emerging Q80K mutation became detectable and remained detectable until the last available visit.

6.1.10 Additional Efficacy Issues/Analyses

Sponsor's Proposed [redacted] (b) (4) :

[redacted] (b) (4)

[redacted] (b) (4) For reference, the complete virologic stopping criteria used in the Phase 3 studies is provided in Table 14 below:

Table 14: Virologic Stopping Rules Used in the Phase 3 Studies (C208, C216, and HPC3007)

Stop TMC435/placebo and continue with PegIFNα-2a and RBV	
Week 4	HCV RNA levels > 1000 IU/mL
Stop PegIFNα-2a and RBV	
Week 12	< 2 $\log_{10}$ IU/mL reduction of HCV RNA compared to baseline
Week 24	Confirmed detectable and HCV RNA levels ≥ 25 IU/mL
Week 36	Confirmed detectable and HCV RNA levels ≥ 25 IU/mL

[redacted] (b) (4)

(b) (4)

[redacted]

Efficacy in the Partial/Null Responder Population:

The Sponsor has requested an indication for treatment of HCV in partial and null responders based on data from study C206. In Study C206, subjects categorized as partial or null responders received 12 weeks of TMC435 in combination with PR, followed by an additional 36 weeks of PR (refer to Section 5.3 for details on the trial design).

The virologic stopping criteria used in Study 206 are provided in Table 16 below for reference:

Table 16: Virologic Stopping Rules Used in Study C206

Stopping Criteria	Stop all Study Medication (TMC435/Placebo, PegIFNα-2a and RBV) in Case of:
Week 4	< 1 $\log_{10}$ IU/mL reduction in HCV RNA compared to baseline
Week 12	< 2 $\log_{10}$ IU/mL reduction in HCV RNA compared to baseline
Week 24	Confirmed detectable HCV RNA (≥ 10 IU/mL)
Week 36	Confirmed detectable HCV RNA (≥ 10 IU/mL)
Viral breakthrough (Day 1 to Week 48)	• Confirmed increase in HCV RNA of > 1 $\log_{10}$ IU/mL compared with the lowest recorded on-treatment value, or· • Confirmed HCV RNA level of >100 IU/mL if previously below lower limit of quantification (25 IU/mL) or undetectable (< 10 IU/mL)

Note: Detectable HCV RNA after previous undetectability must be confirmed by a repeat HCV RNA testing done within 2 weeks. This might require an unscheduled visit.

Source: Clinical Study Report for Study C206

The Sponsor has proposed in the draft label the following treatment algorithm for patients categorized as partial or null responders.

(b) (4)

The SVR24 results (the primary endpoint for this study) from study C206 by study arm and population (including the overall ITT population, prior relapsers, prior partial responders, and prior null responders) are presented in Table 18.

Table 18: SVR24 Rates in Study C206 by Treatment Arm and Prior Treatment Response

Study	C206						
Subjects per Arm	66	66	65	66	66	68	65
Study Arm	PBO	TMC435 100MG/ 12WKS	TMC435 100MG/ 24WKS	TMC435 100MG/ 48WKS	TMC435 150MG/ 12WKS	TMC435 150MG/ 24WKS	TMC435 150 MG/ 48 WKS
	----------N (%) Subjects Achieving SVR24----------						
ITT Population	15/66 (23%)	46/66 (70%)	43/65 (66%)	40/66 (61%)	44/66 (67%)	49/68 (72%)	52/65 (80%)
Relapsers	10/27 (37%)	24/27 (89%)	23/26 (88%)	20/26 (77%)	20/26 (77%)	24/27 (89%)	23/26 (88%)
Partial Responders	2/23 (9%)	16/23 (70%)	11/23 (48%)	12/22 (55%)	15/23 (65%)	18/24 (75%)	19/22 (86%)
Null Responders	3/16 (19%)	6/16 (38%)	9/16 (56%)	8/18 (44%)	9/17 (53%)	7/17 (41%)	10/17 (59%)

In this Reviewer's opinion, it is reasonable to combine the following two study arms for a pooled efficacy analysis: 1) TMC435 100 mg for 12 weeks with PR for 48 weeks and 2) TMC435 150 mg for 12 weeks with PR for 48 weeks. For both of these arms the duration of TMC435 was 12 weeks (the Sponsor's proposed duration for approval). Although the doses in the two arms differ (i.e. 100 mg versus 150 mg), there are no data or scientific reasons to anticipate that the 100 mg dose of TMC435 would prove more effective than the 150 mg dose. Therefore, this would appear to be a conservative pooling. The SVR24 data from this pooled analysis are presented in Table 19 below.

Table 19: SVR24 Rates in Study C206 by Pooled Treatment Arm and Prior Treatment Response

Study	C206			
Subjects per Arm	66	66	66	132
Study Arm	PBO	TMC435 100MG/ 12WKS	TMC435 150MG/ 12WKS	Pooled TMC435 100MG/12WKS and TMC435 150MG/12WKS
	----------N (%) Subjects Achieving SVR24----------			
ITT Population	15/66 (23%)	46/66 (70%)	44/66 (67%)	90/132 (68%)
Relapsers	10/27 (37%)	24/27 (89%)	20/26 (77%)	44/53 (83%)
Partial Responders	2/23 (9%)	16/23 (70%)	15/23 (65%)	31/46 (67%)
Null Responders	3/16 (19%)	6/16 (38%)	9/17 (53%)	15/33 (45%)

In partial responders, the difference in SVR24 rates between the pooled TMC435 groups and placebo group reached statistical significance (2 tailed Fisher Exact Probability Test < 0.00001). In null responders the difference in SVR24 rates between the pooled TMC435 groups and placebo group did not reach statistical significance (2 tailed Fisher Exact Probability Test < 0.114). The lack of statistical significance in the null responder population may relate to the small sample size of the groups and greater than predicted SVR24 rates in the null placebo group (which was more than twice that of the SVR24 rate in the partial responder placebo group).

Based on the above analyses, in this Reviewer's opinion, it is reasonable to extend the indication of TMC435 for the treatment of partial and null responders. Patients in these populations would receive 12 weeks of TMC435 in combination with PR, followed by an additional 36 weeks of PR. However, given the limited data on outcome in partial and null responder patients with the Q80K baseline polymorphism, it is not recommended that these patients receive treatment with TMC435. In addition, this Reviewer recommends that the submission of final data from the ongoing Phase 3 study in partial and null responders (HPC3001) be deemed a post-marketing commitment.

Please refer to the Statistical Review, Virology Review, and Pharmacometrics Review for additional details.

7 Review of Safety

Safety Summary

Many of the adverse events reported in these trials have been well-described with pegylated interferon and ribavirin therapy. As such, the safety assessment focused largely on the first 12 weeks of the study period (i.e. the period during which TMC435 was administered) to allow for a direct comparison of the safety profile of the study drug (plus PR) to that of placebo (plus PR). Efforts were focused on those categories of

adverse events occurring more frequently in the TMC435 group than the placebo group during the first 12 weeks of treatment.

As previously discussed, the Phase 3 trials, C208, C216, and HPC3007 are multicenter, phase 3, randomized, double-blind controlled trials. Apart from differences in the patient populations (treatment-naïve versus relapsers), the three trials are virtually identical with respect to the study design (including the primary objective and endpoint, stratification factors, inclusion/exclusion criteria, and study schema). As such, these Phase 3 trials were pooled to facilitate the primary safety assessment. The primary safety pool included 781 subjects in the TMC435 group and 397 subjects in the placebo group.

Three deaths occurred in the pooled Phase 3 studies. None of these deaths were considered related to TMC435 per investigator (or this Reviewer). In the pooled Phase 3 analysis, 2% of subjects receiving TMC435 had SAEs compared to 3% of subjects in the control arm. Discontinuation of TMC435 or placebo due to an AE occurred in 2% of subjects in the TMC435 group and 1% of subjects in the control group. The most common AEs (by System Organ Class) leading to discontinuation in the TMC435 group was 'Skin and Subcutaneous Tissue Disorders' which led to discontinuation of TMC435 in 1% of subjects.

Based on the known adverse event profile of the approved HCV protease inhibitors and the safety signals identified during the course of this review, the safety assessment primarily focused on the following areas: skin and soft tissue AEs, hepatobiliary AEs, cardiopulmonary AEs, gastrointestinal AEs, musculoskeletal AEs, blood and lymphatic system disorders, neoplasms, and psychiatric AEs (please refer to Section 7.3.5 for details). In order to facilitate the assessment of AE trends, pooled variables for key AEs were constructed (indicated by single parentheses in the following discussion).

In the MedDRA SOC of skin and subcutaneous tissue disorders, there was a higher incidence of AEs (including SAEs) and discontinuations of study drug in the TMC435 group compared to the control group during the first 12 weeks of treatment. Safety analysis led to the identification of three general categories of interest: Pruritis, Rash, and Photosensitivity.

'Pruritis' occurred in 22% of subjects in the TMC435 group and 15% of subjects in the control group during the first 12 weeks of treatment. However, the vast majority of 'pruritis' AEs were of mild or moderate severity, rarely led to discontinuation of TMC435, and were not the cause of any SAEs over the first 12 weeks of treatment.

'Photosensitivity' was reported in 5% of the TMC435 group compared to 1% of the Control group. No discontinuations of TMC435 due to 'photosensitivity' were reported, but two 'photosensitivity' related SAEs (both requiring hospitalization and one requiring

systemic steroids) occurred in the TMC435 group during the first 12 weeks of treatment; while no SAEs occurred in the Control group.

'Rash excluding photosensitivity' events occurred in 25% of subjects in the TMC435 group and 19% of subjects in the Control group during the first 12 weeks of treatment. Of the seven AEs in the SOC category of 'Skin and Subcutaneous Tissue Disorders' leading to discontinuation of TMC435, six were subsumed under the category of 'rash excluding photosensitivity'.

A greater frequency of AEs associated with increased bilirubin (including grade 3 and 4 AEs) occurred in the TMC435 group compared to the Control group. However, little correlation was noted between the development of hyperbilirubinemia and clinical events necessitating discontinuation of study drug or serious adverse events related to study drug use. No association between the bilirubin elevations anticipated with TMC435 use and clinically relevant hepatototoxicty was appreciated. This Reviewer's safety analyses were generally supportive of the Sponsor's view that the increased bilirubin associated with TMC435 use is primarily due to the inhibition of hepatic transporters

The most notable finding with respect to the cardiopulmonary assessment was an increased frequency of 'dyspnea' in the TMC435 group compared to the Control group. The majority of these events occurred in the first 4 weeks of treatment with TMC435. All of these AEs were of mild or moderate severity. There were no grade 3 or 4 AEs, SAEs, or discontinuations due to 'dyspnea' during the first 12 weeks of treatment in the TMC435 group. An analysis to ascertain whether the reported 'dyspnea' events were associated with the presence of anemia was performed and revealed no clear association The reason for the finding of increased rates of 'dyspnea' in the TMC435 group remains unclear.

A higher frequency of gastrointestinal adverse events was noted in the TMC435 group compared to the control group during the first 12 weeks treatment. The difference was largely driven by an increased frequency of nausea and vomiting in the TMC435 group. However, the vast majority of gastrointestinal AEs were of mild or moderate intensity, and SAEs and discontinuations due to gastrointestinal AEs were extremely rare.

Myalgias, arthralgias, and back pain occurred with greater frequency in the TMC435 group compared to the Control group. However, grade 3 events were rare and there were no grade 4 AEs, no SAEs and no discontinuations of TMC435 due to these AEs.

No substantive differences in hematologic AEs or hematologic laboratory abnormalities were noted when comparing the TMC435 group to the control group during the first 12 weeks of treatment. Additionally, there was no consistent evidence of a neoplastic safety signal related to TMC435; and no safety signals related to psychiatric adverse events were noted. The vast majority of the psychiatric AEs reported could be either

fully or partially explained by the concomitant administration of pegylated interferon and ribavirin.

7.1 Methods

As discussed previously, the Phase 3 trials, C208, C216, and HPC3007 are multicenter, phase 3, randomized, double-blind controlled trials. They each include 2 parallel treatment arms: TMC435 150 mg or placebo as part of a treatment regimen including pegylated interferon and ribavirin, in genotype 1 HCV-infected patients, with compensated liver disease including cirrhosis. Study C208 and C216 are evaluating treatment-naïve patients while study HPC3007 is evaluating patients who have relapsed after prior HCV treatment. Apart from differences in the patient populations (treatment-naïve versus relapsers), the three trials are virtually identical with respect to the study design (including the primary objective and endpoint, stratification factors, inclusion/exclusion criteria, and study schema). As such, these Phase 3 trials were pooled to facilitate the primary safety assessment. The primary safety pool included 781 subjects in the TMC435 group and 397 subjects in the placebo group. The safety assessment focused largely on the first 12 weeks of the study period (i.e. the period during which TMC435 was administered) to allow for a direct comparison of the safety profile of the study drug (plus PR) to that of placebo (plus PR). In addition to performing the primary safety assessment, selected safety data from the Phase 2b trials (C205 and C206) were reviewed to enhance the safety analysis.

This Reviewer identified specific adverse events of interest based on the cumulative safety data from the non-clinical studies, Phase 1 through Phase 3 clinical trials of TMC435, and the known safety profiles of the currently approved HCV protease inhibitors. This cumulative data, in addition to adverse events of interest identified during the course of this review, was used to create a specific safety analysis section, 'Submission Specific Primary Safety Concerns' (Section 7.3.5).

The original NDA submission included safety data through Week 60 for trials C208, C216, and HPC3007 using a primary analysis data cut-off of October 2012. A two month Safety Update Report (SUR) was also provided, with a final database cutoff date of March 2013 for the pivotal phase 3 trials. As these clinical trials were not powered to detect statistically significant differences in AEs, when differences in frequency of AEs are noted in the following sections, it does not necessarily imply that these differences are statistically significant.

Overall, the FDA's pooled Phase 3 safety data analyses replicated the Applicant's findings with few exceptions. The exceptions did not lead to a clinically meaningful difference, and were due to methods used in identifying the specific subject population of interest, pooling preferred terms outside of the MedDRA classification scheme or differences in attribution of treatment-relatedness.

All data tables in this section were generated by the primary clinical reviewer from the ISS datasets using JReview unless otherwise specified.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The Applicant's summary of clinical safety in support of TMC435 relied primarily on safety data from three Phase 3 trials (C208, C216, and HPC3007) and two Phase 2 trials (C205 and C206). The Applicant also included high-level safety data from their Phase 1 studies as well as their TMC435 development program in Japan.

This NDA review focuses on the safety data from the three Phase 3 trials (C208, C216, and HPC3007) with periodic use of additional supportive data from the Phase 2 trials (C205 and C206). As mentioned above, safety data from the non-clinical studies, Phase 1 through Phase 3 clinical trials of TMC435, and the known safety profiles of the currently approved HCV protease inhibitors were considered for identification of specific adverse events of interest.

7.1.2 Categorization of Adverse Events

The sponsor coded AEs using MedDRA version 15.0. An assessment of the Applicant's coding of events was performed to assure appropriate mapping of the investigators' verbatim terms to the selected MedDRA Preferred terms. Particular attention was given to serious adverse events, grade 3/4 adverse events, and adverse events that led to study drug discontinuation. Additionally, a random check of adverse events without respect to severity or causality of adverse events was performed. No issues of concern were identified.

The WHO toxicity grading scale was used by the Sponsor for grading AEs in the key Phase 2b (C205, C206) and Phase 3 studies (C208, C216, and HPC3007).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Phase 3 trials were virtually identical in design with the exception of the study population evaluated (treatment naïve patients in C208 and C216 and patients who relapsed after HCV treatment in HPC3007). Therefore, the safety data were pooled for estimating and comparing safety incidence.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A total of 1,153 HCV-infected subjects were treated with TMC435 150 mg q.d. for 12 weeks. The total person-years of exposure to TMC435 was 174.2 in the pooled Phase 3 trials C208, C216, and HPC3007. Given the Applicant's suggested post-approval treatment dosage and duration, this reviewer considers the overall exposure to TMC435 to be adequate.

Please refer to Section 6.1.2 for a summary of participant demographics in the Phase 3 pivotal trials.

7.2.2 Explorations for Dose Response

Dr Jiang Liu (Pharmacometrics) performed analyses assessing the correlation of TMC435 exposure (based on subjects' AUC_{24} values) with adverse event frequency in the pooled Phase 3 trials C208, C216, and HPC3007. In these analyses, anemia, dyspnea, increased bilirubin, pruritis, rash and photosensitivity all demonstrated increased frequency with increasing drug exposures. Please refer to the FDA Pharmacometrics Review for additional details.

Please refer to Section 7.5.1 for a discussion of this Reviewer's analyses of dose dependency for adverse events. The Sponsor also provided analyses with respect to dose response which were duly reviewed.

7.2.3 Special Animal and/or In Vitro Testing

Appropriate preclinical testing was performed as summarized in Section 4.3 of this review. Please refer to the Pharmacology/Toxicology Review by Dr. Janice Lansita for additional details.

7.2.4 Routine Clinical Testing

Routine clinical testing was performed at pre-specified regular intervals during the pivotal Phase 2b and Phase 3 trials. The frequency and scope of this testing was deemed adequate. Safety assessments primarily included the following: physical examinations, measurement of vital signs, clinical laboratory testing, and ECG monitoring. Additional testing was performed as indicated during the trials.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to Section 4.4.2 and 4.4.3 respectively for a discussion of the PD and PK profile of Simeprevir. Please refer to Section 7.5.5 for a discussion of drug-drug interactions.

Please refer to the Clinical Pharmacology Review by Dr. Leslie Chinn for additional details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The known safety profiles of the currently FDA approved HCV protease inhibitors (refer to Section 2.4 for details) were taken into careful account in the selection of safety analyses. Specifically, this Reviewer performed detailed assessments for serious skin reactions/rash, dysguesia, anemia, neutropenia, thrombocytopenia, hyperbilirubinemia, and anorectal disorders based on the AE profile of this drug class.

7.3 Major Safety Results

7.3.1 Deaths

In the pooled Phase 2b and Phase 3 analysis (including Studies C205, C206, C208, C216, and HPC3007), 4 deaths were reported in subjects receiving TMC435. No deaths were reported in the control arms. The events are summarized in Table 20 and described in more detail below.

Table 20: Deaths Listing

Subject ID	Treatment Group	Age	Sex	Race	First Dose TMC435 (Study Day)	Last Dose TMC435 (Study Day)	Death (Study Day)	Cause of Death
Study C206								
206-0278	TMC435	47	M	White	1	Unknown	242	Bacterial Meningitis and Brain Hemorrhage
Study C216								
216-3002	TMC435	49	F	White	1	85	196	Colon Cancer
216-3232	TMC435	62	F	American Indian or Alaska Native	1	83	118	Presumed Cardiopulmonary Event
Study HPC3007								
3007-6252	TMC435	57	F	White	1	84	90	Bilateral Pneumonia and Septic Shock

Subject 206-0278: 47 year old white male with periodontitis and an F2 Metavir score at study entry, experienced a grade 3 convulsion on an unspecified date approximately 9 months after study entry. On Study Day (SD) 227, 6 days after discontinuation of study drugs, the subject was hospitalized and SAEs were subsequently reported for bacterial meningitis, coma, and brain injury. Tests for bacterial meningitis revealed *Streptococcus gordonii*. The events of bacterial meningitis, brain injury, and coma were considered by the investigator to be not related to TMC435/placebo and RBV but probably related to PegIFN-2a. On SD236, the SAE cerebral hemorrhage was reported and the subject died on SD242. No autopsy was performed. [N.B. Available information on this subject was limited].

This reviewer generally concurs with the investigator's assessment. The subject's periodontitis may have led to *S. gordonii* systemic infection (perhaps endocarditis) with subsequent CNS involvement and rapid deterioration in clinical status. PegIFN may have contributed to the risk of infection.

Subject 216-3002: 49 year old white female with a history of supraclavicular lymph node enlargement and an F3 Metavir score received TMC435 from SD1 to SD85. On SD168, she was hospitalized with abdominal pain and diagnosed with colon cancer. Both were considered unrelated to study drugs by the investigator. The subject subsequently underwent surgical resection of the tumor (date not provided) and died on SD196. No autopsy was performed. This reviewer concurs with the investigator's causality assessment.

Subject 216-3232: 62 year old female with an F4 Metavir score at screening and an otherwise unremarkable medical and family history, received TMC435 from SD1 to SD83. On SD105, grade 2 diarrhea and grade 1 rectal hemorrhage were reported. The event of diarrhea was considered not to be related to TMC435, doubtfully related to RBV, and probably related to PegIFNα-2a by the investigator. The event of rectal hemorrhage was considered not to be related to the study medications (TMC435, RBV, and PegIFNα-2a) by the investigator. Laboratory data from SD112 revealed grade 1 hypomagnesemia and grade 1 hypokalemia. No treatment emergent ECG abnormalities were reported. The study medications (PegIFNα-2a, and RBV) were permanently discontinued on SD113 due to the event of diarrhea. No concomitant medications were reported for these events. On SD118, the subject died suddenly, and it was considered to be secondary to a "cardiopulmonary event". An autopsy was not performed. This reviewer agrees that the diarrhea reported 22 days after completion of TMC435 and the presumed cardiopulmonary arrest occurring 35 days after completion of TMC435 are likely not related to TMC435.

Subject 3007-6252: 37 year old white female with a history of opiate addiction (receiving naloxone/buprenorphine), alcoholism, COPD, and an F4 Metavir score at screening received TMC435 from SD2 to SD84. On SD89, the subject was admitted to the hospital and the following grade 4 SAEs were reported: pneumonia, septic shock,

respiratory acidosis, dyspnea, pyrexia, confusional state, and pancytopenia. These SAEs were considered to be not related to TMC435 and RBV, and doubtfully related to PegIFNα-2a. The patient's blood culture and bronchial secretion cultures yielded *Pseudomonas aeruginosa*, and the lung biopsy culture yielded both *P. aeruginosa* and *Enterobacter cloacae*. On SD90, the subject developed bradycardia (grade 4 SAE), hypoxia, and cardiac arrest. Resuscitation efforts failed and the subject died on SD90. The autopsy report indicated the cause of death as bilateral pneumonia and septic shock. This reviewer concurs with the investigator's causality assessment.

7.3.2 Nonfatal Serious Adverse Events

In the pooled Phase 3 analysis, 2% (16/781) of subjects receiving TMC435 had SAEs compared to 3% (10/397) of subjects in the control arm during the first 12 weeks of treatment. The most commonly reported SAE (by MedDRA System Organ Class or SOC) in the TMC435 group was 'psychiatric disorders' reported in 1% of TMC435 recipients. All other SAEs (by SOC) occurred in <1% of TMC435 recipients. Table 21 summarizes all SAEs that occurred in the first 12 weeks of the pooled Phase 3 trials. Multiple AEs were counted only once per subject for each system organ class.

Three subjects (0.4%) in the TMC435 group experienced SAEs which were deemed related (i.e. possibly, probably, or definitely related) to TMC435 by the study investigator. These included the MedDRA preferred terms (PTs) 'Major Depression' in one subject and 'Photosensitivity Reaction' in two subjects.

All SAEs that occurred in the TMC435 group during the first 12 weeks of treatment were reviewed. Please see Section 7.3.5, Submission Specific Primary Safety Concerns, for further details with respect to SAEs of interest related to skin and soft tissue disorders, psychiatric disorders, gastrointestinal disorders, hepatobiliary disorders, cardiopulmonary disorders, hematologic disorders, neoplastic disorders, and musculoskeletal disorders.

Table 21: Serious Adverse Events Occurring in the First 12 Weeks in the Phase 3 Trials

	First 12 Weeks	
	TMC435	PBO
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
Number (%) of Subjects Experiencing Any SAE	16 (2%)	10 (3%)
Psychiatric disorders	4 (1%)	1 (<1%)
Aggression	1 (<1%)	0 (0%)
Anxiety	0 (0%)	1 (<1%)
Depression	2 (<1%)	0 (0%)
Major depression	1 (<1%)	0 (0%)
Infections and infestations	3 (<1%)	2 (1%)
Abscess limb	1 (<1%)	0 (0%)
Bacterial prostatitis	0 (0%)	1 (<1%)
Cellulitis	1 (<1%)	0 (0%)
Lymphadenitis bacterial	1 (<1%)	0 (0%)
Staphylococcal infection	0 (0%)	1 (<1%)
Urinary tract infection	1 (<1%)	0 (0%)
Nervous system disorders	2 (<1%)	3 (1%)
Migraine	0 (0%)	1 (<1%)
Neuropathy peripheral	0 (0%)	1 (<1%)
Syncope	2 (<1%)	0 (0%)
Thoracic outlet syndrome	0 (0%)	1 (<1%)
Hepatobiliary disorders	2 (<1%)	0 (0%)
Bile duct obstruction	1 (<1%)	0 (0%)
Hepatic lesion	1 (<1%)	0 (0%)
Skin and subcutaneous tissue disorders	2 (<1%)	0 (0%)
Photosensitivity reaction	2 (<1%)	0 (0%)
Vascular disorders	1 (<1%)	1 (<1%)
Arterial stenosis limb	0 (0%)	1 (<1%)
Hypotension	1 (<1%)	0 (0%)
Ear and labyrinth disorders	1 (<1%)	0 (0%)
Mixed deafness	1 (<1%)	0 (0%)
Eye disorders	1 (<1%)	0 (0%)
Hyphaema	1 (<1%)	0 (0%)
Gastrointestinal disorders	1 (<1%)	0 (0%)
Abdominal pain	1 (<1%)	0 (0%)
Renal and urinary disorders	1 (<1%)	0 (0%)
Acute prerenal failure	1 (<1%)	0 (0%)
Reproductive system and breast disorders	1 (<1%)	0 (0%)
Vaginal hemorrhage	1 (<1%)	0 (0%)
Injury, poisoning and procedural complications	1 (<1%)	0 (0%)
Overdose	1 (<1%)	0 (0%)

Musculoskeletal and connective tissue disorders	1 (<1%)	0 (0%)
Muscle spasms	1 (<1%)	0 (0%)
Cardiac disorders	0 (0%)	1 (<1%)
Pericarditis	0 (0%)	1 (<1%)
Blood and lymphatic system disorders	0 (0%)	2 (1%)
Anemia	0 (0%)	2 (1%)
Respiratory, thoracic and mediastinal disorders	0 (0%)	1 (<1%)
Pulmonary embolism	0 (0%)	1 (<1%)

7.3.3 Dropouts and/or Discontinuations

Overall, 14/781 subjects (2%) in the TMC435 group and 5/397 subjects (1%) in the control group experienced at least 1 AE leading to discontinuation of TMC435. The most common AEs (by System Organ Class) leading to discontinuation in the TMC435 group included 'Skin and Subcutaneous Tissue Disorders' and 'Psychiatric Disorders' which led to discontinuation of TMC435 in 1% and <1% of subjects respectively. Table 22 summarizes the number (%) of subjects who experienced any AE that led to discontinuation of TMC435 during the first 12 weeks of treatment. Multiple AEs were counted only once per subject for each MedDRA term (SOC and PT).

