CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206843Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 206843 (SDN 2)	Original Submission Date: March 29, 2014
NDA: 206843 (SDN 36)	Resubmission Date: February 13, 2015
Brand Name	Daklinza
Generic Name	Daclatasvir
Reviewer	Stanley Au, Pharm.D., BCPS
Clinical Pharmacology Team Leader	Shirley Seo, Ph.D.
Pharmacometrics Reviewer	Fang Li, Ph.D.
Pharmacometrics Team Leader	Jeffry Florian, Ph.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products
Applicant	Bristol Myers Squibb
Proposed U.S commercially marketed strength and formulation	30 and 60 mg tablets
Proposed dosage regimens	60 mg once daily
	30 mg once daily or 90 mg once daily with strong CYP3A inhibitors or moderate CYP3A inducers, respectively
Proposed Indication for the Application	Treatment of chronic hepatitis C infection
Review Type(s)	505 (b)(1) New Drug Application, Class 2 resubmission

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1   Executive Summary

The applicant, Bristol Myers Squib (BMS), resubmitted a 505(b)(1) New Drug Application (NDA) subsequent to a Complete Response (CR) letter that was issued by the Division of Antiviral Products on November 25, 2014. The CR letter was issued because there was insufficient information to establish the safety and efficacy of daclatasvir subsequent to the withdrawal of the asunaprevir NDA on October 6, 2014.

The resubmission contained the AI444218 trial (ALLY-3), a clinical trial that evaluated the combination of daclatasvir and sofosbuvir in genotype 3 chronic hepatitis C infected, treatment naïve or treatment experienced subjects. The trial evaluated the combination of daclatasvir 60 mg once daily plus sofosbuvir 400 mg once daily which was administered for 12 weeks. For the AI444218 trial, the administered daclatasvir and sofosbuvir formulations were the Phase 3 formulation and the U.S commercially marketed formulations, respectively.

With the exception of the pharmacometrics information for the AI444218 trial, including the population pharmacokinetic (PK) analysis, no new clinical pharmacology information was reviewed as part of the resubmission. For this review, the pharmacometrics review is included in section 3. Daclatasvir clinical pharmacology related review information is provided in the original submission (NDA 206843, SDN 2). The proposed revisions to the relevant clinical pharmacology sections of the proposed daclatasvir U.S. prescribing information are outlined in section 2.

1.1   Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the information in this NDA resubmission and the information provided supports the approval of the application.

1.2   Postmarketing Commitments or Requirements

There are no postmarketing commitments or requirements for this NDA.

2 Labeling Recommendations

(Note: the proposed daclatasvir U.S. prescribing information was not finalized at the time this review was completed)

Section 4

Applicant proposed language	Proposed review team changes
Table 1: Drugs that are Contraindicated with DAKLINZA **Table 1 contents:** 	Mechanism of Interaction	Clinical Comment	Drugs that are Contraindicated with DAKLINZA[a]
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Strong induction of CYP3A by coadministered drug	May lead to loss of virologic response to DAKLINZA	*Anticonvulsants* phenytoin, carbamazepine, (b) (4) *Antimycobacterial agents* rifampin, (b) (4) (b) (4) *Herbal products* St. John's wort (*Hypericum perforatum*) | [a] This table is not a comprehensive list of all drugs that strongly induce CYP3A	*Clinical pharmacology reviewer comment: For the examples of the strong CYP3A inducers, the specific medications were edited to be consistent with the list of strong CYP3A inducers that are included in the draft February 2012 guidance-Drug Interaction Studies-Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations or the available information in the respective U.S. prescribing information. The review team also proposes to shift dexamethasone and rifapentine to section 7, with both medications listed under moderate CYP3A inducers based on the available information in the respective U.S. prescribing information: a) the dexamethasone USPI states that dexamethasone is a moderate CYP3A inducer, and b) according to the rifapentine USPI, the AUC of indinavir, a sensitive CY3A substrate, was decreased by 70% with rifapentine twice weekly dosing.*

Table 1: Drugs that are Contraindicated with DAKLINZA

Mechanism of Interaction	Clinical Comment	Drugs that are Contraindicated with DAKLINZA[a]
Strong induction of CYP3A by coadministered drug	May lead to loss of virologic response to DAKLINZA	*Anticonvulsants* phenytoin, carbamazepine, *Antimycobacterial agents* rifampin *Herbal products* St. John's wort (*Hypericum perforatum*)

[a] This table is not a comprehensive list of all drugs that strongly induce CYP3A

Section 7

Applicant proposed language	Proposed review team changes
Table 3: Established and Other Potentially Significant Drug Interactions (b) (4)	*Clinical pharmacology reviewer comment:* (b) (4) *With the exception of ataznavir/ritonavir, the examples listed below are included in the draft February 2012 drug interaction guidance. Atazanavir/ritonavir was included as a strong CYP3A inhibitor in Table 3 based on the maraviroc drug-drug interaction data.* Table 3: Established and Other Potentially Significant Drug Interactions <table><tr><th>Concomitant Drug Class: Drug Name</th><th>Effect on Concentration[a]</th><th>Clinical Comment</th></tr><tr><td>**Strong CYP3A inhibitors** *atazanavir/ritonavir[b], clarithromycin, indinavir, itraconazole, ketoconazole[b], nefazodone, nelfinavir, posaconazole, saquinavir, telithromycin, voriconazole*</td><td>↑ Daclatasvir</td><td>Decrease DAKLINZA dose to 30 mg once daily when coadministered with strong inhibitors of CYP3A.</td></tr></table> [a] The direction of the arrow (↑ = increase, ↓ = decrease) indicates the direction of the change in pharmacokinetic parameters. [b] These interactions have been studied [*see Clinical Pharmacology (12.3, Table 6 and Table 7)*].

(b) (4)

Applicant proposed language	Proposed review team changes
(b) (4)	*Clinical pharmacology reviewer comment: The separate entries for erythromycin, dilatiazem, and verapamil should be deleted and combined into a single entry for moderate CYP3A inhibitors. The examples listed below are included in the draft February 2012 drug interaction guidance.* Table 3: Established and Other Potentially Significant Drug Interactions

Table 3: Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Comment
Moderate CYP3A inhibitors *atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, verapamil*	↑ Daclatasvir	Monitor for daclatasvir adverse events.

[a] The direction of the arrow (↑ = increase, ↓ = decrease) indicates the direction of the change in pharmacokinetic parameters.

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Applicant proposed language	Proposed review team changes
       (b) (4) 	Table 3: Established and Other Potentially Significant Drug Interactions *Clinical pharmacology reviewer note: the examples listed below are included in the draft February 2012 drug interaction guidance*

Table 3 (upper):

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Comment
Moderate CYP3A inducers *bosentan, efavirenz[b], etravirine, modafinil, nafcillin*	↓ Daclatasvir	Increase DAKLINZA dose to 90 mg once daily when coadministered with moderate inducers of CYP3A.

The direction of the arrow (↑ = increase, ↓ = decrease) indicates the direction of the change in pharmacokinetic parameters.

[b] These interactions have been studied [*see Clinical Pharmacology (12.3, Table 6 and Table 7)*].

<u>Review team changes to the table subsequent to the applicant's acceptance of review team changes for moderate CYP3A inducers</u>

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Comment
Moderate CYP3A inducers *bosentan, dexamethasone, efavirenz[b], etravirine, modafinil, nafcillin, rifapentine*	↓ Daclatasvir	Increase DAKLINZA dose to 90 mg once daily when coadministered with moderate inducers of CYP3A.

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	^a The direction of the arrow (↑ = increase, ↓ = decrease) indicates the direction of the change in pharmacokinetic parameters. ^b These interactions have been studied [*see Clinical Pharmacology (12.3, Table 6 and Table 7)*].

Applicant proposed language	Proposed review team changes

Applicant proposed language

Table 3: Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Comment
Anticoagulants		
Dabigatran etexilate mesylate	↑ Dabigatran	(b) (4)

[a] The direction of the arrow (↑ = increase, ↓ = decrease) indicates the direction of the change in pharmacokinetic parameters.

Proposed review team changes

Table 3: Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Comment
Anticoagulants		
Dabigatran etexilate mesylate	↑ Dabigatran	Use of DAKLINZA with dabigatran etexilate is not recommended in specific renal impairment groups, depending on the indication. Please see the dabigatran U.S. prescribing information for specific recommendations.

[a] The direction of the arrow (↑ = increase, ↓ = decrease) indicates the direction of the change in pharmacokinetic parameters.

Applicant proposed language	Proposed review team changes
Table 3: Established and Other Potentially Significant Drug Interactions	Table 3: Established and Other Potentially Significant Drug Interactions

Applicant proposed language

Table 3: Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Comment
Cardiovascular agents		
Antiarrhythmic: Amiodarone	(b) (4)	(b) (4)

[a] The direction of the arrow (↑ = increase, ↓ = decrease) indicates the direction of the change in pharmacokinetic parameters.

Proposed review team changes

Table 3: Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Comment
Cardiovascular agents		
Antiarrhythmic: Amiodarone	Amiodarone: effects unknown.	Coadministration of amiodarone with DAKLINZA in combination with sofosbuvir is not recommended because it may result in serious symptomatic bradycardia. The mechanism of this effect is unknown. If coadministration is required, cardiac monitoring is recommended [*See Warnings and Precautions (5.2) and Adverse Reactions (6.2).*]

[a] The direction of the arrow (↑ = increase, ↓ = decrease) indicates the direction of the change in pharmacokinetic parameters.

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Applicant proposed language	Proposed review team changes
Table 3: Established and Other Potentially Significant Drug Interactions	Table 3: Established and Other Potentially Significant Drug Interactions

Applicant proposed language

Table 3: Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Comment
Cardiovascular agents		
Antiarrhythmic: Digoxin[b]	↑ Digoxin	(b) (4)

[a] The direction of the arrow (↑ = increase, ↓ = decrease) indicates the direction of the change in pharmacokinetic parameters.

[b] These interactions have been studied [*see Clinical Pharmacology (12.3, Table 6 and Table 7)*].

Proposed review team changes

Table 3: Established and Other Potentially Significant Drug Interactions

Clinical pharmacology reviewer comment: In the U.S prescribing information for digoxin, for drug-drug interactions resulting in an increase in digoxin concentrations greater than 50%, the recommendation states:
Measure serum digoxin concentrations before initiating concomitant drugs. Reduce digoxin concentrations by decreasing dose by approximately 30-50% or by modifying the dosing frequency and continue monitoring.

