Simeprevir

(TMC435)

Presented by
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on behalf of the
Simeprevir (TMC435) Review Team
Division of Antiviral Products

Antiviral Drugs Advisory Committee Meeting
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Key Trials of Simeprevir

Trial Name	Study Design	Population	Simeprevir Dose and Duration	Number Enrolled	Primary Efficacy Endpoint
C208	Phase 3, Randomized, Double-Blinded, Placebo-Controlled	Genotype 1 Treatment-Naïve	150 mg q.d. for 12 Weeks[a]	394	SVR12
C216	Phase 3, Randomized, Double-Blinded, Placebo-Controlled	Genotype 1 Treatment-Naïve	150 mg q.d. for 12 Weeks[a]	393	SVR12
HPC3007	Phase 3, Randomized, Double-Blinded, Placebo-Controlled	Genotype 1 Relapsers	150 mg q.d. for 12 Weeks[a]	393	SVR12
C206	Phase 2b, Randomized, Double-Blinded, Placebo-Controlled	Genotype 1 Relapsers, Null-Responders, & Partial Responders	100 or 150 mg q.d. for 12, 24, or 48 Weeks[b]	462	SVR24

a = In conjunction with pegylated interferon plus ribavirin (PR) for 24 or 48 weeks based on a response guided algorithm

b = in conjunction with PR for 48 weeks

Primary Efficacy Results and Efficacy by Genotype/Subtype

Populations	Naive		Relapsers	
Studies (Number of Subjects)	C208 & C216 (N=785)		HPC3007 (N=393)	
Treatment Arms	Simeprevir	Placebo	Simeprevir	Placebo
Overall SVR12[a]	419/521 (80%)	133/264 (50%)	206/260 (79%)	48/133 (36%)
GT1a	191/254 (75%)	63/131 (48%)	78/111 (70%)	14/54 (26%)
GT1b	228/267 (85%)	70/133 (53%)	128/149 (86%)	34/79 (43%)

[a] *SVR12 is defined as the proportion of subjects with HCV RNA < 25 IU/mL detectable or undetectable 12 weeks after the actual end of treatment.*

Additional Subgroup Analyses

- In both the pooled naïve trials and the relapser trial, SVR12 rates were also substantially higher for the simeprevir treatment group compared to the placebo group regardless of the following:

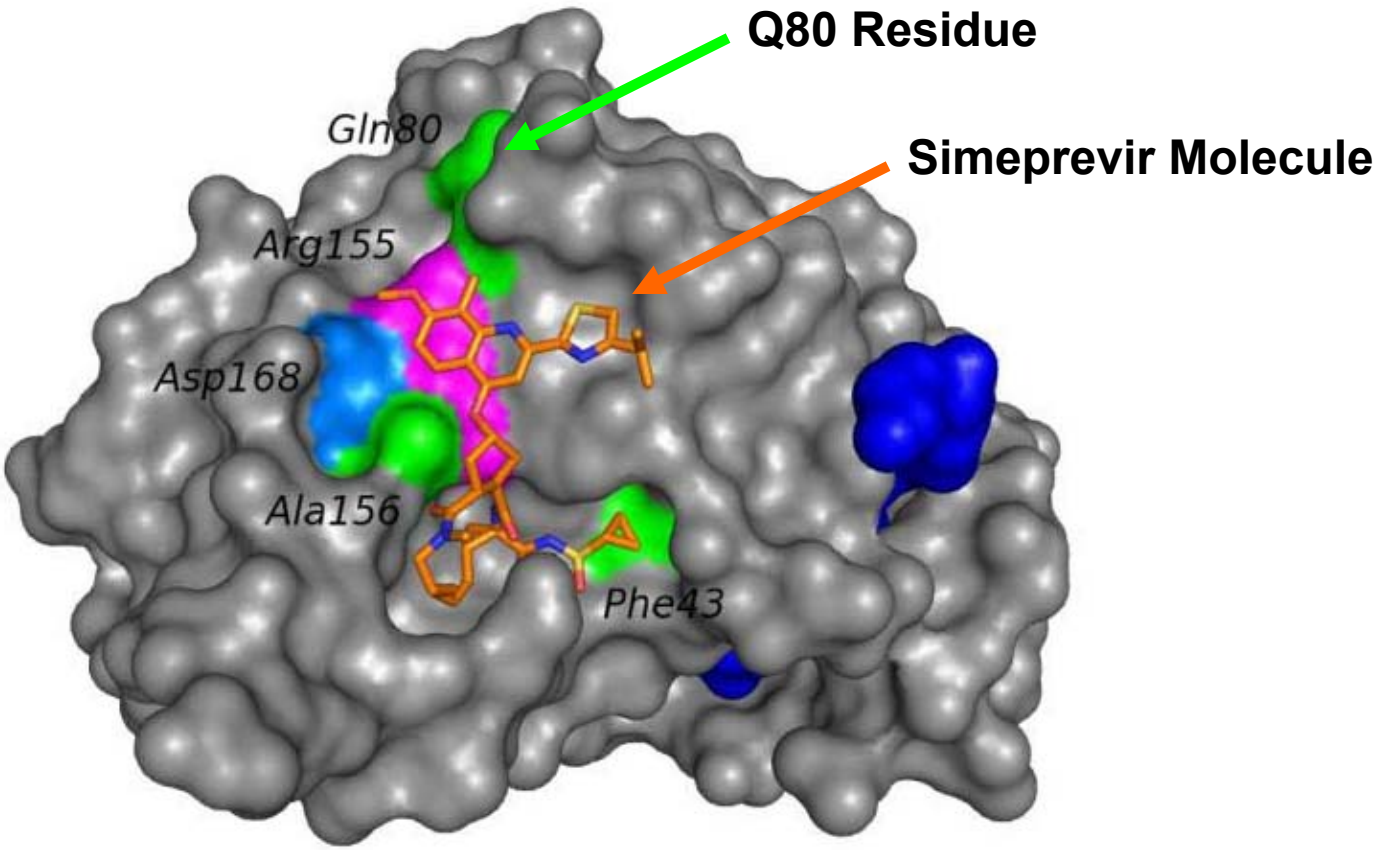
  - Sex
  - Race
  - Baseline HCV RNA load
  - *IL28B* genotype
  - -Age
  - -BMI
  - -METAVIR fibrosis score

- In subjects with HCV GT1a infection having the HCV NS3 Q80K polymorphism at baseline, no substantive difference was observed in SVR12 rates when comparing the simeprevir group to the placebo group in either the naïve or relapser trials

HCV Q80K: Impact on SVR12 Rates

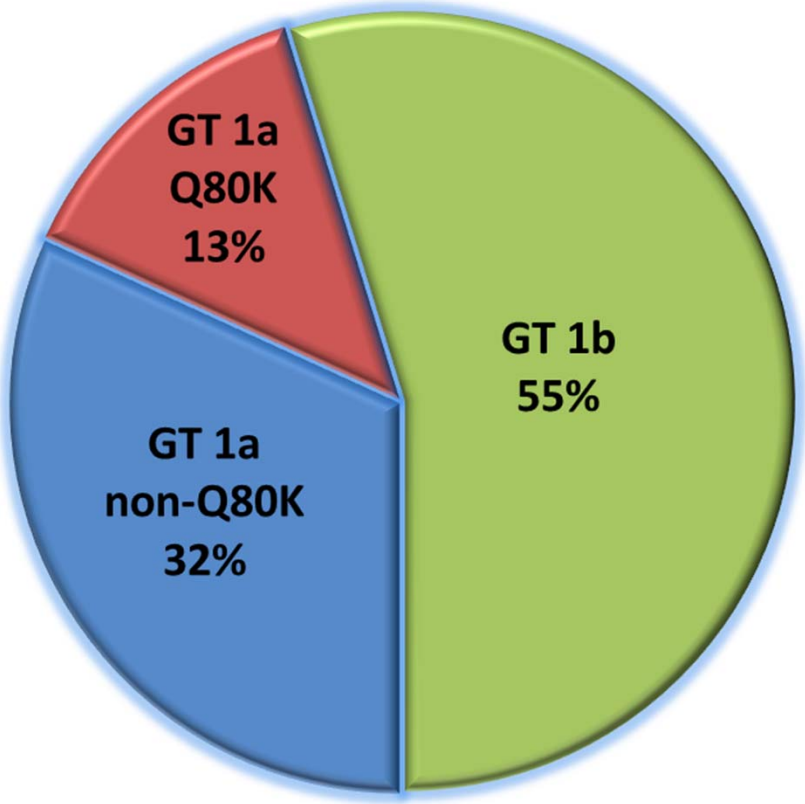
Populations	Naive		Relapsers	
Studies	C208 & C216		HPC3007	
Treatment Arms	Simeprevir	Placebo	Simeprevir	Placebo
	N (%) of subjects achieving SVR12		N (%) of subjects achieving SVR12	
GT1a	191/254 (75%)	63/131 (48%)	78/111 (70%)	14/54 (26%)
Without Q80K	138/165 (84%)	36/83 (43%)	62/79 (78%)	8/34 (24%)
With Q80K	**49/84 (58%)**	**24/44 (55%)**	**14/30 (47%)**	**6/20 (30%)**

NS3 Contact Residues for Simeprevir

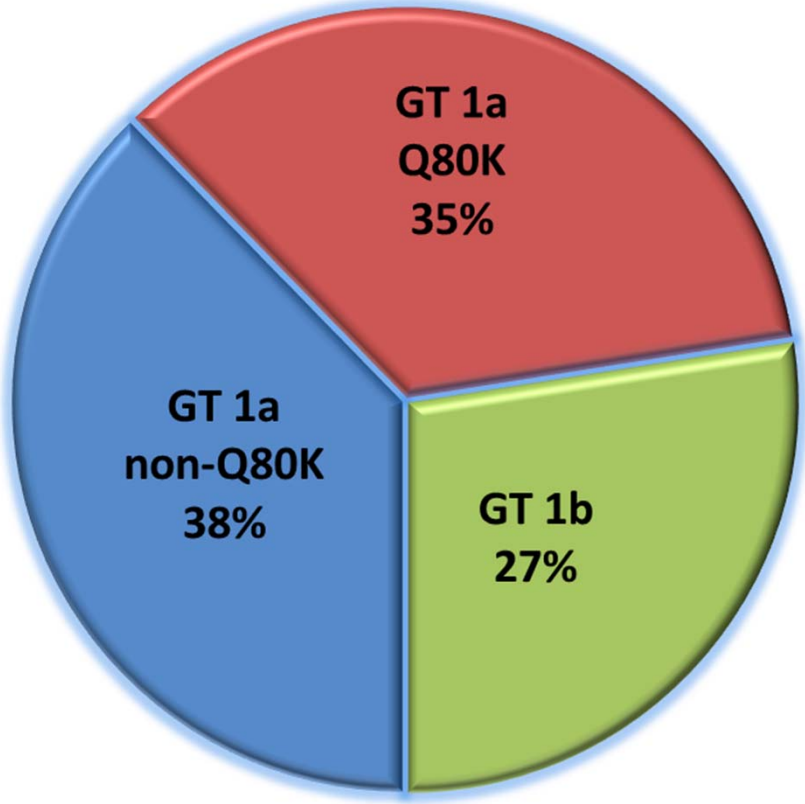


Mod5.3.5.4/TMC435-Cocrystal-AVMR

Distribution of GT1a (with or without Q80K) & GT1b in all Subjects vs. U.S. Subjects in Phase 2b/3 Simeprevir Trials