All AEs leading to discontinuation of TMC435 were reviewed. Please see Section 7.3.5, Submission Specific Primary Safety Concerns, for further details with respect to the discontinuations of TMC435 related to skin and soft tissue disorders, psychiatric disorders, gastrointestinal disorders, hepatobiliary disorders, cardiopulmonary disorders, hematologic disorders, neoplastic disorders, and musculoskeletal disorders. Please refer to section 7.6.2 for details regarding the pregnancy (Subject 208-0409) noted in Table 22.

Table 22: Number (%) of Subjects Experiencing Any AE Leading to Premature Study Drug Discontinuation During the First 12 Weeks (by System Organ Class and Preferred Term)

	First 12 Weeks	
Study Arm	TMC435	PBO
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
Number (%) of Subjects Discontinuing TMC435 due to AE (Presented by SOC and PT)	14 (2%)	5 (1%)
Skin and subcutaneous tissue disorders	7 (1%)	1 (<1%)
Pruritus	1 (<1%)	0 (0%)
Psoriasis	1 (<1%)	0 (0%)
Rash	5 (1%)	0 (0%)
Rash erythematous	1 (<1%)	0 (0%)
Rash maculo-papular	1 (<1%)	1 (<1%)
Skin burning sensation	1 (<1%)	0 (0%)
Psychiatric disorders	3 (<1%)	1 (<1%)
Aggression	1 (<1%)	0 (0%)
Anxiety	1 (<1%)	1 (<1%)
Depression	0 (0%)	1 (<1%)
Major depression	1 (<1%)	0 (0%)
Investigations	2 (<1%)	1 (<1%)
Blood bilirubin increased	1 (<1%)	0 (0%)
Pregnancy test positive	1 (<1%)	0 (0%)
Transaminases increased	0 (0%)	1 (<1%)
Injury, poisoning and procedural complications	1 (<1%)	0 (0%)
Overdose	1 (<1%)	0 (0%)
Gastrointestinal disorders	1 (<1%)	0 (0%)
Stomatitis	1 (<1%)	0 (0%)
Nervous system disorders	1 (<1%)	0 (0%)
Headache	1 (<1%)	0 (0%)
General disorders and administration site conditions	1 (<1%)	1 (<1%)
Fatigue	0 (0%)	1 (<1%)
Pain	1 (<1%)	0 (0%)
Blood and lymphatic system disorders	0 (0%)	1 (<1%)
Neutropenia	0 (0%)	1 (<1%)

7.3.4 Significant Adverse Events

60% of subjects in the TMC435 group experienced an AE of at least moderate severity in the first 12 weeks of treatment compared to 55% of subjects in the control group. Table 23 summarizes the treatment-emergent adverse events of at least moderate

severity reported in at least 2% of subjects in the TMC435 group. Multiple AEs were counted only once per subject for each Preferred Term.

Table 23: Treatment-Emergent Adverse Events of at Least Moderate Severity (Grades 2-4) Reported in at Least 2% of Subjects Receiving TMC435

	First 12 Weeks	
Study Arm	TMC435	PBO
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
MedDRA Preferred Term, Number (%) of Subjects		
Neutropenia	92 (12%)	44 (11%)
Influenza like illness	58 (7%)	16 (4%)
Anemia	52 (7%)	25 (6%)
Headache	52 (7%)	29 (7%)
Fatigue	47 (6%)	34 (9%)
Rash	43 (6%)	10 (3%)
Insomnia	41 (5%)	18 (5%)
Pyrexia	33 (4%)	21 (5%)
Nausea	31 (4%)	9 (2%)
Asthenia	29 (4%)	13 (3%)
Depression	26 (3%)	9 (2%)
Hyperbilirubinemia	25 (3%)	6 (2%)
Thrombocytopenia	23 (3%)	6 (2%)
Myalgia	23 (3%)	7 (2%)
Pruritus	21 (3%)	3 (1%)
Mood altered	19 (2%)	6 (2%)
Back pain	19 (2%)	7 (2%)
Blood bilirubin increased	17 (2%)	3 (1%)
Diarrhea	16 (2%)	7 (2%)
Cough	14 (2%)	3 (1%)
Arthralgia	13 (2%)	4 (1%)
Neutrophil count decreased	13 (2%)	7 (2%)
Anxiety	13 (2%)	9 (2%)

The majority of the events summarized in Table 23 were of moderate (grade 2) severity in both treatment groups. There were 172 (22%) subjects in the TMC435 group, and 94 (24%) subjects in the control group with grade 3 events. There were 23 (3%) subjects in the TMC435 group and 11 (3%) subjects in the control group with grade 4 events.

Table 24 summarizes the grade 3 and grade 4 AEs that occurred in ≥ 2 subjects in the TMC435 group in the first 12 weeks of treatment. Multiple AEs were counted only once per subject for each Preferred Term.

Table 24: Grade 3 and 4 AEs Occurring in ≥ 2 Subjects in the TMC435 Group During the First 12 Weeks

	First 12 Weeks	
Study Arm	TMC435	PBO
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
MedDRA Preferred Term, Number (%) of Subjects		
Neutropenia	72 (9%)	34 (9%)
Thrombocytopenia	11 (1%)	2 (1%)
Hyperbilirubinaemia	9 (1%)	1 (<1%)
Neutrophil count decreased	9 (1%)	5 (1%)
Blood bilirubin increased	7 (1%)	1 (<1%)
Leukopenia	7 (1%)	2 (1%)
Alanine aminotransferase increased	7 (1%)	7 (2%)
Aspartate aminotransferase increased	6 (1%)	4 (1%)
Anemia	6 (1%)	7 (2%)
Headache	5 (1%)	6 (2%)
Pyrexia	4 (1%)	2 (1%)
Influenza like illness	4 (1%)	2 (1%)
Amylase increased	3 (<1%)	0 (0%)
Rash	3 (<1%)	0 (0%)
Back pain	3 (<1%)	1 (<1%)
Platelet count decreased	3 (<1%)	2 (1%)
Fatigue	3 (<1%)	6 (2%)
Lipase increased	2 (<1%)	0 (0%)
Syncope	2 (<1%)	0 (0%)
Nausea	2 (<1%)	0 (0%)
Granulocytopenia	2 (<1%)	1 (0%)
Hemoglobin decreased	2 (<1%)	1 (<1%)
Depression	2 (<1%)	2 (1%)
Asthenia	2 (<1%)	2 (1%)

7.3.5 Submission Specific Primary Safety Concerns

Skin and Soft Tissue Adverse Events

Overview:

There was a higher incidence of skin and subcutaneous tissue disorders (by SOC) in the TMC435 group (49%) compared to the control group (38%) during the first 12 weeks of treatment. The difference in incidence was primarily due to an increase in AEs under

the MedDRA high level group term (HLGT) 'Epidermal and Dermal Conditions'. No other substantive differences were noted based on HLGT between TMC435 and Control groups. Table 25 summarizes the incidence of skin and subcutaneous tissue disorders (by HLGT) during the first 12 weeks of treatment.

Table 25: Skin and Subcutaneous Tissue Disorders by HLGT During the First 12 Weeks of Treatment

	First 12 Weeks	
Study Arm	TMC435	PBO
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
MedDRA HLGT, Number (%) of Subjects		
Epidermal and dermal conditions	352 (45%)	134 (34%)
Skin appendage conditions	73 (9%)	33 (8%)
Skin vascular abnormalities	5 (1%)	1 (<1%)
Angioedema and urticaria	4 (1%)	3 (1%)
Pigmentation disorders	3 (<1%)	1 (<1%)
Skin and subcutaneous tissue disorders NEC	1 (<1%)	0 (0%)
Cornification and dystrophic skin disorders	0 (0%)	3 (1%)

Table 26 details the composition of the AEs under HLGT 'Epidermal and Dermal Conditions' when further stratified by higher level term (HLT). The most common HLTs in both the TMC435 and control groups in this analysis were 'pruritis' and 'rashes, eruptions, and exanthems.' AEs under these HLTs occurred with greater frequency in the TMC435 group than the control group. In addition, AEs under the HLT 'photosensitivity conditions' also occurred with greater frequency in the TMC435 group.

Table 26: AEs Reported Under HLGT 'Epidermal and Dermal Conditions' in the First 12 Weeks of Treatment (Stratified by HLT)

	First 12 Weeks	
Study Arm	TMC435	PBO
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
MedDRA HLT, Number (%) of Subjects		
Pruritus NEC	172 (22%)	59 (15%)
Rashes, eruptions and exanthems NEC	130 (17%)	50 (13%)
Dermal and epidermal conditions NEC	70 (9%)	32 (8%)
Dermatitis and eczema	36 (5%)	13 (3%)
Erythemas	29 (4%)	13 (3%)
Photosensitivity conditions	26 (3%)	2 (1%)
Psoriatic conditions	9 (1%)	1 (<1%)
Papulosquamous conditions	7 (1%)	5 (1%)
Exfoliative conditions	6 (1%)	1 (<1%)
Dermatitis ascribed to specific agent	3 (<1%)	0 (0%)
Bullous conditions	1 (<1%)	1 (<1%)
Skin injuries and mechanical dermatoses	1 (0%)	0 (0%)

The following table details the toxicity grading scale for cutaneous adverse events used in Studies C208, C216, and HPC3007.

Table 27: Toxicity Grading Scale for Cutaneous Adverse Events (Studies C208, C216, and HPC3007)

WHO Toxicity Grade	Definitions
Grade 1	Erythema
Grade 2	Diffuse Maculopapular Rash OR Dry Desquamation
Grade 3	Vesiculation, Moist Desquamation, or ulceration OR Cutaneous reaction with at least 1 of the following*: -Elevations in ALT/AST more than 2 x baseline value -Fever (> 38°C or 100°F); -Serum sickness-like reaction; -Eosinophils > 1000/mm^3
Grade 4	Exfoliative dermatitis; Mucous membrane involvement; Erythema multiforme; Suspected Stevens-Johnson; Necrosis requiring surgery

* This criteria was revised by the Sponsor

A total of 8 subjects in the TMC435 group experienced Grade 3 AEs during the first 12 weeks under the SOC category of 'Skin and Subcutaneous Tissue Disorders.' These AEs (by PT) included the following: alopecia, photosensitivity reaction, pruritis, psoriasis, rash, and rash erythematous. Each of these occurred in only 1 subject except 'rash' which occurred in 3 subjects. No Grade 4 AEs were reported in the TMC435 group during the first 12 weeks of treatment. No Grade 3 or 4 AEs were reported in the control group during this period.

A total of 2 subjects in the TMC435 group and no subjects in the control group experienced an SAE in the SOC category of 'Skin and Subcutaneous Tissue Disorders' during the first 12 weeks of treatment. Both of these were for the AE 'photosensitivity reaction.' These events are summarized in Table 28 and discussed at greater length in the 'photosensitivity' sub-section below.

A total of 7 subjects (1%) discontinued TMC435 during the first 12 weeks of treatment due to an AE under the SOC category of 'Skin and Subcutaneous Tissue Disorders' compared to 1 subject (<1%) in the Control Group (PT 'rash maculo-papular'). All of these events were subsumed under the HLGT 'Epidermal and Dermal Conditions'. These events are summarized in Table 28 and discussed at greater length in the 'rash' sub-section below.

Table 28: Summary of Subjects in the Pooled Phase 3 Studies with SAEs or AEs Leading to Discontinuation of Study Drug Under the MedDRA SOC 'Skin and Subcutaneous Tissue Disorders' During the First 12 Weeks of Treatment

Subject Number	Age Race/ Sex	MedDRA PT (SAE† or led to D/C)	SD (Onset/ Resolution)	Worst Toxicity Grade	Associated Laboratory Findings*/ SD	Associated Mucosal Findings	Systemic Steroids Admin.
TMC435 TREATMENT GROUP							
208-0019	48 W/F	Rash	31/48	3	No	No	No
208-0066	56 W/M	Rash	54/194	2	Grade 1 ALT/ SD86	No	No
208-0243	59 W/F	Rash	61/129	3	No	No	No
208-0416	59 W/M	Rash	67/~240	2	↑Eos (0.73 x 10^9)/ SD86	Apthous Stomatitis/ SD75	Yes
208-0340	46 W/M	Psoriasis	14/ Ongoing	3	No	No	No
216-3022	49 W/F	Rash	52/93	2	No	Mouth Ulceration/ SD57	No
216-3475	40 W/M	Maculo-Papular Rash	32/61	3	No	Apthous Stomatitis/ SD42	No
3007-6128	35 W/M	Photo-sensitivity†	60/86	2	No	No	Yes
3007-6189	44 W/M	Photo-sensitivity†	41/114	3	No	No	No
CONTROL GROUP							
208-0003	38 W/F	Maculo-Papular Rash	44/71	2	↑Eos (0.71 x 10^9)/ SD62	No	No

*Specifically blood eosinophilia and/or presence of transaminitis

The following sub-sections will provide more detail with respect to the AEs which are subsumed under the general categories of pruritis, rash, and photosensitivity. To facilitate review of these AEs, grouped terms were created (defined in detail below). It should be noted, however, that a significant degree of overlap in AE occurrence was noted with respect to these three general categories. In particular, the use of narrow pooling for photosensitivity events may underestimate the actual rate of occurrence of photosensitivity events as some of these events (consistent with photosensitivity) were reported under the more general pooled term of rash.

Pruritis:

Three PTs were reported under the HLT 'Pruritis NEC' during the first 12 weeks of treatment. These included 'pruritis', 'pruritis generalized' and 'rash pruritic.' The PTs

'pruritis' and 'pruritis generalized' were pooled and a new variable termed 'pruritis' was created to facilitate review of this AE. The group term 'pruritis' occurred in 168 subjects (22%) in the TMC435 group and 58 subjects (15%) in the Control group. The investigator deemed 'pruritis' as related to TMC435 or Placebo for TMC435 in 127 subjects in the TMC group (16%) and 34 subjects (9%) of the Control group. Only one subject (<1%) in the TMC435 group and no subjects in the Control group had a grade 3 event in this pooled category during the first 12 weeks of treatment. Only one subject (Subject 208-0243) in the TMC435 group discontinued TMC435 related to an event in this pooled category during the first 12 weeks of treatment. It is notable that this AE was associated with a grade 3 rash which was likely the primary driver of study drug discontinuation (please see individual participant summaries under the rash sub-section for additional details). No discontinuations occurred in the control group related to an AE in this category over the same period of time. No SAEs or grade 4 AEs due to 'pruritis' occurred in either group during the first 12 weeks of treatment.

Additional analyses were performed to ascertain whether an association between pruritis and increased bilirubin or an association between pruritis and rash was present. Of the 168 TMC435 subjects with an AE under the grouped term 'pruritis' during the first 12 weeks of the study, 85/168 (51%) also had graded elevations in bilirubin reported during that time period [grade 1 in 50/85 (30%) subjects, grade 2 in 27/85 (16%) subjects, grade 3 in 6/85 (4%) subjects, and grade 4 in 2/85 (1%) subjects]. As the overall frequency and distribution of graded bilirubin abnormalities was very similar in subjects with 'pruritis' compared to that of the TMC435 study population as a whole (which had a frequency of 50% for graded bilirubin abnormalities), no clear association between 'pruritis' and elevated bilirubin levels could be established. Of the 168 TMC435 subjects with an AE under the grouped term 'pruritis' during the first 12 weeks of the study, 76/168 (45%) also had an AE under the grouped term 'rash' reported during that time period. As the frequency of 'rash' for the TMC435 study population as whole during that period was 28% (compared to 45% in the sub-population with 'pruritis'), it appears that an association was present between rash and pruritis in the pooled Phase 3 studies.

Photosensitivity:

In vitro studies revealed that TMC435 was phototoxic after UVA exposure and photosensitivity reactions were reported with clinical experience. Therefore, as a precaution, subjects were asked to adhere to the following sun-protection measures during TMC435 administration and up to 1 month post administration in the Phase 2b and III protocols: *Extreme exposure to the sun or sunbathing should be avoided, as well as the use of tanning devices (e.g., sunbed, solarium) from baseline until last intake of TMC435/placebo. Ideally, outdoor activities should be scheduled outside the hours that UV radiation is most intense or should be performed in the shade. Wide-brim hats, sunglasses, and use of sunscreens are recommended to maximize sun protection.*

However, based on the results of study C125 showing that TMC435 was not associated with a delayed photosensitizing effect (refer to Section 7.4.5 for details) the sun-protective measures in the Phase 3 protocols were removed. However, these sun-protection measures were removed in an amendment which became effective only after all subjects had completed treatment with TMC435. Thus, 100% of subjects in the Phase 2b and Phase 3 studies completed treatment with TMC435 prior to the discontinuation of these measures.

In order to facilitate the review of photosensitivity related AEs, this Reviewer created a new grouped variable termed 'photosensitivity.' The grouped variable 'photosensitivity' includes the following PTs: photodermatosis, photosensitivity reaction, polymorphic light eruption, solar dermatitis, and sunburn. During the first 12 weeks of treatment 'photosensitivity' was reported in 38 subjects (5%) of the TMC435 group compared to 3 subjects (1%) in the Control group. The investigator deemed 'photosensitivity' as related to TMC435 or Placebo for TMC435 in 29 subjects in the TMC group (4%) and 2 subjects (1%) of the Control group.

Only one 'photosensitivity' event met either grade 3 or grade 4 criteria. That event was a grade 3 SAE under the PT 'photosensitivity reaction' in the TMC435 Group in Subject 3007-6189 which is described below. No discontinuations of TMC435 due to the pooled AE 'photosensitivity' were reported. However, per protocol, Subject 3007-6189 who developed the grade 3 photosensitivity AE should have permanently discontinued all study medications (including TMC435); continuing this patient on study medications was later deemed a protocol deviation. Two 'photosensitivity' related SAEs (both under the PT 'photosensitivity reaction') occurred in the TMC435 group during the first 12 weeks of treatment. No 'photosensitivity' related SAEs occurred in the Control group during the same time period. The following are summaries of the SAEs in the TMC435 group:

Subject 3007-6128: 35 year old white male with an unremarkable medical history and a screening Metavir score of F0-F1, developed the grade 1 AE 'sunburn' on SD60. The investigator considered this event as possibly related to the study medications (TMC435, RBV, and PegIFNα-2a). On SD69, the subject presented to the hospital with complaints of facial swelling and pain. Treatment included prednisone 100 mg IV daily. The subject was discharged on SD70. The physical examination on the following day showed partly oozing erythematous scaly lesions on the forehead, nasal hump, and lips due to sunburn; an SAE of photosensitivity reaction of grade 2 severity was reported. The investigator considered this event as possibly related to the study medications (TMC435, RBV, and PegIFNα-2a). Treatment with TMC435 was interrupted on SD70 due to this event. No action was taken with RBV and PegIFNα-2a due to this event. The event was reported as resolved on SD86. The subject completed the study treatment and received his last dose of TMC435 on SD84 and PegIFNα-2a and RBV on SD169. This Reviewer agrees that photosensitivity reaction was related to TMC435.

Subject 3007-6189: 44 year old white male with a history of asthma and a screening Metavir score of F3, developed grade 1 sunburn on SD 6 which resolved on SD9 and was deemed unrelated to study medications (TMC435, PegIFNα-2a, and RBV). On SD40, he developed a febrile syndrome following unprotected sun exposure the previous day. On SD41, he developed blisters on his arms, neck, head, ears, and nose with associated left arm edema. He was subsequently hospitalized and a grade 3 SAE photosensitivity reaction was reported which was considered to be probably related to TMC435 and not related to PegIFNα-2a and RBV. TMC435 treatment was interrupted during his hospitalization (due to lack of access to the drug), but no formal action was taken with the study medications due to the events of peripheral edema and photosensitivity reaction. The subject was discharged on SD44. He had rapid scarring of the cutaneous lesions by SD46. On SD50, the infiltrative lesions recurred on the neck and ears after a brief sun exposure, despite adequate protective clothing. More bullous lesions were reported on the back of the hands, vertex and ears and the subject was re-hospitalized. Urine porphyrines test results showed an increase of coproporphyrines, hexacarboxyporphyrines, and uroporphyrines. However, a skin biopsy excluded the diagnosis of porphyria cutanea tarda and was judged consistent with an eczematous-like drug eruption. Immunofluorescent investigation showed several granular deposits of C3 in the dermo-epidermal junction and in dermal vessels. Liver function tests were normal, except for slightly elevated lactate dehydrogenase. Treatment of the subject included topical betamethasone and sulfadiazine silver. The subject was discharged on SD52. By SD57, the event of photosensitivity reaction improved in severity, and was reported as a grade 2 AE. The subject completed treatment with TMC435, with the last dose received on SD87. The events of peripheral edema and photosensitivity reaction were reported as resolved on SD114. This reviewer concurs with the investigator's assessment of causality.

Rash:

In order to facilitate the review of rash events, a grouped term 'rash' was created which includes the following MedDRA PTs: Rash, Erythema, Eczema, Rash maculo-papular, Rash macular, Dermatitis, Rash papular, Skin exfoliation, Rash pruritic, Rash erythematous, Urticaria, Rash generalized, Drug eruption, Dermatitis allergic, Dermatosis, Vasculitic rash, Toxic skin eruption, Exfoliative rash, Generalised erythema, Dermatitis exfoliative, Cutaneous vasculitis, Photosensitivity reaction, Polymorphic light eruption, Solar dermatitis, Photodermatosis, and Sunburn.

The overall frequency of 'rash' and the individual MedDRA PTs that comprised this pooled term are outlined in Table 29 below. Overall, 'rash' occurred in 28% of subjects in the TMC435 group and 20% of subjects in the Control group during the first 12 weeks of treatment.

Table 29: Pooled Rash AEs Occurring During the First 12 Weeks of Treatment

	First 12 Weeks	
Study Arm	TMC435	PBO
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
Rash (Pooled Variable) Number (%) of Subjects	218 (28%)	79 (20%)
Pooled Rash by Component MedDRA PT, Number (%) of Subjects		
Rash	106 (14%)	44 (11%)
Erythema	24 (3%)	11 (3%)
Photosensitivity reaction	24 (3%)	2 (1%)
Eczema	18 (2%)	8 (2%)
Sunburn	17 (2%)	1 (<1%)
Rash maculo-papular	14 (2%)	3 (1%)
Dermatitis	11 (1%)	2 (1%)
Rash macular	11 (1%)	2 (1%)
Rash papular	7 (1%)	4 (1%)
Skin exfoliation	5 (1%)	1 (<1%)
Rash erythematous	4 (1%)	2 (1%)
Rash pruritic	4 (1%)	1 (<1%)
Urticaria	4 (1%)	3 (1%)
Rash generalised	3 (<1%)	1 (<1%)
Dermatitis allergic	2 (<1%)	1 (<1%)
Drug eruption	2 (<1%)	0 (0%)
Exfoliative rash	1 (<1%)	0 (0%)
Polymorphic light eruption	1 (<1%)	0 (0%)
Solar dermatitis	1 (<1%)	0 (0%)
Toxic skin eruption	1 (<1%)	0 (0%)
Vasculitic rash	1 (<1%)	0 (0%)

The following figure displays the timing of onset of 'rash' in the 218 subjects in the TMC435 group who developed 'rash' during the first 12 weeks of the Phase 3 trials. Fifty-six percent of the 'rash' cases in the TMC435 group occurred during the first 4 weeks of treatment with TMC435, with 42% of cases occurring in the first 2 weeks. Please note that the percentages displayed in the graph are based on a denominator of 781 subjects. The timing of onset of rash in the Control group (not shown in Figure 4) demonstrated a similar pattern with early onset of rash predominating.

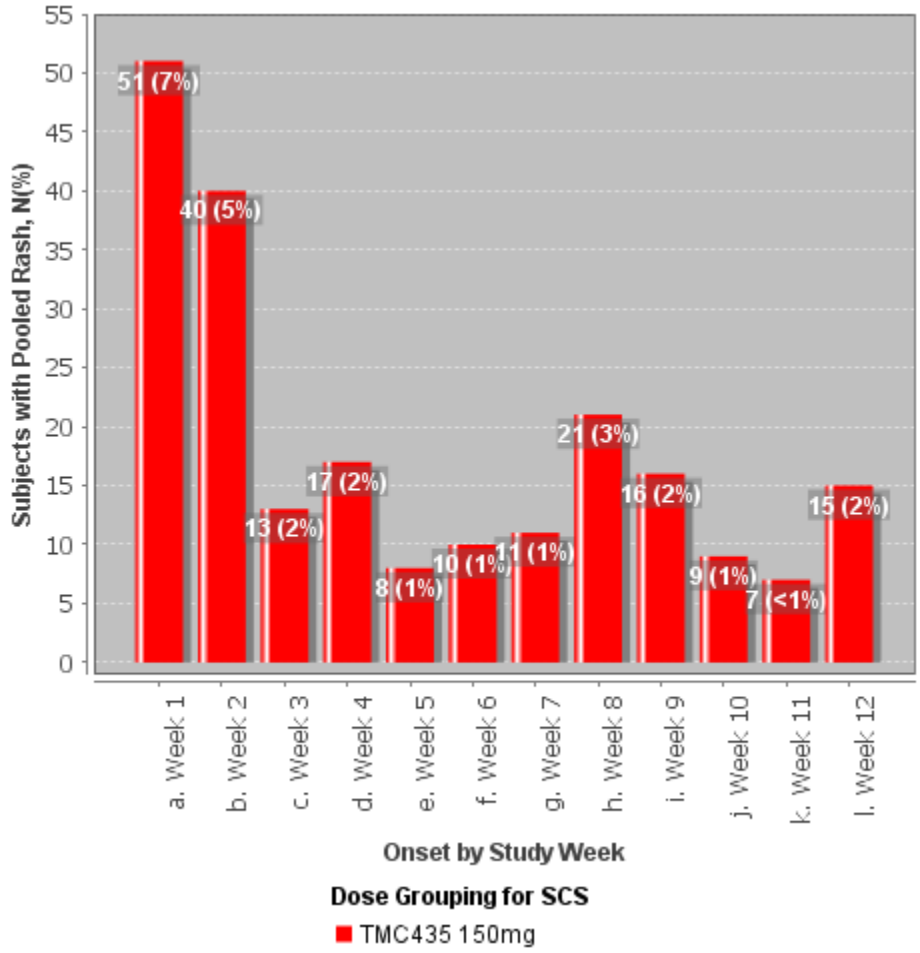


Figure 4: Timing of Onset of 'Rash' in the TMC435 Group during the First 12 Weeks of the Pooled Phase 3 trials

Of note, the grouped term 'rash' also includes the MedDRA PTs that comprise the 'photosensitivity' grouped variable. In order to also assess 'rash' in the absence of the photosensitivity related PTs, a new variable termed 'rash excluding photosensitivity' was created. 'Rash excluding photosensitivity' occurred in 25% of subjects in the TMC435 group and 19% of subjects in the Control group during the first 12 weeks of treatment.