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Comment
Cardiovascular agents		
Antiarrhythmic: Digoxin[b]	↑ Digoxin	Patients already receiving daclatasvir initiating digoxin: Initiate treatment using the lowest appropriate digoxin dosage. Monitor digoxin concentrations; adjust digoxin doses if necessary and continue monitoring. Patients already receiving digoxin prior to initiating daclatasvir: Measure serum digoxin concentrations before initiating daclatasvir. Reduce

			digoxin concentrations by decreasing dosage by approximately 30-50% or by modifying the dosing frequency and continue monitoring.

[a] The direction of the arrow (↑ = increase, ↓ = decrease) indicates the direction of the change in pharmacokinetic parameters.

[b] These interactions have been studied [*see Clinical Pharmacology (12.3, Table 6 and Table 7)*].

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Applicant proposed language	Proposed review team changes

Table 3: Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Comment
Lipid-lowering agents		
HMG-CoA reductase inhibitors: Rosuvastatin[b] Atorvastatin Fluvastatin Pitavastatin Pravastatin Simvastatin	↑ Rosuvastatin ↑ Atorvastatin ↑ Fluvastatin ↑ Pitavastatin ↑ Pravastatin ↑ Simvastatin	(b) (4)

[a] The direction of the arrow (↑ = increase, ↓ = decrease) indicates the direction of the change in pharmacokinetic parameters.
[b] These interactions have been studied [*see Clinical Pharmacology (12.3, Table 6 and Table 7)*].

Table 3: Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	Effect on Concentration[a]	Clinical Comment
Lipid-lowering agents		
HMG-CoA reductase inhibitors: Atorvastatin Fluvastatin Pitavastatin Pravastatin Rosuvastatin[b] Simvastatin	↑ Rosuvastatin ↑ Atorvastatin ↑ Fluvastatin ↑ Pitavastatin ↑ Pravastatin ↑ Simvastatin	Monitor for HMG-CoA reductase inhibitor associated adverse events such as myopathy.

[a] The direction of the arrow (↑ = increase, ↓ = decrease) indicates the direction of the change in pharmacokinetic parameters.
[b] These interactions have been studied [*see Clinical Pharmacology (12.3, Table 6 and Table 7)*].

Applicant proposed language	Proposed review team changes
Section 7.4-Other Drugs *Drugs without Clinically Significant Interactions with DAKLINZA* Based on the results of drug interaction trials [*see Clinical Pharmacology (12.3)*], no clinically relevant changes in exposure were observed for ▓▓ (b) (4) cyclosporine, escitalopram, ▓▓ (b) (4) methadone, midazolam, ▓▓ (b) (4) tacrolimus, or tenofovir. No clinically relevant interaction (b) (4) ▓▓	<u>Original review team recommendations and comments</u> *Section 7.4 was shifted to section 12.3. Additionally, the list of medications was edited to include only medications that were evaluated in drug-drug interaction trials. The information in sections 7.1 and 7.2 provides sufficient guidance to clinicians regarding medications that would be anticipated not to interact with daclatasvir or vice versa based on mechanistic considerations and deleting the list avoids ambiguity regarding the rationale for listing medications that were not evaluated in drug-drug interaction trials.* ▓▓ (b) (4) *Drugs without Clinically Significant Interactions with DAKLINZA* Based on the results of drug interaction trials, no clinically relevant changes in exposure were observed for cyclosporine, escitalopram, ethinyl estradiol/norgestimate, methadone, midazolam, tacrolimus, or tenofovir with concomitant use of daclatasvir. No clinically relevant changes in daclatasvir exposure were observed with cyclosporine, escitalopram, famotidine, omeprazole, tacrolimus, or tenofovir.

	<u>Review team edits and comments subsequent to applicant's request to retain list of medications and in section 7</u>

The retention of this information in section 7 was acceptable.

Any medications that are listed in the USPI that are predicted to either not interact with daclatasvir or vice versa should be based on the entire drug-drug interaction profile that includes not only cytochrome P450 mediated interactions but also transporter based interactions. Therefore DAVP has edited the list to only include medications where data currently exists that supports the lack of a predicted interaction (if data [e.g. transporter info] is not available to make a determination, the medication was also excluded).

The inclusion of peginterferon alfa, ribavirin, or antacids was considered acceptable based on the available supportive information that was included as part of the original DCV NDA submission.

Drugs without Clinically Significant Interactions with DAKLINZA

Based on the results of drug interaction trials [*see Clinical Pharmacology (12.3)*], no clinically relevant changes in exposure were observed for cyclosporine, escitalopram, ethinyl estradiol/norgestimate, methadone, midazolam, tacrolimus, or tenofovir with concomitant use of daclatasvir. No clinically relevant changes in daclatasvir exposure were observed with cyclosporine, escitalopram, famotidine, omeprazole, sofosbuvir, tacrolimus, or tenofovir. No clinically relevant interaction is anticipated for daclatasvir or the following concomitant medications: peginterferon alfa, ribavirin, or antacids. |

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Section 12.2-Pharmacodynamics

Applicant proposed language	Proposed review team changes
Cardiac Electrophysiology (b) (4)	Cardiac Electrophysiology At a dose 3 times the maximum recommended dose, daclatasvir does not prolong the QT interval to any clinically relevant extent.

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Section 12.3-Pharmacokinetics

Applicant proposed language	Proposed review team changes (text changes are highlighted)
The pharmacokinetic properties of daclatasvir were evaluated in healthy adult subjects and in subjects with chronic HCV. (b) (4) [redacted] Administration of daclatasvir tablets in HCV-infected subjects resulted in approximately dose-proportional increases in C_{max}, AUC, and C_{min} up to 60 mg once daily. Steady state [redacted] (b) (4) after 4 days of once-daily administration. Exposure of daclatasvir [redacted] (b) (4) HCV-infected subjects.	Clinical pharmacology reviewer note: *Based on the long term stability data referenced under method validation report TNJR11-132, the generated long term stability data appears to cover the duration of long term stability data necessary for daclatasvir from the AI444218 trial.* The pharmacokinetic properties of daclatasvir were evaluated in healthy adult subjects and in subjects with chronic HCV. Administration of daclatasvir tablets in HCV-infected subjects resulted in approximately dose-proportional increases in C_{max}, AUC, and C_{min} up to 60 mg once daily. Steady state is ==anticipated== after ==approximately== 4 days of once-daily ==daclatasvir== administration. Exposure of daclatasvir was similar between healthy and HCV-infected subjects. **Table X: Population Pharmacokinetic Estimates for Daclatasvir 60 mg Once Daily in Chronic Hepatitis C Infected Subjects Receiving Daclatasvir 60 mg Once Daily and Sofosbuvir 400 mg Once Daily**

Parameters	Daclatasvir 60 mg once daily (N=152)
AUC_{0-24h} (ng.h/mL)	
Mean ± standard deviation	10973 ± 5288
Median (range)	9680 (3807-41243)

C_{24h} (ng/mL)		
Mean ± standard deviation	182 ± 137	
Median (range)	148(21-1050)	

Applicant proposed language	Proposed review team changes
Absorption and Bioavailability In HCV-infected subjects following multiple oral doses of daclatasvir tablet ranging from 1 mg to 100 mg once daily, peak plasma concentrations occurred ⬜ (b) (4) 2 hours post dose. *In vitro* studies with human Caco-2 cells indicated that daclatasvir is a substrate of P-gp. The absolute bioavailability of the tablet formulation is 67%.	**Absorption and Bioavailability** In HCV-infected subjects following multiple oral doses of daclatasvir tablet ranging from 1 mg to 100 mg once daily, peak plasma concentrations occurred within 2 hours post dose. *In vitro* studies with human Caco-2 cells indicated that daclatasvir is a substrate of P-gp. The absolute bioavailability of the tablet formulation is 67%.

Applicant proposed language	Proposed review team changes (changes are highlighted)
Effect of Food on Oral Absorption In healthy subjects, administration of a daclatasvir 60 mg tablet after a high-fat, high-caloric meal (951 total kcal) decreased daclatasvir C_{max} and $AUC_{(0\text{-}inf)}$ by 28% and 23%, respectively, compared with fasted conditions. Administration of a daclatasvir 60 mg tablet after a low-fat, low-caloric meal (277 total kcal) ⬜ (b) (4) compared with fasted conditions [*see Dosage and Administration (2)*].	*Clinical pharmacology reviewer comment: the breakdown of the calories for the specified meal was added, consistent with the current recommendations for section 12 labeling.* **Effect of Food on Oral Absorption** In healthy subjects, administration of a daclatasvir 60 mg tablet after a high-fat, high-caloric meal (approximately 951 total kcal, 492 kcal from fat, 312 kcal from carbohydrates, 144 kcal from protein) decreased daclatasvir C_{max} and $AUC_{(0\text{-}inf)}$ by 28% and 23%, respectively, compared with fasted conditions. A food effect was not observed with administration of a daclatasvir 60 mg tablet after a low-fat, low-caloric meal (approximately 277 total kcal, 41 kcal from fat, 190 kcal from carbohydrates, 44 kcal from protein) compared with fasted conditions [*see Dosage and Administration (2)*].

Applicant proposed language	Proposed reviewer changes (changes are highlighted)
Distribution Protein binding of daclatasvir in HCV-infected subjects was approximately 99% and independent of dose at the dose range studied (1-100 mg). In subjects who received daclatasvir 60 mg tablet orally followed by 100 μg [^{13}C,^{15}N]-daclatasvir intravenous dose, estimated volume of distribution at steady state was 47.1 L.	**Distribution** ==With multiple dosing==, protein binding of daclatasvir in HCV-infected subjects was approximately 99% and independent of dose at the dose range studied (1-100 mg). In subjects who received daclatasvir 60 mg tablet orally followed by 100 μg [^{13}C,^{15}N]-daclatasvir intravenous dose, estimated volume of distribution at steady state was 47 L.

Applicant proposed language	Proposed review team changes (changes are highlighted)
Metabolism _____ (b) (4) daclatasvir is a substrate of CYP3A, with CYP3A4 being the primary CYP isoform responsible for metabolism. Following single-dose oral administration of 25 mg ^{14}C-daclatasvir in healthy subjects, the majority of radioactivity in plasma was predominately attributed to parent drug ((b) (4) % or greater).	**Metabolism** ==Daclatasvir== is a substrate of CYP3A, with CYP3A4 being the primary CYP isoform responsible for metabolism. Following single-dose oral administration of 25 mg ^{14}C-daclatasvir in healthy subjects, the majority of radioactivity in plasma was predominately attributed to parent drug (==97%== or greater).