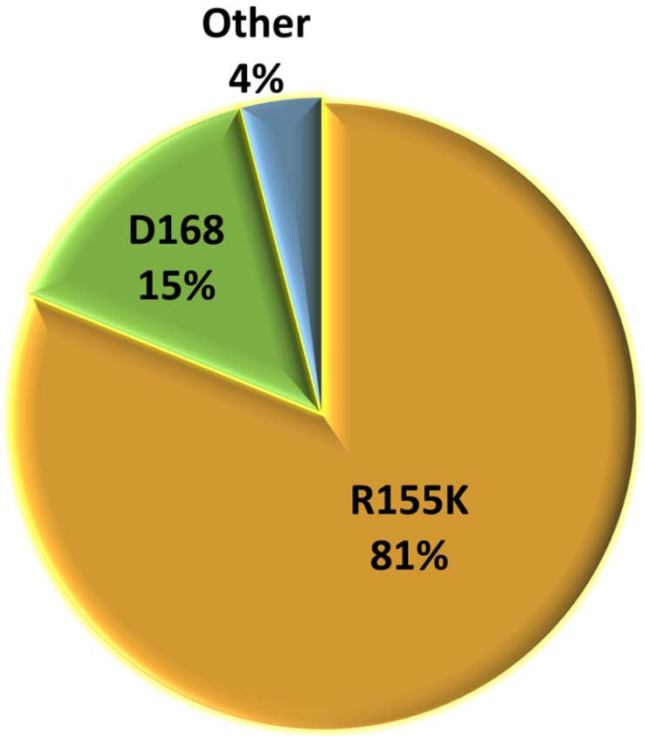


Overall (N=1,997)

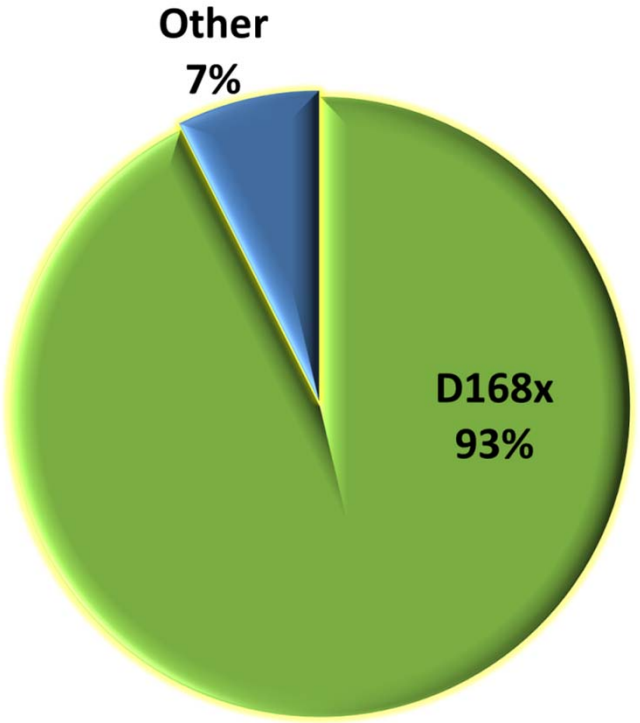


U.S. (N=411)

Treatment-Associated Emergence of Simeprevir Resistance in GT1a and GT1b-Infected Subjects



GT1a (n=122)



GT1b (n=81)

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

R155K and Cross-Resistance

FDA-APPROVED HEPATITIS C VIRUS (HCV) DRUGS

MUTATIONS IN THE HCV PROTEASE GENE ASSOCIATED WITH RESISTANCE TO NONSTRUCTURAL PROTEIN 3 (NS3) PROTEASE INHIBITORS

	V	T	V			R	A	V		I*V	M
	36	54	55			155	156	158		170	175
Boceprevir	A M	A S G C	A I			K T	S T V	I		F*A T*T	L
	V	T		I		R	A		D		
Telaprevir	36	54		132		155	156		168		
	A M G L	A S		V**		K T G M	S T V		N**		

INVESTIGATIONAL HCV DRUGS[a]

MUTATIONS IN THE HCV PROTEASE GENE ASSOCIATED WITH RESISTANCE TO NONSTRUCTURAL 3 PROTEIN (NS3) PROTEASE INHIBITORS

	V	F	T	Q	S	S	R	A	D
	36	43	54	80	122	138	155	156	168
Simeprevir	M	S	S	K R L	A R	T	K	T V	A V E H T

IAS-USA. Drug Resistance in HCV (2012)

Efficacy in Partial and Null Responders

- Data from the Phase 2b trial, C206, support an indication for simeprevir treatment in patients with GT1 infection who were partial or null responders to prior treatment with interferon (± ribavirin)

- In C206, subjects received 12, 24, or 48 weeks of simeprevir (at daily doses of either 100 or 150 mg) in combination with PR for 48 weeks

Efficacy in Partial and Null Responders in C206

SVR24 Results

Study	C206						
Treatment Arm	Simeprevir 100MG/ 12WKS	Simeprevir 100MG/ 24WKS	Simeprevir 100MG/ 48WKS	Simeprevir 150MG/ 12WKS	Simeprevir 150MG/ 24WKS	Simeprevir 150 MG/ 48 WKS	Placebo
	----------N (%) Subjects Achieving SVR24----------						
Partial Responders	17/23 (74%)	11/23 (48%)	12/22 (55%)	15/23 (65%)	18/24 (75%)	19/22 (86%)	2/23 (9%)
Null Responders	6/16 (38%)	9/16 (56%)	8/18 (44%)	9/17 (53%)	7/17 (41%)	10/17 (59%)	3/16 (19%)

Efficacy in Partial and Null Responders in C206

SVR24 Results

Study	C206						
Treatment Arm	Simeprevir 100MG/ 12WKS	Simeprevir 100MG/ 24WKS	Simeprevir 100MG/ 48WKS	Simeprevir 150MG/ 12WKS	Simeprevir 150MG/ 24WKS	Simeprevir 150 MG/ 48 WKS	Placebo
	----------N (%) Subjects Achieving SVR24----------						
Partial Responders	17/23 (74%)	11/23 (48%)	12/22 (55%)	15/23 (65%)	18/24 (75%)	19/22 (86%)	2/23 (9%)
Null Responders	6/16 (38%)	9/16 (56%)	8/18 (44%)	9/17 (53%)	7/17 (41%)	10/17 (59%)	3/16 (19%)

Efficacy in Partial and Null Responders in C206

SVR24 Results

Study	C206	
Treatment Arm	Simeprevir 100MG/12WKS AND Simeprevir 150MG/12WKS	Placebo
	----------N (%) Subjects Achieving SVR24----------	
Partial Responders	32/46 (70%)	2/23 (9%)
Null Responders	15/33 (45%)	3/16 (19%)

Efficacy in More Difficult to Treat Subpopulations

Pooled Treatment Naïve Trials

Combined Baseline Factors	SVR12, n/N (%)	
	Simeprevir	Placebo
IL28B Non-CC Genotypes AND MFS F3-F4 AND Baseline HCV RNA ≥ 800 KIU/mL	37/73 (51%)	3/38 (8%)

Efficacy Summary

- Simeprevir in combination with PR was superior to placebo (in combination with PR) in achieving SVR in both treatment-naïve subjects and in subjects who relapsed after prior interferon (± ribavirin) therapy
- In the subgroup of subjects with the viral Q80K polymorphism at baseline, a substantial impact on the efficacy of simeprevir was observed
- DAVP intends to recommend that all GT1a patients undergo screening for this baseline polymorphism prior to treatment with simeprevir and that alternative treatment options be considered for patients infected with this polymorphic variant
- DAVP believes that there is sufficient evidence to support an indication to include HCV GT1 infected patients classified as treatment naïve, prior relapsers, prior partial responders and prior null responders

Safety Review Strategy

- The safety review was based primarily on data from the Phase 3 trials: C208, C216, and HPC3007
- As their study design (apart from the patient population) was virtually identical, the safety analysis was conducted by pooling the safety data from the three Phase 3 trials
- In addition, results from two Phase 2b trials (C205 and C206) provided supportive safety data
- The safety review focuses primarily on the first 12 weeks of treatment (the simeprevir administration period) in the pooled Phase 3 trials

Deaths

Pooled Phase 2b and Phase 3 Trials, 72 Week Follow-up Data

Trial (Treatment Group)	Age/ Sex	Race	First Dose Simeprevir (SD)	Last Dose Simeprevir (SD)	Death (SD)	Cause of Death
Study C206						
C206 (Simeprevir)	47/ M	White	1	Unknown	242	Bacterial Meningitis and Brain Hemorrhage
Study 216						
C216 (Simeprevir)	49/ F	White	1	85	196	Colon Cancer
C216 (Simeprevir)	62/ F	American Indian or Alaska Native	1	83	118	Presumed Cardiopulmonary Event
Study HPC3007						
HPC3007 (Simeprevir)	57/ F	White	1	84	90	Bilateral Pneumonia and Septic Shock

SD = Study Day

Non-Fatal Serious Adverse Events (SAEs) and Adverse Events (AEs) Leading to Premature Study Drug Discontinuation

	Simeprevir	Placebo
Study Phase	First 12 Weeks	First 12 Weeks
Studies (Number of Subjects)	C208, C216, HPC3007 (N=781)	C208, C216, HPC3007 (N=397)
Any SAE* (%)	2%	3%
Any AE Leading to Premature Study Drug Discontinuation (%)	2%	1%

**Includes all SAEs regardless of relationship to study drug. SAEs judged related to simeprevir per investigator included the MedDRA preferred terms 'major depression' in one subject and 'photosensitivity reaction' in two subjects*

AEs Occurring ≥ 3% More Frequently in the Simeprevir Group versus the Control Group

	Simeprevir	Placebo
	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 (including Photosensitivity)*	218 (28%)	79 (20%)
Pruritus*	168 (22%)	58 (15%)
Nausea	173 (22%)	70 (18%)
Myalgia	126 (16%)	53 (13%)
Dyspnea*	92 (12%)	30 (8%)
Increased Bilirubin*	61 (8%)	11 (3%)

* Indicates grouped term

Dyspnea

Pooled Phase 3 Trials, First 12 Weeks

- An increased frequency of dyspnea was noted in the simeprevir group compared to the placebo group (12% versus 8% respectively)
- The majority of cases (61%) occurred during the first 4 weeks of treatment with simeprevir
- There were no grade 3 or 4 AEs, SAEs, or discontinuations due to dyspnea in the simeprevir group
- 89% of the subjects in the simeprevir group with dyspnea reported during the first 12 weeks of the study were reported as "Recovered/Resolved" with respect to this AE, based on the available data
- An analysis to determine whether the reported dyspnea events were associated with the presence of anemia was performed and no association was apparent

Increased Bilirubin

Background & Pooled Phase 3 Trial Data

- From early in clinical development, hyperbilirubinemia was known to be associated with use of simeprevir and was considered an adverse event of special interest
- The higher incidence of bilirubin elevations in simeprevir-treated subjects appears to be primarily attributable to a decrease in bilirubin elimination related to inhibition of the hepatic transporters OATP1B1 and MRP2
- In the pooled phase 3 trials, graded bilirubin laboratory abnormalities occurred in 49% of subjects in the simeprevir group compared to 26% of subjects in the placebo group during the first 12 weeks of treatment
  - This difference was primarily driven by grade 1 and 2 laboratory abnormalities