A total of 4 subjects (1%) of the TMC435 group and no subjects in the Control group had a grade 3 AEs reported in the category of 'rash excluding photosensitivity.' Those grade 3 AEs occurred in subjects 208-0019, 208-0243, 216-3453, and 216-3475. All of these subjects (except Subject 216-3453) discontinued study drug and their narratives are found below. Subject 216-3453, a 53 year old Black, Latino female developed a grade 1 rash on SD42 deemed possibly related to study drugs by the investigator. The rash progressed to involve the neck, lower back and abdomen and reached a maximum toxicity grade of three.

No grade 4 AEs or SAEs under the category 'rash excluding photosensitivity' occurred in the TMC435 group during the first 12 weeks.

A total of 7 subjects (1%) discontinued TMC435 during the first 12 weeks of treatment due to an AE under the SOC category of 'Skin and Subcutaneous Tissue Disorders' compared to 1 subject (<1%) in the Control Group (PT 'rash maculo-papular'). These events were previously presented in Table 28. All seven of the AEs in the TMC435 group were subsumed under the HLGT 'Epidermal and Dermal Conditions.' Six of the seven AEs leading to discontinuation of TMC435 were subsumed under the category of 'rash excluding photosensitivity.' Summaries of the seven events in the TMC435 group are provided below:

Subject 208-0019: 48-year-old White female with a Metavir score of F0-F1 who developed a Grade 1 AE of 'skin burning sensation' and a Grade 3 AE of 'rash' involving the chest on SD31. There was no associated eosinophilia, hepatic abnormalities, or mucosal findings. The AEs of rash and skin burning sensation were considered not related to TMC435, RBV and PegIFNα-2a by the investigator. TMC435 was discontinued on SD40. On SD42, the AE of skin burning sensation was reported as resolved. On SD43 the AE of rash improved in severity to grade 1 and was reported as resolved on SD48. This reviewer does not concur with the investigator's assessment of causality and would judge these events at least possibly related to study drugs.

Subject 208-0066: 56 year old white male with a history of celiac disease and a screening Metavir score of F0-F1. The subject developed a grade 1 AE 'photosensitivity reaction' on SD51 which was judged as very likely related to TMC435 by the investigator and reported as resolved the same day. However, on SD54 the subject developed a grade 1 'rash' judged possibly related to the study drug. The rash persisted and was changed to grade 2 on SD65 and judged very likely related to TMC435. There was no eosinophilia or mucosal findings, but grade 1 ALT increase was temporally associated with this event. TMC435 was discontinued on SD67. On SD114 the AE of rash improved in severity to grade 1 and was reported as resolved on SD194. This reviewer concurs with the investigator's assessment of causality.

Subject 208-0243: 59 year old white female with a screening Metavir score of F3, developed the Grade 2 AEs 'rash' and 'pruritis' on SD61. The rash involved the upper body, torso, and legs. These AEs were judged as probably related to study drugs and study drugs were discontinued. The subject received the last dose of TMC435 on SD78, the last dose of PegIFNα-2a on SD86, and the last dose of RBV on SD88. On SD88, the AE of rash worsened in severity to grade 3, and now also involved the face. The AE of rash was considered to be not related to TMC435, RBV, or PegIFNα-2a by the investigator. The subject was treated with topical steroids. On SD97, the AE of rash improved in severity to grade 2 and on SD100 the AEs of rash and pruritus improved in severity to grade 1. The AEs of rash and pruritus were reported as resolved on SD129. There was no associated eosinophilia, hepatic abnormalities or mucosal findings related

to these events. This reviewer does not concur with the investigator's assessment of causality and would judge all of these events at least possibly related to study drugs (including TMC435).

Subject 208 0416: 59 year old white male with a history of asthma and a screening Metavir score of F4, developed the grade 2 AE 'rash' on SD67. The rash involved the abdomen, legs, arms, and back. This AE was considered to be probably related to TMC435 and RBV and doubtfully related to PegIFNα-2a by the investigator. The subject received his last dose of TMC435 on SD73, his last weekly dose PegIFNα-2a on SD151, and his last dose of RBV on SD152. Associated AEs included grade 1 apthous stomatitis occurring on SD75. The investigator considered the rash and apthous stomatitis to be discrete, unrelated events. Serum eosinophils were reported to be elevated to a level of 0.73×10^9 on SD86. The subject was treated with diphenhydramine hydrochloride, glaxal base (a moisturizing emollient), and oral prednisone for the rash. The AE of rash was reported as resolved on an unspecified date in April 2012 (~6 months after AE onset). This reviewer concurs with the investigator's assessment of TMC435 causality with respect to the rash, but not with respect to the oral lesions. This reviewer considers the oral lesions at least possibly related to TMC435 and possibly linked to the rash.

Subject 208-0340: 46 year old white male with a Metavir score of F2 and an otherwise unremarkable medical history developed grade 1 'psoriasis' on SD14. The AE was considered to be probably related to PegIFNα-2a, doubtfully related to RBV, and not to be related to TMC435 by the investigator. On SD22, the psoriasis worsened in severity to grade 3. This AE was considered to be possibly related to PegIFNα-2a, and not to be related to TMC435 and RBV by the investigator. The subject received the last dose of PegIFNα-2a on SD15, and the last dose of TMC435 and RBV on SD21. The subject was treated with calcipotriol (a synthetic derivative of calcitriol or vitamin D). The AE of psoriasis was still ongoing at the time of the report. This Reviewer generally agrees with the investigator with respect to causality as the exacerbation and occurrence of psoriasis in hepatitis C patients treated with IFN-α has been well described[2].

Subject 216 3022: 49 year old white female with a history of allergic dermatitis/eczema and a screening Metavir score of F0-F1, developed the grade 2 AE 'rash' on SD52. This AE was considered to be very likely related to TMC435 and RBV, and doubtfully related to PegIFNα-2a by the investigator. Treatment with TMC435 was discontinued due to this AE with the last dose received on SD57. There was no associated eosinophilia or hepatic abnormalities. Associated AEs included grade 2 mouth ulceration on SD57 and pruritis on SD61. The investigator considered the rash and mouth ulceration to be discrete, unrelated events. Concomitant medications reported for these AEs included topical hydrocortisone and hydroxyzine hydrochloride. The AEs of rash and pruritis were considered resolved on SD93 and the AE of mouth ulcerations was considered resolved on SD95. This reviewer concurs with the investigator's assessment of TMC435 causality with respect to the rash, but not with respect to the oral lesions. This reviewer

considers the oral lesions at least possibly related to TMC435 and possibly linked to the rash.

Subject 216 3475: 40 year old white male with an unremarkable medical history and a screening Metavir score of F0-F1, developed the grade 2 AE 'maculopapular rash' on SD32. On SD52, the subject was reported with grade 3 AE of erythematous rash. Both of these AEs were considered to be probably related to TMC435 and RBV and not related to PegIFNα-2a by the investigator. The subject was treated with topical steroids. The subject received the last dose of PegIFNα-2a on SD50 and the last doses of TMC435 and RBV on SD52. The AEs of maculopapular rash and erythematous rash were considered resolved on SD61. Concurrent AEs of interest included grade 2 aphthous stomatitis (onset SD42, resolution SD66). The oral lesions consisted of 4 painful, 2 mm round ulcers located on the lower lip. These were assumed to be of herpetic origin; however, HSV PCR testing of the lesions was negative. The oral lesions were not considered to be related to study medications per investigator. There was no associated eosinophilia or transaminase increases. This reviewer concurs with the investigator's assessment of TMC435 causality with respect to the rash, but not with respect to the oral lesions. This reviewer considers the oral lesions at least possibly related to TMC435 and possibly linked to the rash.

Pooled Phase 2b Studies:

Additional analyses were also conducted by pooling data from Phase 2b studies (C205 and C206) to better define the skin and soft tissue safety profile of TMC435. These studies included TMC435 doses ranging from 75mg to 150 mg and TMC435 durations ranging from 12 weeks to 48 weeks (refer to Section 5.3 for additional details).

The grouped variable 'pruritis' occurred in 33 subjects (23%) in the Control arm and in 204 subjects (29%) in the pooled TMC435 arms in pooled Studies C205 and C206 during the first 12 weeks of treatment. There were two grade 3 AEs reported for 'pruritis' in the TMC435 group (Subjects 205-0455 and 206-0166) and none in the Control group during the first 12 weeks. There were no grade 4 AEs or SAEs reported for 'pruritis' in either group in the first 12 weeks. There was one discontinuation of study drug related to 'pruritis' in the TMC435 group (Subject 205-0085) and no discontinuations in the Control group during the first 12 weeks of treatment.

The pooled variable 'photosensitivity' occurred in 1 subject (1%) in the control arm and in 11 subjects (2%) in the pooled TMC435 arms in pooled Studies C205 and C206 during the first 12 weeks. There were no grade 3 or 4 AEs, SAEs, or discontinuations of TMC435 related to 'photosensitivity' in the pooled Phase 2b studies.

The grouped variable 'rash excluding photosensitivity' occurred in 27 subjects (19%) in the pooled Control group and in 165 subjects (23%) in the TMC435 group during the first 12 weeks of treatment. There were three subjects with grade 3 AEs in the TMC435

group and no subjects with grade 3 events in the control group under this grouped variable during the first 12 weeks of treatment. The three grade 3 AEs were the 'drug eruption' (subject 206-0292) and 'rash' (subjects 205-0505 and 206-0426). Summaries of these events are provided below under the discussion of AEs leading to study drug discontinuation.

Table 30 describes, by treatment arm, the AEs under the SOC 'skin and subcutaneous tissue disorders' leading to discontinuation of TMC/placebo during Studies C205 and C206.

Table 30: Skin and Soft Tissue AEs Leading to Discontinuation of TMC435/Placebo in Studies C205 and C206

Studies	C205 and C206 Pooled						
Subjects per Arm	143	66	66	143	147	78	705
Study Arm	PBO	TMC435 100MG/12 WKS	TMC435 100MG/48 WKS	TMC435 150MG/12 WKS	TMC435 150MG/24 WKS	TMC435 75MG/12 WKS	Pooled TMC435 Arms
MedDRA PT, N (%) of Subjects							
Dermatitis exfoliative	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	1 (<1%)
Drug eruption	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (<1%)
Pruritus	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	1 (<1%)
Rash	1 (1%)	1 (2%)	1 (2%)	0 (0%)	3 (2%)	0 (0%)	5 (1%)
Cutaneous vasculitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (<1%)
Total Subjects	1 (1%)	1 (2%)	1 (2%)	1 (1%)	4 (3%)	1 (1%)	8 (1%)

A total of 8 subjects (1%) in the TMC435 group discontinued study drug versus 1 subject (1%) in the Control group during the period of TMC435/placebo +PR administration. Two of the discontinuations in the TMC435 group were classified as SAEs (Subjects 206-0292 and 205-0371). These were the only SAEs in the TMC435 group reported under the SOC 'skin and subcutaneous tissue disorders' during the period of TMC435 administration; no SAEs were reported in the placebo group. Table 31 provides a summary of the characteristics of the subjects who discontinued TMC435 due to an AE under the category of 'skin and subcutaneous tissue disorders' during the period of TMC435 administration. Additional narrative information on these subjects follows the table summary.

Table 31: Summary of Subjects in the Pooled Phase 2b Studies with AEs Leading to Discontinuation of Study Drug Under the MedDRA SOC 'Skin and Subcutaneous Tissue Disorders' During the TMC435/PBO + PR Period of Administration

Subject Number	Age Race/ Sex	MedDRA PT	SD (Onset/ Resolution)	Worst Toxicity Grade	Associated Laboratory Findings*/ SD	Associated Mucosal Findings	Systemic Steroids Admin.
TMC435 TREATMENT GROUP							
205-0505	56 W/F	Dermatitis Exfoliative	68/ Ongoing	3	↑Eos 13%/ SD84	No	Yes
205-0455	44 W/F	Rash	43/141	2	↑Eos 8%/ SD50	No	No
205-0085	32 W/F	Rash	13/ Ongoing	2	No	No	No
205-0371	46 W/F	Cutaneous Vasculitis†	63/ Ongoing	2	No	No	Yes
206-0426	55 W/F	Rash	22/ Ongoing	3	No	No	No
206-0485	44 W/F	Rash	173/254	2	No	No	No
206-0292	27 W/M	Drug Eruption†	29/87	3	↑Eos 13% (0.7 x 10^9)/ SD56	No	No
206-0512	65 W/M	Rash	7/161	1	No	Oral herpes/SD7	No
CONTROL GROUP							
205-0049	21 WM	Rash	81/169	2	↑Eos 14%/ SD140	No	No

*Specifically blood eosinophilia and/or presence of transaminitis
† = SAE

Brief Summaries of the events leading to discontinuation of study drug follow:

Subject 205-0049 (Placebo Group): 21 year old white male on 24 week placebo/48 week PR arm discontinued placebo on SD113 due to a grade 2 rash involving the trunk and upper extremities. The rash resolved by SD169.

Subject 206-0426 (TMC435 100mg/12wks): 55 year old white female developed a grade 3 rash on SD22 deemed possibly related to all study drugs. The rash was described as a 3 cm erythematous circular lesion on the right upper thigh with small vesicles. TMC435 was discontinued on SD22, and the subject withdrew consent on the same day.

Subject 206-0485 (TMC435 100mg/48wks): 44 year old white female developed a grade 2 rash on SD173 deemed probably related to TMC435 and not related to PR. TMC435 was discontinued on SD175, the subject received treatment with topical steroids, and the rash resolved by SD197.

Subject 205-0505 (TMC435 150mg/12wks): 56 year old white female developed grade 2 exfoliative dermatitis on SD68 deemed probably related to TMC435 and not related to PR. TMC435 was discontinued on SD72, the subject was treated with topical steroids, and the rash resolved by SD197. The exfoliative dermatitis resolved on SD74. The same day, grade 3 rash was reported and was treated oral prednisone. PR was discontinued on SD84 due to the rash. The investigator considered rash to be probably related to TMC435, PegIFNα-2a, and RBV.

Subject 205-0455 (TMC435 150mg/24wks): 44 year old white female developed grade 2 rash on SD43 deemed probably related to TMC435 and possibly related to PR. TMC435 was discontinued on SD52, the subject was treated with topical steroids, and the rash resolved by SD141.

Subject 206-0292 (TMC435 150mg/24wks): 27 year old white male developed grade 2 rash on SD29 deemed possibly related to TMC435, probably related to RBV and not related to PegIFN. The patient was treated with topical steroids. On SD57, the event of rash worsened in severity and the subject complained of low grade fever and itchy rash affecting the face, neck, hands, and axillae with serous discharge. The absolute eosinophil count was elevated at 0.7 (13%). The subject was evaluated by a dermatologist. Skin examination revealed erythema, edema, green crusts and desquamation on the face, neck and ears. Drug eruption was diagnosed, and was reported as a medically significant grade 3 SAE. A skin biopsy from the right forearm on SD58 showed focal prekeratosis, spongiosis, and chronic inflammatory mononuclear infiltrate mixed with a few eosinophils and fresh blood in the upper dermis. The AE of drug eruption was considered to be possibly related to TMC435, probably related to RBV and not related to PegIFN. Treatment with the study medications (TMC435 and PR) was permanently discontinued on SD 57 and 58 respectively. The subject was treated with IM and topical steroids. The drug eruption was considered as resolved on SD86.

Subject 205-0085 (TMC435 150mg/24wks): 33 year old white female with reported grade 2 dyspnea on SD11 and grade 2 rash and pruritis on SD13. These AEs were considered possibly related to all study drugs by the investigator. No evidence of concurrent transaminitis or eosinophilia was present. TMC435 was discontinued on SD13 and the rash, pruritis, and dyspnea was considered resolved on SD23.

Subject 206-0512 (TMC435 150mg/24wks): 65 year old white male with reported grade 1 rash, grade 1 arthralgias, and grade 1 oral herpes simplex infection on SD7. The rash was considered possibly related to all study drugs and prompted discontinuation of study drugs on SD141. No evidence of concurrent transaminitis or eosinophilia was present. The rash was considered resolved on SD168

Subject 205-0371 (TMC435 75mg/12wks): 46 year old white female developed a painful, swollen, purple lesion on the anterior surface of her right leg on SD63. She was

hospitalized on SD76 as well as SD82 and diagnosed with grade 2 cutaneous vasculitis, which was reported as an SAE. The investigator considered the SAE to be possibly related to TMC435, probably related to PegIFNα-2a, and doubtfully related to RBV. Study medication (TMC435, PegIFNα-2a, and RBV) was permanently discontinued due to this SAE on SD83. The subject was discharged from the hospital on SD84, and treated with oral steroids. The cutaneous vasculitis was considered ongoing at the last follow-up visit.

Global Assessment of Potentially Life-Threatening Cutaneous Events:

The Sponsor was specifically queried as to whether any subjects receiving TMC435 in any study to date (including the studies conducted in Japan for which limited safety data was provided with this NDA submission) have been diagnosed with any of the following conditions: erythema multiforme (EM), Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), or drug reaction with eosinophilia and systemic symptoms (DRESS). Per Sponsor, no subjects have been diagnosed with SJS, TEN, or DRESS in any studies of TMC435 to date.

A total of three subjects have been diagnosed with EM. All of these subjects were enrolled in studies in Japan. Brief narratives of these subjects' events follow:

Subject 3004-31-073, a 61 year old Asian subject with no reported medical history was receiving a treatment regimen consisting of TMC435 100 mg for 24 weeks in conjunction with PR for 24 or 48 weeks based on RGT. On SD 69, the subject experienced EM reported as an AE of grade 3 severity. The AE was deemed to be probably related to TMC435 and RBV and doubtfully related to PegINFα-2a by the investigator. The rash was present on the upper and lower extremities, trunk, back, and buttocks. No mucus membrane involvement or desquamation was associated with this AE and the subject did not require hospitalization. Treatment for this AE included oral prednisolone. Skin biopsy revealed superficial perivascular dermatitis with lymphocytic and eosinophilic infiltrates. All study medications were discontinued on SD 83 and the AE was reported as resolved on SD 112. This reviewer agrees with the investigator's causality assessment with respect to TMC435.

Subject 3010-26-318 was diagnosed with grade 2 EM (no bullous or mucosal lesions) on SD 52. No biopsy was performed and no details with respect to treatment were provided. Treatment with TMC435, PegIFNα-2b and RBV was interrupted from Week 8 to Week 9 and was completed at Week 12 (TMC435) and Week 24 (PegIFNα-2b and RBV), respectively. EM was reported as resolved on SD 98 (Week 14). The investigator considered EM to be probably related to TMC435 and PegIFNα-2b and possibly related to RBV. This reviewer agrees with the investigator's causality assessment with respect to TMC435.

Subject 3004-02-052, a 67-year-old Asian female was receiving a treatment regimen consisting of TMC435 in conjunction with PR. This subject completed her course of TMC435 on SD83. Sixty-three days later (on SD 146), she was diagnosed with EM which was reported as a grade 3 SAE. There was no mucous membrane involvement in this subject and the event was not considered as life-threatening. The rash was present on the proximal lower and upper limbs, distal lower and upper limbs, and neck. The texture and surface was smooth and sclerotic. There was no evidence for desquamation. Treatment with PegIFNα-2a and RBV was discontinued at Weeks 22 and 23, respectively, due to EM. The subject was admitted to the hospital at Week 23 (SD 160) for IV steroid treatment. She was discharged 10 days after admission and EM was reported as being resolved by SD 328. The investigator considered EM to be probably related to TMC435, PegIFNα-2a and RBV. Based on the greater than two month delay between the onset of EM and the completion of treatment with TMC435, this reviewer would consider a causal relationship between EM and TMC435 in this subject to be doubtful, and more likely related to PegIFNα-2a and RBV.

Summary:

A safety signal was noted with respect to rash and/or photosensitivity events in the Phase 2b (C205 & C206) and pivotal Phase 3 trials (C208, C216, and HPC3007). This included an increased frequency and severity of rash and/or photosensitivity adverse events and serious adverse events, as well as an increase in rates of discontinuation of TMC435 due to rash and/or photosensitivity related adverse events. Per Sponsor, there were no life-threatening rash events or deaths related to rash reported in any study of TMC435 to date.

A significant degree of overlap was noted between adverse events strictly categorized as rash, and those strictly categorized as photosensitivity. The use of narrow pooling for photosensitivity events may have underestimated the actual rate of occurrence of photosensitivity events as some of these events which were consistent with photosensitivity were reported under the more general pooled term of rash. It was also noted that all of the subjects in these Phase 2b and Phase 3 trials completed treatment with TMC435 prior to the discontinuation of the sun protection measures specified per protocol.

This Reviewer recommends that a discussion of rash and photosensitivity events be included in the Warnings and Precautions section of the product label. This would include a recommendation that sun protection measures (consistent with those used in the pivotal trials) be initiated in all patients receiving TMC435.

Psychiatric Adverse Events:

The use of alpha interferon treatment is associated with neuropsychiatric AEs including but not limited to depression, suicidal/homicidal ideation, and suicide. As such, the focus of this safety analysis was to assess for substantive differences in the frequency and/or severity of psychiatric AEs in the TMC435 group compared to the Control Group.

There was an equal incidence of psychiatric disorders (by SOC) in the TMC435 group (38%) and the control group (38%) during the first 12 weeks treatment. A small increase in incidence was noted for AEs in the TMC435 group under the MedDRA HLGT 'Anxiety disorders and symptoms'. No other substantive increases were noted in the TMC435 group compared to the control group based on HLGT. Table 32 summarizes the incidence of psychiatric disorders (by HLGT) during the first 12 weeks of treatment.

Table 32: Psychiatric Disorders by HLGT During the First 12 Weeks of Treatment

	First 12 Weeks	
Study Arm	TMC435	PBO
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
MedDRA HLGT, Number (%) of Subjects		
Sleep disorders and disturbances	170 (22%)	88 (22%)
Mood disorders and disturbances NEC	99 (13%)	59 (15%)
Depressed mood disorders and disturbances	86 (11%)	45 (11%)
Anxiety disorders and symptoms	52 (7%)	21 (5%)
Sexual dysfunctions, disturbances and gender identity disorders	11 (1%)	3 (1%)
Personality disorders and disturbances in behaviour	6 (1%)	1 (<1%)
Deliria (incl confusion)	6 (1%)	2 (1%)
Psychiatric disorders NEC	3 (<1%)	1 (<1%)
Suicidal and self-injurious behaviours NEC	1 (<1%)	1 (<1%)
Changes in physical activity	1 (<1%)	2 (1%)
Somatoform and factitious disorders	0 (0%)	1 (<1%)

A total of 5 subjects (1%) in the TMC435 group and 7 subjects (2%) in the Control group experienced and Grade 3 AEs during the first 12 weeks under the SOC category of 'Psychiatric Disorders.' The AEs (by PT) in the TMC435 group included the following: aggression, burnout syndrome, depression, major depression and suicidal ideation. Each subject had only 1 event except for 1 subject with both 'depression' and 'suicidal ideation' reported.' No Grade 4 AEs occurred in the TMC435 group during the first 12 weeks of treatment. One Grade 4 AE ('anxiety') occurred in the control group during this period.

A total of 3 subjects (<1%) discontinued TMC435 during the first 12 weeks of treatment versus 1 subject (<1%) in the Control group due to an AE under the SOC category of

'Psychiatric Disorders.' The specific AEs in the TMC435 group were 'aggression,' 'anxiety,' and 'major depression.' Summaries of the adverse events in the TMC435 group which led to discontinuation of study drug are provided below:

Subject 208-0172: 53 year old white female with history of depression and psychosis experienced the grade 3 AE 'major depression' on SD47 which led to discontinuation of all study medications on SD51. The AE was considered to be very likely related to PegIFNα-2a, possibly related to TMC435 and doubtfully related to RBV by the investigator. This Reviewer concurs with the Investigator's causality assessment.

Subject 216-3261: 35 year old white male with a history of mild depression experienced grade 1 depression on SD43 deemed possibly related to the study medications (TMC435, PegIFNα-2a, and RBV). Treatment included venlafaxine. On SD68, the subject became violent, and aggression was reported as a grade 3 SAE. Treatment with the study medications (TMC435, PegIFNα-2a, and RBV) was permanently discontinued on SD 68 due to this event. On SD84, the subject was forgetful and had difficulty controlling his temper. He was voluntarily admitted to a mental health institution. Memory impairment was reported as a grade 3 SAE. The events of aggression and memory impairment were considered to be not related to the study medications (TMC435, PegIFNα-2a, and RBV). Treatment with venlafaxine was discontinued, and treatment with aripiprazole was commenced. The events of aggression and memory impairment were reported as resolved on SD101. This Reviewer concurs with the Investigator's causality assessment with respect to TMC435.

Subject 3007-6027: 60 year old white male with a history of anxiety experienced grade 2 AEs of anxiety, headache, and pain on SD5. The AE of anxiety was considered not to be related to TMC435, RBV, and PegIFNα-2a by the investigator. The AEs of headache and pain were considered not to be related to TMC435 and RBV, and very likely related to PegIFNα-2a by the investigator. Treatment with TMC435, PegIFNα-2a and RBV was permanently discontinued on SD6 due to the AEs of anxiety, headache, and pain. The AEs anxiety, headache, and pain were reported as resolved on SD14. Based on the limited information available, this Reviewer would consider the AE of anxiety to be possibly related to TMC435, although confounded by a history of anxiety and the concurrent use of PR.