Applicant proposed language	Proposed review team changes (changes are highlighted)
Elimination Following single-dose oral administration of 25 mg ^{14}C-daclatasvir in healthy subjects, 88% of total radioactivity was recovered in feces (53% of the dose as unchanged (b) (4)) and 6.6% of the dose was excreted in the urine (primarily as unchanged (b) (4)). Following multiple-dose administration of daclatasvir in HCV-infected subjects, with doses ranging from 1 mg to 100 mg once daily, the terminal elimination half-life of daclatasvir ranged from approximately 12 to 15 hours. In subjects who received daclatasvir 60 mg tablet orally followed by 100 µg [^{13}C,^{15}N]-daclatasvir intravenous dose, the total clearance was 4.24 L/h.	**Elimination** Following single-dose oral administration of 25 mg ^{14}C-daclatasvir in healthy subjects, 88% of total radioactivity was recovered in feces (53% of the dose as unchanged daclatasvir) and 6.6% of the dose was excreted in the urine (primarily as unchanged daclatasvir). Following multiple-dose administration of daclatasvir in HCV-infected subjects, with doses ranging from 1 mg to 100 mg once daily, the terminal elimination half-life of daclatasvir ranged from approximately 12 to 15 hours. In subjects who received daclatasvir 60 mg tablet orally followed by 100 µg [^{13}C,^{15}N]-daclatasvir intravenous dose, the total clearance was 4.2 L/h.

Applicant proposed language	Proposed review team changes (changes are highlighted)
Specific Populations *Renal Impairment* The pharmacokinetics of daclatasvir following a single 60 mg oral dose was studied in non–HCV-infected subjects with renal impairment. Using a regression analysis, the predicted $AUC_{(0\text{-}inf)}$ of daclatasvir was estimated to be $26^{(b)}_{(4)}$%, $^{(b)(4)}$%, and $^{(b)(4)}$% higher in subjects with creatinine clearance (CLcr) values of 60, 30, and 15 mL/min, respectively, relative to subjects with normal renal function (CLcr of 90 mL/min, defined using the Cockcroft-Gault CLcr formula) $^{(b)(4)}$ daclatasvir unbound $AUC_{(0\text{-}inf)}$ was predicted to be $18^{(b)}_{(4)}$%, $39^{(b)}_{(4)}$% and $51^{(b)}_{(4)}$% higher for subjects with CLcr values of 60, 30 and 15 mL/min, respectively, relative to subjects with normal renal function. Using observed data, subjects with end-stage renal disease requiring hemodialysis had a $^{(b)(4)}$% increase in daclatasvir $AUC_{(0\text{-}inf)}$ and a $20^{(b)}_{(4)}$% increase in unbound $AUC_{(0\text{-}inf)}$ compared to subjects with normal renal function. [*See Use in Specific Populations (8.6).*] Daclatasvir is highly protein bound to plasma proteins and is unlikely to be removed by dialysis.	*Clinical Pharmacology reviewer comment: The unbound concentrations referenced in the applicant's original proposed language were analyzed using a partially validated LC/MS/MS method in EDTA anticoagulated plasma by* $^{(b)(4)}$ *(TNJM08147.00). Based on the long term stability data referenced in another method validated under study number TNJS07-177a, the generated long term stability data appears to cover the duration of long term stability data necessary for daclatasvir unbound concentrations from the AI444063 trial (no specific information was provided regarding whether fresh calibration standards were used for the long term stability experiments).* Original review team recommendation **Specific Populations** *Renal Impairment* The pharmacokinetics of daclatasvir following a single 60 mg oral dose was studied in non–HCV-infected subjects with renal impairment. Using a regression analysis, the predicted $AUC_{(0\text{-}inf)}$ of daclatasvir was estimated to be 26%, 60%, and 80% higher in subjects with creatinine clearance (CLcr) values of 60, 30, and 15 mL/min, respectively, relative to subjects with normal renal function (CLcr of 90 mL/min, defined using the Cockcroft-Gault CLcr formula). Using observed data, subjects with end-stage renal disease requiring hemodialysis had a 27% increase in daclatasvir $AUC_{(0\text{-}inf)}$ compared to subjects with normal renal function as defined using the Cockcroft-Gault CLcr formula [*See Use in Specific Populations (8.6).*] Daclatasvir is highly protein bound to plasma proteins and is unlikely to

	be removed by dialysis.
	Review team comments subsequent to applicant's request to retain unbound daclatasvir data
	The retention of unbound daclatasvir data was acceptable.

Applicant proposed language	Proposed review team changes (changes are highlighted)
Specific Populations *Hepatic Impairment* The pharmacokinetics of daclatasvir following a single 30 mg oral dose was studied in non–HCV-infected subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment compared to a corresponding matched control group. The C_{max} and $AUC_{(0-inf)}$ of total daclatasvir (free and protein-bound drug) were lower by (b)(4)% and (b)(4)%, respectively, in Child-Pugh A subjects; by 45(b)(4)% and (b)(4)%, respectively, in Child-Pugh B subjects; and by (b)(4)% and 36(b)(4)%, respectively, in Child-Pugh C subjects. The C_{max} and $AUC_{(0-inf)}$ of unbound daclatasvir were lower by 43(b)(4)% and (b)(4)%, respectively, in Child-Pugh A subjects; by 14(b)(4)% and (b)(4)%, respectively, in Child-Pugh B subjects; and by (b)(4)% and 5(b)(4)%, respectively, in Child-Pugh C subjects [*see Use in Specific Populations (8.7)*].	*Clinical Pharmacology reviewer comment: The magnitude of change in unbound daclatasvir concentrations in the daclatasvir hepatic impairment trial (AI444013) is summarized below.* *The unbound concentrations were analyzed using a partially validated LC/MS/MS method in EDTA anticoagulated plasma by (b)(4) (TNJM08147.00). Based on the long term stability data referenced in another method validated under study number TNJS07-177a, the generated long term stability data appears to cover the duration of long term stability data necessary for daclatasvir unbound concentrations from the AI444013 trial (no specific information was provided regarding whether fresh calibration standards were used for the long term stability experiments).*

Treatment and Comparison	$Cmax_u$ (ng/mL) Adjusted Geo.Mean	AUC(INF)$_u$ (ng•h/mL) Adjusted Geo.Mean
A	2.33	25.6
Control	4.06	42.4
	GMR(90% CI)	GMR(90% CI)
A vs. Control	0.574 (0.399,0.825)	0.604(0.402,0.908)
B	3.49	41.6
Control	4.06	42.4
	GMR(90% CI)	GMR(90% CI)
B vs. Control	0.860(0.639,1.156)	0.981(0.699,1.376)
C	2.73	40.1
Control	4.06	42.4
	GMR(90% CI)	GMR(90% CI)
C vs. Control	0.674(0.448,1.013)	0.946(0.607,1.474)
(A+B+C)	2.81	34.9
Control	4.06	42.4
	GMR(90% CI)	GMR(90% CI)
(A+B+C) vs. Control	0.693(0.507,0.947)	0.824(0.583,1.166)

A: Child-Pugh A hepatically-impaired subjects; B: Child-Pugh B hepatically-impaired subjects; C: Child-Pugh C hepatically-impaired subjects; Control: healthy subjects/normal hepatic function

Specific Populations

Hepatic Impairment

The pharmacokinetics of daclatasvir following a single 30 mg oral dose was studied in non–HCV-infected subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment compared to a corresponding matched control group. The C_{max} and $AUC_{(0-inf)}$ of total daclatasvir (free and protein-bound drug) were lower by 46% and 43%, respectively, in Child-Pugh A subjects; by 45% and 38%, respectively, in Child-Pugh B subjects; and by 55% and 36%, respectively, in Child-Pugh C subjects. The C_{max} and $AUC_{(0-inf)}$ of unbound daclatasvir were lower by 43% and 40%, respectively, in Child-Pugh A subjects; by 14% and 2%, respectively, in Child-Pugh B subjects; and by 33% and 5%, respectively, in Child-Pugh C subjects [*see Use in Specific Populations (8.7)*].

Applicant proposed language	Proposed review team changes
Specific Populations *Gender* Population pharmacokinetic analyses in HCV-infected subjects (b) (4)	**Specific Populations** *Gender* Population pharmacokinetic analyses in HCV-infected subjects estimated female subjects have a 30% higher daclatasvir AUC compared to male subjects. This difference in daclatasvir AUC is not considered clinically relevant.

Applicant proposed language	Proposed review team changes (changes highlighted)
Drug Interactions *Transporters* Daclatasvir is a substrate of P-gp. However, cyclosporine, which inhibits multiple transporters including P-gp, did not have a clinically relevant effect on the pharmacokinetics of daclatasvir. Daclatasvir, *in vitro*, did not inhibit organic cation transporter (OCT) 2 and did not have a clinically relevant effect on the pharmacokinetics of tenofovir, a substrate of organic anion transporters (OAT) ^{(b) (4)}. Daclatasvir demonstrated inhibitory effects on digoxin (a P-gp substrate) and rosuvastatin (an OATP 1B1, OATP 1B3, and BCRP substrate) in drug-drug interaction trials.	**Drug Interactions** *Transporters* Daclatasvir is a substrate of P-gp. However, cyclosporine, which inhibits multiple transporters including P-gp, did not have a clinically relevant effect on the pharmacokinetics of daclatasvir. Daclatasvir, *in vitro*, did not inhibit organic cation transporter (OCT) 2 and did not have a clinically relevant effect on the pharmacokinetics of tenofovir, an organic anion transporter (OAT) substrate. Daclatasvir demonstrated inhibitory effects on digoxin (a P-gp substrate) and rosuvastatin (an OATP 1B1, OATP 1B3, and BCRP substrate) in drug-drug interaction trials.

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Applicant proposed language	Proposed review team changes
Table 4:-Effect of DAKLINZA on the Pharmacokinetics of Concomitant Drugs	*Clinical Pharmacology reviewer comment: in Table 4, for certain concomitant medications, the drug-drug interaction data was recommended for deletion since the 90% CIs for C_{max}, AUC, and C_{min} were within 80% to 125%.*

Table 4:-Effect of DAKLINZA on the Pharmacokinetics of Concomitant Drugs

Concomitant Drug	Co administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min} [a]
Cyclosporine	400 mg single dose	60 mg QD			(b) (4)

Concomitant Drug	Co administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min} [a]
Escitalopram	10 mg QD	60 mg QD			(b) (4)

Concomitant Drug	Co administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min} [a]
					(b) (4)

Concomitant Drug	Co administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min} [a]
					(b) (4)

Concomitant Drug	Co administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}[a]
					(b) (4)

Concomitant Drug	Co administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}[a]
					(b) (4)
Tenofovir disoproxil fumarate	300 mg QD	60 mg QD			

[a] C_{min} was defined as either the C_{tau} or the C_{trough} concentration value.