Increased Bilirubin

Pooled Phase 3 Trials

- Elevations in bilirubin occurred early after initiation of simeprevir, peaked by the 2nd week of treatment and returned to near baseline values by four weeks following completion of treatment with simeprevir
- Although a greater frequency of AEs related to increased bilirubin occurred in the simeprevir group compared to the placebo group (8% versus 3% respectively), no association between bilirubin elevation and clinically relevant hepatotoxicity was appreciated

Skin and Soft Tissue Assessment

Pooled Phase 3 Trials, First 12 Weeks

- There was a higher incidence of skin and subcutaneous tissue disorders* in the simeprevir group (49%) compared to the placebo group (38%) during the first 12 weeks of treatment

- Safety analysis led to the identification of three general categories of interest: Pruritus, Photosensitivity and Rash

- In order to facilitate the assessment of AE trends, grouped variables for each of these categories were constructed

*by MedDRA System Organ Class

Warnings and Precautions

- Guidance for Industry
  - **Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products**

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
October 2011

Warnings and Precautions

Overview

- The Warnings and Precautions section is intended to identify and describe a discrete set of adverse reactions and other potential safety hazards that are *serious* or are *otherwise clinically significant* because they have implications for prescribing decisions or for patient management
- To include an adverse event in the section, there should be reasonable evidence of a causal association between the drug and the adverse event, but a causal relationship need not have been definitively established

Warnings and Precautions

Defining Serious Adverse Events

- An AE that results in any of the following outcomes should be considered serious*
  - Death
  - A life threatening AE
  - Inpatient hospitalization or prolongation of existing hospitalization
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - A congenital anomaly or birth defect

*Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the above outcomes

Warnings and Precautions

Defining "Clinically Significant" Events

- The following types of adverse reactions could be considered otherwise clinically significant:
  - An adverse reaction that may lead to a potentially serious outcome unless the dosage or regimen is adjusted, the drug is discontinued, or another drug is administered to prevent the serious outcome
  - An adverse reaction that could be prevented or managed with appropriate patient selection, monitoring, or avoidance of concomitant therapy, and prevention or management of the adverse reaction is needed to avoid a potentially serious outcome
  - An adverse reaction that can significantly affect patient compliance, particularly when noncompliance has potentially serious consequences

Warnings and Precautions

Anticipated Adverse Reactions

- There are circumstances in which an adverse reaction that has not been observed with a drug can nonetheless be anticipated to occur
- The Warnings and Precautions section should include serious or otherwise clinically significant adverse reactions that are anticipated to occur with a drug if it appears likely that the adverse reaction will occur with the drug based on what is known about the pharmacology, chemistry, or class of the drug

Phototoxicity vs. Erythema Multiforme

Phototoxicity

- Exaggerated Sunburn
- Photo-distributed eruption
  - Face, V of the neck, forearms, hands
- Preventative measures (sun avoidance, protective clothing, sun block) are indicated
- Management requires discontinuation of the offending drug

Erythema Multiforme

- Variable morphologic characteristics (typical targetoid lesions or atypical lesions)
- Lesions are most commonly in an acral distribution with predilection for extensor surfaces
- Lesions may spread in a centripetal fashion
- May involve mucous membranes
- Management requires discontinuation of the offending drug

Drucker, Drug Saf 2011; Sokumbi, International J of Dermatology 2012

Photosensitivity

Results In Vitro and in Healthy Subjects

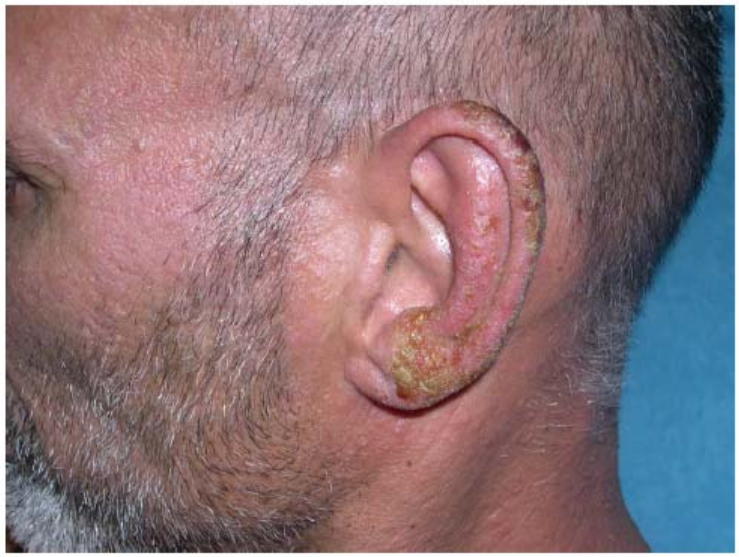
- In vitro studies revealed that simeprevir was phototoxic after UVA exposure and photosensitivity reactions were reported with early clinical experience
- Subjects were asked to adhere to sun-protection measures during simeprevir administration in the pivotal trials
- A dedicated photosensitivity study performed in healthy subjects revealed evidence of immediate photosensitivity in 33% of subjects in the simeprevir group and in no subjects in the positive control (ciprofloxacin) or placebo groups
  - There was a positive association in this study between higher exposures to simeprevir and the development of immediate photosensitivity reactions.
  - The anticipated AUC for simeprevir in patients with chronic hepatitis C infection is 2 to 3-fold higher than that of healthy subjects

Photosensitivity

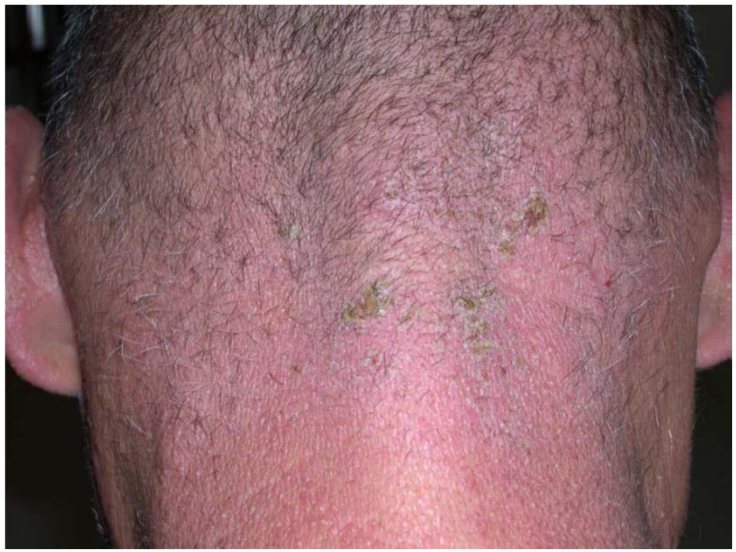
Pooled Phase 3 Trials, First 12 Weeks

- Photosensitivity (grouped term) was reported in 5% of simeprevir subjects and 1% of placebo subjects
- 2 SAEs reported as “photosensitivity reactions” occurred in the simeprevir group
  - 44 year old WM blisters on his arms, neck, head, ears, and nose; hospitalized on two occasions related to this event
  - 35 year old WM with facial swelling and pain; required hospitalization and systemic steroids
- No discontinuations of simeprevir due to photosensitivity were reported

AE Reported as "Photosensitivity"



SD 43



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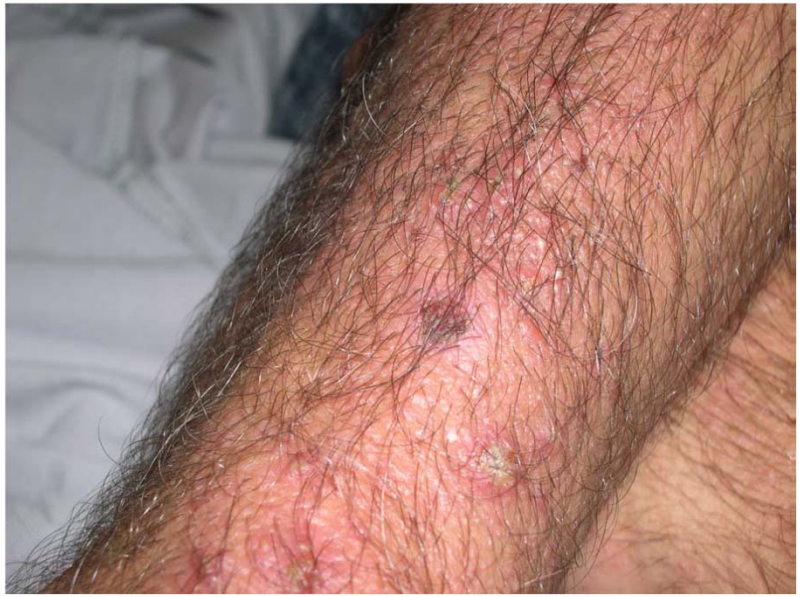
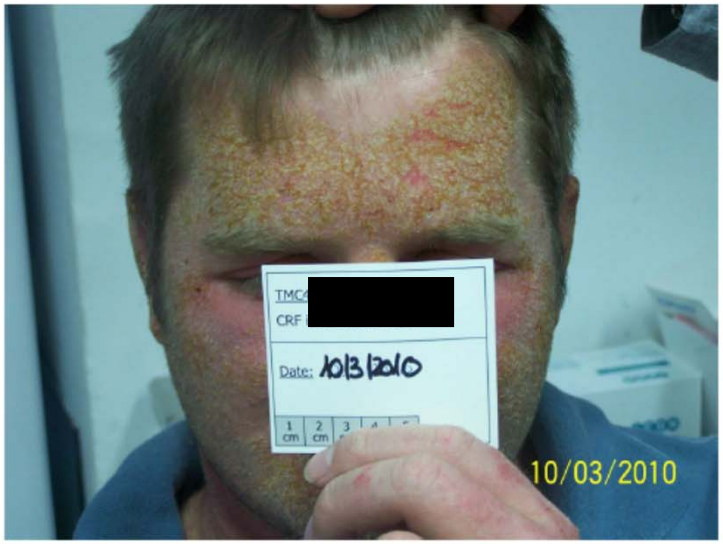


Subject #9

SD 43

AE Reported as “Drug Eruption”



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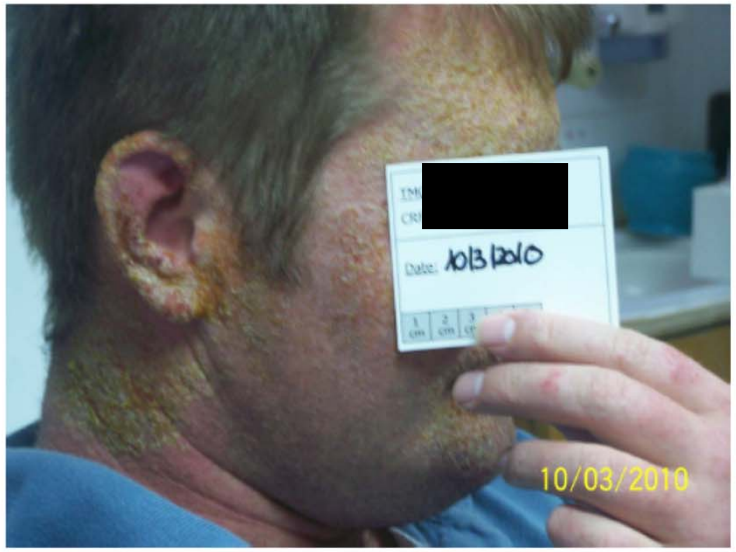