A total of 4 subjects (1%) in the TMC435 group and 1 subject in the control group (<1%) experienced an SAE in the SOC category of 'Psychiatric Disorders' during the first 12 weeks of treatment. The SAEs in the TMC435 group included the following: aggression (1 subject), depression (1 subject), depression and suicidal ideation (1 subject), and major depression (1 subject). The SAE in the Control Group was 'anxiety.' The following are summaries of the events in the TMC435 group:

Subject 208-0440: 53 year old black or African American female with a history of depression received TMC435 until SD35 at which point it was discontinued due to

virologic stopping criteria. On SD44, the subject was hospitalized with depression and suicidal ideation, which were reported as AEs of grade 3 severity and were considered to be probably related to PegIFNα-2a and doubtfully related to TMC435 and RBV by the investigator. The treatment with RBV and PegIFNα-2a was withdrawn due to these AEs. On SD81, the AE of suicidal ideation was reported as resolved. On SD82, the AE of depression improved to grade 1 and was ongoing at the time of this report. This Reviewer concurs with the Investigator's causality assessment.

Subject 3007-6128: 35 year old white male with an unremarkable medical history experienced a grade 2 AE of depression on SD10. The investigator considered this event not to be related to TMC435 and RBV and probably related to PegIFNα-2a. On SD240 (156 days after completing TMC435 and 71 days after completing PR) the subject was hospitalized with a grade 3 SAE for depression and a grade 2 SAE for alcohol poisoning. Neither SAE was considered related to study drugs by the investigator. This Reviewer concurs with the Investigator's SAE causality assessment.

Summaries for Subjects 208-0172 and 216-3261 are presented above in the section discussing AEs leading to study drug discontinuation.

Summary: Based on an assessment of the pooled Phase 3 data, no significant safety signals related to psychiatric adverse events were noted. The vast majority of the psychiatric AEs reported could be either fully or partially explained by the concomitant administration of pegylated interferon and ribavirin.

Gastrointestinal Adverse Events:

There was a higher incidence of gastrointestinal disorders (by SOC) in the TMC435 group (45%) compared to the control group (40%) during the first 12 weeks treatment. That difference appeared to be driven largely by an increased frequency of AEs under the HLT 'nausea and vomiting symptoms' in the TMC435 group. No other substantive increases were noted in the TMC435 group compared to the control group based on HLT. Table 33 summarizes the frequency of gastrointestinal AEs (by HLT) which occurred in ≥ 3% of the TMC435 group during the first 12 weeks of treatment. The PTs subsumed under the HLT 'nausea and vomiting' are also described in the table. Of interest, dysguesia (which occurred with increased frequency in the licensure trials of boceprevir) did not occur with increased frequency in the TMC435 group during the first 12 weeks of treatment (4% of TMC435 subjects and 5% of control subjects).

Table 33: Gastrointestinal AEs (by HLT) which Occurred in ≥ 3% of the TMC435 Group during the First 12 Weeks of Treatment

	First 12 Weeks	
Study Arm	TMC435	PBO
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
MedDRA HLT, Number (%) of Subjects		
Nausea and vomiting symptoms	194 (25%)	80 (20%)
Nausea*	173 (22%)	70 (18%)
Vomiting*	51 (7%)	20 (5%)
Diarrhea (excl infective)	86 (11%)	45 (11%)
Gastrointestinal and abdominal pains (excl oral and throat)	55 (7%)	35 (9%)
Gastrointestinal atonic and hypomotility disorders NEC	28 (4%)	14 (4%)
Oral dryness and saliva altered	27 (3%)	7 (2%)
Dyspeptic signs and symptoms	27 (3%)	10 (3%)
Stomatitis and ulceration	25 (3%)	14 (4%)

*MedDRA PT

There were a total of 6 subjects (1%) in the TMC435 group and 3 subjects in the Control group (1%) with grade 3 AEs under the SOC 'gastrointestinal disorders.' In the TMC435 group, this included 2 subjects with nausea, 1 subject with upper abdominal pain, 1 subject with abdominal pain, 1 subject with diarrhea, and 1 subject with stomatitis. There were no grade 4 events in either group. There was one discontinuation of TMC435 for stomatitis (Subject 216-3151) and one SAE for 'abdominal pain' (Subject 3007-6100) reported in the TMC435 group. Summaries of these two events are provided below:

Subject 216-3151: 36 year old white male with a non-contributory medical history experienced grade 3 stomatitis on SD 75. This AE was considered to be very likely related to TMC435 and not related to PegIFNα-2b and RBV by the investigator. Treatment with TMC435 was discontinued due to this AE on SD78. No action was taken with PegIFNα-2a and RBV due to this AE. The AE of stomatitis was considered resolved on SD94. There was no rash temporally associated with this event. This reviewer agrees that the stomatitis may have been related to the use of TMC435.

Subject 3007-6100: 42 year old Asian female with a grade 2 AEs of abdominal pain and vaginal hemorrhage on SD47 and SD51 respectively. All these AEs were considered not to be related to the study medications (TMC435, RBV, and PegIFNα-2a) and no action was taken with the study medications due to these events. On SD57, the events of abdominal pain and vaginal hemorrhage worsened, and were reported as SAEs of grade 3 severity. The subject was hospitalized on the same day. On SD60, the subject's condition improved and the events of abdominal pain and vaginal hemorrhage were reported as grade 2 and grade 1 AEs, respectively. The event of vaginal

hemorrhage was reported as resolved on SD62. The event of abdominal pain was reported as ongoing. This reviewer agrees with the investigator's causality assessment.

An assessment of anorectal AEs was specifically performed given the known safety profile of telaprevir (refer to Section 2.4 for details). No anorectal safety signal was appreciated. Table 34 summarizes AEs by MedDRA PT under the following HLTs: 'anal and rectal disorders NEC,' 'anal and rectal pains,' 'anal and rectal signs and symptoms,' and 'anal and rectal ulcers and perforations.' All AEs displayed in Table 34 were reported as grade 1 events.

Table 34: Anorectal AEs during the First 12 Weeks of Treatment

	First 12 Weeks	
Study Arm	TMC435	PBO
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
MedDRA PT, Number (%) of Subjects		
Anal fissure	1 (<1%)	0 (0%)
Rectal prolapse	0 (0%)	1 (<1%)
Proctalgia	1 (<1%)	1 (<1%)
Anal pruritus	2 (<1%)	0 (0%)

Summary: A higher frequency of gastrointestinal adverse events was noted in the TMC435 group compared to the control group during the first 12 weeks treatment. The difference was largely driven by an increased frequency of nausea and vomiting in the TMC435 group. However, the vast majority of gastrointestinal AEs were of mild or moderate intensity, and SAEs and discontinuations due to gastrointestinal AEs were extremely rare.

Hepatobiliary and Pancreatic Adverse Events:

From early in clinical development, hyperbilirubinemia was known to be associated with use of TMC435 and was considered an adverse event of special interest. However, per Sponsor, the higher incidence of bilirubin elevations in TMC435-treated subjects is primarily attributed to a decrease in bilirubin elimination related to inhibition of the hepatic transporters OATP1B1 and MRP2. OATP1B1 transports both unconjugated and conjugated bilirubin; MRP2 transports conjugated bilirubin.

Table 35 below describes hepatobiliary AEs (by PT) which occurred under the SOCs 'Investigations' or 'Hepatobilary Disorders' during the first 12 weeks of treatment. The vast majority of the AEs in the TMC435 group described in Table 35 were related to an increase in bilirubin. As such, the following PTs were pooled to facilitate comparison of the groups: hyperbilirubinemia, blood bilirubin increased, jaundice, blood bilirubin unconjugated increased, and bilirubin conjugated increased. When those terms were

pooled, the grouped term 'increased bilirubin' occurred in 8% of subjects in the TMC435 group and 3% of subjects in the Control group during the first 12 weeks of treatment. No other safety signals with respect to hepatobiliary or pancreatic AEs in the TMC435 group were identified.

Table 35: Hepatobiliary AEs (by PT) Occuring under the SOCs 'Investigations' or 'Hepatobilary Disorders' during the First 12 Weeks of Treatment in either Treatment Group

	First 12 Weeks	
	TMC435	PBO
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
MedDRA PT, Number (%) of Subjects		
Increased Bilirubin (Grouped Term)*	61 (8%)	11 (3%)
Alanine aminotransferase increased	8 (1%)	11 (3%)
Amylase increased	7 (1%)	1 (<1%)
Aspartate aminotransferase increased	7 (1%)	8 (2%)
Gamma-glutamyltransferase increased	4 (1%)	6 (2%)
Lipase increased	3 (<1%)	1 (<1%)
Transaminases increased	3 (<1%)	2 (1%)
Hepatic pain	2 (<1%)	1 (<1%)
Bile duct obstruction	1 (<1%)	0 (0%)
Blood alkaline phosphatase increased	1 (<1%)	0 (0%)
Cholelithiasis	1 (<1%)	0 (0%)
Hepatic enzyme increased	1 (<1%)	0 (0%)
Hepatic lesion	1 (<1%)	0 (0%)
Hepatomegaly	1 (<1%)	0 (0%)
Liver palpable subcostal	1 (<1%)	0 (0%)
Urine bilirubin increased	1 (<1%)	0 (0%)
Urobilinogen urine increased	1 (<1%)	0 (0%)
Gallbladder disorder	0 (0%)	1 (<1%)
Hepatic function abnormal	0 (0%)	1 (<1%)
Liver function test abnormal	0 (0%)	1 (<1%)

* The Grouped term 'Increased Bilirubin' includes the following MedDRA PTs: hyperbilirubinemia, blood bilirubin increased, jaundice, blood bilirubin unconjugated increased, and bilirubin conjugated increased

Grade 3 adverse events due to a hepatobiliary or pancreatic AE under the SOC categories of 'hepatobiliary disorders' or 'investigations' are presented in Table 36 below. Grade 3 AEs under the grouped term "increased bilirubin" occurred in 2% of subjects in the TMC435 group and 1% of subjects in the Control group during the first 12 weeks of treatment.

Table 36: Grade 3 Hepatobiliary AEs (by PT) Occuring under the SOCs 'Investigations' or 'Hepatobilary Disorders' during the First 12 Weeks of Treatment

	First 12 Weeks	
	TMC435	PBO
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
MedDRA PT, Number (%) of Subjects		
Hyperbilirubinaemia	9 (1.2%)	1 (0.3%)
Alanine aminotransferase increased	6 (0.8%)	6 (1.5%)
Aspartate aminotransferase increased	6 (0.8%)	3 (0.8%)
Blood bilirubin increased	6 (0.8%)	1 (0.3%)
Amylase increased	3 (0.4%)	0 (0.0%)
Lipase increased	2 (0.3%)	0 (0.0%)
Bile duct obstruction	1 (0.1%)	0 (0.0%)
Gamma-glutamyltransferase increased	1 (0.1%)	2 (0.5%)
Hepatic enzyme increased	1 (0.1%)	0 (0.0%)
Hepatic lesion	1 (0.1%)	0 (0.0%)
Transaminases increased	1 (0.1%)	1 (0.3%)
Urine bilirubin increased	1 (0.1%)	0 (0.0%)
Hepatic function abnormal	0 (0.0%)	1 (0.3%)

Grade 4 events due to a hepatobiliary or pancreatic AE under the SOC categories of 'hepatobiliary disorders' or 'investigations' are presented in Table 37 below. Grade 4 AEs under the grouped term "increased bilirubin" occurred in < 1% of subjects in the TMC435 group and no subjects in the Control group during the first 12 weeks of treatment.

Table 37: Grade 4 Hepatobiliary AEs (by PT) Occuring under the SOCs 'Investigations' or 'Hepatobilary Disorders' during the First 12 Weeks of Treatment

	First 12 Weeks	
	TMC435	PBO
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
MedDRA PT, Number (%) of Subjects		
Alanine aminotransferase increased	2 (0.3%)	2 (0.5%)
Blood bilirubin increased	2 (0.3%)	0 (0.0%)
Aspartate aminotransferase increased	0 (0.0%)	2 (0.5%)
Gamma-glutamyltransferase increased	0 (0.0%)	1 (0.3%)

A total of 2 subjects in the TMC435 group and no subjects in the control group experienced an SAE in the SOC categories 'hepatobiliary disorders' and 'investigations.' These included the AE 'bile duct obstruction' in Subject 208-0461 and 'hepatic lesion' in Subject 208-0445. The following are summaries of these events:

Subject 208-0461: 54 year old white female with a history of diabetes mellitus (DM), a screening Metavir score of F2, and a BMI of 23 kg/m^2, developed the grade 1 AE 'abdominal pain' and the grade 2 AE 'jaundice' on SD25. On SD31, the subject was hospitalized and was diagnosed with grade 3 bile duct obstruction and grade 2 cholelithiasis both of which were considered to be not related to TMC435, PegIFNα-2a or RBV by the investigator. The Subject subsequently underwent endoscopic retrograde cholangiopancreatography and cholecystectomy. No action was taken with TMC435, PegIFNα-2a and RBV. On SD37, the AEs of abdominal pain, jaundice, cholelithiasis, and bile duct obstruction were reported as resolved. This reviewer concurs with the investigator's assessment of causality. That conclusion was, in part, based on the fact that this was the only subject in the pooled Phase 3 studies with the AEs of 'bile duct obstruction' or 'cholelithiasis' reported and that the subject had several risk factors for gallstones including her race, age, sex, and history of DM.

Subject 208-0445: 45 year old white female was hospitalized on SD54 with a lacerated liver, shoulder pain and chest contusion due to a motor vehicle accident. The 'hepatic lesion' was reported as a grade 3 AE and was considered to be not related to TMC435, PegIFNα-2a and RBV by the investigator. No action was taken with TMC435, PegIFNα-2a and RBV. On SD68, the AE of hepatic lesion was reported as resolved. This reviewer concurs with the investigator's assessment of causality.

One subject in the TMC435 Group and 1 Subject in the Control group discontinued TMC435/PBO during the first 12 weeks of treatment due to a hepatobiliary AE under the SOC categories of 'hepatobiliary disorders' and 'investigations.' The specific AE in the TMC group was 'blood bilirubin increased' while the AE in the Control group was 'transaminases increased.' A summary of the event in the TMC group is provided below:

Subject 208-0111: 35 year old white male with a Metavir score was F4, baseline ALT of 122 U/L (normal range: 6-43 U/L), AST of 158 U/L (normal range: 11-36 U/L), total bilirubin of 28 µmol/L (normal range: 3-21 µmol/L), and indirect bilirubin of 17 µmol/L (normal range: 0-21 µmol/L). Pertinent medical history included portal hypertension, splenomegaly, spider naevi, and palmer erythema. On SD15, a grade 4 AE 'blood bilirubin increased' and a grade 2 AE 'jaundice' were reported (total bilirubin: 111 µmol/L, and indirect bilirubin: 62 µmol/L). On the same day the subject's ALT was 44 U/L and AST was 66 U/L. The AEs 'blood bilirubin increased' and 'jaundice' were considered to be very likely related to TMC435, possibly related to RBV, and doubtfully related to PegIFNα-2a by the investigator. No action was taken with RBV and PegIFNα-2a due to these events; however treatment with TMC435 was permanently discontinued

due to the event 'blood bilirubin increased'. The subject received the last dose of TMC435 on SD35. On SD50, the AE 'blood bilirubin increased' improved in severity to grade 3. The AEs 'blood bilirubin increased' and 'jaundice' were reported as resolved on SD114 (total bilirubin: 39 µmol/L and indirect bilirubin: 26 µmol/L). This reviewer agrees with the investigator's causality assessment with respect to TMC435.

Hy's Law

Hy's Law refers to the observation made by Dr. Hy Zimmerman that drug induced hepatocellular injury (i.e. aminotransferase elevation) accompanied by jaundice had a poor prognosis. Hepatocellular injury sufficient to impair bilirubin excretion has been used at the FDA to identify drugs likely to cause severe liver injury. The definition used by the FDA as indicator of clinical concern for drug-induced liver injury includes: ALT or AST > 3x upper limit of normal (ULN), total bilirubin > 2x ULN without an initial increase in alkaline phosphatase, and no other explanations for the increases in liver enzymes (e.g. viral hepatitis, pre-existing or acute liver disease, another drug capable of causing the observed injury).

Due to a number of confounding factors, the appropriate application and interpretation of Hy's Law in the setting of treatment trials for chronic hepatitis C in general and TMC435 in particular, is unknown. All of the subjects in the pivotal Phase 3 trials of TMC435 were chronically infected with HCV and 27% of subjects in the TMC435 pooled group were classified as Metavir Fibrosis Score F3 or F4. All subjects in the pivotal Phase 3 trials were co-administered PR, and the administration of interferon is known to increase the risk of hepatitis exacerbations and hepatic failure in patients with cirrhosis. In addition, TMC435 is known to the increase bilirubin levels due to the inhibition of hepatic transporters, further confounding the interpretation of the analysis.

Despite the above caveats, a modified Hy's Law analysis was conducted in the TMC435 group in the pooled Phase 3 trials (C208, C216, and HPC3007). A search was conducted for subjects with simultaneous elevation of ALT or AST > 3x ULN and total bilirubin > 2x ULN with alkaline phosphatase < 2x ULN during the first 12 weeks of the trial (i.e. during the period of TMC435 administration).

A total of 21 subjects in the TMC435 group (n = 781) were identified using the above search parameters.

- 12 subjects had a progressive decline in ALT levels (which were elevated at baseline) during the first 12 weeks of treatment. The subjects included 208-0111, 208-0201, 208-0266, 208-0380, 216-3057, 216-3297, 216-3333, 216-3420, 216-3447, 3007-6252, 3007-6281, and 3007-6324.
- 4 subjects had an isolated treatment emergent increase in ALT and/or AST. (An isolated increase is being defined as a laboratory abnormality which was not present at either the visit immediately preceding or immediately following the visit

which yielded the abnormal result). The isolated elevations in these subjects were not associated with HCV viremia. The subjects included 208-0160, 208-0366, 216-3158, and 216-3362.

- 5 subjects had a treatment emergent elevation in ALT and/or AST persisting over 2 or more visits. Four of these 5 subjects were categorized as MFS F3 or F4 and all cases were confounded either by concomitant medication administration (including interferon) or by alcohol abuse. Little correlation was present between the pattern of elevation/resolution of bilirubin and that of ALT and/or AST. A brief summary of these five cases follows:

    - 1 subject (208-0290), a 51 year old White male with an F4 MFS and baseline ALT of 53 U/L, had an elevation in ALT (maximum 143 U/L) documented from Weeks 2-5 which returned to baseline levels (48 U/L) by Week 10 on treatment. The subject's bilirubin level was 32 μmol/L at baseline (normal range 3-21 μmol/L), 31 μmol/L at Week 2 and 50 μmol/L at Week 5. Bilirubin levels peaked at Week 8 and Week 12 reaching 77 μmol/L and declined to a level of 41 μmol/L by Week 14. The elevation in ALT was not associated with HCV viremia. The subject was administered bactrim from SD3-12 which preceded the elevation in ALT; bactrim was also administered from SD111-125 with no apparent impact on transaminase values. Trimethoprim-sulfmethoxazole has been implicated in reports of hepatotoxicity.[3]
    - 1 subject (216-3093), a 64 year old White female with an F3 MFS had an initial decline in ALT (from a baseline level of 147 U/L) to a nadir of 63 U/L at week 8 of treatment. The subject then had an elevation in ALT at Week 12 and 14 (peak level of 123 U/L) before completely normalizing by Week 17 (ALT 40 U/L). The subject's bilirubin was 12 μmol/L at baseline and increased to a peak of 43 μmol/L at Week 2. It then declined on Weeks 4 and 8 to 26 μmol/L and 22 μmol/L respectively, followed by a peak on Week 12 of 43 μmol/L before declining to 21 μmol/L at Week 14 and 12 μmol/L at Week 17. The elevation in ALT was not associated with HCV viremia. The subject received augmentin from SD72-82, shortly preceding the documented increase in ALT. He also received Tylenol from SD3-104. Both amoxicillin-clavulanic acid and acetaminophen have been associated with drug-induced hepatitis.[4,5]
    - 1 subject (216-3125), a 44 year old White male with an F4 MFS and baseline AST/ALT values of 75/85 U/L, had an initial decline in transaminase values through Week 2 (nadir values AST/ALT of 51/57 U/L), followed by a gradual increase in values peaking at Week 12 (AST/ALT 124/109 U/L). The subject's bilirubin level steadily increased from a baseline level of 14 μmol/L to a peak level of 50 μmol/L on Week 8, and then declined to 26 μmol/L on Week 14 and 17 μmol/L on Week 16. The elevation in transaminases was not associated with HCV viremia.

The AST/ALT values declined to 93/97 U/L at Week 14 and 80/80 U/L by Week 15. The subject completed the TMC435 treatment course. The subject received Tylenol (650 mg po tid) from SD3-169.

- 1 subject (3007-6249), a 53 year old White male with an F2 MFS and baseline AST/ALT values of 43/39 U/L, had an increase in transaminase values occurring (and peaking) at Week 4 with AST/ALT of 145/108 U/L respectively. The subject's baseline bilirubin was 14 μmol/L and increased steadily on treatment reaching a peak of 50 μmol/L on Week 12 and declined to 39 μmol/L on Week 13. The elevation in ALT was not associated with HCV viremia or administration of concomitant medications. AST/ALT values declined to 99/76 U/L by Week 8 and to 79/67 U/L by Week 12. The subject completed treatment with TMC435, but PR was discontinued at Week 13 due to the AE 'alcohol abuse.' This case is clearly confounded by the subject's active alcohol abuse. The subject's AST/ALT ratio (with AST > ALT) is also supportive of the role of alcohol in this case.
- 1 subject (3007-6223), a 32 year old White male with an F3 MFS and a baseline ALT of 135 U/L, had an elevation in ALT to 260 U/L noted at Week 4. The subject's ALT remained elevated throughout treatment with TMC435 (which was completed at Week 12). The subject's ALT reached a peak level of 383 U/L at Week 16. The subject's baseline bilirubin was 9 μmol/L and steadily increased on treatment reaching a peak of 57 μmol/L on Week 12 with a decline to level of 22 μmol/L by Week 16. The elevation in ALT was not associated with HCV viremia. The subject received allopurinol from SD 15-57 and SD 94-116 and transaminase levels appeared to increase approximately 2 weeks following each administration (compared to pre-administration values). Of note, allopurinol has been associated with drug-induced hepatotoxicity.[6] Treatment with pegylated interferon and ribavirin was stopped at approximately Week 16 due to elevated liver enzymes. The subject's ALT declined to a level of 196 U/L by Week 20. Approximately 6 months later, the AE of hepatic enzyme increased was reported as resolved (ALT values corresponding to this time point are not available).

Given the multiple confounding factors present in this population in general and this subset of subjects in particular, this Reviewer does not find a hepatic safety signal of concern based on the modified Hy's Law analysis.

Summary:

As anticipated, this Reviewer discovered a greater frequency of AEs associated with increased bilirubin (including grade 3 and 4 AEs) in the TMC435 group compared to the Control group. However, little correlation was noted between the development of hyperbilirubinemia and clinical events necessitating discontinuation of study drug or

serious adverse events related to study drug use. This tends to lend credence to the Sponsor's view that the increased bilirubin associated with TMC435 use is primarily due to the inhibition of hepatic transporters; a view which is also supported by this Reviewer's analysis of the hepatic laboratory parameters (see Section 7.4.2 for additional details).

Cardiopulmonary Adverse Events

This section includes an assessment of AEs under the SOC Respiratory, Thoracic and Mediastinal Disorders and the SOC Cardiac and Vascular Disorders.

Respiratory, Thoracic and Mediastinal Disorders:

The only HLT (under the SOC Respiratory, Thoracic, and Mediastinal Disorders) which occurred with a notable difference in frequency between TMC435 and Control groups was 'Breathing Abnormalities.' This difference was driven by the PTs 'dyspnea' and 'exertional dyspnea,' both of which occurred more frequently in the TMC435 group. Table 38 summarizes the incidence of Respiratory, Thoracic, and Mediastinal Disorders (by HLT and select PT) during the first 12 weeks of treatment.

Table 38: Respiratory, Thoracic, and Mediastinal Disorders by HLT Occurring in ≥ 1% of Subjects in the TMC435 Group During the First 12 Weeks of Treatment

	First 12 Weeks	
Study Arm	TMC435	PBO
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
MedDRA HLT, Number (%) of Subjects		
Breathing abnormalities	93 (12%)	30 (8%)
Dyspnea	60 (8%)	22 (6%)
Dyspnea Exertional	32 (4%)	8 (2%)
Sleep Apnea Syndrome	1 (<1%)	0 (0%)
Coughing and associated symptoms	77 (10%)	38 (10%)
Upper respiratory tract signs and symptoms	36 (5%)	22 (6%)
Nasal disorders NEC	15 (2%)	6 (2%)
Paranasal sinus disorders (excl infections and neoplasms)	7 (1%)	1 (<1%)
Nasal congestion and inflammations	6 (1%)	4 (1%)
Bronchospasm and obstruction	4 (1%)	3 (1%)

Of the 92 subjects with either 'dyspnea' or 'dyspnea exertional,' in the TMC435 group, there were no grade 3 or 4 AEs, no SAEs, and no discontinuations due to either 'dyspnea' or 'dyspnea exertional' during the first 12 weeks of treatment.

Of the 92 subjects with either 'dyspnea' or 'dyspnea exertional,' in the TMC435 group, 38 subjects (or 41%) had events deemed related to TMC435. Of the 30 subjects with either 'dyspnea' or 'dyspnea exertional,' in the control group, 10 subjects (or 33%) had events deemed related to placebo.

In order to facilitate analysis, a grouped variable 'dyspnea' was created which included both the PTs 'dyspnea' and 'exertional dyspnea.' 'Dyspnea' tended to occur early in the TMC435 treatment course with 61% of cases (57/92 subjects) occurring during the 1st four weeks of treatment (see Figure 5 below).