Applicant proposed language	Proposed review team changes

Applicant proposed language

Table 5:Effect of Coadministered Drugs on DAKLINZA Pharmacokinetics

Concomitant Drug	Co administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min} [a]
Atazanavir/ ritonavir	300 mg/100 mg QD	20 mg QD, (b) (4)			(b) (4)

Concomitant Drug	Co administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min} [a]
Efavirenz	600 mg QD	120 mg QD, (b) (4)	1.67 (1.51, 1.84)	1.37 (1.21, 1.55)	0.83 (0.69, 1.00)
					(b) (4)

[a] C_{min} was defined as either the C_{tau} or the C_{trough} concentration value.

Proposed review team changes

Clinical pharmacology reviewer note: The data for daclatasvir was revised to display non dose normalized data only because dose proportionality for daclatasvir could not be definitely concluded.

Table 5:Effect of Coadministered Drugs on DAKLINZA Pharmacokinetics

Concomitant Drug	Co administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min} [a]
Atazanavir/ ritonavir	300 mg/100 mg QD	60 mg once daily (reference arm) 20 mg once daily (test arm)	*Non dose normalized* 0.45 (0.41, 0.49)	0.70 (0.65, 0.75)	1.22 (1.08, 1.37)

Concomitant Drug	Co administered Drug Dose	<TRADE -NAME- DCV> Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}^{a}
Efavirenz	600 mg once daily	60 mg once daily (reference arm) 120 mg once daily (test arm)	*Non dose normalized* 1.67 (1.51, 1.84,	1.37 (1.21, 1.55)	0.83 (0.69, 1.00)

[a] C_{min} was defined as either the C_{tau} or the C_{trough} concentration value.

Applicant proposed language	Proposed review team changes (changes highlighted)
Table 5:Effect of Coadministered Drugs on DAKLINZA Pharmacokinetics	Table 5:Effect of Coadministered Drugs on DAKLINZA Pharmacokinetics

Applicant proposed language

Table 5:Effect of Coadministered Drugs on DAKLINZA Pharmacokinetics

Concomitant Drug	Co administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}[a]
Famotidine	40 mg single dose	60 mg single dose	0.56 (0.46, 0.67)	0.82 (0.70, 0.96)	0.89 (0.75, 1.06)

[a] C_{min} was defined as either the C_{tau} or the C_{trough} concentration value

Proposed review team changes (changes highlighted)

Table 5:Effect of Coadministered Drugs on DAKLINZA Pharmacokinetics

Concomitant Drug	Co administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}[a]
Famotidine	40 mg single dose	60 mg single dose (2 hours after famotidine administration)	0.56 (0.46, 0.67)	0.82 (0.70, 0.96)	0.89 (0.75, 1.06)

[a] C_{min} was defined as either the C_{tau} or the C_{trough} concentration value

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Applicant proposed language	Proposed review team changes (changes highlighted)
Table 5:Effect of Coadministered Drugs on DAKLINZA Pharmacokinetics	Table 5:Effect of Coadministered Drugs on DAKLINZA Pharmacokinetics

Applicant proposed language

Table 5:Effect of Coadministered Drugs on DAKLINZA Pharmacokinetics

Concomitant Drug	Co administered Drug Dose	\<TRADE-NAME-DCV\> Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}[a]
Omeprazole	40 mg QD	60 mg single dose	0.64 (0.54, 0.77)	0.84 (0.73, 0.96)	0.92 (0.80, 1.05)

[a] C_{min} was defined as either the C_{tau} or the C_{trough} concentration value

Proposed review team changes (changes highlighted)

Table 5:Effect of Coadministered Drugs on DAKLINZA Pharmacokinetics

Concomitant Drug	Co administered Drug Dose	\<TRADE-NAME-DCV\> Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}[a]
Omeprazole	40 mg single dose	60 mg single dose	0.64 (0.54, 0.77)	0.84 (0.73, 0.96)	0.92 (0.80, 1.05)

[a] C_{min} was defined as either the C_{tau} or the C_{trough} concentration value

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Applicant proposed language	Proposed review team changes
Table 5:Effect of Coadministered Drugs on DAKLINZA Pharmacokinetics	*Clinical pharmacology reviewer comment: in Table 5, for concomitant use of daclatasvir* (b) (4)

Concomitant Drug	Co administered Drug Dose	\<TRADE-NAME-DCV\> Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min} [a] (b) (4)

C_{min} was defined as either the C_{tau} or the C_{trough} concentration value

Patient prescribing information

Applicant proposed changes	Proposed review team changes
	(b) (4)

Applicant proposed changes	Proposed review team changes
	(b) (4)

3   Pharmacometrics review

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

NDA	206843 (SDN36)
Submission Date	February 13, 2015
Brand Name	DAKLINZA
Generic Name	Daclatasvir
Applicant	Bristol-Myers Squibb
Submission Type	Complete Response Resubmission
Formulation	Tablet 30 mg, 60 mg
Indication	For the treatment of chronic HCV genotype 3 infection (b) (4) in adults.
OCP Division	Division of Clinical Pharmacology IV
OND Division	DAVP
OCP Reviewer	Stanley Au, Pharm.D.
PM Reviewer	Fang Li, Ph.D.
OCP Team Leader	Shirley Seo, Ph.D.
PM Team Leader	Jeffry Florian, Ph.D.

1   SUMMARY OF FINDINGS

1.1   Key Review Questions

The purpose of this review is to address the following key questions:

1.1.1   What covariates significantly influence daclatasvir pharmacokinetics and are any dose adjustments necessary based on these changes?

Several covariates such as body weight, sex, and baseline creatinine clearance were identified to have significant impact on daclatasvir pharmacokinetics and exposure. Of note, female subjects were estimated to have a 25% lower clearance and a 31% higher AUC relative to male subjects. However, the higher AUC is considered not clinically significant. All of the other factors that were evaluated, such as age, race and cirrhosis, had less effect on daclatasvir exposure, and these changes in exposure were also considered to be not clinically relevant.

In applicant's updated population PK analysis for daclatasvir, data from 12 clinical studies were combined. The final population PK dataset has a total of 20615 quantifiable plasma concentrations from 2301 HCV-infected subjects, including 1080 additional PK samples from all 152 subjects in study AI444218 who were treated with daclatasvir 60 mg QD and SOF 400 mg QD. The model structure and covariates in the updated model

were the same as the previous model with the exception of including sofosbuvir treatment as a covariate on CL/F and F. Daclatasvir PK in HCV-infected subjects was described by a two-compartment model, with absorption modeled as a zero-order release followed by first-order absorption into the central compartment. PK parameter estimates were of no significant difference with the previous model. Identified covariates that affect daclatasvir exposure were the same as identified in the previous analysis (Clinical Pharmacology Review for daclatasvir, NDA 206843, SDN 2).

The applicant's updated model was assessed by the FDA reviewer. The model is adequate and deemed acceptable for describing the observed exposures from the studies included in the analysis. The reviewer's analysis of covariates effect on daclatasvir PK was similar to that of the applicant. The effects of sex, race, body weight, and some other laboratory parameters on daclatasvir clearance (CL/F) are presented in Figure 1.

Covariates of interest that may affect daclatasvir exposure include race, body weight, and age. Black subjects have 13% higher AUC than white subjects. Subjects >=65 years old have 10.5% higher AUC than those < 65 years old. All of these differences were in the range of 80-125% and were not considered clinically significant. Therefore, no dose adjustments based on race, age were necessary.

Female subjects were estimated to have a 25% lower clearance and a 31% higher AUC relative to male subjects. This exposure change was investigated further as female subjects were also observed to have a higher SVR12 rate (93.6%) than male subjects (85.6%) in study AI444218 who were infected with HCV genotype 3. However, the observed difference in SVR12 rate may also be confounded by baseline cirrhosis status instead of exposure. The SVR12 rate was much lower in cirrhotic subjects (62.5%) compared to that in non-cirrhotic subjects (96.3%). Furthermore, in study AI444218, male subjects were more likely to have cirrhosis than female subjects (27% male subjects and 13% female subjects were cirrhotic, respectively). Given that other patient factors may be contributing to the observed difference in response rate between males and females and as a 30% difference in exposure does not warrant dose adjustment for other intrinsic and extrinsic factors, this difference in exposure between genders is not considered to be clinically relevant.

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Figure 1: Daclatasvir PK-covariates of Interest (SVR12, Body weight, Baseline ALT, Sex, Race, and CrCL) Relationship to Daclatasvir
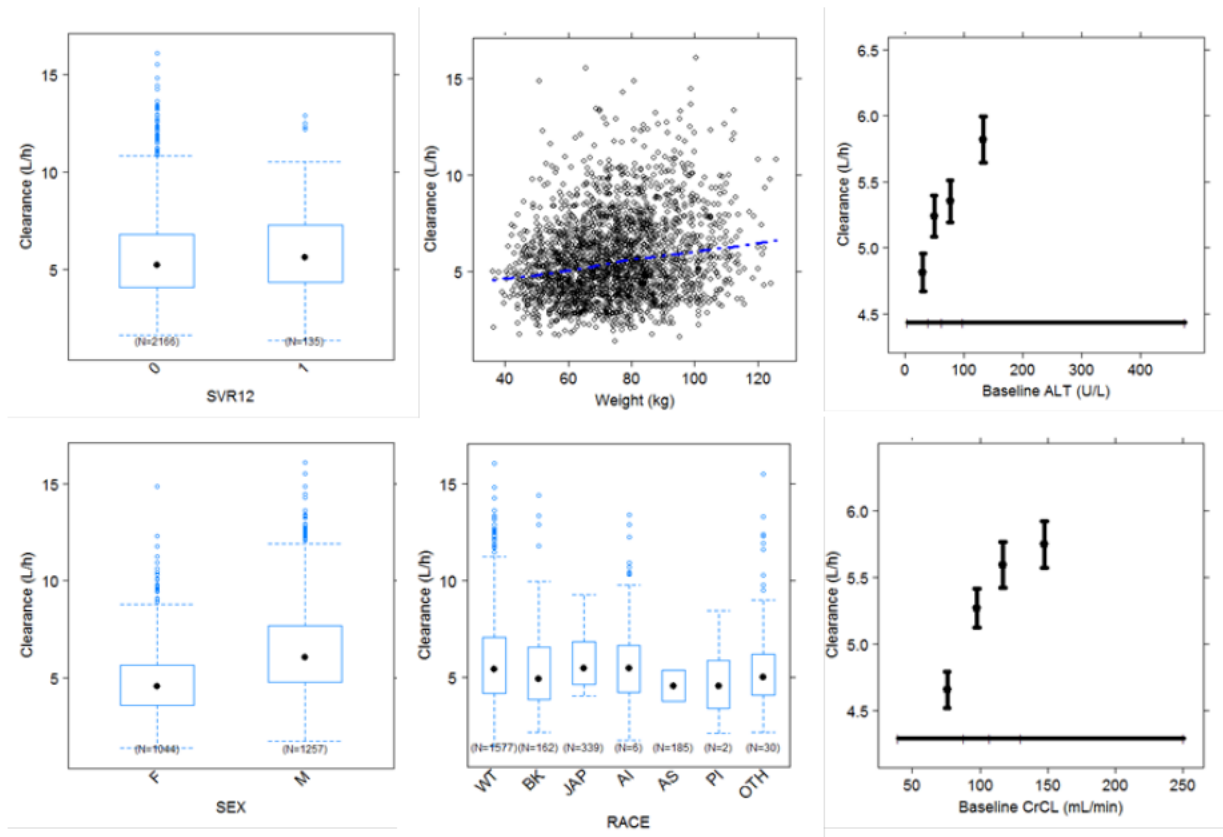
1.2 Recommendations

The Division of Pharmacometrics in the Office of Clinical Pharmacology has reviewed this application from a clinical pharmacology perspective and recommends approval of daclatasvir 60 mg once daily for the treatment of chronic HCV genotype 3 infection in combination with sofosbuvir 400 mg once daily. The reviewer agrees with the applicant's conclusions from the updated population PK analyses for daclatasvir and has included a summary table of AUC and C_{0h} from AI444218 in the label.