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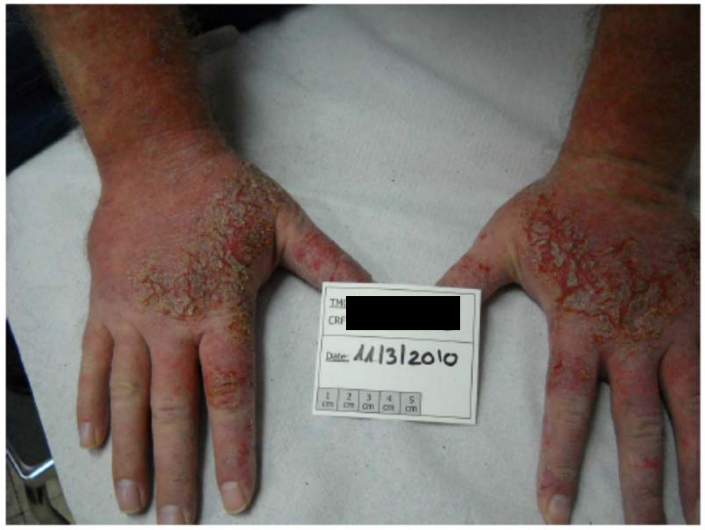


SD 58

Subject #17

Photosensitivity

DAVP's Rationale for a Warning and Precaution

- Evidence of causality
  - Positive preclinical findings
  - Increased frequency in simeprevir group compared to the placebo group in the clinical trials
  - Exposure response relationship in both healthy and HCV infected subjects
  - Temporal association between simeprevir administration and reactions
- Serious adverse events reported
  - Hospitalizations and use of systemic steroids required
- The provision of guidance for prevention (sun protection measures) and management (discontinuation of simeprevir) is indicated to avoid a potentially serious outcome

Rash

Pooled Phase 3 Trials, First 12 Weeks

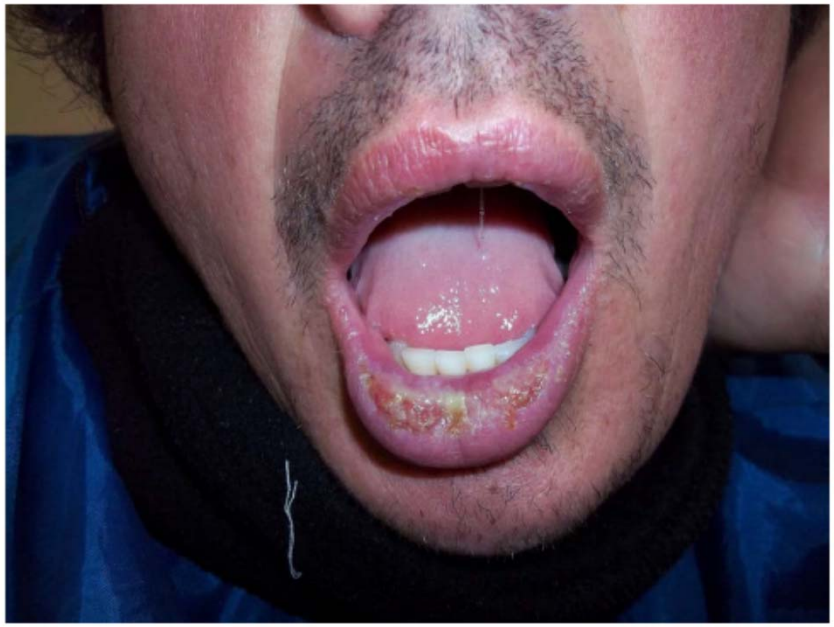
- Rash (grouped term excluding photosensitivity events) occurred in 25% of subjects in the simeprevir group and 19% of subjects in the placebo group
- 56% of rash events in the simeprevir group occurred during the first 4 weeks of treatment; 43% occurring in the first 2 weeks
- Grade 3 rash was reported in 1% of the simeprevir group and in no subjects in the placebo group
- No grade 4 AEs or SAEs due to rash were reported in the simeprevir or placebo groups
- 1% of subjects discontinued simeprevir due to rash compared to <1% of subjects in the placebo group

Rash Leading to Discontinuation of Study Drug

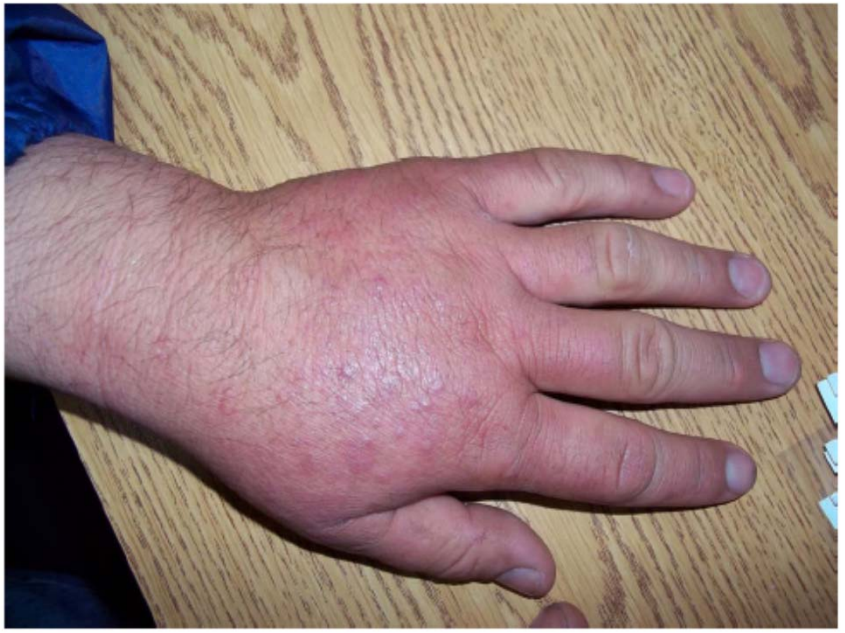
Study #/ Subject #	Age Race/ Sex	MedDRA PT	Study Day (Onset/ Resolution)	Worst Toxicity Grade	Associated Laboratory Findings*/ Study Day	Associated Mucosal Findings/ Study Day	Systemic Steroids Admin.
SIMEPREVIR GROUP							
C208/ 1	48 W/F	Rash	31/49	3	No	No	No
C208/ 2	56 W/M	Rash	54/194	2	Grade 1 ALT/ SD86	No	No
C208/ 3	59 W/F	Rash	61/129	3	No	No	No
C208/ 4	**59 W/M**	**Rash**	**67/~240**	**2**	**↑Eos (0.73 x 10^9)/ SD86**	**Apthous Stomatitis/ SD75**	**Yes**
C208/ 5	46 W/M	Psoriasis	14/ Ongoing	3	No	No	No
C216/ 6	**49 W/F**	**Rash**	**52/93**	**2**	**No**	**Mouth Ulceration/ SD57**	**No**
C216/ 7	**40 W/M**	**Maculo-Papular Rash**	**32/61**	**3**	**No**	**Conjunctivitis/ SD23 Apthous Stomatitis/ SD42**	**No**
PLACEBO GROUP							
C208/ 8	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

AE Reported as “Maculopapular Rash”



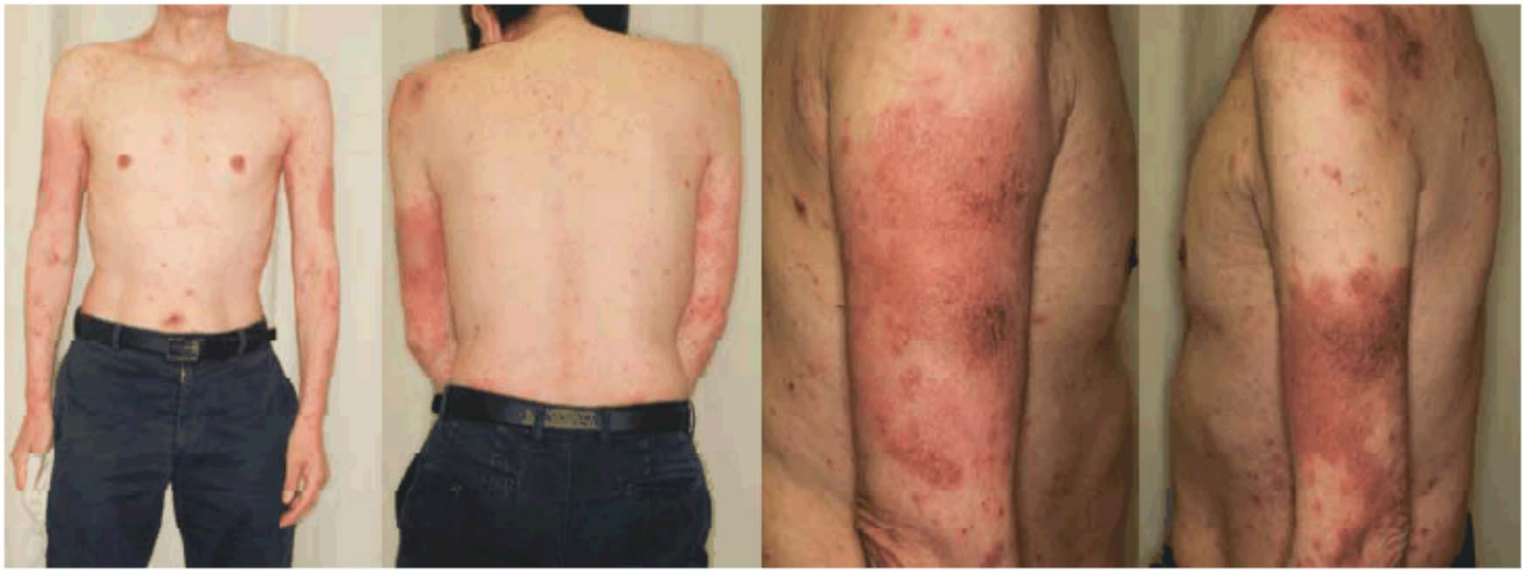
SD 53



SD 53

Subject #7

AE Reported as “Erythema Multiforme”