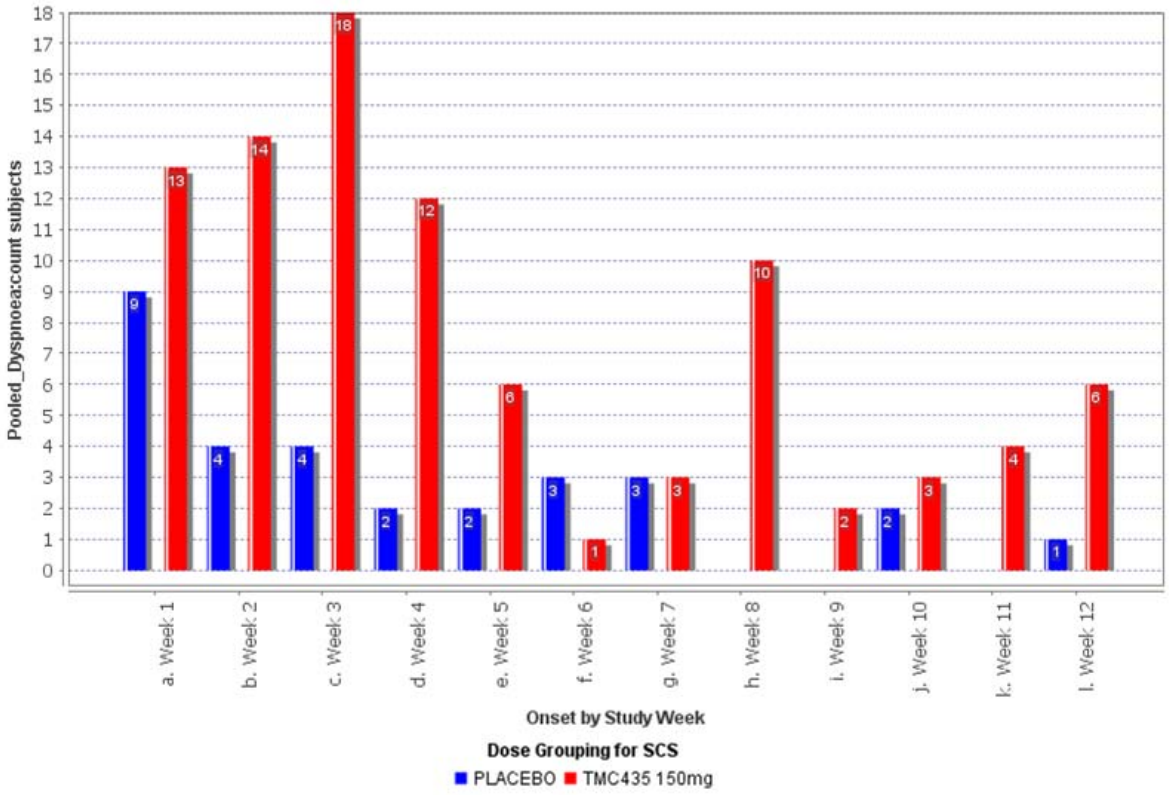


Figure 5: Timing of Onset of 'Dyspnea' in the TMC435 Group during the First 12 Weeks of the Pooled Phase 3 trials

Of the 92 subjects with 'dyspnea' reported during the first 12 weeks of the study, 82 subjects (89%) were in the outcome category of "Recovered/Resolved" with respect to this AE and 9 subjects (10%) were in the AE outcome category of "Not Recovered/Not Resolved" based on the available data.

A separate analysis was performed to factor in the possibility of anemia as a driver for the increased frequency of 'dyspnea' events in the TMC435 group. For this analysis, an additional grouped variable 'anemia' was also created and included the following PTs: 'anemia', 'hemoglobin decreased', 'hemolytic anemia', 'hematocrit decreased', and 'red blood cell count decreased.' Of the 92 subjects with 'dyspnea' reported during the first

12 weeks of treatment in the TMC435 group, 22 subjects (or 24%) also had 'anemia' reported during the first 12 weeks. In the control group, 6 subjects (or 20%) had both 'anemia' and 'dyspnea' reported during the first 12 weeks of treatment. Based on this analysis which controlled for 'anemia', the frequency of 'dyspnea' was 9% (70/781) in the TMC435 group and 6% (24/397) in the Control group. Therefore, irrespective of controlling for 'anemia', dyspnea rates were 50% higher in the TMC435 group compared to the Control group.

Under the SOC Respiratory, Thoracic, and Mediastinal Disorders, there was one grade 3 AE ('cough' in Subject 208-0315) in the TMC435 group and two grade 3 AEs in the Control group ('pulmonary embolism' and 'oropharyngeal pain') during the first 12 weeks of treatment. There were no grade 4 AEs under the SOC Respiratory, Thoracic, and Mediastinal Disorders during the first 12 weeks of treatment in either group.

There were no SAEs in the TMC435 group and only 1 SAE in the control group (PT 'pulmonary embolism') under the SOC Respiratory, Thoracic, and Mediastinal Disorders during the first 12 weeks of treatment.

There were no discontinuations of TMC435 due to an AE under the SOC Respiratory, Thoracic, and Mediastinal Disorders during the first 12 weeks of treatment in either group.

Cardiac and Vascular Disorders:

Table 39 summarizes (by PT) the frequency of any AEs under the SOCs Cardiac Disorders and Vascular Disorders occurring during the first 12 weeks of treatment in the TMC435 group.

Table 39: Cardiac Disorders and Vascular Disorders by PT Occurring in ≥ 1 Subject in the TMC435 Group During the First 12 Weeks of Treatment

	First 12 Weeks	
	TMC435	PBO
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
MedDRA PT, Number (%) of Subjects		
Tachycardia	6 (1%)	0 (0%)
Hypotension	5 (1%)	0 (0%)
Hot flush	5 (1%)	1 (<1%)
Palpitations	4 (1%)	2 (1%)
Hypertension	4 (1%)	3 (1%)
Pallor	2 (<1%)	0 (0%)
Arrhythmia	1 (<1%)	0 (0%)
Angina pectoris	1 (<1%)	0 (0%)
Conduction disorder	1 (<1%)	0 (0%)
Intra-abdominal haematoma	1 (<1%)	0 (0%)
Supraventricular extrasystoles	1 (<1%)	0 (0%)
Myocardial ischaemia	1 (<1%)	1 (<1%)
Sinus tachycardia	1 (<1%)	1 (<1%)
Hypertensive crisis	1 (<1%)	1 (<1%)
Flushing	1 (<1%)	1 (<1%)

There was only one grade 3 or 4 event listed in the Table above. That event, 'hypotension,' was categorized as a grade 3 SAE and is summarized below:

Subject 208-0006: 60 year old white male with a history pertinent for hypertension (receiving amlodipine and Co-diovan), low back pain (receiving morphine sulfate), and a screening Metavir score of F3 was hospitalized on SD13 with syncope, acute pre-renal failure, and hypotension, reported as AEs of grade 3 severity. These AEs were considered not to be related to TMC435, PegIFNα-2a, and RBV by the investigator. The suspected causes of these events were dehydration, anti-hypertensive therapy and morphine sulfate. The treatment with TMC435 and RBV was interrupted from SD13-15 while no action was taken with PegIFNα-2a. On SD15, the events of syncope, acute prerenal failure and hypotension were reported as resolved and the subject was discharged. The subject completed the study treatment with TMC435 on SD82. This reviewer concurs with the investigator's assessment of causality.

There were no other SAEs in the TMC435 group occurring in the first 12 weeks under the SOCs Cardiac Disorders or Vascular Disorders. There were no discontinuations of TMC345 for any AEs in the first 12 weeks under the SOCs Cardiac Disorders or Vascular Disorders.

Summary:

The most notable finding with respect to the cardiopulmonary assessment was an increased frequency of 'dyspnea' in the TMC435 group compared to the Control group. The majority of these events occurred in the first 4 weeks of treatment with TMC435. All of these AEs were of mild or moderate severity. There were no grade 3 or 4 AEs, SAEs, or discontinuations due to 'dyspnea' during the first 12 weeks of treatment in the TMC435 group. An analysis to ascertain whether the reported 'dyspnea' events were associated with the presence of anemia was performed and failed to demonstrate a clear association. The reason for the finding of increased rates of 'dyspnea' in the TMC435 group remains unclear.

Blood and Lymphatic System Disorders:

As background, the use of erythropoiesis-stimulating agents (ESA) was prohibited in the pivotal Phase 3 studies. ESA use was reported in only two subjects (0.3%) in the TMC435 group. The use of neutropoiesis-stimulating agents was infrequent in both the TMC435 group (24 subjects or 3.4%) and the placebo group (15 subjects or 4.2%).

Adverse events in the SOC 'Blood and Lymphatic System Disorders' combined with the HLGT 'Hematologic Investigations' occurred in 31% of subjects in the TMC435 group and 28% of subjects in the Control group during the first 12 weeks of treatment. Table 40 summarizes all of the AEs by PT under the SOC 'Blood and Lymphatic System Disorders' and the HLGT 'Hematology Investigations' under the SOC "Investigations' which occurred during the first 12 weeks of treatment.

Table 40: AEs (by PT) Under the SOC 'Blood and Lymphatic System Disorders' and the HLGT 'Hematology Investigations' Occurring in the First 12 Weeks of Treatment

	First 12 Weeks	
	TMC435	PBO
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
MedDRA PT, Number (%) of Subjects		
Neutropenia	109 (14%)	50 (13%)
Anemia	93 (12%)	40 (10%)
Thrombocytopenia	33 (4%)	9 (2%)
Neutrophil count decreased	21 (3%)	10 (3%)
Leukopenia	14 (2%)	7 (2%)
Hemoglobin decreased	11 (1%)	4 (1%)
Platelet count decreased	6 (1%)	6 (2%)
Hemolytic anaemia	3 (<1%)	0 (0%)
Granulocytopenia	3 (<1%)	2 (1%)
White blood cell count decreased	3 (<1%)	5 (1%)
Activated partial thromboplastin time prolonged	2 (<1%)	2 (1%)
Hemolysis	1 (<1%)	0 (0%)
White blood cell count increased	1 (<1%)	0 (0%)
Hematocrit decreased	1 (<1%)	1 (<1%)
Coagulopathy	0 (0%)	1 (<1%)
Red blood cell count decreased	0 (0%)	1 (<1%)
Lymphopenia	0 (0%)	1 (<1%)
Activated partial thromboplastin time shortened	0 (0%)	2 (1%)
Prothrombin time prolonged	0 (0%)	2 (1%)

A slightly higher frequency of the AEs by PT 'neutropenia', 'anemia', and 'thrombocytopenia' were noted. Given the similarity of many of the AE terms related to neutropenia, anemia, thrombocytopenia, and leukopenia, separate analyses were performed using the following grouped variables to allow a clearer assessment of AE trends:

1. 'Neutropenia' = PTs ('neutropenia', 'neutrophil count decreased' and 'granulocytopenia')
2. 'Leukopenia' = PTs ('leukopenia' and 'white blood cell count decreased')
3. 'Thrombocytopenia' = PTs ("thrombocytopenia', 'platelet count decreased')
4. 'Anemia' = PT ('anemia', 'hemoglobin decreased', 'hemolytic anemia', 'hematocrit decreased', 'red blood cell count decreased')

The analysis using grouped termed revealed a slightly higher frequency of anemia in the TMC435 group than the control group during the first 12 weeks of treatment (see Table 41 below).

Table 41: AEs (by Grouped Terms) Under the SOC 'Blood and Lymphatic System Disorders' and the HLGT 'Hematology Investigations' Occurring in the First 12 Weeks of Treatment

	First 12 Weeks	
	TMC435	PBO
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
Grouped Term, Number (%) of Subjects		
Neutropenia	132 (17%)	62 (16%)
Anemia	105 (13%)	44 (11%)
Thrombocytopenia	39 (5%)	15 (4%)
Leukopenia	17 (2%)	12 (3%)

The frequency of grade 3 and grade 4 AEs under the SOC 'Blood and Lymphatic System Disorders' combined with the HLGT 'Hematologic Investigations' was similar between groups (refer to Table 42 below).

Table 42: Grade 3 or 4 AEs (by Grouped Term) Under the SOC 'Blood and Lymphatic System Disorders' and the HLGT 'Hematology Investigations' Occurring in the First 12 Weeks of Treatment

	First 12 Weeks	
	TMC435	PBO
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
Grouped Term, Number (%) of Subjects		
Neutropenia	83 (11%)	40 (10%)
Anemia	8 (1%)	8 (2%)
Thrombocytopenia	14 (2%)	4 (1%)
Leukopenia	7 (1%)	2 (1%)

There were no SAEs or discontinuations due to AEs under the SOC category of 'Blood and Lymphatic System Disorders' or the HLGT 'Haematologic Investigations' reported in the TMC435 group during the first 12 weeks of treatment.

Summary: A slightly higher frequency of 'anemia' occurred in the TMC435 group (13%) compared to the Control group (11%) during the first 12 weeks of treatment. However the frequency of grade 3 or 4 'anemia' AEs was higher in the Control group over this period of time. No substantive differences in the frequency of AEs in the categories of 'neutropenia', 'leukopenia', or 'thrombocytopenia' were noted during the first 12 weeks

of treatment. There were no SAEs or discontinuations due to hematologic AEs reported in the TMC435 group during the first 12 weeks of treatment.

Neoplasms (Benign, Malignant, and Unspecified):

During the 72 Week reporting period, AEs under the SOC 'Neoplasms' occurred in 11/781 (1.4%) of subjects in the TMC435 group and 1/397 (0.3%) of subjects in the Control group. Table 43 describes all neoplasms (by PT) which occurred over the 72 Week reporting period. Although a greater frequency of events occurred in the TMC435 group, no clustering of cases by HLGT, HLT, or PT within the TMC435 group was noted.

Table 43: All Neoplasms (by PT) Occurring over the 72 Week Reporting Period in the Pooled Phase 3 Studies

	72 Week Reporting Period	
	TMC435	PBO
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
MedDRA PT, Number (%) of Subjects		
Breast cancer	1 (0.1%)	0 (0.0%)
Colon cancer	1 (0.1%)	0 (0.0%)
Granular cell tumour	1 (0.1%)	0 (0.0%)
Hepatic neoplasm malignant	1 (0.1%)	0 (0.0%)
Laryngeal cancer	1 (0.1%)	0 (0.0%)
Lipoma	1 (0.1%)	0 (0.0%)
Melanocytic naevus	1 (0.1%)	0 (0.0%)
Renal cell carcinoma	1 (0.1%)	0 (0.0%)
Seborrhoeic keratosis	0 (0.0%)	1 (0.3%)
Skin papilloma	2 (0.3%)	0 (0.0%)
Uterine leiomyoma	1 (0.1%)	0 (0.0%)

In order to further investigate the overall trend of increased neoplasms in the TMC435 group, additional analyses were conducted using the pooled 2b studies C205 and C206. In these pooled Studies, AEs under the SOC 'Neoplasms' (including both benign and malignant neoplasms) occurred in 25 subjects (4%) in the TMC435 group and 8 subjects (6%) in the Control group during the 72 week reporting period . Table 44 presents only the malignant neoplasms from Study C205 and C206 for comparison. In the pooled TMC435 group there were 11/705 subjects (1.6%) with AEs reported for malignant neoplasms compared to 5/143 subjects (3.4%) in the pooled Control group during the 72 week reporting period.

Table 44: All Malignant Neoplasms (by PT) Occurring over the 72 Week Reporting Period in the Pooled Phase 2b Studies

	72 Week Reporting Period	
	TMC435	PBO
Studies (Number of Subjects)	C205 and C206 (N=705)	C205 and C206 (N=143)
MedDRA PT, Number (%) of Subjects		
Basal cell carcinoma	3 (<1%)	0 (0%)
Breast cancer	3 (<1%)	0 (0%)
Breast cancer in situ	1 (<1%)	0 (0%)
Cervix carcinoma	1 (<1%)	0 (0%)
Hepatic neoplasm	0 (0%)	1 (1%)
Hepatic neoplasm malignant	1 (<1%)	0 (0%)
Histiocytosis haematophagic	0 (0%)	1 (1%)
Neoplasm skin	0 (0%)	1 (1%)
Ovarian neoplasm	0 (0%)	1 (1%)
Rectal cancer	1 (<1%)	0 (0%)
Squamous cell carcinoma	1 (<1%)	1 (1%)

Summary: After assessing the totality of data (including the pivotal phase 3 studies and supportive phase 2b studies), this Reviewer has not found consistent evidence that a neoplastic signal of concern is present. As discussed in Section 4.3, no carcinogenicity studies of TMC435 were required as the Sponsor's proposed treatment duration of TMC435 is only 12 weeks. TMC435 was not found to be genotoxic in a series of tests including the Ames test, mouse lymphoma test and mouse bone marrow micronucleus test.

Musculoskeletal:

During the first 12 weeks of treatment, AEs under the SOC 'Musculoskeletal' occurred in 33% of subjects in the TMC435 group and 29% of subjects in the Control group. This difference was largely driven by an increase in three specific PTs in the TMC435 group: myalgia, arthralgia, and back pain. Table 45 describes the AE under the SOC 'Musculoskeletal' that occurred in ≥ 1% of subjects in the TMC435 group by HLT and also describes the specific PTs mentioned above.

Table 45: AE under the MedDRA SOC 'Musculoskeletal' (Stratified by HLT) that occurred in ≥ 1% of Subjects in the TMC435 Group during the First 12 Weeks of Treatment

	First 12 Weeks	
	TMC435	PBO
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
MedDRA HLT, Number (%) of Subjects		
Muscle pains	126 (16%)	53 (13%)
Myalgia*	126 (16%)	53 (13%)
Joint related signs and symptoms	80 (10%)	31 (8%)
Arthralgia*	80 (10%)	31 (8%)
Musculoskeletal and connective tissue pain and discomfort	75 (10%)	34 (9%)
Back Pain*	49 (6%)	17 (4%)
Muscle related signs and symptoms NEC	17 (2%)	13 (3%)
Bone related signs and symptoms	5 (1%)	4 (1%)

*MedDRA PT

With respect to the PTs 'myalgia,' 'arthralgia,' and 'back pain,' there were no grade 4 AEs, no SAEs and no discontinuations of TMC435 due to these AEs. There were 3 subjects (< 1%) with the grade 3 AE 'back pain' in the TMC435 group and 1 subject (<1%) with this grade 3 AE in the Control group.

Summary: Myalgias, arthralgias, and back pain occurred with somewhat greater frequency in the TMC435 group compared to the Control group. However, grade 3 events were rare and there were no grade 4 AEs, no SAEs and no discontinuations of TMC435 due to these AEs. Additionally, no rhabdomyolysis adverse events were reported in TMC435 treated subjects in either the Phase 2b (C205 and C206) or Phase 3 studies (C208, C216, and HPC3007).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 46 presents all AEs by MedDRA PT that occurred in ≥3% of subjects in the TMC435 group during the first 12 weeks of treatment.

Table 46: AEs Occurring in ≥3% of Subjects in the TMC435 Group During the First 12 Weeks of Treatment

	TMC435	PBO
	First 12 Weeks	First 12 Weeks
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
MedDRA Preferred Term n (%)		
Fatigue	278 (36%)	157 (40%)
Headache	259 (33%)	141 (36%)
Influenza like illness	203 (26%)	84 (21%)
Pyrexia	184 (24%)	104 (26%)
Nausea	173 (22%)	70 (18%)
Pruritus	161 (21%)	54 (14%)
Insomnia	131 (17%)	67 (17%)
Myalgia	126 (16%)	53 (13%)
Asthenia	125 (16%)	71 (18%)
Decreased appetite	120 (15%)	56 (14%)
Neutropenia	109 (14%)	50 (13%)
Rash	106 (14%)	44 (11%)
Anemia	93 (12%)	40 (10%)
Diarrhea	86 (11%)	45 (11%)
Arthralgia	80 (10%)	31 (8%)
Mood altered	74 (9%)	46 (12%)
Cough	72 (9%)	36 (9%)
Chills	68 (9%)	41 (10%)
Depression	60 (8%)	29 (7%)
Dyspnea	60 (8%)	22 (6%)
Dry skin	60 (8%)	27 (7%)
Vomiting	51 (7%)	20 (5%)
Back pain	49 (6%)	17 (4%)
Dizziness	48 (6%)	20 (5%)
Injection site erythema	44 (6%)	22 (6%)
Alopecia	44 (6%)	21 (5%)
Anxiety	40 (5%)	17 (4%)
Sleep disorder	36 (5%)	22 (6%)
Thrombocytopenia	33 (4%)	9 (2%)
Dyspnea exertional	32 (4%)	8 (2%)
Abdominal pain upper	31 (4%)	18 (5%)
Hyperbilirubinemia	29 (4%)	8 (2%)
Disturbance in attention	29 (4%)	13 (3%)
Dyspepsia	27 (3%)	10 (3%)
Dysgeusia	27 (3%)	17 (4%)
Blood bilirubin increased	27 (3%)	3 (1%)
Weight decreased	26 (3%)	6 (2%)
Dry mouth	25 (3%)	7 (2%)
Erythema	24 (3%)	11 (3%)

Photosensitivity reaction	24 (3%)	2 (1%)
Oropharyngeal pain	23 (3%)	10 (3%)

Table 47 presents the AEs by PT and grouped term that occurred ≥3% more frequently in the TMC435 group compared to the Control group during the first 12 weeks of treatment.

Table 47: AEs by PT and Grouped Term that Occurred ≥3% More Frequently in the TMC435 Group Compared to the Control Group during the First 12 Weeks of Treatment.

	TMC435	Control
	First 12 Weeks	First 12 Weeks
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
Preferred Term or Grouped Term, n (%)		
Rash[1]	218 (28%)	79 (20%)
Influenza like illness	203 (26%)	84 (21%)
Pruritis[2]	168 (22%)	58 (15%)
Nausea	173 (22%)	70 (18%)
Myalgia	126 (16%)	53 (13%)
Dyspnea[3]	92 (12%)	30 (8%)
Increased Bilirubin[4]	61 (8%)	11 (3%)
Photosensitivity[5]	38 (5%)	3 (1%)

1. Grouped term 'Rash' includes the following preferred terms: Rash, Erythema, Eczema, Rash maculo-papular, Rash macular, Dermatitis, Rash papular, Skin exfoliation, Rash pruritic, Rash erythematous, Urticaria, Rash generalized, Drug eruption, Dermatitis allergic, Dermatosis, Vasculitic rash, Toxic skin eruption, Exfoliative rash, Generalised erythema, Dermatitis exfoliative, Cutaneous vasculitis, Photosensitivity reaction, Polymorphic light eruption, Solar dermatitis, Photodermatosis, and Sunburn
2. Grouped term 'Pruritis' includes the following preferred terms: pruritis and pruritis generalized
3. Grouped term 'Dyspnea' includes the following preferred terms: dyspnea and dyspnea exertional
4. Grouped term 'Increased Bilirubin' includes the following preferred terms: hyperbilirubinemia, blood bilirubin increased, jaundice, blood bilirubin unconjugated increased, and bilirubin conjugated increased
5. Grouped term 'Photosensitivity' includes the following preferred terms: photodermatosis, photosensitivity reaction, polymorphic light eruption, solar dermatitis, and sunburn

The relevant subsections of Section 7.3.5 provide detailed discussions of each of the AEs (with the exception of 'influenza like illness' described below) that occurred ≥3% more frequently in the TMC435 group compared to the Control group during the first 12 weeks of treatment.

As noted in Table 47, the AE 'influenza like illness' was reported in 26% of TMC435 subjects and 21% of Control subjects during the first 12 weeks of treatment. Only 1% of TMC435 treated subjects and 1% of Control subjects had grade 3 events and no grade 4 events were reported for either group. There were no SAEs or discontinuations of study drug reported for either group related to the AE 'influenza like illness.'

7.4.2 Laboratory Findings

Hepatic and Pancreatic Laboratory Abnormalities:

Table 48 summarizes the hepatic and pancreatic laboratory abnormalities by severity grade. The analysis set was limited to subjects with at least one post-baseline laboratory value for each test. Subjects were counted only once for their post-baseline maximum severity for each laboratory test.

Table 48: Hepatic and Pancreatic Laboratory Abnormalities by Severity Grade During the First 12 Weeks of Treatment

	TMC435	PBO
	First 12 Weeks	First 12 Weeks
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
Maximum toxicity grade, n(%)		
Aspartate Aminotransferase (U/L)		
Grade 1 (1.25 to 2.5 x ULN)	65 (8%)	49 (12%)
Grade 2 (>2.5 to 5 x ULN)	28 (4%)	13 (3%)
Grade 3 (>5 to 10 x ULN)	8 (1%)	5 (1%)
Alanine Aminotransferase (U/L)		
Grade 1 (1.25 to 2.5 x ULN)	47 (6%)	30 (8%)
Grade 2 (>2.5 to 5 x ULN)	23 (3%)	11 (3%)
Grade 3 (>5 to 10 x ULN)	10 (1%)	8 (2%)
Bilirubin (umol/L)		
Grade 1 (>1 to 1.5 x ULN)	208 (27%)	61 (15%)
Grade 2 (>1.5 to 2.5 x ULN)	143 (18%)	36 (9%)
Grade 3 (>2.5 to 5 x ULN)	32 (4%)	6 (2%)
Grade 4 (>5 x ULN)	3 (<1%)	0 (0%)
Alkaline Phosphatase (U/L)		
Grade 1 (1.25 to 2.5 x ULN)	26 (3%)	5 (1%)
Grade 2 (>2.5 to 5 x ULN)	1 (<1%)	0 (0%)
Gamma Glutamyl Transferase (U/L)		
Grade 1 (1.25 to 2.5 x ULN)	36 (5%)	35 (9%)
Grade 2 (>2.5 to 5 x ULN)	16 (2%)	17 (4%)
Grade 3 (>5 to 10 x ULN)	2 (0%)	5 (1%)
Grade 4 (>10 x ULN)	1 (0%)	2 (1%)
Amylase (U/L)		
Grade 1 (>1 to 1.5 x ULN)	116 (15%)	57 (14%)
Grade 2 (>1.5 to 2.0 x ULN)	38 (5%)	22 (6%)
Grade 3 (>2.0 to 5 x ULN)	27 (3%)	11 (3%)
Lipase (U/L)[1]		
Grade 1 (>1 to 1.5 x ULN)	19 (2%)	8 (2%)
Grade 2 (>1.5 to 3.0 x ULN)	6 (1%)	6 (2%)
Grade 3 (>3.0 to 5 x ULN)	5 (1%)	3 (1%)

There was no evidence of a concerning trend with respect to graded elevations in AST, ALT, GGT, amylase or lipase in the TMC435 group compared to the Control group. As a normalization of AST and ALT levels are anticipated early after initiation of HCV treatment, an additional analysis was performed to assess the highest toxicity grade reported following achievement of nadir AST and ALT levels. Again, no concerning trends were noted in this analysis (refer to Table 49 below).