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in <u>underline blue font</u>.

12.3 Pharmacokinetics

The pharmacokinetic properties of daclatasvir were evaluated in healthy adult subjects and in subjects with chronic HCV. Following Administration of daclatasvir tablets in HCV-infected subjects resulted in approximately dose-proportional increases in C_{max}, AUC, and C_{min} up to 60 mg once daily. Steady state is anticipated after approximately

4 days of once-daily daclatasvir administration. Exposure of daclatasvir was similar between healthy and HCV-infected subjects.

Table X: Population Pharmacokinetic Estimates for Daclatasvir in Chronic Hepatitis C Infected Subjects Receiving Daclatasvir 60 mg Once Daily and Sofosbuvir 400 mg Once Daily

Parameters	Daclatasvir 60 mg once daily (N=152)
AUC_{0-24h} (ng.h/mL)	
Mean ± standard deviation	10973 ± 5288
Median (range)	9680 (3807-41243)
C_{24h} (ng/mL)	
Mean ± standard deviation	182± 137
Median (range)	148(21-1050)

Gender

Population pharmacokinetic analyses in HCV-infected subjects estimated that female subjects have a 30% higher daclatasvir AUC compared to male subjects. This difference in daclatasvir AUC is not considered clinically relevant.

2   PERTINENT REGULATORY BACKGROUND

BMS resubmitted NDA206843 for daclatasvir to support the use of daclatasvir (DCV) in combination with other antiviral agent (sofosbuvir, SOF) for the treatment of chronic hepatitis C virus genotype 3 (GT-3) infection. In this resubmission for DCV, the applicant submitted efficacy and safety data from a new pivotal phase 3 study AI444218 (N=152) that was conducted in HCV GT-3 infected treatment-experienced and treatment-naïve subjects with and without cirrhosis. An updated population PK study that contains PK data from AI444218 was included in this resubmission. The focus of this pharmacometrics review is to evaluate the population PK and assess covariate effects on DCV pharmacokinetics.

3   RESULTS OF APPLICANT'S ANALYSIS

3.1   Population PK Analysis

Objectives: the primary objectives of the submitted population PK analysis were to:

- Update the prior PPK analysis (11 clinical studies) with new data from study AI444218 (GT-3 HCV subjects)

- Evaluate the influence, in any, of sofosbuvir on the pharmacokinetics of DCV.

- Estimate pharmacokinetic (PK) parameters for each subject for subsequent evaluation of the exposure SVR 12 response (E-R) relationship.

Data: The updated population PK datasets included 2301 HCV-infected subjects and 20165 quantifiable plasma concentrations from 12 clinical studies, adding 152 subjects

and 1080 PK concentrations from study AI444218 (N=152). All subjects in study AI444218 were HCV genotype (GT) 3 positive and received SOF as a concomitant medication, in addition to the 211 subjects in the previous analysis from study AI444040.

The baseline demographics of subjects included in the population PK datasets is summarized in Table 1.

Table 1: **Summary of Baseline Demographics of the Final Dataset for Population PK Analysis**

Covariate	Summary N= 2301
Age (years)	
Mean (SD)	53.66 (10.52)
Median (Min, Max)	55.00 (18.00, 79.00)
Body Weight (kg)	
Mean (SD)	74.29 (16.46)
Median (Min, Max)	73.40 (36.00, 125.90)
Gender N (%)	
Female	1044 (45.37)
Male	1257 (54.63)
Race N (%)	
WHITE	1577 (68.54)
BLACK/AFRICAN AMERICAN	162 (7.04)
AMERICAN INDIAN/ALASKA NATIVE	6 (0.26)
ASIAN	178 (7.74)
ASIAN INDIAN	4 (0.17)
ASIAN OTHER	3 (0.13)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	2 (0.09)
OTHER	30 (1.30)
JAPANESE	339 (14.73)

Source: Table 4.1.4.3-1 on page 25 of applicant's population PK report

Population PK Models:

Base Model: The applicant used the previously developed model structure as the base model for the revised analysis. The base model had the same model structure and covariate effects as the prior final model, however, the parameters were re-estimated using the augmented dataset. The effect of SOF treatment was evaluated in a univariate screen on CL/F, F (with and without IIV) and Vc/F and those interactions that were determined to be significant were added to the final model.

The base model of daclatasvir was a two-compartment model with zero-order release and first order absorption, as shown in Figure 2.

Figure 2: Two-Compartmental PK Model with Zero-order Release and First-order Absorption
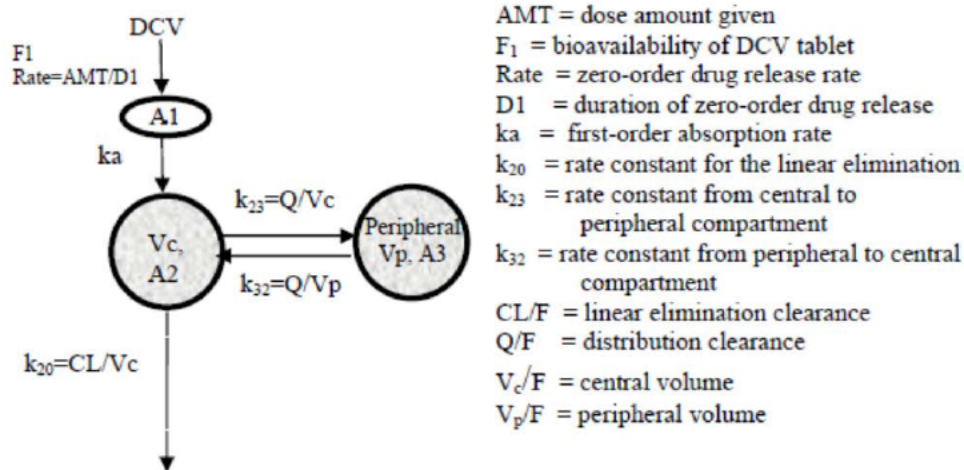
Source: *Figure 4.2.1-1 of applicant's population PK report*

Full Covariate Model: After an evaluation of the base model with the augmented dataset, a full-covariate model was developed by incorporating the effect of the SOF-parameter relationship. The full covariate model was developed in two steps: first, the covariate (SOF)-parameter relationships of interest were screened separately, followed by the incorporation of uncorrelated covariates into the full covariate model. In this analysis, all prior covariates were retained from the previously reported final model and the impact of SOF on CL/F, Vc/F and F was assessed. For effects of SOF on F, changes in the relative bioavailability were modeled as a function of SOF treatment, where F was fixed to a value of 1 in those subjects who did not receive SOF.

Final Model: Lastly, the final model was developed by retaining only the statistically significant covariate-parameter relationships. The final model was obtained by removing each covariate one-at-a-time and recording the minimum objective function (MOF) value for each run. The covariate with the smallest change in MOF was removed from the model, and the process repeated. In the final model, all covariates retained were significant at $p < 0.01$.

The uncertainty of the final PPK model parameter was estimated using the $COV step in NONMEM.

Table 2 summarized the parameter estimates and their 95% confidence intervals of the updated final model. The extent of shrinkage of estimation derived from the final model was assessed for each inter-individual variability term (η) as well as for residual error (ε) by the following formulas:

$$\eta_{shrinkage} = 1 - \frac{SD\left(\hat{\eta}_{EBE}\right)}{\omega}$$

$$\varepsilon_{shrinkage} = 1 - SD(IWRES)$$

Modest inter-individual variability was observed, 35.6% for CL/F and 27.0% for Vc/F. Shrinkage estimates for CL/F, Vc/F, and Ka were 5.7%, 16.4%, and 29.2%, respectively.

Table 2: **Parameter Estimate of the Updated Final Model**

Name [a] [Units]	Symbol	Estimate [b]	Standard Error (RSE%) [c]	95% Confidence Interval [d]
Fixed Effects				
CL/F [L/hr]	θ_1	1.74	0.0165 (0.948)	1.71, 1.77
Vc/F [L]	θ_2	4.06	0.02 (0.493)	4.02, 4.1
Q/F [L/hr]	θ_3	1.04	0.0757 (7.28)	0.892, 1.19
Vp/F [L]	θ_4	3.45	0.0721 (2.09)	3.31, 3.59
ka [1/hr]	θ_5	1.15	0.0498 (4.33)	1.05, 1.25
D1 [hr]	θ_6	-0.131	0.0328 (25)	-0.195, -0.0667
WT ON Vc/F	θ_7	0.597	0.0476 (7.97)	0.504, 0.69
GENDER F ON CL/F	θ_8	-0.264	0.0172 (6.52)	-0.298, -0.23
GENDER F ON Vc/F	θ_9	-0.221	0.0239 (10.8)	-0.268, -0.174
RACE BLACK ON CL/F	θ_{10}	-0.0959	0.0272 (28.4)	-0.149, -0.0426
RACE ASIAN ON CL/F	θ_{11}	0.0646	0.0202 (31.3)	0.025, 0.104
RACE OTHER ON CL/F	θ_{12}	-0.15	0.0608 (40.5)	-0.269, -0.0308
RACE BLACK ON Vc/F	θ_{13}	0.00133	0.021 (1580)	-0.0398, 0.0425
RACE ASIAN ON Vc/F	θ_{14}	0.196	0.0284 (14.5)	0.14, 0.252
RACE OTHER ON Vc/F	θ_{15}	-0.175	0.0763 (43.6)	-0.325, -0.0255
ALT TIME	θ_{16}	-0.0333	0.00658 (19.8)	-0.0462, -0.0204
BCRCL ON CL/F	θ_{17}	0.142	0.0247 (17.4)	0.0936, 0.19
GENO TYPE 1A ON CL/F	θ_{18}	0.0777	0.0139 (17.9)	0.0505, 0.105
SOF on F	θ_{19}	0.937	0.0218 (2.33)	0.894, 0.98
SOF on CL/F	θ_{20}	0.0445	0.0181 (40.7)	0.00902, 0.08
Random Effects				
CL/F [-]	$\omega_{1,1}$	0.127 (0.356)	0.00457 (3.6)	0.118, 0.136
Vc/F [-]	$\omega_{2,2}$	0.0728 (0.27)	0.00767 (10.5)	0.0578, 0.0878
ka [-]	$\omega_{4,4}$	2.28 (1.51)	0.124 (5.44)	2.04, 2.52
CL/F:Vc/F [-]	$\omega_{1,2}$	0.0873 (0.908)	0.00515 (5.9)	0.0772, 0.0974
Residual Error				
ADDITIVE	$\sigma_{1,1}$	0.166 (0.407)	0.00384 (2.31)	0.158, 0.174