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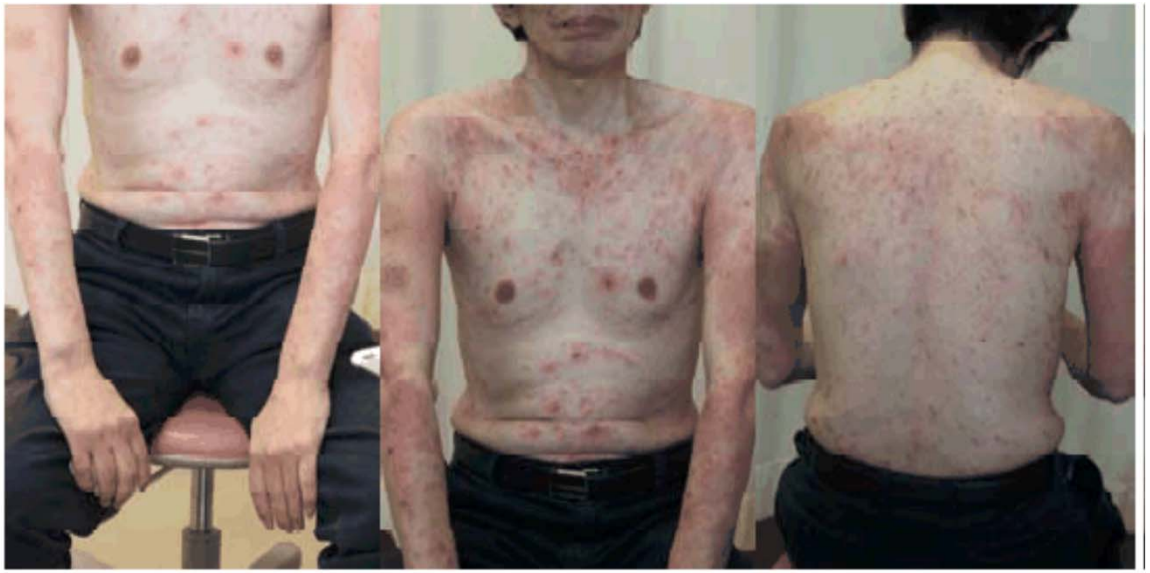


SD 83

Subject X

Rash

DAVP's Rationale for a Warning and Precaution

- Evidence of causality
  - Increased frequency and severity of rash in the simeprevir group compared to the placebo group in the clinical trials
  - Exposure response relationship for rash in subjects in the Phase 3 trials
  - Temporal association between simeprevir administration and rash
- Rash could be considered a "clinically significant" event
  - Leading cause of AEs leading to discontinuation of simeprevir
  - Erythema multiforme has been reported in the Japanese trials
  - Severe rash has been reported with other drugs in the same class
  - The provision of guidance for rash management (discontinuation of simeprevir for severe or progressive rash) is indicated to avoid a potentially serious outcome

Safety Summary

- A safety signal was noted with respect to photosensitivity reactions and rash
- DAVP is considering including photosensitivity reactions and a recommendation for sun protection measures in the Warnings and Precautions section of the simeprevir prescribing information
- DAVP is also considering the inclusion of a separate discussion of rash in the Warnings and Precautions section of the simeprevir prescribing information

Highlights of Simeprevir Clinical Pharmacology

Leslie W. Chinn, Ph.D.
Office of Clinical Pharmacology,
Office of Translational Sciences

Outline

- ADME
- Drug-drug interactions
- Exposure-response relationships
- Exposure differences in patient subpopulations

Simeprevir ADME

- Absorption: Orally bioavailable
  - Food increases exposures by 60-70%
- Distribution: Highly plasma-protein bound (>99.9%)
  - Distributes to liver via active process
- Metabolism:
  - Not extensively metabolized
  - CYP3A; possible contributions from CYP2C8 and CYP2C19
  - Plasma: 85% unchanged drug
- Excretion: Hepatobiliary
  - Feces: 91% of radioactivity (31% unchanged drug)
  - Urine: <0.05% of radioactivity

Simeprevir as a Victim of Drug-Drug Interactions

Interaction	Effect on simeprevir	Recommendation
CYP3A inhibitors (moderate or strong)		
↑ simeprevir	AUC increased >7-fold in presence of ritonavir or erythromycin	**Do not coadminister**
CYP3A inducers (moderate or strong)		
↓ simeprevir	C_{trough} decreased >90% in presence of rifampin or efavirenz	**Do not coadminister**

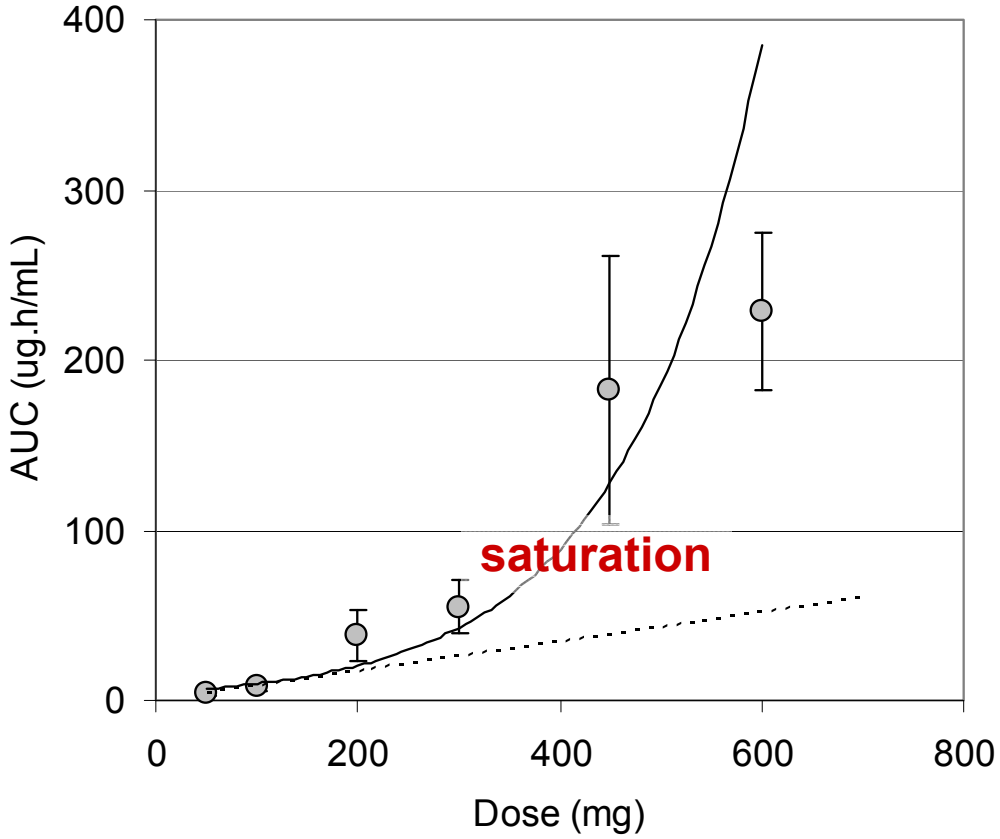
CYP3A: cytochrome P450 isoform 3A

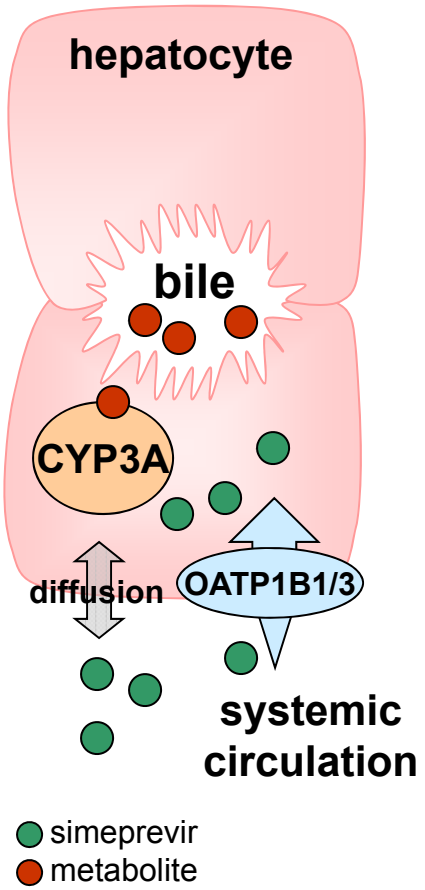
Simeprevir as a Perpetrator of Drug-Drug Interactions

Interaction	Effect of simeprevir	Recommendation
OATP1B1/3 substrates		
↑ substrates	Atorvastatin, rosuvastatin, simvastatin AUC and C_{max} increased 1.5- to 3-fold in presence of simeprevir	**Plasma concentrations may increase due to inhibition OATP1B1/3;** recommendations vary
CYP3A substrates		
↑ or ↔ substrates	Oral midazolam AUC and C_{max} increased ~25%; no change in IV midazolam AUC or C_{max}	**Plasma concentrations may increase due to intestinal CYP3A inhibition;** recommendations vary

OATP1B1/3: organic anion transporting polypeptide 1B 1 and 3 transporters

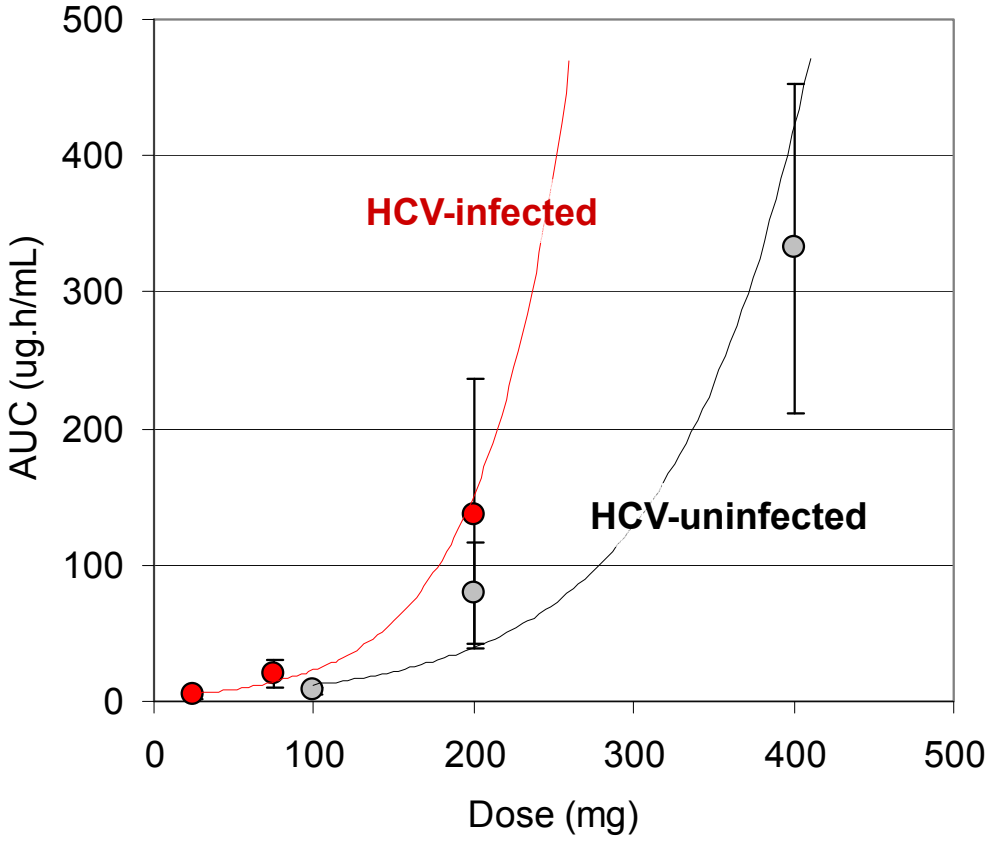
Simeprevir Exhibits Non-Linear Pharmacokinetics