Table 49: Highest Toxicity Grade Reported following Achievement of Nadir AST and ALT Levels

	TMC435	PBO
	First 12 Weeks	First 12 Weeks
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
Maximum toxicity grade, n(%)		
Aspartate Aminotransferase (U/L)		
Grade 1 (1.25 to 2.5 x ULN)	42 (5%)	27 (7%)
Grade 2 (>2.5 to 5 x ULN)	22 (3%)	9 (2%)
Grade 3 (>5 to 10 x ULN)	8 (1%)	3 (1%)
Alanine Aminotransferase (U/L)		
Grade 1 (1.25 to 2.5 x ULN)	29 (4%)	18 (5%)
Grade 2 (>2.5 to 5 x ULN)	14 (2%)	9 (2%)
Grade 3 (>5 to 10 x ULN)	6 (1%)	5 (1%)

Both ALT and AST (not shown) demonstrated a similar decline in levels early post-treatment initiation (see Figure 6 below).

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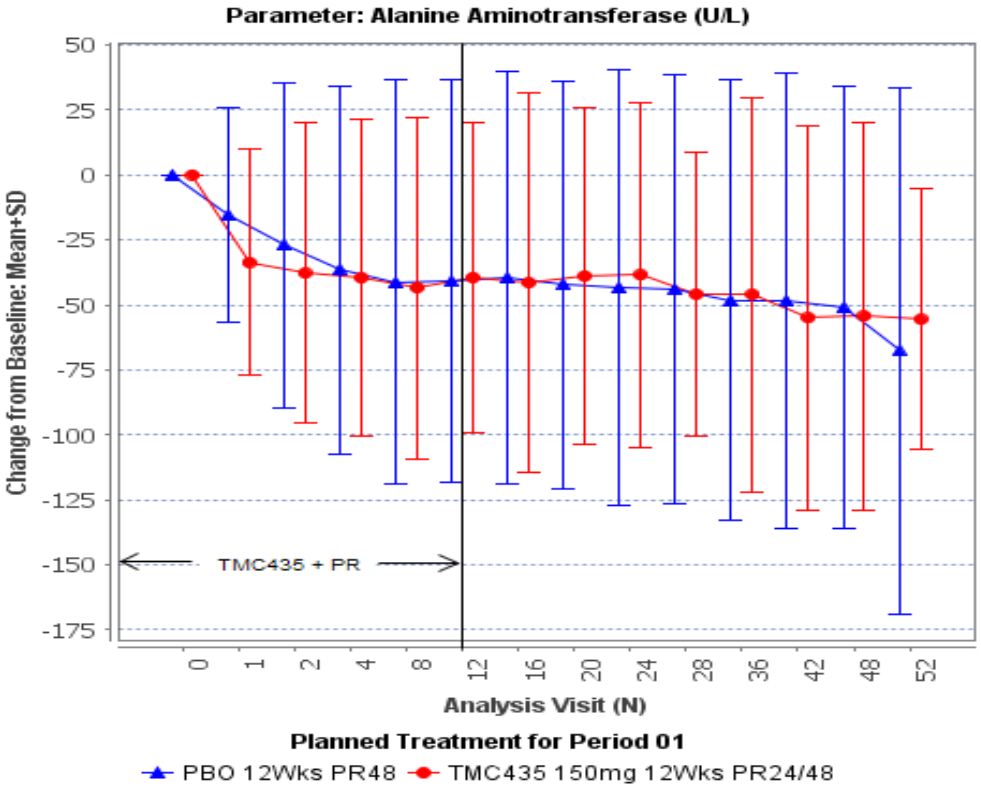

Figure 6: Alanine Aminotransferease (ALT)--Change from Baseline Over Time (in Weeks)

A marked increase in frequency of graded bilirubin elevations in the TMC435 group (49%) compared to the Control group (26%) was noted. This difference was primarily driven by grade 1 and 2 laboratory abnormalities. Any elevation in direct bilirubin was reported in 28% of TMC435 subjects and in 10% of Control subjects. Any elevation in indirect bilirubin was noted in 25% of TMC435 subjects and in 12% of Control subjects. Elevations in bilirubin occurred early after treatment initiation, peaking by Week 2. By four weeks following completion of TMC435 treatment (i.e. Week 16), levels were shown to return to near baseline values. The following graph summarizes the time course of bilirubin elevation in the Phase 3 trials.

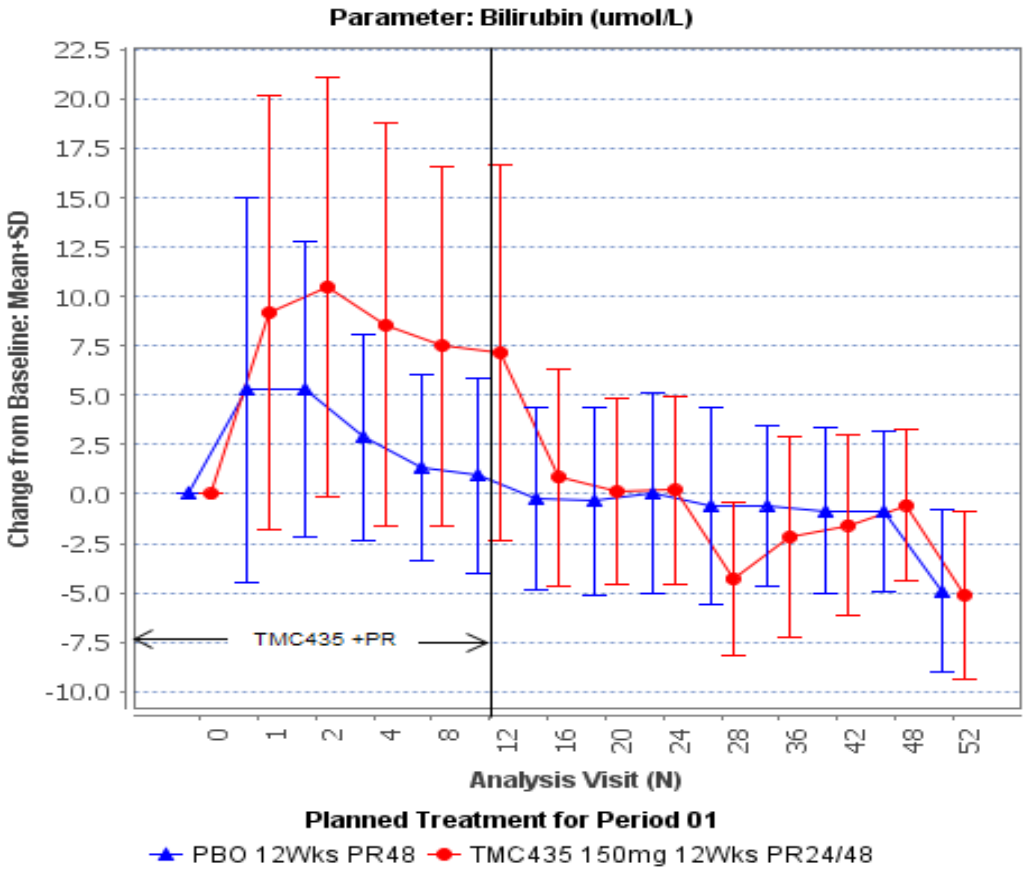

Figure 7: Serum Bilirubin--Change from Baseline Over Time (in Weeks)

An increase in reported elevations in alkaline phosphatase in the TMC group (4%) compared to the Control group (1%) was also noted. All alkaline phosphatase laboratory abnormalities were grade 1 or 2 in severity. Elevations in alkaline phosphatase increased steadily upon treatment initiation, peaking at Week 8 and rapidly declining to baseline levels upon completion of TMC435 treatment. The following graph summarizes the time course alkaline phosphatase elevation.in the Phase 3 trials.

Of note, there was no evidence an increased frequency of bile duct obstruction or cholestatic hepatotoxicity in the TMC435 group compared to the Control group. As discussed in detail in Section 7.3.5, there was only one subject (Subject 208-0461) or 0.1% of the TMC435 group with a reported AE related to cholelithiasis and biliary obstruction.

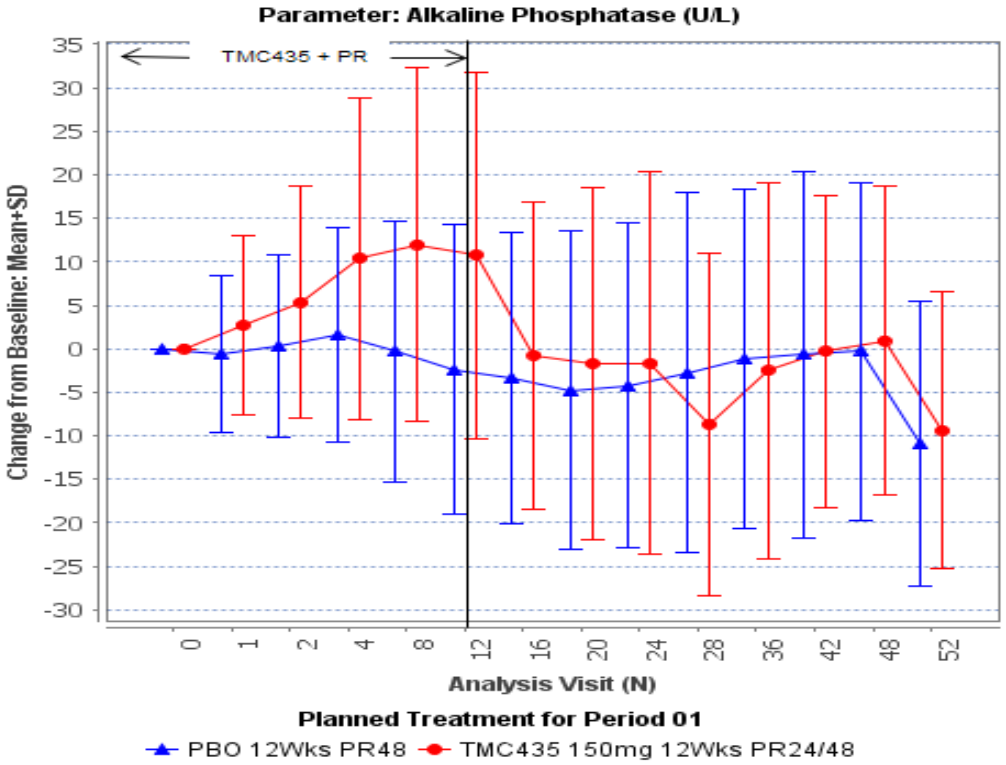

Figure 8: Serum Alkaline Phosphatase--Change from Baseline Over Time (in Weeks)

Hematologic Laboratory Abnormalities:

Table 50 summarizes the hematologic laboratory abnormalities by severity grade. The analysis set was limited to subjects with at least one post-baseline laboratory value for each test. Subjects were counted only once for their post-baseline maximum severity for each laboratory test. There is no evidence of a concerning trend with respect to hematologic laboratory findings in the TMC435 group compared to the Control group. Of note, Prothrombin time and Activated Partial Thromboplastin Time were also assessed in these studies and no difference in frequency of graded events between groups for these indices was appreciated.

Table 50: Hematologic Laboratory Abnormalities by Severity Grade During the First 12 Weeks of Treatment

	TMC435	PBO
	First 12 Weeks	First 12 Weeks
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
Maximum toxicity grade, n(%)		
Hemoglobin (g/L)		
Grade 1 (9.5-10.5 gm/dL)	121 (15%)	59 (15%)
Grade 2 (8.0 to < 9.5 gm/dL)	41 (5%)	19 (5%)
Grade 3 (6.5 to < 8.0 gm/dL)	6 (1%)	7 (2%)
Neutrophils (x10^9/L)		
Grade 1 (1000-1500/mm³)	314 (40%)	149 (38%)
Grade 2 (750-999/mm³)	159 (20%)	93 (23%)
Grade 3 (500-749/mm³)	96 (12%)	52 (13%)
Grade 4 (<500/mm³)	23 (3%)	11 (3%)
Platelets (x10^9/L)		
Grade 1 (75,000 to < 100,000/mm^3)	101 (13%)	54 (14%)
Grade 2 (50,000 to < 75,000/mm^3)	44 (6%)	37 (9%)
Grade 3 (20,000 to < 50,000/mm^3)	13 (2%)	3 (1%)

Renal and Electrolyte Laboratory Abnormalities:

Table 51 summarizes the renal and electrolyte laboratory abnormalities by severity grade. The analysis set was limited to subjects with at least one post-baseline laboratory value for each test. Subjects were counted only once for their post-baseline maximum severity for each laboratory test. There is no evidence of a concerning trend with respect to the renal or electrolyte laboratory findings in the TMC435 group compared to the Control group.

Table 51: Renal and Electrolyte Laboratory Abnormalities by Severity Grade During the First 12 Weeks of Treatment

	TMC435	PBO
	First 12 Weeks	First 12 Weeks
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
maximum toxicity grade, n (%)		
Serum Creatinine		
Grade 1 (≥1.1 to ≤1.5 x ULN)	16 (2%)	10 (3%)
Grade 2 (>1.5 to ≤3.0 x ULN)	1 (<1%)	3 (1%)
Serum Phosphate (Hypophosphatemia)		
Grade 1 (2.0-2.4 mg/dL)	164 (21%)	77 (19%)
Grade 2 (1.5-1.9 mg/dL or replacement Rx required)	29 (4%)	11 (3%)

Grade 3 (1.0-1.4 mg/dL intensive Rx or hospitalization required)	0 (0%)	4 (1%)
Serum Magnesium (Hypomagnesemia)		
Grade 1 (1.4-1.2 mEq/L)	30 (4%)	18 (5%)
Grade 2 (1.1-0.9 mEq/L)	1 (<1%)	1 (<1%)
Serum Potassium (Hypokalemia)		
Grade 1 (3.0-3.4 mEq/L)	52 (7%)	23 (6%)
Grade 2 (2.5-2.9 mEq/L)	1 (<1%)	2 (1%)
Serum Potassium (Hyperkalemia)		
Grade 1 (5.6-6.0 mEq/L)	3 (<1%)	3 (1%)
Serum Glucose (Hypoglycemia)		
Grade 1 (55-64 mg/dL)	18 (2%)	15 (4%)
Grade 2 (40-54 mg/dL)	4 (1%)	3 (1%)
Serum Glucose (Hyperglycemia)		
Grade 1 (116-160 mg/dL)	108 (14%)	55 (14%)
Grade 2 (161-250 mg/dL)	23 (3%)	9 (2%)
Grade 3 (251-500 mg/dL)	6 (1%)	3 (1%)
Serum Calcium (Hypocalcemia)		
Grade 1 (8.4-7.8 mg/dL)	29 (4%)	12 (3%)
Grade 2 (7.7-7.0 mg/dL)	3 (<1%)	6 (2%)
Serum Calcium (Hypercalcemia)		
Grade 1 (10.6-11.5 mg/dL)	7 (1%)	1 (<1%)
Serum Sodium (Hyponatremia)		
Grade 1 (130-135 mEq/L)	40 (5%)	19 (5%)
Grade 2 (123-129 mEq/L)	6 (1%)	2 (1%)
Serum Sodium (Hypernatremia)		
Grade 1 (146-150 mEq/L)	81 (10%)	40 (10%)
Grade 2 (151-157 mEq/L)	4 (1%)	1 (<1%)

7.4.3 Vital Signs

Pulse and blood pressure (BP) parameters were monitored and recorded during the Phase 3 trials. Table 52 summarizes the clinically relevant abnormalities reported for these parameters during the first 12 Weeks in the pooled Phase 3 studies. No substantive differences were noted between the TMC435 and the Control groups for any of the parameters assessed.

Table 52: Pulse and BP Parameters During the First 12 Weeks of the Phase 3 Trials

	TMC435	PBO
	First 12 Weeks	First 12 Weeks
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
Parameter, n(%)		
Supine Pulse Rate (beats/min)		
Abnormally Low	5 (<1%)	2 (1%)
Abnormally High	0 (0%)	1 (<1%)
Supine Systolic Blood Pressure (mmHg)		
Abnormally Low	23 (3%)	9 (2%)
Grade 1	53 (7%)	33 (8%)
Grade 2	15 (2%)	8 (2%)
Grade 3	3 (<1%)	1 (<1%)
Supine Diastolic Blood Pressure (mmHg)		
Abnormally Low	9 (1%)	4 (1%)
Grade 1	39 (5%)	26 (7%)
Grade 2	12 (2%)	13 (3%)
Grade 3	2 (<1%)	1 (<1%)

7.4.4 Electrocardiograms (ECGs)

ECGs were performed on a scheduled basis during the Phase 3 studies. Table 53 summarizes selected ECG abnormalities reported for these parameters during the first 12 Weeks in the pooled Phase 3 studies. No substantive differences were noted between the TMC435 and the Control groups for any of the parameters assessed. For QRS, the Sponsor defined "abnormally low" as ≤ 50 ms and "abnormally high" as ≥ 120 ms. For QTc, the Sponsor defined the abnormalities as follows: "borderline" as 450< QTc ≤ 480 ms; "prolonged" as 480< QTc ≤ 500 ms; and "pathologically prolonged" as QTc > 500 ms. For the PR interval, the Sponsor defined "abnormally high" as ≥ 210 ms.

Table 53: Selected ECG Parameters During the First 12 Weeks of the Phase 3 Trials

	TMC435	PBO
	First 12 Weeks	First 12 Weeks
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
Parameter, n(%)		
PR Interval (msec)		
Abnormally Low	0 (0%)	0 (0%)
Abnormally High	8 (1%)	7 (2%)
QRS Interval (msec)		
Abnormally Low	0 (0%)	0 (0%)
Abnormally High	1 (<1%)	1 (<1%)
QTC Interval Bazett (msec)		
Borderline	30 (4%)	17 (4%)
Pathologically Prolonged	1 (<1%)	0 (0%)
Prolonged	3 (<1%)	1 (<1%)
QTC Interval Fridericia (msec)		
Borderline	11 (1%)	2 (1%)
Pathologically Prolonged	0 (0%)	0 (0%)
Prolonged	0 (0%)	0 (0%)

Please refer to Section 7.4.5, 'QT Assessment Study' for a detailed description of the dedicated QT study performed in support of this application.

7.4.5 Special Safety Studies/Clinical Trials

QT Assessment Study:

Study TMC435-TiDP16-C117 was a double-blind, double-dummy, randomized, 4-period cross-over, placebo and positive controlled (moxifloxacin) study to evaluate the effect of TMC435 on the QTc interval in healthy subjects.

The following summary of findings is based on the review of the Interdisciplinary Review Team (IRT) for QT studies:

No significant QTc prolongation effect of TMC435 was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between TMC435 and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time was adequately demonstrated indicating that assay sensitivity was established. See Table 54 below for details.

Table 54: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for TMC435 and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time	ΔΔQTcF (ms)	90% CI (ms)
TMC435 150 mg	3	0.8	(-1.0, 2.6)
TMC435 350 mg	3	1.2	(-0.6, 3.0)
Moxifloxacin 400 mg*	4	10.9	(9.0, 12.8)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 8.3 ms.

Source: IRT Review

The 150 mg once daily dose (q.d.) was the highest dose of TMC435 studied in the phase 2b and phase 3 clinical trials and is proposed dose for post-approval use. The pharmacokinetics of TMC435 appears to be substantially more than dose proportional when the dose is higher than 75 mg q.d. In the current trial, the mean values of C_{max} and AUC_{24h} on day 7 at the supratherapeutic TMC435 dose of 350 mg q.d. were roughly 10 times those at the therapeutic dose of 150 mg q.d. This is higher than the expected high clinical exposure of a drug-drug interaction with ritonavir (Study C104), which was an average increase in C_{max} of 4.7-fold.

Renal Impairment Study:

Study TMC435-TiDP16-C126 was a phase 1, open-label study to investigate the steady-state plasma pharmacokinetics and short-term safety and tolerability of TMC435 in subjects with severe renal impairment compared to matched healthy subjects with normal renal function. Severe renal impairment was defined by an estimated glomerular filtration rate (eGFR) ≤ 29 mL/min/1.73m^2 as determined by the Modification of Diet in Renal Disease (MDRD) equation. Subjects with severe renal impairment requiring dialysis were excluded from enrollment. Normal renal function was defined as an eGFR ≥ 80 mL/min/1.73m^2 (MDRD).

The study population consisted of a total of 16 subjects between 36 and 67 years of age. Eight healthy subjects (7 male, 1 female) with normal renal function and 8 subjects (7 male, 1 female) with severe renal impairment were enrolled. A healthy subject was matched to a subject with severe renal impairment with regards to sex, race, age (± 10 years), and body mass index (BMI) (± 20%). All subjects received TMC435 150 mg once daily (q.d.) for 7 days.

Per Sponsor, steady-state conditions were generally achieved prior to full pharmacokinetic blood sampling on Day 7 for most subjects. However, for some subjects concentrations were still increasing, both in renally impaired subjects and matched healthy controls. For subjects with severe renal impairment, C_{min}, C_{max}, and AUC_{24h} of TMC435 were about 71%, 34%, and 62% higher, respectively, as compared to matched healthy subjects, based on the ratios of the least squares (LS) means. The

90% confidence intervals for the LS mean ratios were wide. The mean values of the fraction of TMC435 unbound to protein in plasma at pre-dose and 4 hours after dosing was about 0.0001 for subjects with severe renal impairment and for matched healthy subjects.

None of the subjects died during the study or permanently discontinued TMC435 treatment prematurely due to an AE. One (12.5%) renally impaired subject had an SAE (rhabdomyolysis). Two (25.0%) renally impaired subjects had laboratory abnormalities that were reported during the treatment phase as an AE [hyperbilirubinemia (grade 1) and blood ALP increased (grade 1)]. One (12.5%) healthy subject had a laboratory-related AE (hyperbilirubinemia) during the treatment phase. All AEs were grade 1 or 2 in severity, except for the SAE rhabdomyolysis, which was grade 3 in severity and is described in detail below.

Subject 126-0016, a 56-year old White man with a history of hypertension, diabetes mellitus, peripheral artery disease, coronary artery disease, and left ventricular dysfunction, received 150 mg TMC435 q.d. from SD1 to SD8 per protocol. Concomitant medications included allopurinol, amlodipine, carvedilol, furosemide, gliquidone, potassium chloride, ramipril, telmisartan, trimetazine, and fenofibrate at 267 mg daily. It was also reported that the subject was receiving a statin which was stopped 14 days prior to initiation of study drug. At baseline, serum creatinine was grade 3 (4.7 mg/dL), AST was grade 1 increased (51.0 U/L), LDH was above normal (313.2 U/L), and ALT, total bilirubin, direct bilirubin, and indirect bilirubin were normal. On SD4, the subject had grade 2 myalgia from which he recovered one day later. No action was taken with respect to TMC435 due to this AE. On SD8, the subject had grade 4 increased AST (506.4 U/L), grade 2 increased ALT (160.8 U/L), elevated LDH (1413.0 U/L), and total bilirubin and direct bilirubin levels above normal (21.0 and 7.4 µmol/L, respectively). Serum creatinine remained at a grade 3 elevation (4.1 mg/dL). Treatment with fenofibrate, which the subject was receiving to treat dyslipoproteinemia, was stopped on SD8. Rhabdomyolysis was confirmed on SD9 by the results of creatine kinase (CK) (96.76 µkat/L, i.e., 18.8 x ULN), creatine kinase muscle brain fraction (CK-MB) (20.84 and 19.45 µg/L, i.e., 7.2 and 6.8 x ULN), and myoglobin (1200, 1475, and 1476 µg/L, i.e., 16.7, 20.5, and 20.5 x ULN). Rhabdomyolysis was reported as a grade 3 SAE with a start date of SD8. On SD10, the subject was hospitalized for 3 days. From SD12 onwards, the subject received 500 mg ademetionine (S-adenosyl methionine) q.d. A gradual decrease in laboratory parameters was observed from SD10 onwards. The CK level had decreased to 4.3 µkat/L on SD20). On SD37, the AST, ALT, total bilirubin, and direct bilirubin levels had returned to normal (34.8 U/L, 28.2 U/L, 13.4 µmol/L, and 3.7 µmol/L, respectively). The subject's LDH level was still above normal, but had decreased to 291.6 U/L. The CK-MB and myoglobin had improved to 1.5 µg/L and 80 µg/L, respectively. The subject was considered recovered from rhabdomyolysis on SD37.

Rhabdomyolysis was considered probably related to TMC435 treatment by the investigator. The elevation in hepatic enzymes was interpreted by the investigator as a reflection of the rhabdomyolysis; the subject's increase in direct bilirubin possibly an indication of degradation of myoglobin. According to the investigator, the SAE could have been caused by a too short of a wash out period for the statin, an interaction of TMC435 and fenofibrate, or another drug/food combination. Of note, the AUC_{24} for TMC435 for subject 126-0016 was essentially at the mean level for this study as demonstrated in the figure below.

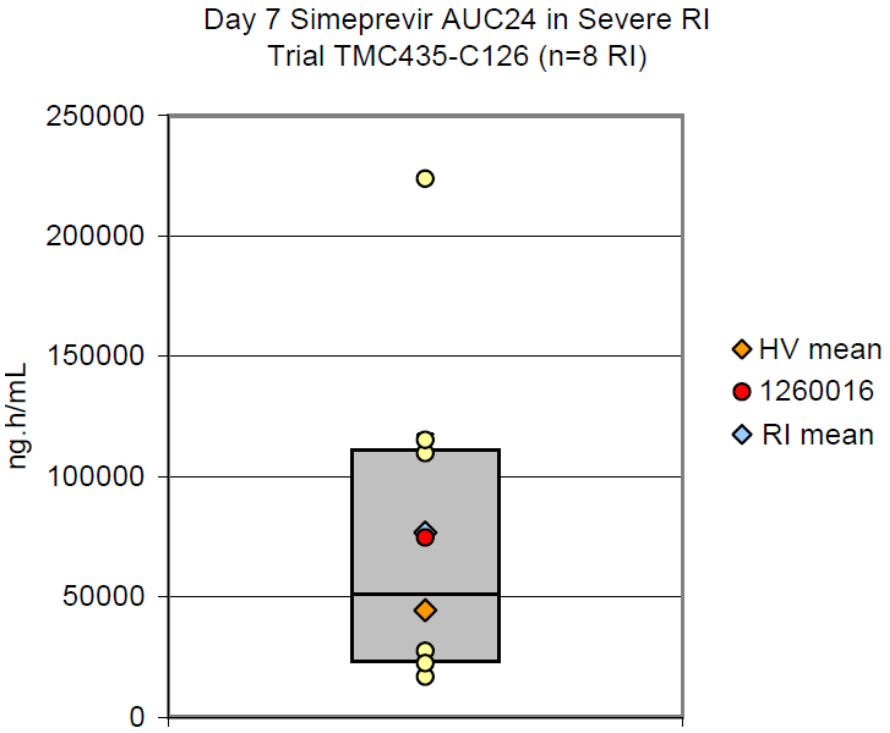

Figure 9: AUC_{24} Distribution of Subjects in Study C126; HV = healthy volunteers, RI = renal insufficiency subjects
Source: Clinical Pharmacology Review by Dr. Leslie Chinn

This Reviewer is concerned about the development of severe rhabdomyolysis necessitating hospitalization in even 1 subject with severe renal insufficiency given the small number of subjects studied in this population (N=8). However, no events of rhadbomyolysis were reported in either the Phase 2b (C205 and C206) or Phase 3 studies (C208, C216, and HPC3007). Additionally, higher TMC435 drug exposures were reported in other subjects (both within this study and in other studies) with no associated reports of rhabdomyolysis. Finally, this subject did have potentially confounding factors related to concomitant medication administration (i.e. statins and fenofibrate). In this Reviewer's opinion, and assuming concurrence of the clinical

pharmacology review team, it is not unreasonable to grant approval for careful use of TMC435 in this patient population.