Source: Table 6.1.3-1 on page 53 of applicant's population PK report

Model Evaluation: The final model was evaluated with the goodness-of-fit (GOF) plots produced with S-PLUS (Version 8.1) or R. Prediction corrected visual predictive check (pcVPC) was created to show the time course of the predicted mean and spread of

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concentrations (5th to 95th percentile) versus the observed data for all studies in the augmented dataset.

Goodness-of-fit plots of the updated final model are demonstrated in Figure 3. The visual predictive check of all data is demonstrated in Figure 4.

Figure 3: Goodness-of-fit Plots of the Updated Final Population PK Model
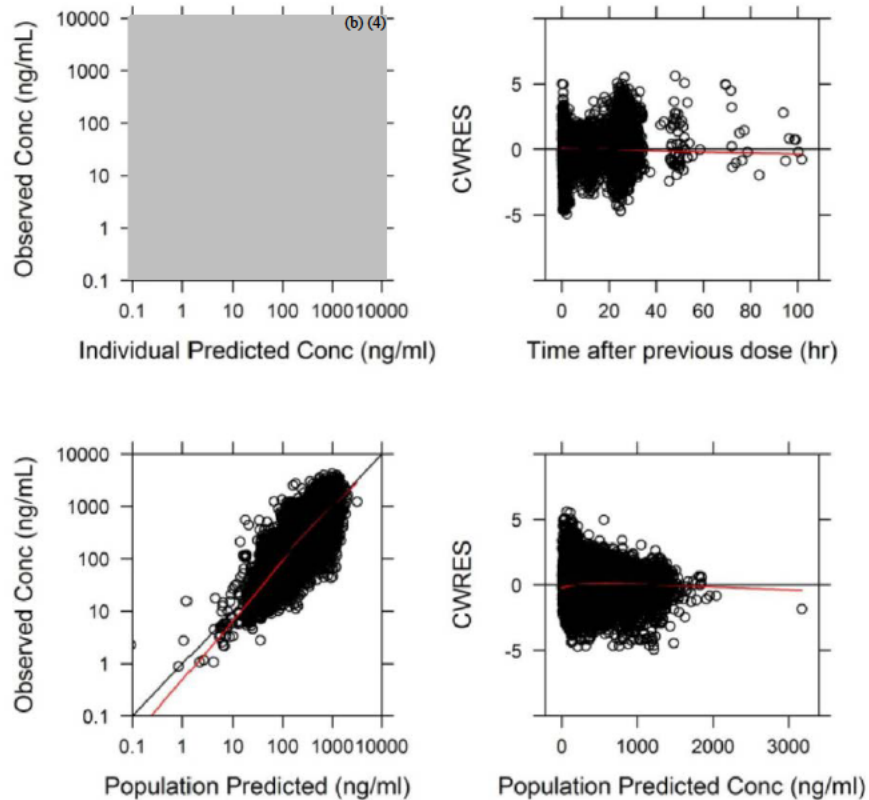
Note: Black line is unity line, red line is loess line

Source: Figure 6.1.3-1 on page 55 of applicant's population PK report

Figure 4: **Visual Predictive Check for All Data**
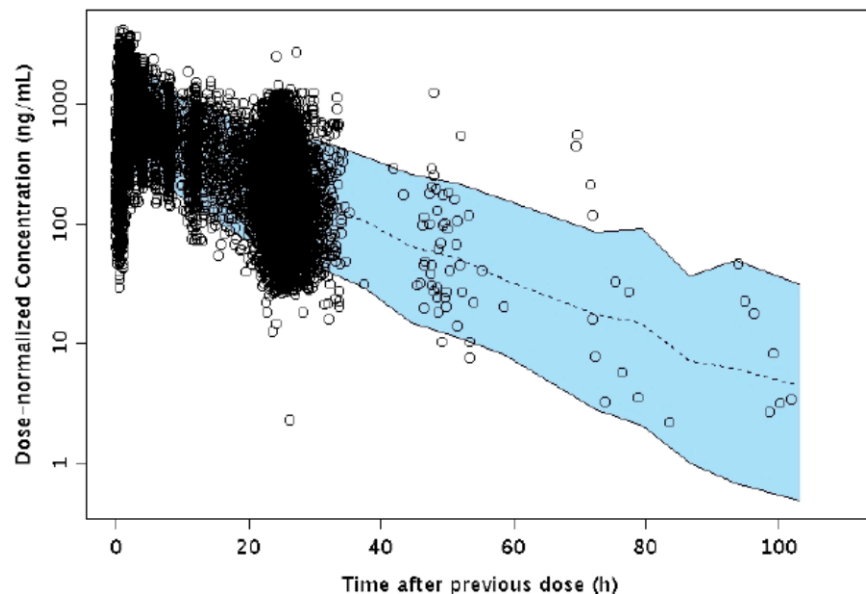
Note: Circles are observed DCV plasma concentrations, dashed black lines represent the median observed value, and the blue shaded area represents the 5th percentile and 95th percentiles of the observed values. PK concentrations were normalized to 60 mg QD.

Source: Figure 6.1.3-2 on page 56 of applicant's population PK report

Reviewer's Comments:

- *The applicant's population PK analysis is appropriate and acceptable. The goodness-of-fit plots and the visual predictive check indicate that the updated population PK model is adequate in characterizing the PK profile of daclatasvir in subjects with HCV infections. The inter-individual variability for CL/F and Vc/F are modest. Shrinkages for CL/F, Vc/F and Ka are small. The estimated PK parameters, such as CL/F and Vc/F appear reasonable. The applicant's analyses were verified by the reviewer, with no significant discordance identified (see reviewer's analysis).*

Effect of Covariates on daclatasvir PK

Covariates retained in the previous model included sex, baseline body weight, race, ALT, baseline creatinine clearance (CRCL), and virus genotype (GT1A vs. non-GT1A). In the updated model, in addition to these covariates, additional covariate of sofosbuvir (SOF) on daclatasvir PK parameters was estimated. The impact of significant covariates on the daclatasvir PK parameters is illustrated in Figure 5. Of note, females subjects have a 25% lower CL/F than male subjects.

The impact of covariates on AUC is presented in Figure 6. Female subjects were estimated to have a 30% higher AUC than male subjects. Black subjects were estimated to have an AUC 10% higher than white and Asian subjects. Subjects co-administered SOF were estimated to have a 10% lower AUC than those subjects not administered SOF.

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Figure 5: **Impact of Covariates on PK Parameters of the Updated Model**
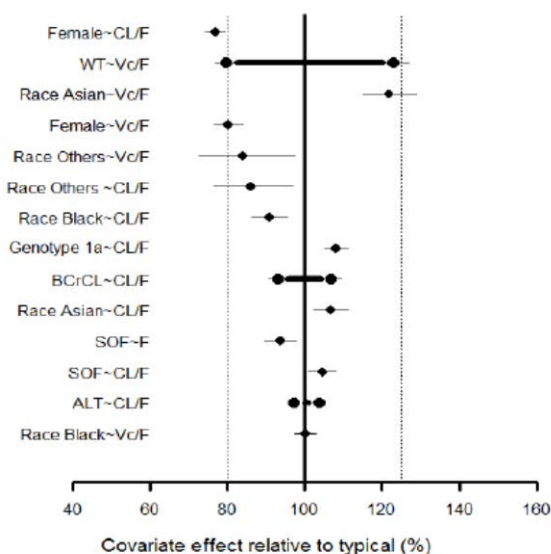
Note: Typical PK parameters were estimated for a white, 70 kg, male, genotype 1b treatment naive HCV-infected subject with baseline ALT of 60 IU/L and BCrCL of 100 mL/min. PK parameters at 5th percentile and 95th percentile of the population values of WT and BCrCL, or at different levels of the categorical covariates was compared with typical PK estimates. Dashed vertical lines indicate 80% and 125% difference from typical. Horizontal error bars indicate 95% CI of the values.

Source: Figure 6.1.4.1-1 on page 58 of applicant's population PK report

Figure 6: **Impact of Covariates on AUC$_{ss}$**
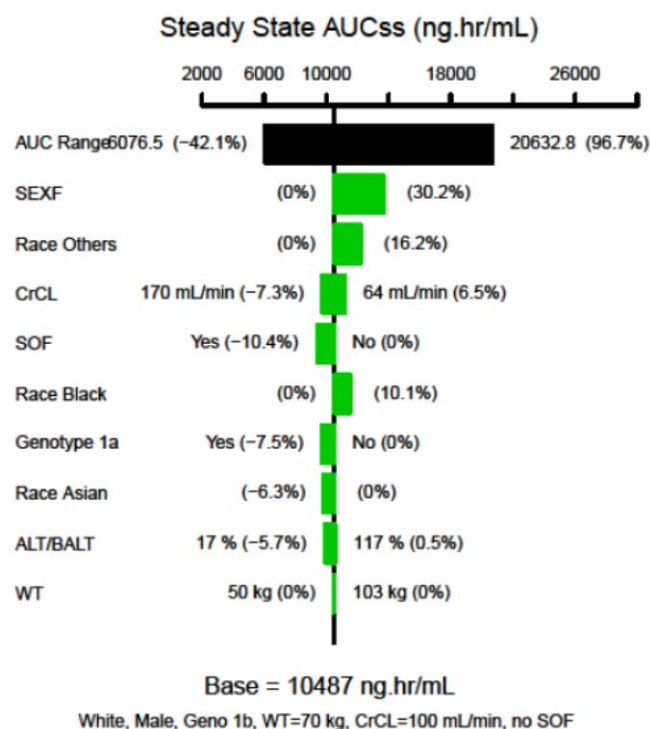
Source: Figure 6.1.4.2-1 on page 59 of applicant's population PK report

Reviewer's comments: The impact of covariates on daclatasvir AUC (≤30%) is not likely to be clinically relevant. In study AI444218, the major covariate that significantly impacts SVR12 rate is cirrhosis status. In a total of 152 subjects in study AI444218, subjects without cirrhosis achieved a SVR12 rate of 96.3%, while subjects with cirrhosis achieved cirrhosis of 62.5%. Daclatasvir exposure in subjects with or without cirrhosis is similar.