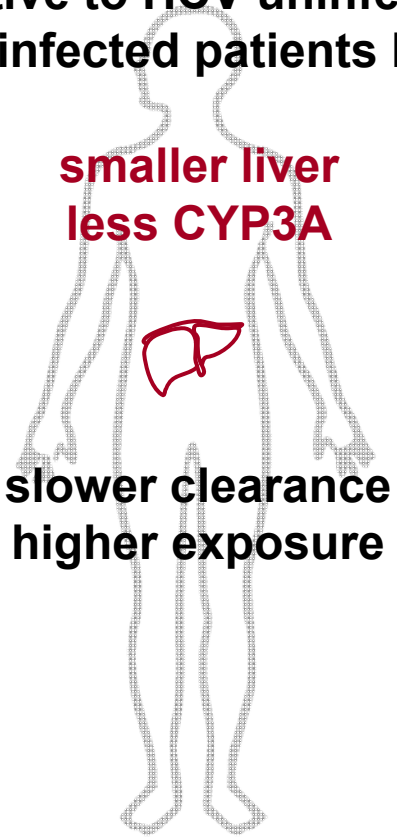


Trial C101 (healthy subjects)

Systemic Exposures are Higher in HCV-Infected Patients

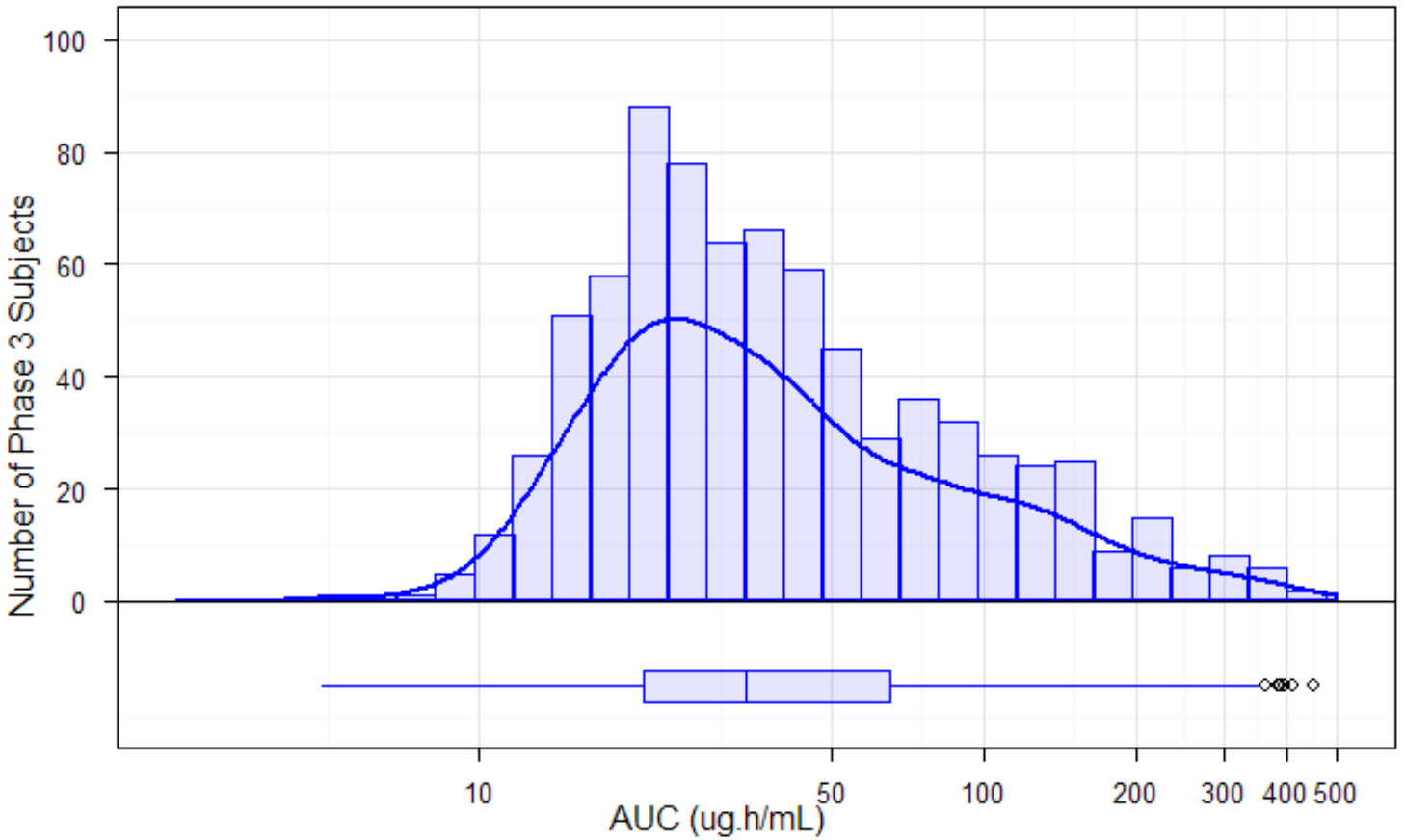


Relative to HCV-uninfected, HCV-infected patients have:



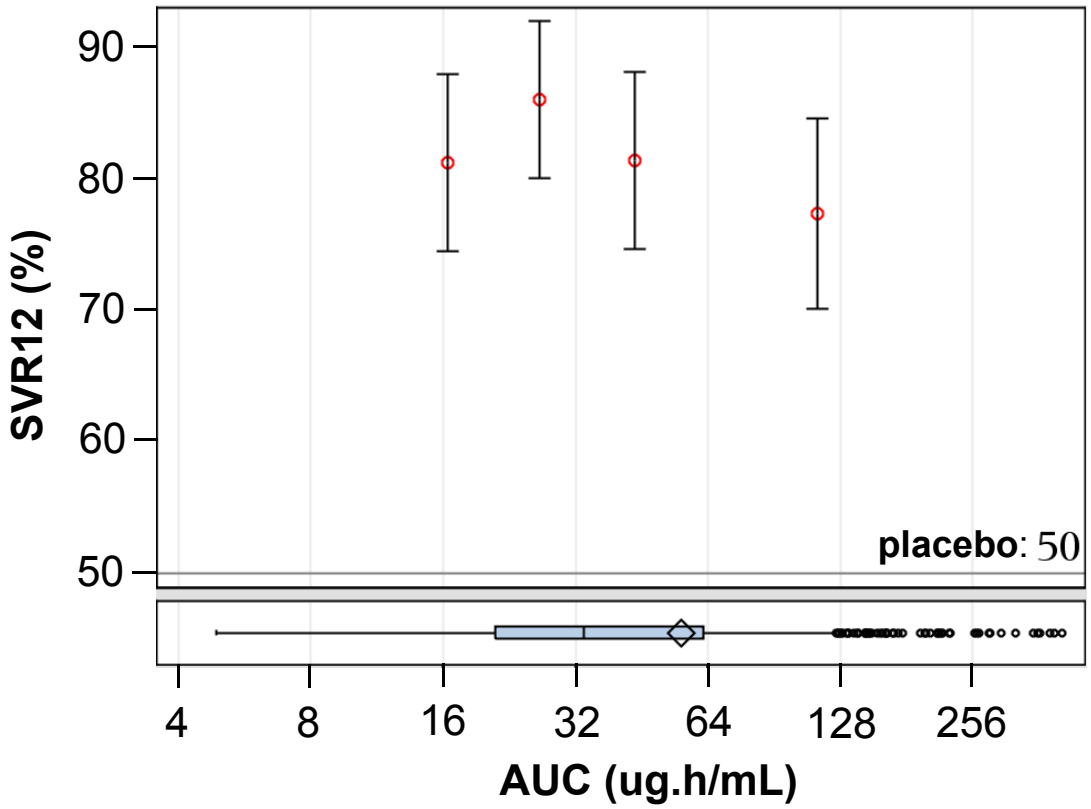
Trials C101 (HCV-uninfected) and C201 (HCV-infected); Nakai et al. 2008, Johnson et al. 2010

Systemic Exposures are Highly Variable in HCV-Infected Patients



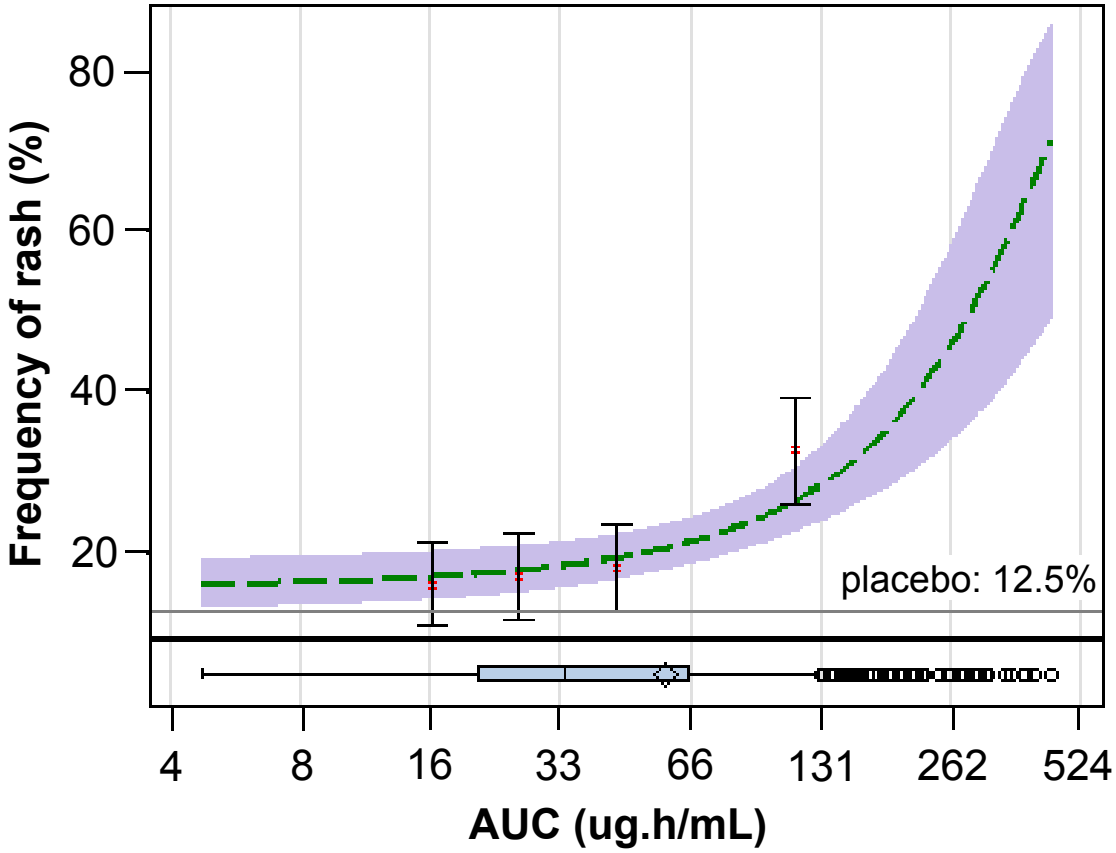
Phase 3 trials (C208, C216, HPC3007)

No Correlation Between Efficacy (SVR12) and Exposures Achieved with 150 mg QD



Phase 3 trials (C208, C216)

An Increased Incidence of Rash was Associated with Higher Exposures in Phase 3



Similar relationships between exposures and:

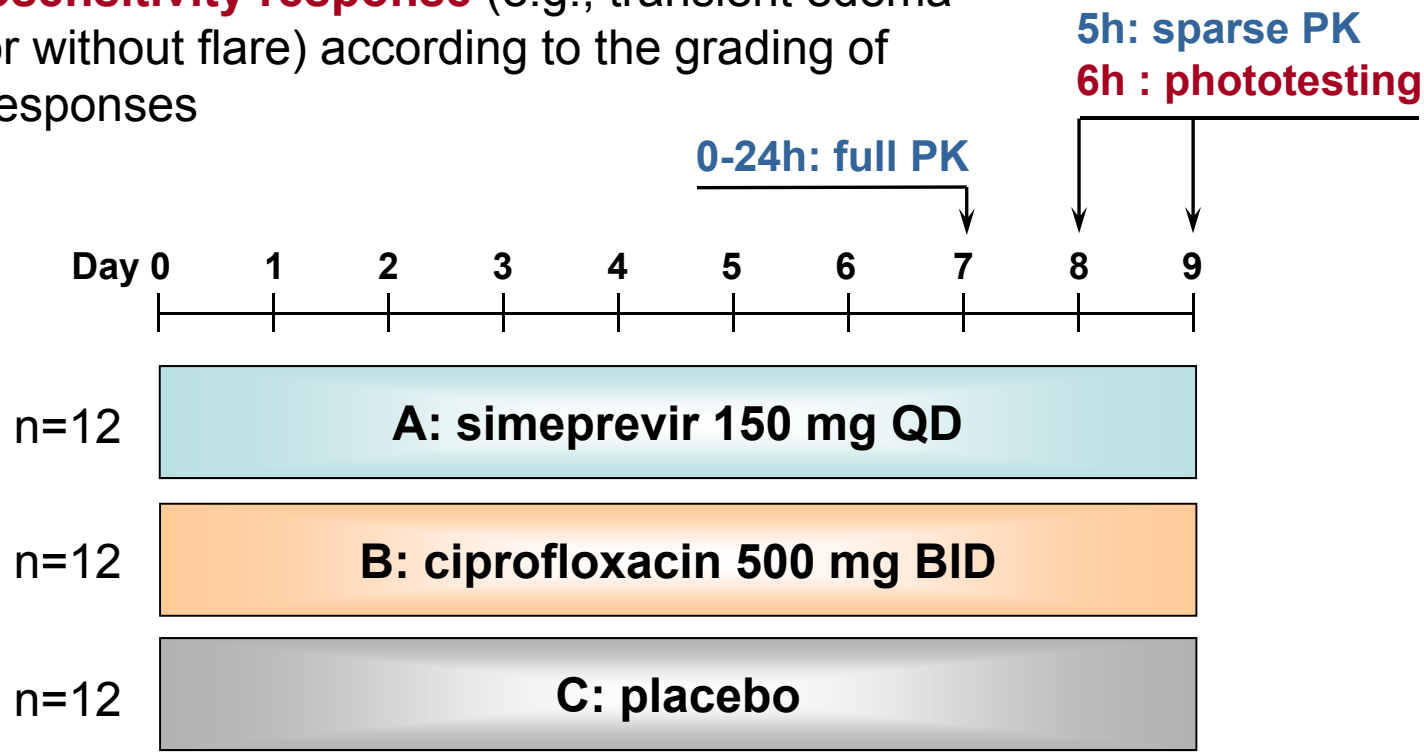
- photosensitivity
- pruritus
- dyspnea
- increased bilirubin

Phase 3 trials (C208, C216, HPC3007)

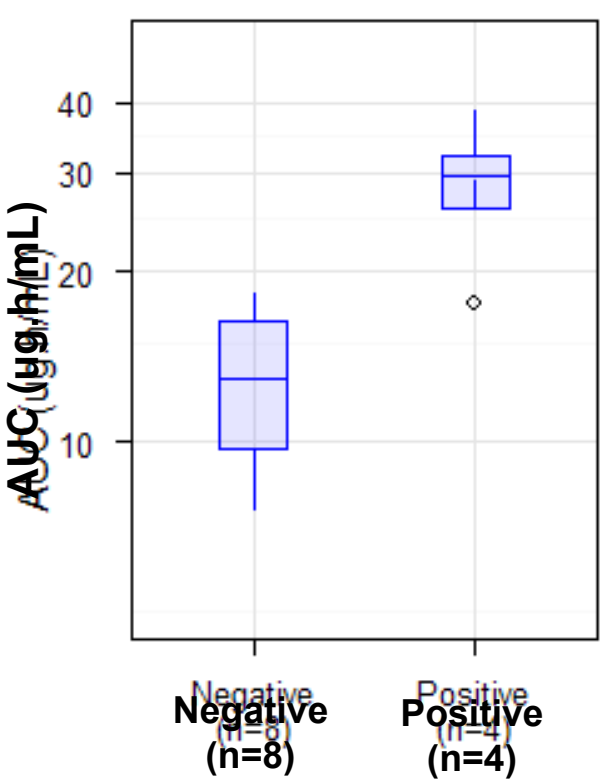
C125: Photosensitivity Trial Design

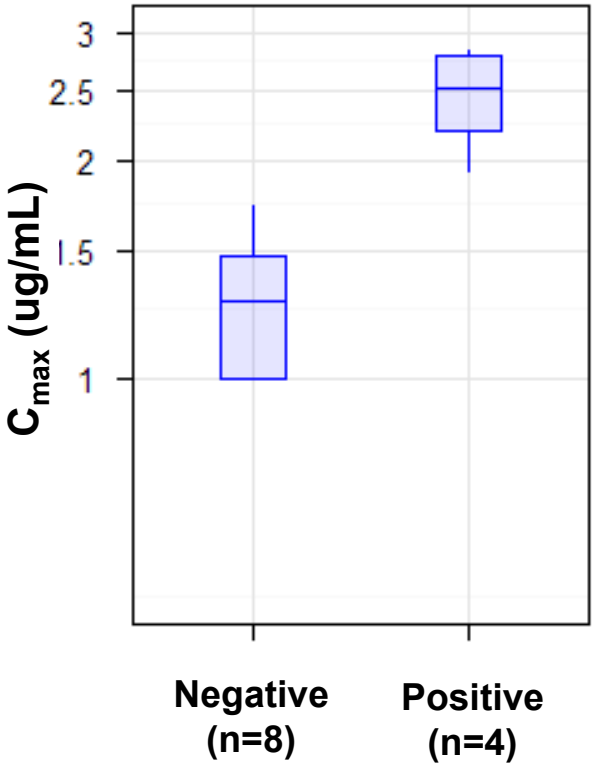
Two photosensitivity endpoints:

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



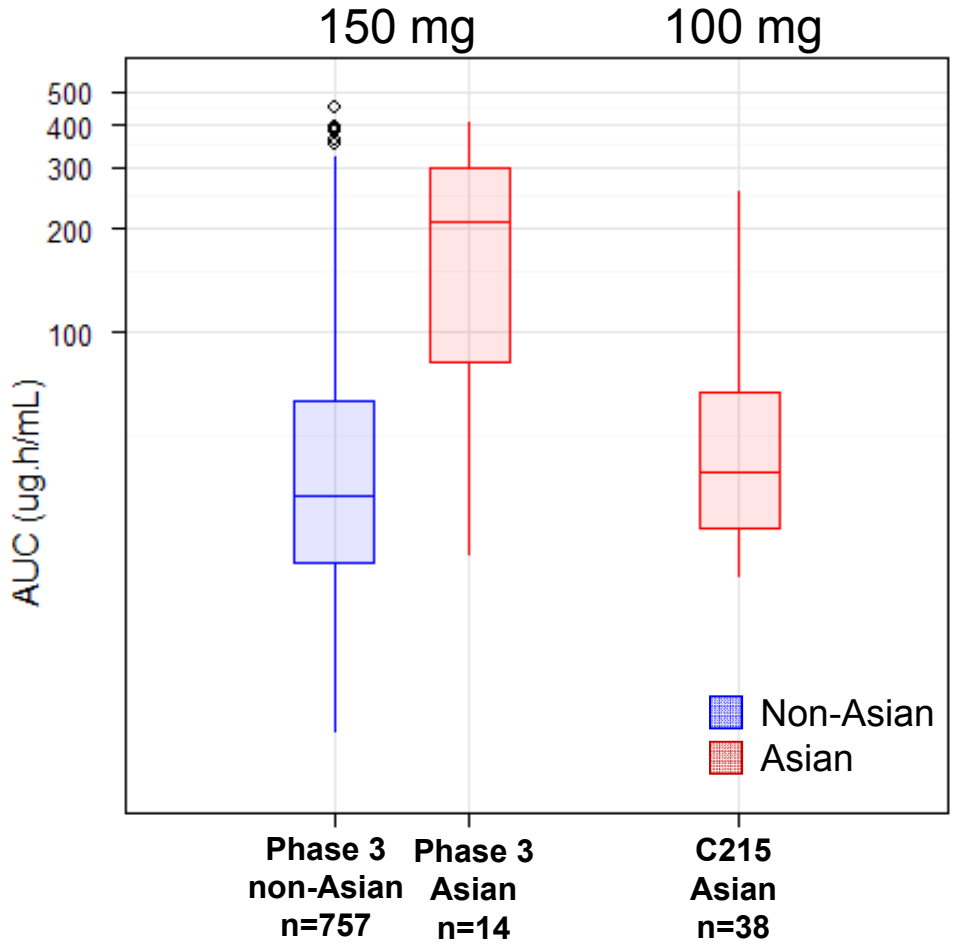
Photosensitivity Events were Associated with Higher Exposures in Healthy Subjects





Trial C125; endpoint: immediate photosensitivity response following controlled light exposures