Hepatic Insufficiency Study:

Study TMC435-TiDP16-C113 was a phase 1, open-label, sequential trial to investigate the steady-state pharmacokinetics and short-term safety and tolerability of TMC435 in subjects with moderate or severe hepatic impairment.

The trial population consisted of a total of 24 subjects between 42 and 65 years of age. Panel A consisted of 8 subjects (6 male, 2 female) with moderate hepatic impairment (Child-Pugh B) and 8 matched controls (6 male, 2 female) with normal hepatic function. Panel B consisted of 8 subjects (6 male, 2 female) with severe hepatic impairment (Child-Pugh C). Control subjects were matched to subjects with hepatic impairment based on sex, race, age (± 5 years and within the age limits as specified in the inclusion criterion), body mass index (BMI) (± 15% and within the BMI limits as specified in the inclusion criterion), and smoking status.

Dosing in Panel A and Panel B occurred sequentially. Subjects in Panel A received TMC435 150 mg q.d. for 7 days. After review of the safety, tolerability and pharmacokinetic data from Panel A, the dose to be administered for subjects in Panel B (severe hepatic impairment) was determined to be 150 mg q.d. for 7 days and a decision was made that no matched controls were to be included in Panel B. TMC435 pharmacokinetic data from Panels A and B were compared to data obtained from genotype 1 hepatitis C virus (HCV)-infected subjects from study C201 (150 mg q.d. dose cohort), since, per Sponsor, these subjects reflect the intended patient population better than young healthy volunteers. In addition, TMC435 pharmacokinetic data and safety results from Panels A and B were compared to each other.

In subjects with moderate hepatic impairment, C_{max} and AUC_{24h} values for TMC435 at Day 7 were, respectively, 1.71 and 2.44 fold higher as compared to matched control subjects with normal hepatic function, based on the ratios of the LSmeans. For subjects with severe hepatic impairment, C_{max} and AUC_{24h} values for TMC435 at Day 7 were, respectively, 3.13 and 5.22 fold higher than (non-matched) control subjects with normal hepatic function and 1.83 and 2.14 fold higher than subjects with moderate hepatic impairment, based on the ratios of the LSmeans.

Compared to historical data in patients with chronic HCV infection and compensated liver disease (results from study TMC435-C201 [150 mg q.d. dose cohort]), C_{max} was 0.93 fold lower and AUC_{24h} was 1.30 fold higher in moderately hepatic impaired subjects, while in severely hepatic impaired subjects C_{max} and AUC_{24h} for TMC435 were, respectively, 1.69 fold and 2.78 fold higher, based on the ratios of the LSmeans. As background, data from prior trials with TMC435 have indicated that TMC435 plasma exposure is generally 2 to 3-fold greater in HCV-infected subjects compared to healthy

volunteers. The 90% CIs for the LSmean ratios were wide, especially for the comparisons with historic control data from study TMC435-C201. The unbound fraction of TMC435 in plasma was very low in all subjects (≤ 0.064%) and was similar at 4 hours, 6 hours, and 24 hours after dosing on Day 7.

No deaths were reported during this trial and none of the subjects permanently discontinued study medication because of an AE. All AEs were grade 1 or 2 in severity except for one grade 4 SAE (pneumonia) which occurred in a subject with moderate hepatic impairment 8 days after the last intake of TMC435 and is described below.

Subject 113-0015, a 50-year-old White female with a history significant for type II diabetes and cirrhosis, received TMC435 150 mg q.d. for 7 days starting on 28 April 2010. On 8 May 2010, i.e., 4 days after last intake of TMC435, the subject experienced a sore throat, which progressed to swelling in the throat. On (b) (6), she was admitted to the intensive care unit with complaints of shortness of breath and was diagnosed with bilateral pneumonia. The subject was treated with broad spectrum antibiotics, but became hypoxic and required intubation on (b) (6). Oseltamivir phosphate was added to her treatment regimen the following day. It was reported that a throat culture was positive for *Streptococcus sp.* and a urine culture was positive for *Escherichia coli*; a test for H1N1 and blood cultures were negative. The subject was discharged from the hospital on (b) (6) and recovered from the event of bilateral pneumonia on (b) (4) after a duration o (b) (6) days. The subject completed the trial on 11 June 2010. The pneumonia was considered not related to the study medication in the opinion of the investigator. This Reviewer agrees that the pneumonia was unlikely to be related to study drug despite the relatively close proximity of the onset of the SAE to the completion of study drug.

No grade 4 laboratory abnormalities were observed during the treatment phase in this trial. Treatment-emergent grade 3 toxicities were observed for pancreatic amylase, platelets, and hyperbilirubinemia in 5 subjects with hepatic impairment. Of note, all of these subjects had grade 2 abnormalities in these laboratory indices at baseline. None of the observed laboratory abnormalities were reported as an AE.

Please refer to Section 4.4.3 and the Clinical Pharmacology Review for additional details related to dosing recommendations in this population resulting from this study.

Photosensitivity Study

Study TMC435-TiDP16-C125 was a randomized, double-blind, double-dummy, placebo- and positive controlled, parallel group Phase 1 trial that compared the cutaneous photosensitizing potential of multiple oral doses of TMC435 150 mg q.d. to that observed in subjects administered multiple oral doses of placebo. Ciprofloxacin was used as a positive control.

The primary objective of the trial was to assess the cutaneous photosensitizing potential (as determined by using the phototoxicity index for delayed erythema) of multiple oral daily doses of TMC435 150 mg once daily. There were 2 photosensitivity endpoints: (1) the phototoxicity index for delayed erythema at each waveband and solar simulator assessed at 24 hours post-irradiation and; (2) the presence or absence of an immediate photosensitivity response (e.g., transient edema with or without flare) according to the grading of skin responses.

The trial consisted of 3 phases: Screening, Treatment, and Follow-Up. The Screening phase began up to 21 days before the start of the Treatment phase. Subjects who met the eligibility criteria proceeded to baseline phototesting to assess the immediate photosensitivity response, and to determine the baseline minimum erythema dose (MED) value for delayed erythema. This baseline testing occurred on 3 consecutive days during the Screening phase. After screening, subjects were randomized in a 1:1:1 ratio to 1 of 3 treatments: TMC435 150 mg q.d. (Treatment A), ciprofloxacin 500 mg twice daily (b.i.d.) (Treatment B), or placebo (Treatment C). All treatments were administered for 9 days. Full pharmacokinetic profiles of TMC435 and ciprofloxacin were determined on Day 7. Subjects underwent a series of photosensitivity testing on Days 8-10.

Due to issues with the medication (leakage of capsules), this trial was temporarily interrupted. At the time of interruption, 13 subjects (i.e., 4 subjects each in the TMC435 and ciprofloxacin group and 5 subjects in the placebo group) had received at least one dose of study medication. For 6 of these subjects (2 in each treatment group), treatment was ongoing (Day 1 or 2 of study medication intake, except for 2 subjects who had reached Day 8), while 7 subjects had already completed the treatment phase. After resolution of the medication quality issues, the trial restarted with a completely new set of subjects. The Sponsor's main analysis population is the second set of subjects, while the first set of subjects was included in the General, Adverse Events, and Laboratory analyses only.

Thirty-six subjects were enrolled in the main analysis population: 12 in Group A (11 male, 1 female), 12 in Group B (10 male, 2 female), and 12 in Group C (all male). All subjects were white, and only one subject was Hispanic or Latino in ethnicity. Ages ranged from 18-52 years old across groups with similar mean ages (~28).

In the main analysis population, there were no deaths or discontinuations due to an AE. Two subjects experienced an SAE. These included head injury (grade 3) in a single subject in the ciprofloxacin group and amnesia (grade 2) in a single subject in the TMC435 group one day after the last dose of study medication. Two subjects experienced a skin event of interest. These included varicella (grade 2) in a single subject in the placebo group and contact dermatitis (grade 1) in a single subject in the TMC435 group. All other AEs were grade 1 or 2 in severity. No grade 3 or grade 4 treatment-emergent laboratory abnormalities were observed during the trial. The safety

profile for the first set of enrolled subjects was generally unremarkable (no deaths, SAEs, or discontinuations due to AEs).

As noted earlier, the photosensitivity endpoints included an assessment of both immediate and delayed responses.

Immediate Responses: In the TMC435 group, 4 subjects (33.3%) showed an immediate photosensitivity response (erythema with evidence of edema that was itchy in 2 subjects) post irradiation at the 335±30 nm or 365±30 nm waveband on Day 8 or Day 9. However, no abnormalities were detected when tested with physiological irradiances, i.e., half and 1/10th of the monochromator outputs. In the ciprofloxacin and placebo groups, no subjects had an immediate photosensitivity response after irradiation on Day 8 and/or Day 9.

Delayed Responses: Individual subjects were considered photosensitive to a study medication at that specific waveband, if the postdose minimal erythemal dose (MED) was ≥ 40% lower than the baseline MED (i.e., phototoxicity index ≥ 1.67). In the TMC435 group, only one subject was considered photosensitive, with phototoxicity indexes graded as mild (phototoxicity index: 1.67-3.0) at the 335±30 nm and 365±30 nm wavebands. In the ciprofloxacin group, 11 subjects (91.7%) were considered photosensitive to at least one waveband. Four of these subjects showed moderate and/or severe phototoxicity at one or more wavebands. In the placebo group, 4 subjects (33.3%) showed at least mild phototoxicity at some wavebands, one of these subjects (i.e., the subject who had been enrolled with a concomitant active skin condition on the back, which was reported as major protocol deviation) showed moderate phototoxicity on the 365±30 nm waveband.

It should be noted that this study was performed in healthy subjects and that the anticipated AUC for TMC435 is 2 to 3-fold lower in a healthy population than a population with chronic hepatitis C infection. This may account, in part, for the apparent discrepancy between the results of this study (i.e. the absence of delayed photosensitivity responses) and the clinical findings related to photosensitivity in the phase 2b and 3 trials. As discussed above, it is also important to note that immediate photosensitivity responses (a secondary endpoint of the study) were demonstrated in the TMC435 group. Please refer to the dermatology consultation by Dr. Brenda Carr for additional details on the interpretation of the results of this study.

HIV-HCV Co-infection Study:

Study C212 is an ongoing open-label, single arm clinical study to evaluate the safety, tolerability and efficacy of TMC435 in combination with PegIFNα-2a and RBV (PR) in adult chronic hepatitis C genotype-1 infected subjects who are co-infected with human immunodeficiency virus type 1 (HIV-1). Subjects were classified based on their HCV treatment history (HCV treatment-naïve, prior HCV relapser, prior null responder, prior

partial responder) and also by HIV treatment experience (on antiretroviral therapy [ART], not on ART).

The criteria with respect to allowable ART were largely based on the results of DDI studies which had been performed using the following ART components: raltegravir, efavirenz, rilpivirine, tenofovir, darunavir/ritonavir, and ritonavir. Based on these studies all PIs and all NNRTIs except rilpivirine were disallowed in Study C212 (see Table 55 below):

Table 55: Allowed ART Components for Study C212

Table 21: Allowed HIV Medication – Study C212		
ART Class	**Allowed**	**Disallowed***
PIs	-	• all PIs.
NRTIs	lamivudine, emtricitabine, tenofovir disoproxil fumarate, abacavir	• didanosine, and stavudine in combination with PegIFNα -2a/RBV • generic version of NRTIs not approved in the participating countries
NNRTIs	rilpivirine (TMC278)	• NNRTIs other than rilpivirine
Fusion Inhibitors	enfuvirtide	-
Integrase Inhibitors	raltegravir	-
Entry Inhibitors	maraviroc	-
HIV Vaccines	-	• All HIV vaccines

* After treatment with TMC435, all ARVs were allowed, with the exception of atazanavir, didanosine and stavudine if combined with PegIFNα-2a/RBV.

Source: Janssen's Protocol for Study C212

The HCV treatment regimen for HCV treatment-naïve subjects and prior HCV relapsers without cirrhosis includes 12 weeks of TMC435 150 mg once daily plus RGT with PR for 24 or 48 weeks. The treatment regimen for prior HCV null responders, partial responders, and all subjects with cirrhosis includes 12 weeks of TMC435 150 mg once daily plus 48 weeks of PR.

The primary efficacy endpoint for the study is SVR12. Major secondary endpoints include the following: SVR24, meeting RGT criteria for shortened treatment to 24 weeks, on- and post-treatment failure with respect to HCV, HIV viral load and CD4+ cell count over time, confirmed HIV virologic failure rates, and safety and tolerability.

The study enrolled 106 subjects, 53 were HCV treatment-naïve and 53 were HCV treatment experienced (15 prior relapsers, 10 prior partial responders, and 28 prior null responders). The majority of subjects (82%) had HCV genotype 1a. Approximately half of the subjects were enrolled in North America (46%) and the remainder (54%) in Europe. The median age was 48 years. The majority of subjects were white (82%) and male (85%); 14% of the subjects were black or African American. A total of 27% of subjects had IL28B genotype CC, 56% had IL28B genotype CT, and 17% had IL28B genotype TT. The median log10 HCV RNA level at baseline was 6.51 IU/mL. Twelve percent (12%) of the overall population had cirrhosis at baseline, with a higher proportion of subjects (29%) with cirrhosis in the null responder population. The

majority (88%) of subjects were receiving ART at baseline. The mean baseline CD4+ cell count (absolute) was 663 cells/uL with a range of 311-1404 cells/uL. The U.S. Centers for Disease Control and Prevention HIV classification of subjects[7] at baseline was as follows: 67% Category A, 21% Category B, and 12% Category C.

At the time of the Week 24 interim analysis, 91% of subjects had completed treatment with TMC435. The majority of the treatment-naïve and prior relapser subjects (72% and 87%, respectively) completed all study therapy at Week 24. The majority of the prior partial and non-responder subjects were still on treatment (80% and 68%, respectively). Preliminary efficacy results including SVR4 and SVR12 are presented in Table 56 below.

Table 56: Preliminary Efficacy Results from Study C212

	TMC435 150 mg 12 Wks PR 24/48	
	SVR4	SVR12
ITT Population Overall	30/35 (86%)	10/13 (77%)
Treatment Naïve Subjects	21/25 (84%)	6/8 (75%)
Prior Relapsers	9/10 (90%)	4/5 (80%)

Safety Results: This Reviewer's safety assessment focused on comparing the high level safety profile (i.e. grade 3/4 AEs, SAEs and AEs leading to discontinuation of TMC435) of subjects in this study to date to that of the pooled Phase 3 pivotal trials (C208, C216, and HPC3007). It should be noted, however, that such a comparison does not account for the impact of HIV disease, HIV treatment, and differences in subject demographics between the trials.

The following table presents all grade 3/4 AEs reported during the TMC435 + PR phase of the trial to date. A total of 32 subjects (30%) in C212 had grade 3/4 AEs during this period as compared to 23% of subjects in the pooled Phase 3 trials over the same period. A very similar distribution of grade 3/4 AEs was demonstrated in the pooled Phase 3 trials. However, a greater percentage of grade 3/4 AEs were reported in subjects from study C212 for neutropenia (16% versus 9%), anemia (3% versus 1%), and increases in ALT (3% versus 1%) and AST (3% versus 1%) compared to subjects in the pooled Phase 3 studies.

Table 57: Grade 3 and 4 AEs Occurring During the TMC + PR Phase

Studies (Number of Subjects)	C212 (N=106)
Phase	TMC435 + PR
MedDRA Preferred Term, Number (%) of Subjects	
Neutropenia	17 (16%)
Anemia	3 (3%)
Aspartate aminotransferase increased	3 (3%)
Alanine aminotransferase increased	3 (3%)
Neutrophil count decreased	2 (2%)
Dry skin	1 (1%)
Dyspnea exertional	1 (1%)
Fatigue	1 (1%)
General physical health deterioration	1 (1%)
Depression	1 (1%)
Hypertriglyceridemia	1 (1%)
Hypoalbuminemia	1 (1%)
Intervertebral disc protrusion	1 (1%)
Lipase increased	1 (1%)
Malnutrition	1 (1%)
Mental status changes	1 (1%)
Mood altered	1 (1%)
Anger	1 (1%)
Hyperbilirubinemia	1 (1%)
Thoracic vertebral fracture	1 (1%)
Thrombocytopenia	1 (1%)

There were no deaths reported in this trial. A total of 5 subjects (5%) in study C212 had SAEs reported during the TMC435 + PR phase of the trial compared to 2% of subjects in the pooled Phase 3 trials over the same period. The subjects in C212 and their reported SAEs follow: Subject 0014 (Mental Status Changes); Subject 0058 (General Physical Health Deterioration, Malnutrition); Subject 0136 (AST increased, hyperbilirubinemia); Subject 0138 (Pneumothorax, Thoracic Vertebral Fracture); Subject 0141 (Intervertebral Disc Protrusion).

A total of 4 subjects (4%) in study C212 discontinued TMC435 during the TMC435 + PR phase of the trial compared to 2% of subjects in the pooled Phase 3 trials over the same period. The subjects in C212 and their reported AEs leading to discontinuation of TMC435 follow: Subject 0014 (Mental Status Changes); Subject 0076 (Anemia); Subject 0136 (AST increased, Hyperbilirubinemia, Hypoalbuminemia); Subject 0148 (Burning Sensation, Erythema, Diarrhea, Nausea, Hyperhidrosis, Paranoia).

Of the 7 subjects with either SAEs or AEs leading to discontinuation reported, only 3 subjects had events deemed related to TMC435 by investigator (subject 0058, Subject 0136, and Subject 0148). These cases were reviewed in detail. The causality assessment of the SAEs (general physical health deterioration, malnutrition) in Subject 0058 was confounded by her complicated baseline medical history (including but not limited to cirrhosis, HIV infection since 1990, hypertension, and coronary artery disease) and the concomitant use of PR. The causality assessment of the SAEs (reported on SD1) and AE leading to discontinuation in Subject 0136 was confounded by his baseline hepatic abnormalities (including an F3 Metavir Score and abnormal AST, ALT, bilirubin and alkaline phosphatase values). The AEs leading to discontinuation (Burning Sensation, Erythema, Diarrhea, Nausea, Hyperhidrosis, Paranoia) in Subject 0148 all occurred on SD1 and reached a maximal severity of grade 2 prior to discontinuation of study drugs on SD3.

Table 58 presents the grade 3/4 laboratory abnormalities reported during the TMC + PR period. Thirty six subjects (34%) had grade 3/4 laboratory abnormalities reported compared to 26% in the pooled Phase 3 trials over the same treatment period. Most notable was the increased frequency of grade 3/4 neutropenia (22% versus 15%) and grade 3 elevations in amylase (9% versus 4%) compared to the pooled Phase 3 trials. However, grade 3/4 elevations in lipase were uncommon and no cases of pancreatitis were reported (as AEs). Also the demographics of this study differed from that of the pooled Phase 3 trials with a greater proportion of Black/African American subjects enrolled in C212 as compared to the pooled trials (12% versus 4% respectively). This difference in demographics may account, in part, for the differences noted in rates of grade 3/4 neutropenia.

Table 58: Grade 3 and 4 Laboratory Abnormalities Occurring During the TMC435 + PR Phase

Studies (Number of Subjects)	C212 (N=106)	
Phase	TMC435 + PR	
Parameter	Analysis Toxicity Grade	
Neutrophils and Precursors (x10E9/L)	Grade 3	18 (17%)
	Grade 4	5 (5%)
Amylase (U/L)	Grade 3	10 (9%)
Hemoglobin (g/L)	Grade 3	2 (2%)
Bilirubin (umol/L)	Grade 3	2 (2%)
Aspartate Aminotransferase (U/L)	Grade 3	2 (2%)
Alanine Aminotransferase (U/L)	Grade 3	1 (1%)
Triacylglycerol Lipase (U/L)	Grade 3	1 (1%)
	Grade 4	1 (1%)
Sodium (mmol/L)	Grade 4	1 (1%)

Potential impact on HIV treatment outcome was also evaluated as a safety parameter. Two out of 93 (2%) subjects on HAART had confirmed HIV virologic failure based on confirmed HIV RNA ≥50 copies/mL after previous <50 copies/mL. However, at subsequent time points these subjects had a HIV viral load <50 copies/mL without any

change in HAART. None of the subjects had confirmed ≥200 copies/mL after previous <50 copies/mL. Based on these findings, this Reviewer would not consider these events to be true virologic failure, but rather "blips" in HIV RNA levels. A decrease in absolute CD4+ cell count was observed during treatment (considered to be due to interferon-induced lymphopenia by the Applicant). However, the percentage of CD4+ cells remained stable over time.

In summary, an increased frequency of grade 3/4 AEs, SAEs, discontinuations due to AE, and grade 3/4 laboratory abnormalities were noted to date in Study C212 as compared to the pooled phase 3 trials. However, this Reviewer still finds the safety profile acceptable taking into account the impact of HIV disease, HIV treatment, and differences in demographics between the trials.

7.4.6 Immunogenicity

As Simeprevir is a small molecule and not a peptide, immunogenicity effects were not anticipated and therefore not specifically assessed during the clinical trials.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Table 59 displays selected pooled AEs of interest reported during treatment with various doses of TMC435 (75 mg, 100 mg, and 150 mg) over a fixed duration of 12 Weeks. There appears to be a dose response with respect to the pooled variables 'photosensitivity' and 'increased bilirubin,' with increasing frequencies of AEs seen with increasing doses of TMC435. Despite pooling data from the Phase 2b and Phase 3 trials, the small numbers of subjects in several of the subgroups may limit the interpretability of these data.

Table 59: Dose Dependency for Selected Adverse Events Using Derived Pooled Variables

Studies	C205, C206, C208, C216 & HPC3007 Pooled			
Study Arm	PBO	TMC435 75MG	TMC435 100MG	TMC435 150MG
Phase	First 12 Weeks	First 12 Weeks	First 12 Weeks	First 12 Weeks
Subjects per Arm	540	153	197	1136
Pooled Variable, N (%) of Subjects				
Rash (excluding Photosensitivity)	103 (19%)	39 (26%)	35 (18%)	283 (25%)
Pruritis	91 (17%)	36 (24%)	54 (27%)	282 (25%)
Photosensitivity	4 (1%)	0 (0%)	2 (1%)	47 (4%)
Anemia	60 (11%)	18 (12%)	24 (12%)	152 (13%)
Thrombocytopenia	20 (4%)	5 (3%)	6 (3%)	55 (5%)
Neutropenia	87 (16%)	37 (24%)	35 (18%)	212 (19%)

Leukopenia	13 (2%)	1 (1%)	2 (1%)	34 (3%)
Dyspnea	47 (9%)	29 (19%)	28 (14%)	140 (12%)
Increased Bilirubin	15 (3%)	3 (2%)	11 (6%)	95 (8%)

7.5.2 Time Dependency for Adverse Events

Table 60 displays selected pooled AEs of interest reported during varying durations of dosing (12, 24, or 48 Weeks) with 150 mg of TMC435. Increased rates of AEs with greater duration of exposure occurred in virtually all selected AEs with the possible exception of increased bilirubin. Some of the increase in rates was likely due to the contribution of the PR component of therapy. Despite pooling data from the Phase 2b and Phase 3 trials, the small numbers of subjects in several of the subgroups limit the interpretability of these data.

Table 60: Time Dependency for Selected Adverse Events Using Derived Pooled Variables

Studies	C205, C206, C208, C216 & HPC3007 Pooled					
	TMC435+PR 12wks		TMC435+PR 24wks		TMC435+PR 48wks	
Study Arm	PBO	TMC435 150MG	PBO	TMC435 150MG	PBO	TMC435 150MG
Subjects per Arm	397	924	77	147	66	65
Pooled Variable, N (%) of Subjects						
Rash (excluding Photosensitivity)	60 (15%)	225 (24%)	23 (29%)	47 (32%)	15 (25%)	23 (35%)
Pruritis	50 (13%)	211 (23%)	34 (44%)	55 (37%)	9 (14%)	25 (38%)
Photosensitivity	2 (1%)	43 (5%)	0 (0%)	4 (3%)	1 (2%)	11 (17%)
Anemia	36 (9%)	121 (13%)	14 (18%)	31 (21%)	13 (20%)	14 (22%)
Thrombocytopenia	12 (3%)	42 (5%)	3 (4%)	8 (5%)	4 (6%)	6 (9%)
Neutropenia	53 (13%)	162 (18%)	16 (21%)	36 (24%)	12 (18%)	22 (34%)
Leukopenia	11 (3%)	21 (2%)	2 (3%)	9 (6%)	2 (3%)	5 (8%)
Dyspnea	26 (7%)	110 (12%)	12 (16%)	20 (14%)	7 (11%)	12 (18%)
Increased Bilirubin	11 (3%)	76 (8%)	2 (3%)	16 (11%)	2 (3%)	4 (6%)

7.5.3 Drug-Demographic Interactions

Table 61 summarizes the AEs by MedDRA PT that occurred with a ≥ 3% difference between men and women in the TMC435 Groups in the pooled Phase 3 studies. The majority of the AEs which show gender differences in the TMC435 group are mirrored by similar findings in the Control group. This Reviewer would conclude, therefore, that these differences are primarily driven by the PR component of therapy. Notable exceptions include impact on elevations of bilirubin, which appear to be more frequent in men receiving TMC435 and are not mirrored by similar findings in the Control group.