4   REVIEWER'S ANALYSIS

4.1   Introduction

The submitted population PK model included data from 12 clinical studies. This model is updated from that provided in the original submission and includes patients administered daclatasvir with sofosbuvir. As this is the regimen under consideration for approval, it is of interest to know the adequacy of the model in describing the observed data and the effects of covariates of interest (such as age, race, and body weight) on daclatasvir PK. As such, the pharmacometrics reviewer performed independent analysis with an aim to evaluate the submitted model and assessed the effect of covariates on daclatasvir exposure. The primary objective was to evaluate whether the results from population PK analysis will support the applicant's claims in the label and to inform summary PK parameters (AUC and C_{0h}) in the label.

4.2   Objectives

Analysis objectives are to:

1. Evaluate the adequacy of the applicant's final model in describing the observed daclatasvir concentrations after the proposed dosing regimen.

2. Evaluate the effect of covariates of interest, such as, age, weight, race, and other factors, on daclatasvir exposure (steady state AUC).

3. Estimate the pre-dose plasma concentration of daclatasvir at steady state under the proposed dosing regimen

4.3   Methods

4.3.1   Data Sets

Data sets used are summarized in Table 3.

Table 3: Analysis Data Sets

Study Number	Name	Link to EDR
AI444218	ppk.xpt	\\cdsesub1\evsprod\NDA206843\0034\m5\datasets\dcv-pop-pk-ally-3\analysis\legacy\datasets

4.3.2   Software

NONMEM (Version 7.2) installed on a 48-core Linux cluster was used for the population PK analysis. An R package "popPK" developed by FDA was used for population PK

graphing and reporting; SAS for windows 9.3 was used for all other graphing and statistical analyses.

4.3.3   Models

The applicant's population PK datasets and final model were used for testing the adequacy of the submitted final model and estimating PK parameters. The dataset name and its location are summarized in Table 3.

4.4   Results

4.4.1   Population PK Analysis

The reviewer conducted population PK analysis with the applicant's models. The results of the applicant's population PK analysis can be repeated. The PK parameter estimates from the reviewer's model were similar to those of the applicant's analysis (Table 4).

4.4.2   Goodness-of-fit plots for the final model

The final model was evaluated by assessing the goodness-of-fit plots as shown in Figure 7, which shows the population prediction and individual prediction versus observed daclatasvir concentrations for all subjects. The individual predictions versus observed concentrations stratified by study are shown in Figure 8. As shown, the fittings are good across all studies, suggesting that the observations were well captured.

Figure 7: Predicted versus Observed Plasma Daclatasvir concentrations (the black lines are line of identity and the dashed red lines are smooth lines)
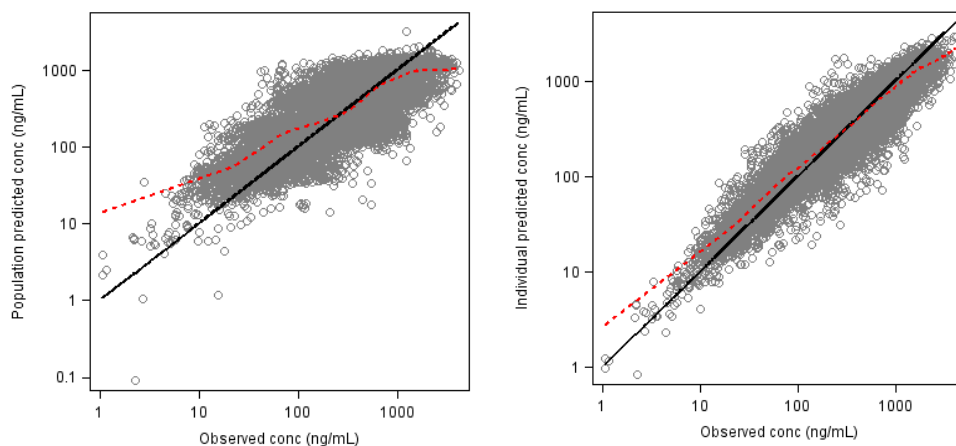
Figure 8: Individual Predicted Concentrations versus Observed Plasma Concentrations by Study
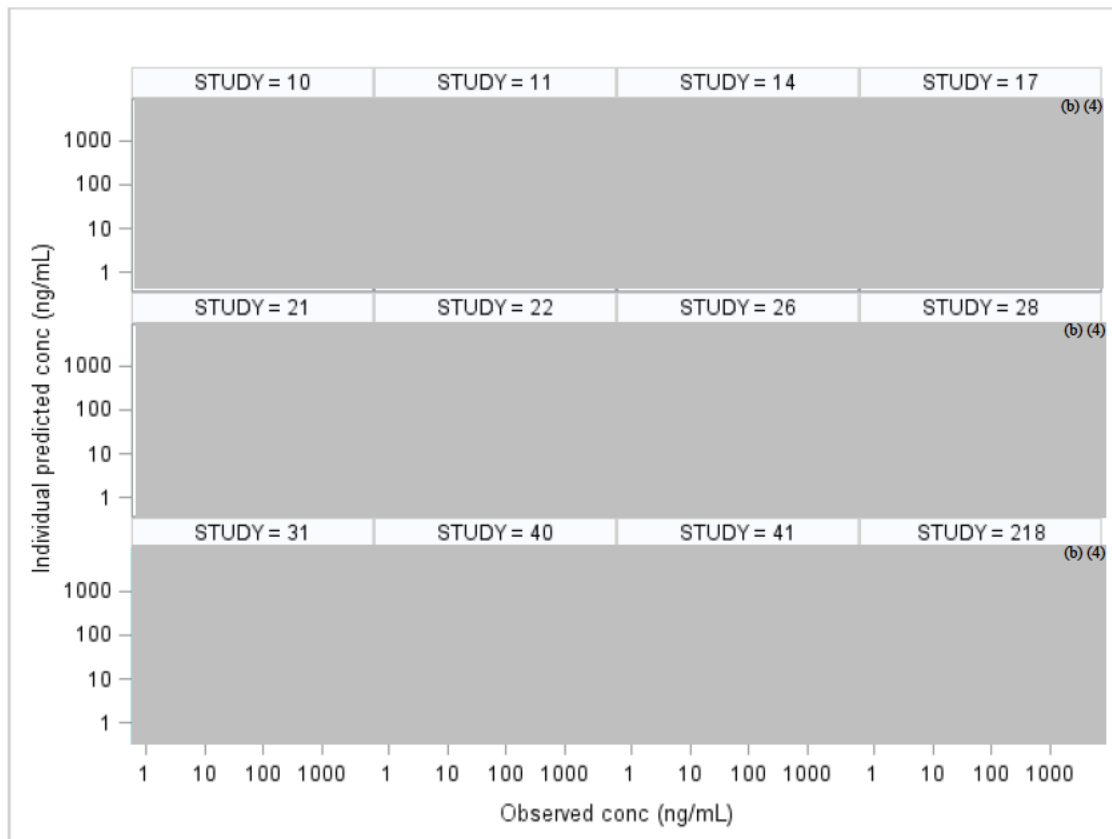
4.4.3 Parameter Estimates

The reviewer's population PK parameter estimates for the final PK model are shown in Table 4. The results were similar to those from the applicant.

Summary of post-hoc estimates of daclatasvir individual clearance and AUC_{0-24} after 60 mg QD dose is shown in Table 5. There was no clinically relevant difference in exposure among different race, sex, or age groups.

Table 4: Reviewer's final PK model parameter estimates.

Parameter	Estimate	RSE(%)
CL (Clearance (L/hr))	1.74	0.9%
Vc/F(L)	4.06	0.5%
Q/F (L)	1.04	7.2%
Vp/F (L)	3.45	2.1%
Ka: First order absorption rate (1/hr)	1.15	4.3%
D1 (hr)	-0.131	25%

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Parameter	Estimate	RSE(%)
CL (Clearance (L/hr))	1.74	0.9%
Weight on Vc/F	0.597	7.8%
GENDER F on CL/F	-0.264	6.6%
V2-IBW (Power of IBW on Central Volume	-0.221	10.9%
Race Black on CL/F	-0.0959	27.7%
Race Asian on CL/F	0.0645	31.3%
Race Other on CL/F	-0.15	39.9%
Race Black on Vc/F	0.00132	1417.7%
Race ASIAN on Vc/F	0.196	14.5%
Race Other oON	-0.175	44.1%
ALT Time Varying on CL/F	-0.0331	19.1%
Baseline CRCL on CL/F	0.142	16.8%
GENO type 1A ON CL/F	0.0778	17.5%
SOF on F	0.937	2.4%
SOF on CL/F	0.0446	41%
Inter-Individual Variability Estimates (omega^2)		
Omega(CL)	0.127	3.6%
Omega(Vc)	0.0728	11%
Omega(KA)	2.28	5.5%
Residual Error		
Additive	0.166(2.2%)	

Table 5: Summary of Individual Empirical Bayes' Estimates

Parameters		N	Mean	SD	5th percentile	95th percentile
CL/F (L/h)	White	1577	5.90	2.25	5.79	6.01
	Black	162	5.44	2.28	5.09	5.79
	Asian but not Japanese	185	5.75	2.12	5.44	6.06
	Japanese	339	5.41	1.83	5.22	5.61
	Male	1257	6.51	2.27	3.47	10.64
	Female	1044	4.87	1.69	2.65	8.05
	< 65 years	1984	5.86	2.20	2.97	10.05
	≥ 65 years	317	5.18	2.02	2.82	9.44
$AUC_{ss(0-24)}$ (µg h/mL)	White	1577	11719	4634	11490	11948
	Black	162	12887	5031	12017	13668
	Asian but not Japanese	185	11908	4622	11237	12578
	Japanese	339	12279	3988	11853	12705
	Other					
	Male	1257	10378	3751	5640	17280
	Female	1044	13811	4831	7446	22612
	< 65 years	1984	11732	4554	5968	20184
	≥ 65 years	317	13215	4705	6355	21314

With the updated model, the exposure (AUC_{0-24} and C_{24h}) of daclatasvir after 60 mg once daily in adult subjects with HCV infections was estimated. The steady state trough concentration 24 hours after the previous dose was estimated. The results are summarized in Table 6. The population estimated exposure to daclatasvir was found in agreement with the observed values.