Systemic Exposures were Higher in Asian Patients in Phase 3 trials



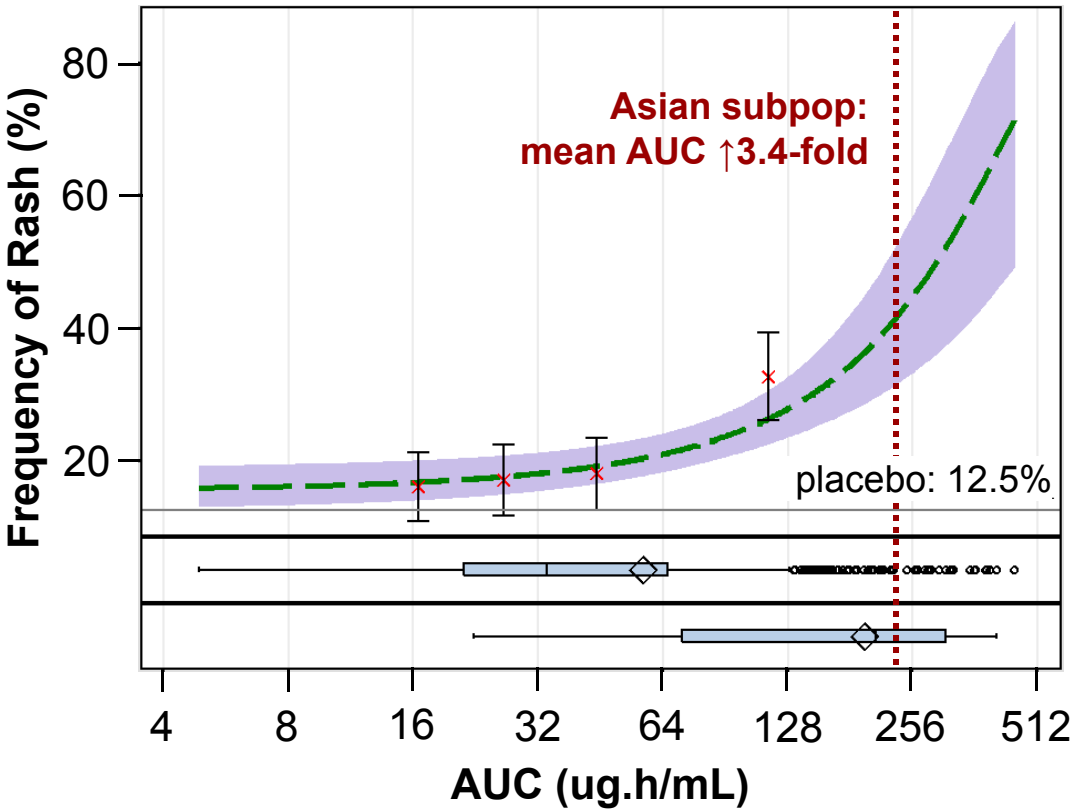
Relative to Caucasian subjects, Asian subjects have:

smaller liver
less CYP3A
less OATP1B1

slower clearance
higher exposure

Phase 3 trials (C208, C216, HPC3007); Yang et al. 2012, Tomita et al. 2013

There are Limited Safety Data to Support SMV 150 mg QD in Asian Patients

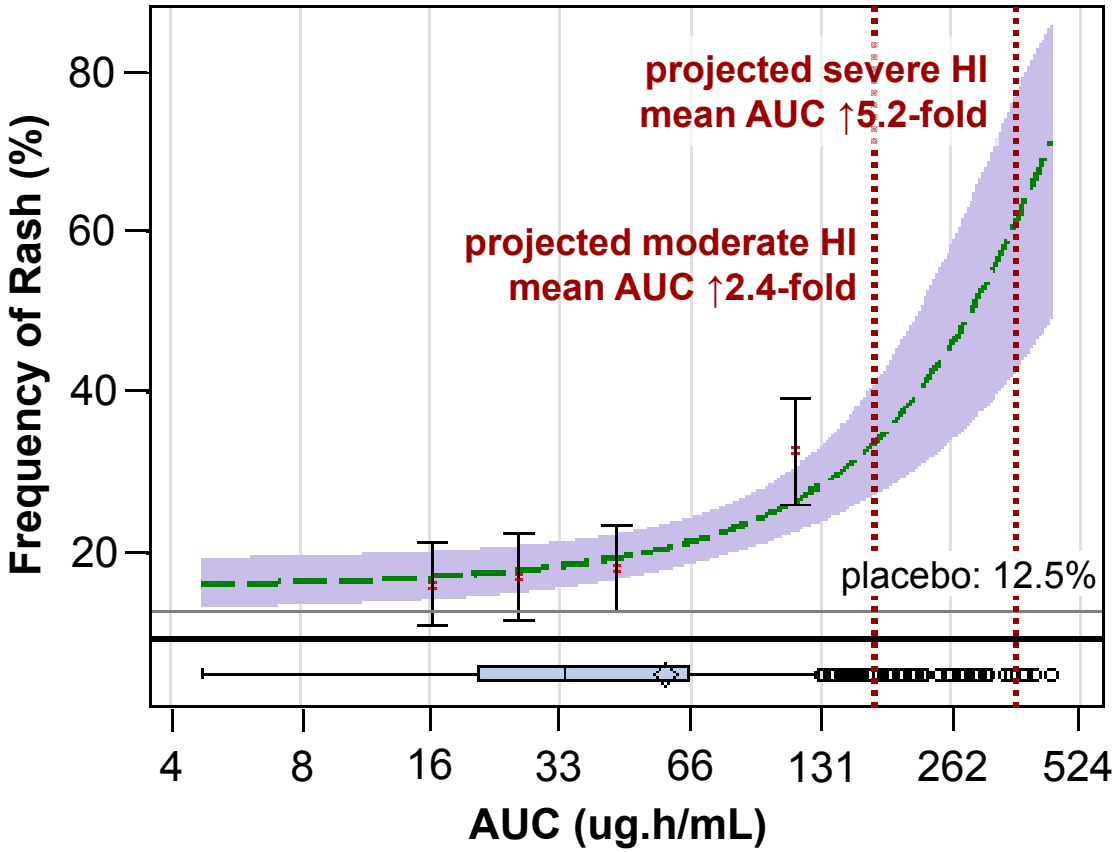


Phase 3 trials (C208, C216, HPC3007)

Unresolved Dosing Issue: Patients with East Asian Ancestry

- The Division recommends inclusion of the following in prescribing information
  - Higher exposures in patients with East Asian ancestry
  - Observed relationship between higher exposures and increased frequency of adverse events, including rash and photosensitivity
- Evaluation of simeprevir pharmacokinetics and identification of an appropriate dose is ongoing
  - In progress: simeprevir 150 or 100 mg QD in China and Korea
  - Approved: simeprevir 100 mg QD in Japan

HCV-Uninfected Subjects with Moderate or Severe Hepatic Impairment had Higher Exposures Compared to Healthy Controls



- PegIFN is contraindicated in Child-Pugh class B or C
- Simeprevir PK will be evaluated in patients with moderate or severe hepatic impairment during ongoing IFN-free development

Phase 3 trials (C208, C216, HPC3007)

Conclusions

- Simeprevir is a substrate of CYP3A – do not coadminister with moderate or strong CYP3A inducers or inhibitors
- Simeprevir inhibits OATP1B1/3 and intestinal CYP3A
- Systemic exposures increase supraproportionally
- Simeprevir exposures are higher in populations with lower amounts of CYP3A and/or OATP1B1/3:
  - HCV-infected patients
  - Patients with East Asian ancestry
  - Subjects with moderate or severe hepatic impairment
- The frequency of rash, photosensitivity, and other adverse events increases with higher systemic exposures

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Back-Up Slides Shown

Selected Pooled AEs of Interest
Asian Subjects, First 12 Weeks, Phase 3 Trials

Studies	C208, C216, HPC3007			
Treatment Period	First 12 Weeks			
Study Arm (Number of Subjects)	Simeprevir (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%)

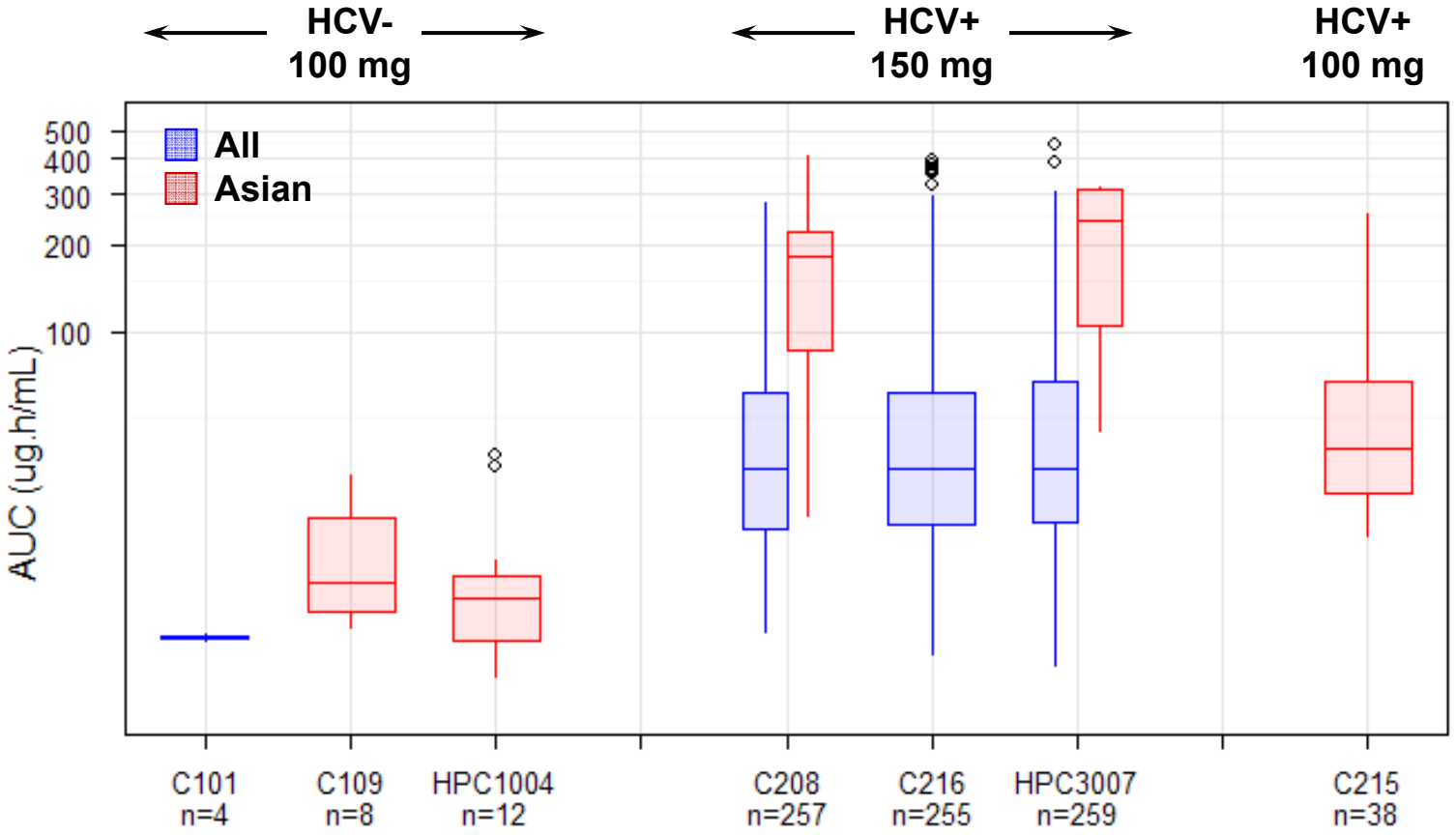
Suggested W&P for Photosensitivity (1)

- Photosensitivity reactions have been observed with TRADENAME in combination with peginterferon alfa and ribavirin, including serious reactions which resulted in hospitalization [see Adverse Reactions (6.1)]. Photosensitivity reactions occurred with greatest frequency during the first 4 weeks of treatment with TRADENAME in combination with peginterferon alfa and ribavirin, but can occur at any time during treatment. 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, and dorsa of the hands). Manifestations may include burning, erythema, exudation, blistering, and edema.

Suggested W&P for Photosensitivity (2)

- Avoid excess exposure to sun and use sun protective measures during treatment of TRADENAME in combination with peginterferon alfa and ribavirin. Avoid use of tanning devices during treatment of TRADENAME in combination with peginterferon alfa and ribavirin [see Patient Counseling Information, Photosensitivity (17.2)]. TRADENAME should be discontinued if a photosensitivity reaction occurs and patients should be monitored until the reaction has resolved.

Higher systemic exposures have been observed in Asians throughout development



Smaller liver size, decreased functional CYP3A and OATP1B1 contribute to lower clearance