Table 61: Common AEs that Occurred with a ≥ 3% Difference Between Sexes in the Pooled Phase 3 Trials

Studies	C208, C216, HPC3007			
Treatment Period	First 12 Weeks			
Study Arm (Number of Subjects)	TMC435 150mg (N=781)		PBO (N=397)	
Sex (N)	Male (N=467)	Female (N=314)	Male (N=230)	Female (N=167)
MedDRA PT, Number (%) of Subjects				
Fatigue	151 (32%)	127 (40%)	88 (38%)	69 (41%)
Headache	141 (30%)	118 (38%)	75 (33%)	66 (40%)
Nausea	72 (15%)	101 (32%)	30 (13%)	40 (24%)
Influenza like illness	128 (27%)	75 (24%)	56 (24%)	28 (17%)
Decreased appetite	59 (13%)	61 (19%)	32 (14%)	24 (14%)
Anemia	34 (7%)	59 (19%)	12 (5%)	28 (17%)
Rash	53 (11%)	53 (17%)	20 (9%)	24 (14%)
Neutropenia	58 (12%)	51 (16%)	23 (10%)	27 (16%)
Vomiting	19 (4%)	32 (10%)	7 (3%)	13 (8%)
Alopecia	12 (3%)	32 (10%)	7 (3%)	14 (8%)
Dizziness	21 (4%)	27 (9%)	10 (4%)	10 (6%)
Chills	47 (10%)	21 (7%)	27 (12%)	14 (8%)
Dry mouth	10 (2%)	15 (5%)	1 (0%)	6 (4%)
Urinary tract infection	2 (0%)	15 (5%)	0 (0%)	6 (4%)
Injection site erythema	34 (7%)	10 (3%)	18 (8%)	4 (2%)
Hyperbilirubinaemia	23 (5%)	6 (2%)	5 (2%)	3 (2%)
Blood bilirubin increased	22 (5%)	5 (2%)	3 (1%)	0 (0%)

Table 62 summarizes selected grouped AEs of interest by gender during the first 12 weeks in the Phase 3 studies. This analysis revealed similar findings to the preceding analysis, namely an increased frequency of hyperbilirubinemia in men versus women in the TMC435 group which was not noted in the Control group. An increase in 'rash excluding photosensitivity' events in women was noted in both the TMC435 group and control group, although the increase was greater in the TMC435 group. A notable, but anticipated increase in anemia events occurred in women compared to men in both the TMC435 and Control groups.

Table 62: Selected Pooled AEs of Interest by Gender during the First 12 Weeks in the Phase 3 studies

Studies	C208, C216, HPC3007			
Treatment Period	First 12 Weeks			
Study Arm (Number of Subjects)	TMC435 150mg (N=781)		PBO (N=397)	
Sex (N)	Male (N=467)	Female (N=314)	Male (N=230)	Female (N=167)
Grouped Term, N (%) of Subjects				
Rash (excluding Photosensitivity)	99 (21%)	93 (30%)	40 (17%)	36 (22%)
Pruritis	97 (21%)	71 (23%)	30 (13%)	28 (17%)
Photosensitivity	19 (4%)	19 (6%)	3 (1%)	0 (0%)
Anemia	39 (8%)	66 (21%)	14 (6%)	30 (18%)
Thrombocytopenia	25 (5%)	14 (4%)	8 (3%)	7 (4%)
Neutropenia	74 (16%)	58 (18%)	30 (13%)	32 (19%)
Leukopenia	9 (2%)	8 (3%)	4 (2%)	8 (5%)
Dyspnea	59 (13%)	33 (11%)	19 (8%)	11 (7%)
Increased Bilirubin	47 (10%)	14 (4%)	8 (3%)	3 (2%)

An additional analysis was performed to assess for differences by gender in laboratory bilirubin abnormalities (refer to Table 63 below). This analysis revealed an increased frequency of graded hyperbilirubinemia in men in both the TMC435 and Control groups, but more pronounced in the TMC435 group. This finding may be explained in part by the increased plasma concentrations of bile acids in males compared to females.

Table 63: Graded Bilirubin Abnormalities Stratified by Gender in the Phase 3 Studies

Studies	C208, C216, HPC3007			
Study Period	First 12 Weeks		First 12 Weeks	
Study Group	TMC435		Control	
Sex	Male	Female	Male	Female
Number of Subjects	467	314	230	167
Bilirubin (umol/L)				
Grade 1 (>1 to 1.5 x ULN)	137 (29%)	71 (23%)	40 (17%)	21 (13%)
Grade 2 (>1.5 to 2.5 x ULN)	105 (22%)	38 (12%)	25 (11%)	11 (7%)
Grade 3 (>2.5 to 5 x ULN)	23 (5%)	9 (3%)	5 (2%)	1 (1%)
Grade 4 (>5 x ULN)	3 (1%)	0 (0%)	0 (0%)	0 (0%)
All Grades	268 (57%)	118 (38%)	70 (31%)	33 (21%)

A safety analysis by Asian race was performed due to the finding of significantly higher mean TMC435 exposures in this population (refer to Section 4.4.3 for details) and the

correlation of increased TMC435 exposure with a number of adverse events (refer to Section 7.2.2 for additional details). Table 64 summarizes the findings from this analysis. In the TMC435 group, rash, anemia, thrombocytopenia, increased bilirubin, and dyspnea were reported at higher rates in Asians than in all races combined. The same was true only for dyspnea in the Control group. However, the low number of Asian subjects (N=20) enrolled in the pivotal trials greatly limits the interpretability of this data.

Table 64: Comparison of Grouped AEs of Interest in Asian Subjects versus Subjects of All Races in the Pooled Phase 3 Studies

Studies	C208, C216, HPC3007			
Treatment Period	First 12 Weeks			
Study Arm (Number of Subjects)	TMC435 150mg (N=781)		PBO (N=397)	
Sex (N)	Asian (N=15)	All Races (N=781)	Asian (N=5)	All Races (N=397)
Grouped Term, N (%) of Subjects				
Rash (excluding Photosensitivity)	7 (47%)	192 (25%)	1 (20%)	76 (19%)
Pruritis	3 (20%)	168 (22%)	0 (0%)	58 (15%)
Photosensitivity	0 (0%)	38 (5%)	0 (0%)	3 (1%)
Anemia	5 (33%)	105 (13%)	0 (0%)	44 (11%)
Thrombocytopenia	2 (13%)	39 (5%)	0 (0%)	15 (4%)
Neutropenia	1 (7%)	132 (17%)	0 (0%)	62 (16%)
Leukopenia	0 (0%)	17 (2%)	0 (0%)	12 (3%)
Dyspnea	3 (20%)	92 (12%)	1 (20%)	30 (8%)
Increased Bilirubin	2 (13%)	61 (8%)	0 (0%)	11 (3%)

7.5.4 Drug-Disease Interactions

These safety analyses focused on the impact of liver fibrosis on AEs and laboratory abnormalities by stratifying the subjects by Metavir Fibrosis score. Table 65 summarizes selected pooled AEs of interest stratified by Metavir score. Several of the pooled variables showed an increase in frequency with increasing Metavir score (e.g. anemia, thrombocytopenia) but only increased bilirubin (and to a lesser degree rash excluding photosensitivity) showed an increase in the TMC435 group that was not accompanied by similar changes in the Control group.

Table 65: Selected Pooled AEs of Interest Stratified by Metavir Fibrosis Score

Studies	C208, C216, HPC3007					
Study Period	First 12 Weeks			First 12 Weeks		
Study Arm	TMC435			Control		
Metavir Score	F0-F2	F3	F4	F0-F2	F3	F4
Number of Subjects	545	126	87	290	55	51
Pooled Variable, N (%) of Subjects						
Rash (excluding Photosensitivity)	130 (24%)	28 (22%)	29 (33%)	51 (18%)	13 (24%)	12 (24%)
Pruritis	115 (21%)	23 (18%)	25 (29%)	39 (13%)	7 (13%)	12 (24%)
Photosensitivity	22 (4%)	9 (7%)	5 (6%)	2 (1%)	1 (2%)	0 (0%)
Anemia	61 (11%)	23 (18%)	19 (22%)	27 (9%)	10 (18%)	7 (14%)
Thrombocytopenia	20 (4%)	7 (6%)	12 (14%)	5 (2%)	5 (9%)	5 (10%)
Neutropenia	92 (17%)	18 (14%)	17 (20%)	43 (15%)	8 (15%)	10 (20%)
Leukopenia	13 (2%)	1 (1%)	3 (3%)	13 (2%)	1 (1%)	3 (3%)
Dyspnea	68 (12%)	11 (9%)	9 (10%)	22 (8%)	4 (7%)	4 (8%)
Increased Bilirubin	36 (7%)	8 (6%)	13 (15%)	8 (3%)	2 (4%)	1 (2%)

Table 66 summarizes the graded bilirubin laboratory abnormalities stratified by Metavir Fibrosis score. The frequency and severity of graded bilirubin elevations in the TMC435 group increased with increasing Metavir score. Grade 3 elevations in bilirubin rose from 2% with Metavir scores F0-F2, to 4% with Metavir scores of F3, to 14% with Metavir scores of F4.

Table 66: Graded Bilirubin Laboratory Abnormalities Stratified by Metavir Scores

Studies	C208, C216, HPC3007					
Study Period	First 12 Weeks			First 12 Weeks		
Study Arm	TMC435			Control		
Metavir Score	F0-F2	F3	F4	F0-F2	F3	F4
Number of Subjects	545	126	87	290	55	51
Bilirubin (umol/L)						
Grade 1 (>1 to 1.5 x ULN)	147 (27%)	33 (26%)	21 (24%)	45 (16%)	10 (18%)	6 (12%)
Grade 2 (>1.5 to 2.5 x ULN)	93 (17%)	25 (20%)	20 (23%)	25 (9%)	4 (7%)	7 (14%)
Grade 3 (>2.5 to 5 x ULN)	13 (2%)	5 (4%)	12 (14%)	1 (<1%)	3 (6%)	2 (4%)
Grade 4 (>5 x ULN)	2 (<1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
All Grades	255 (46%)	63 (50%)	54 (62%)	71 (25%)	17 (31%)	15 (30%)

7.5.5 Drug-Drug Interactions

Please refer to Sections 4.4.2 and 4.4.3 for a discussion of the PD and PK properties of TMC435.

The primary enzyme involved in the biotransformation of TMC435 is CYP3A. Co-administration of TMC435 with drugs that are strong inhibitors of CYP3A may significantly increase the plasma exposure of TMC435; co-administration of TMC435 with drugs that are strong inducers of CYP3A may significantly decrease the plasma exposure of TMC435. As such, it is not recommended that TMC435 be co-administered with drugs that are either strong inhibitors or strong inducers of CYP3A. Please refer to the Clinical Pharmacology Review for a detailed discussion of the completed drug-drug interaction studies as well as recommendations pertaining to co-administration of TMC435 with drugs either demonstrated or anticipated to interact with TMC435.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Please refer to Section 7.3.5 under the subsection entitled, “Neoplasms (Benign, Malignant, and Unspecified)” for a discussion of neoplastic events in the Phase 3 pivotal and Phase 2b supportive trials.

7.6.2 Human Reproduction and Pregnancy Data

Pregnancy or plans to become pregnant in female subjects and partners of male subjects was an exclusion criterion for all clinical studies conducted to date. In clinical studies with TMC435, female subjects of childbearing potential and male subjects having a female partner of childbearing potential were required to use 2 effective birth control methods. In addition, TMC435 had to be discontinued per protocol if a pregnancy was reported during the treatment period.

The following information on pregnancy outcomes in female subjects and female partners of male subjects was collected and provided by the sponsor:

In all completed and ongoing clinical studies (including studies conducted in Japan) with TMC435, a total of 9 pregnancies were reported up to the cut-off date of 18 January 2013. Of these, 6 were reported in female subjects and 3 in partners of male subjects. The majority of the pregnancies (8/9) involved exposure to TMC435/PBO before or after the subject or subject's partner’s pregnancy.

Only one case involved exposure of the female subject to TMC435/PBO during pregnancy (C208-0409). The subject received TMC435/PBO from 02 August 2011 to 07 August 2011, RBV from 02 August 2011 to 08 August 2011, and PegIFN from 02

August 2011 (end date not provided). The pregnancy was confirmed on [redacted] and the date of conception was estimated to be [redacted]. All three study drugs were withdrawn. Following 39 weeks of gestation, the subject delivered a baby on [redacted]. [redacted] he baby was normal. The hospitalization was not prolonged and the baby did not receive any medical therapy other than standard newborn care.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and efficacy of Simeprevir has not been established in the pediatric population.

The Applicant has requested a partial waiver of pediatric studies for pediatric subjects less than 3 years of age. The Applicant's rationale is that the necessary studies are impossible or highly impracticable because the pathophysiology of chronic HCV in children < 3 years of age is relatively benign and spontaneous clearance is possible in this age group. This rationale was deemed acceptable by the Primary Clinical Reviewer.

The Applicant has requested a deferral for studies in subjects ≥ 3 to < 18 years of age pending availability of an interferon (IFN)-free and/or INF/RBV-free combination direct acting antiviral (DAA) treatment regimen. The Applicant provided the following rationale for the deferral request: 1) Children with a chronic HCV infection are often asymptomatic and usually experience slow disease progression; 2) The safety concerns associated with current PegIFN-based regimens, outweigh the benefit of immediate treatment and a potential cure with an IFN-based regimen in children ≥ 3 to < 18 years of age; 3) Preliminary data from select TMC435-containing IFN-free regimens appear promising. The Applicant's rationale was deemed acceptable by the Primary Clinical Reviewer.

The Applicant has proposed a pediatric plan encompassing two clinical studies:

[redacted]

(b) (4)

The Applicant's Pediatric Plan and waiver/deferral requests will be reviewed by the FDA's Pediatric Review Committee on 17 October 2013. The applicant will be asked to include long-term (3 years at minimum) follow-up for pediatric patients enrolled in this protocol in order to assess long-term safety and efficacy in this population. In addition, it will be recommended that SVR12 rather than SVR24 be used as the primary efficacy endpoint.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The following information was provided by the Sponsor. Seven cases of overdose, including 3 cases of overdose involving the intake of TMC435/PBO doses above the intended dose per protocol, have been reported during TMC435 development (including studies conducted in Japan) up to the cut-off date of 18 January 2013.

In none of the 3 cases involving TMC435/PBO was the blind broken. One subject in study HPC3001 was to receive TMC435/PBO 150 mg q.d. and telaprevir/PBO 750 mg 3 times/day + PegIFN/RBV. The subject took 2 TMC435 capsules by error in 1 day. No AEs were reported. No action was taken and the subject recovered from the overdose the same day. Note that this study has not been unblinded. The other 2 cases were considered serious due to hospitalization. Additional detail on these cases is provided below:

The first subject (205-0412) was receiving TMC435 75 mg q.d. plus PR and experienced a multiple drug overdose, which was considered an impulsive act. The subject took 3 doses of TMC435/PBO, 9 doses of 200 mg RBV, 8 doses of 60 mg duloxetine hydrochloride, and 12 doses of 5 mg diazepam. The subject went to the emergency department and discharged himself feeling drowsy but otherwise well and recovered from the overdose on the same day. The subject had no reported previous history of overdose, suicide attempt or depression. However, the use of duloxetine raises the question of whether the subject had an unreported underlying psychiatric

condition. No action was taken with regard to the study drugs and the event was considered not related to any of the study drugs.

The second subject (study HPC3007) was receiving TMC435 150 mg q.d. plus PR and experienced an overdose, which was considered a suicide attempt. The subject took 12 doses of TMC435/PBO, 18 doses of 200 mg RBV, and 27 doses of 30 mg duloxetine. No AEs were reported in association with the overdose, and the subject recovered approximately 13 days after the event. She had a relevant history of alcohol abuse and depression and was being treated for the depression with duloxetine at time of the event.

The abuse potential of simeprevir is anticipated to be low based on the pharmacology and mechanism of action of the drug. Per Applicant, there is no information to indicate that withdrawal and rebound occur with simeprevir. Viral resistance to simeprevir may develop in subjects who fail on treatment with simeprevir-containing regimens (please refer to Section 4.2 for details).

7.7 Additional Submissions / Safety Issues

The Sponsor submitted a 2 month safety update report (SUR) with a final database cut-off date of March 2013 for the pivotal Phase 3 studies. No additional safety issues were identified in the review of the SUR which have not already been discussed in the preceding text.

8 Postmarket Experience

This product has not yet been approved for marketing in any country. As such, there is no postmarketing experience at this time.

9 Appendices

9.1 Literature Review/References

1. W.L. Chuang, M.L. Yu, "Host factors determining the efficacy of hepatitis C treatment," *Journal of Gastroenterology*, vol. 48, Issue 1, pp. 22-30, January 2013.

2. S. Imafaku, J. Nakayama, "Profile of patients with psoriasis associated with hepatitis C virus infection," *J Dermatol*, Feb 18, 2013. [Epub ahead of print]

3. F. Zaman, G. Ye, K.D. Abreo, et al. "Successful orthotopic liver transplantation after trimethoprim-sulfamethoxazole associated fulminant liver failure," *Clin Transplant*, vol. 15(5), pp. 461-4, October 2003.

4. J. Cundiff, S. Joe. "Amoxicillin-clavulanic acid–induced hepatitis," *American Journal of Otolaryngology–Head and Neck Medicine and Surgery,* vol. 28, pp. 28-30, 2007.

5. D. Larrey, T. Vial, A. Micaleff, et al. "Hepatitis associated with amoxycillin-clavulanic acid combination report of 15 cases." *Gut*, vol. 33, pp. 368-371, 1992.

6. F. H. Al-Kawas, L. B. Seeff, R. A. Berendson, et al. "Allopurinol Hepatotoxicity: Report of Two Cases and Review of the Literature." *Ann Intern Med*, vol. 95(5), pp. 588-590, 1981

7. Centers for Disease Control and Prevention. *1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults*. MMWR Recomm Rep. 1992 Dec 18;41(RR-17):1-19.

9.2 Labeling Recommendations

The proposed package insert (PI or label) is being reviewed by all disciplines involved in the review of this application. As discussed at length in Sections 1 and 6 of this Review, a number of critical virology/efficacy revisions to the PI are currently under discussion, including screening all patients for the Q80K polymorphism and revising the Sponsor's proposed treatment algorithm. From the clinical pharmacology perspective, a dose reduction in patients of Asian ancestry and in patients with moderate hepatic insufficiency is under consideration (refer to Section 4.4.3 for details). From the non-clinical perspective, a more complete discussion of reproductive toxicity findings and a revision to the proposed pregnancy category is also under discussion (refer to Section 4.3 for details). The following important safety related revisions are being considered:

<u>Section 5 (Warnings and Precautions):</u>

- Include a discussion of photosensitivity and rash (with recommendations for sun protection measures and management recommendations)

Section 6.1 (Clinical Studies Experience):

- Limit this section to focus on the Phase 3 trials (C208, C216, and HPC3007)
- Replace the proposed [redacted] (b) (4) with a table describing AEs (all grades and all causality) occurring with at least 3% higher frequency among patients in the TMC435 group compared to subjects in the Control group during the first 12 weeks of treatment in the pooled Phase 3 studies
- Include a safety summary related to 'dyspnea'
- Include additional information in the laboratory safety section on hyperbilirubinemia (e.g. time course, direct and indirect components, reversibility, etc.)
- Remove [redacted] (b) (4)

Discussions regarding the labeling recommendations are ongoing at this time and have not been finalized with the Applicant. The final agreed upon PI will be available at the time of approval.

9.3 Advisory Committee Meeting

The Antiviral Drugs Advisory Committee meeting is being convened by the Division on 23 October 2013 to solicit the committee's comments and recommendations regarding this application. The preliminary (draft) questions/issues which will be addressed and discussed are listed below. Detailed information on the Advisory Committee discussions and recommendations will be accessible in the transcripts after the committee meeting.

1. Please comment on the safety profile of TMC435 focusing on rash and photosensitivity events reported during the clinical trials.

   a. In the committee's opinion, are any of the serious adverse events and/or discontinuations related to rash and/or photosensitivity in the TMC435 group consistent with severe cutaneous adverse reactions (e.g. DRESS, SJS, etc.)?

   b. Do the rash/photosensitivity events merit special attention in the product label?

   c. Based on the available clinical trials experience, should sun-protection measures be recommended for all patients receiving TMC435?

2. Considering the overall risks and benefits, do the available data from studies C208, C216, and HPC3007 support approval of TMC435 in combination with pegylated interferon and ribavirin for treatment of HCV infection in treatment-naïve adults and in adults who have relapsed after prior interferon-based HCV treatment?

    a. Should screening for the Q80K polymorphism be performed on these patients prior to initiation of TMC435 with the object of excluding patients from treatment if the polymorphism is present?

3. Considering the overall risks and benefits, do the available data from study C206 support approval of TMC435 in combination with pegylated interferon and ribavirin for treatment of HCV infection in adults categorized as partial responders and null responders to prior interferon-based HCV treatment?

    a. Should screening for the Q80K polymorphism be performed on these patients prior to initiation of TMC435 with the object of excluding patients from treatment if the polymorphism is present?

4. At the proposed dose of TMC435 150 mg once daily, mean exposures were approximately 3.4-fold higher in individuals of East Asian ancestry compared to the pooled Phase 3 population. Similarly, TMC435 150 mg once daily provided 2.4-fold higher exposures in subjects with moderate hepatic impairment compared to healthy volunteers. Considering the positive relationship between TMC435 exposures and the incidence of adverse events (including rash, photosensitivity, anemia, dyspnea, pruritus, and increased bilirubin), should the dose strength of TMC435 be reduced in the following patient subgroups:

    a. patients of East Asian ancestry
    b. patients with moderate hepatic insufficiency

5. Are there post marketing studies that should be conducted to further define risks or optimal use of TMC435?

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

/s/

ADAM I SHERWAT
08/25/2013

MARY E SINGER
08/26/2013
I concur with Dr. Sherwat's assessments and conclusions in this review.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205123 **Applicant:** Janssen **Stamp Date:** 03/28/2013

Drug Name: Simeprevir (TMC435) **NDA/BLA Type:** Original NDA submission; 505 (b)(1)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD format
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			Yes, a Clinical Overview, and Clinical Efficacy and Safety Summaries have been provided.
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Yes, under 5.3.5.3 with a link to 2.7.4.
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Yes, under 5.3.5.3 with a link to 2.7.3.
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			The Clinical Overview contains a "Benefits and Risks Conclusions" section (section 9.0).
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505 (b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: C205 Study Title: A Phase IIb, randomized, double-blind, placebo-controlled trial to investigate the efficacy, tolerability, safety and pharmacokinetics of TMC435 as	X			

	Content Parameter	Yes	No	NA	Comment
	part of a treatment regimen including peginterferon alfa-2a and ribavirin in treatment –naïve genotype 1 hepatitis C-infected subjects. Sample Size: 386 Arms: 1. 75 mg q.d. TMC (12 weeks) + PR (24 weeks) 2. 75 mg q.d. TMC (24 weeks) + PR (24 weeks) 3. 150 mg q.d. TMC (12 weeks) + PR (24 weeks) 4. 150 mg q.d. TMC (24 weeks) + PR (24 weeks) 5. PR (48 weeks) Location in submission: Section 5.3.5.1 Study Number: C206 Study Title: 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. Sample Size: 462 Arms: 1. 100 mg q.d. TMC (12 weeks) + PR (48 weeks) 2. 100 mg q.d. TMC (24 weeks) + PR (48 weeks) 3. 100 mg q.d. TMC (48 weeks) + PR (48 weeks) 4. 150 mg q.d. TMC (12 weeks) + PR (48 weeks) 5. 150 mg q.d. TMC (24 weeks) + PR (48 weeks) 6. 150 mg q.d. TMC (48 weeks) + PR (48 weeks) 7. PR (48 weeks) Location in submission: Section 5.3.5.1				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? The following three pivotal studies were provided to support the following proposed indication: X Pivotal Study #1 C208: 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 alfa-2a and ribavirin in treatment-naïve, genotype 1 hepatitis Cinfected subjects. Sample Size: 394 Pivotal Study #2 C216: A Phase III, randomized, double-blind, placebo-	X			

	Content Parameter	Yes	No	NA	Comment
	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 nfected subjects. Sample Size: 393 <u>Pivotal Study #3</u> HPC3007: 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 alfa-2a and ribavirin in hepatitis C, genotype 1 infected subjects who relapsed after previous interferon-based therapy. Sample Size: 393				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Yes, the primary endpoint for the pivotal studies (C208, C216, and HPC 3007) was sustained virologic response 12 weeks after the planned end of treatment (SVR12).
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			The Sponsor provided, in Section 1.2, a document entitled "Acceptance of Foreign Clinical Studies." That document primarily concentrates on the acceptability of the foreign data from a GCP perspective. It should be noted that the Q80K baseline polymorphism has been shown to negatively impact the efficacy of TMC435 and that this polymorphism was

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	Content Parameter	Yes	No	NA	Comment
					most prevalent in subjects from North America (see Clinical Overview Section 4.7.1.1 for details).
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			Yes, a dedicated QT assessment study, C117, has been completed and the data previously submitted for review and also included with this submission (Section 5.3.4.1).
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			N.B. The Sponsor is conducting a separate development program in Japan and provided the requested safety data from this program.
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			1846 HCV-infected subjects and 806 healthy subjects have received TMC435. A total of 1153 HCV-infected subjects have been treated with TMC435 150 mg for 12 weeks.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		X		
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			Yes, specifically rash, anemia, neutropenia, and increased bilirubin were treated as adverse events of special/clinical

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					interest.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Yes, narrative summaries for all deaths, AE leading to dropout and SAEs have been provided for studies C205, C206, C208, C216 and HPC3007
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The Sponsor provided a waiver request for children < 3 years of age (Section 1.9.1) and a deferral request for children 3-18 years of age (Section 1.9.2).
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			See comment in #17 above.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			See Section 1.3.4

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

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

1. Please provide a "coding dictionary" or, if already provided, indicate its location in the submission. The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

Adam Sherwat

Reviewing Medical Officer Date

Mary Singer

Clinical Team Leader Date

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

/s/

ADAM I SHERWAT
04/23/2013

MARY E SINGER
04/24/2013