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Table 6: Population pharmacokinetic Estimates of Daclatasvir 60 mg Once Daily in Subjects with HCV infections

Parameter	Study AI444218 DCV 60 mg QD+SOF 400 mg QD N=152	Study AI447028 DCV 60 mg QD+ASV: 100 mg BID N=640	Study AI444011 DCV 60 mg QD +P/R N=194	Combined Study of AI444010, AI444021,AI444040, AI447026,AI444011, AI444024,AI447011, AI447028,AI444014, AI444031,AI447017, AI444218 N=1888
AUC_{24h} (ng·h/mL)				
Mean ± SD	10973±5288	12283±4519	10905±4363	12212±4607
Median (Range) (5th to 95th percentile)	9680 (3807-41243) (4951-20327)	11740 (4190-33856)	9811 (4060-29878)	11457 (3808-41243)
C_{0h} (ng/mL)				
Mean ± SD	182±137	222±116	189±113	215±119
Median Range 5th to 95th percentile	148 (21-1050) (54-420)	197 (40-842) (82-437)	148 (48-762) (62-408)	189 (21-1050) (77-437)

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
Run48.sas	Post NONMEM analysis of the final model	~\Daclatasvir_NDA206843_034_FL\Daclatasvir_NDA206843S34_F\PPK Analyses\Ex17_daclatasvir_ally3_nm_output
Run50.sas	Post NONMEM analysis of the final model for estimating C_{0h}	Daclatasvir_NDA206843_034_FL\ l\PPK Analyses\Ex17_daclatasvir_ally3\nm_output\run50

Reference ID: 3785161

BIOPHARMACEUTICS REVIEW

Office of New Drug Quality Assessment

Application No.:	NDA 206-843 (000)	**Reviewer:** Sandra Suarez Sharp, Ph.D.	
Division:	DAP		
Applicant:	Bristol –Myers Squibb (BMS)	**Team Leader:** Angelica Dorantes, Ph.D.	
Trade Name:	-----	**Acting Biopharmaceutics Supervisor:** Paul Seo, Ph.D.	
Generic Name:	Daclatasvir dihydrochloride (DCV) IR ⬚ (b) (4) tablets	**Date Assigned:**	March 31, 2014
Indication:	Chronic Hepatitis C Infection	**Date of Review:**	Aug 26, 2014
Formulation/strength	IR Tablets 30 mg and 60 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates 02/28/14 06/25/14 07/22/14	Date of informal/Formal Consult	Primary Review Due in DARRTS
	March 31, 2014	Aug 29, 2014

Type of Submission:	Original NDA (Priority Review)
Key review points	1. Dissolution method and acceptance criterion 2. Bridging Across Phases of Drug Development 3. Biowaiver request for the 30 mg strength 4. Role of dissolution on supporting several drug product specifications

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18. Is there any in vitro alcohol dose-dumping information submitted? What data are provided to support the Applicant's claim (e.g. lack of dose-dumping in the presence of alcohol)?

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21. Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution? What is the risk assessment been performed to evaluate the criticality of dissolution?

22. What biopharmaceutics information is available to support the clinical relevance of the proposed design space?

23. Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?

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BIOPHARMACEUTICS ASSESSMENT

I) SUMMARY OF BIOPHARMACEUTICS FINDINGS

BMS is seeking approval of Declatasvir (DCV; BMS-790052) as an oral film-coated tablet for the treatment of chronic hepatitis C virus (HCV) infection. The recommended dose for DCV is 60 mg administered orally QD without regard to meals in adults. A 30 mg QD dose is being proposed for dose adjustments of DCV to 30 mg QD or 90 mg QD when co-administered with strong CYP3A4/P-gp inhibitors or moderate CYP3A4 inducers, respectively.

The biopharmaceutics program is based primarily on 4 key DCV studies; 2 relative bioavailability and food effect studies (AI444009 and AI444039), an absolute BA study (AI444044) and a proton pump inhibitor study (AI444024). These studies provide the data needed to bridge findings from the capsule formulation utilized in early clinical development (Phase 1) with the Phase 2 tablet and Phase 3 tablet formulations and their application to understanding the expected pharmacokinetics (PK), safety and efficacy profile of the proposed commercial tablet formulation. All these studies will be reviewed by the Clinical Pharmacology Reviewer at OCP.

DCV is classified as a Biopharmaceutical Classification System (BCS) Class II compound (low solubility/high permeability). There were no formulation changes between the Phase 3 and commercial formulations. The tablets compositions, excipient to active drug ratios, color, and tablet shape (pentagonal) for Phase 3 and commercial 30 mg and 60 mg tablets are identical. The two strengths are proportionally similar in composition.

The biopharmaceutics review is being focus on the evaluation and acceptability of the data provided to support; **1)** the dissolution method and acceptance criterion, **2)** biowaiver request for the 30 mg strength, **3)** appropriate bridging of formulations used across the developmental phases and, **4)** the role of dissolution to support the drug product specification ranges.

1) Dissolution Method and Acceptance Criterion:

The following originally submitted dissolution method and dissolution acceptance criterion was found acceptable for the proposed drug product (30 mg and 60 mg) for release and on stability.

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
II	75 rpm	1000 mL	37°C	50 mM potassium phosphate buffer at pH 6.8 with 0.75% Brij 35	Q= (b)(4) % in 30 min

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The Applicant submitted adequate/sufficient information to support the discriminating ability of the dissolution method. The setting of the dissolution acceptance criterion was based on the mean dissolution profiles of pivotal clinical batches.

2) Biowaiver Request of the BA/BE requirements for the 30 mg Tablet

The purpose of the waiver was to support the approval of the 30 mg strength since it was not tested in phase 3 clinical trials and there is no PK information on the final formulation. The following information/data was submitted to support the biowaiver:

- **Formulation composition:** The 60-mg tablets (reference) and the 30-mg tablets (test) are manufactured using ▊▊▊▊ (b) (4) therefore, the composition of the ingredients in ▊▊ (b) (4) both strengths ▊▊▊ (b) (4). The only differences between the two dose strengths are the tablet weight, color and ▊▊▊ (b) (4) ▊▊▊▊

- **Dissolution profile comparisons in four different media (pH** ▊▊ (b) (4) **and proposed QC medium).**

Comparative dissolution was conducted in three dissolution conditions ▊▊▊ (b) (4) ▊▊▊▊▊▊▊▊ and in dissolution medium intended to release commercial product (potassium phosphate buffer, pH 6.8 with 0.75% Brij 35). The results demonstrated that the 30 mg tablet is dose-proportional to the 60 mg tablets as demonstrated by similarity factors > 50).

3) Appropriate Bridging Across Phases of Drug Development

There were some major process and formulation changes implemented to the Phase 1 and Phase 2 and between the phase 2 and phase 3 clinical trial formulations. These changes are supported by the result of several BA studies linking the early formulations to the to-be-marketed formulation as described in formulation development section. These studies have been reviewed by OCP. Study A1444099 (BA study) is considered not pivotal from biopharmaceutics perspective for the approval of the drug product since it was conducted to bridge a formulation tested in earlier phases of development (phase 1) and there is PK data for the phase 3/TBM formulation (60 mg tablet).

According to the Applicant, the phase 2 formulation (30 mg) tablet was BE to the phase 3 formulation (60 mg tablet) (refer to OCP review by Dr. Stanley Au for more details). There were no formulation changes between the Phase 3 and commercial formulations.

There is only one manufacturing site being proposed, Bristol-Myers Squibb Company, Indiana, US.

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4) The Role of Dissolution in Supporting Several Drug Product Specifications

The effect of drug substance particle size and process parameters such as hardness and ▨▨▨▨ (b) (4) and their impact on dissolution were evaluated during development. The results from these studies indicated that there are no critical process parameter (CPPs) identified that could have a direct impact on the critical quality attributes (including dissolution) for daclatasvir dihydrochloride tablets. In addition, based on the long-term stability there was no change in the dissolution performance under the conditions studied. Therefore, the risk mitigation approach for dissolution is acceptable (see table below).

NDA Risk Assessment Table

From Initial Biopharmaceutics Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations/ Comments
Dissolution	None identified	M	• An adequate, discriminating dissolution method was developed.	Acceptable	• The NDA's dissolution method and acceptance criteria were found acceptable.

The proposed specifications for tablet weight ▨ (b) (4) (▨▨▨ (b) (4) % for the 30 mg and 60 mg strength, respectively); hardness (▨▨▨▨ (b) (4) for the 30 mg and 60 mg strength, respectively); and drug substance particle size (D90 ▨ (b) (4) ▨) are supported by the dissolution data.

II)   RECOMMENDATION
From the Biopharmaceutics perspective, NDA 206-843 for Daclatasvir dihydrochloride IR ▨▨ (b) (4) tablets, 30 mg and 60 mg, is recommended for **APPROVAL**.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

III) QUESTION BASED REVIEW APPROACH

A) GENERAL ATTRIBUTES

1. ***What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?***

Drug Substance
Daclatasvir is a first-in-class, highly selective nonstructural protein 5a (NS5A) replication complex inhibitor (RCI) with picomolar potency and broad genotypic coverage in vitro.

DCV is a   (b) (4) of daclatasvir. It contains (b) (4)

. DCV is classified as low solubility drug as per Biopharmaceutics Classification System (BCS). A summary of the physicochemical properties of DCV is presented in Table 1. The pH solubility profile is presented in Figure 1.

Table 1. Physicochemical properties of DCV

Physical Parameters	
Description	White to yellow powder
Melting Point/Range	206° - 253°C (b) (4)
Hygroscopicity	(b) (4)
Powder X-Ray Diffraction	(b) (4)
Form	
Solution Parameters	
Specific Rotation at (b) (4)	(b) (4)
Solubility Profile at 24°C ± 3°C	Solvent Solubility (mg/mL)
	Water > 700
	(b) (4)
Solution pH at 24°C ± 3°C	(b) (4)
pKa at 24°C ± 3°C	(b) (4)
Distribution Coefficient (b) (4)	(b) (4)
pH-Solubility Profile at (b) (4)	Final pH of Solution Solubility (mg/mL)
	(b) (4)

Figure 1.   Ambient Temperature Equilibrium Aqueous Solubility of Daclatasvir Dihydrochloride.

Drug Product

DCV Film-Coated Tablets, 30 mg and 60 mg (as the free base), contain daclatasvir dihydrochloride drug substance. A ⬛⬛⬛⬛⬛ (b) (4) with a 22% w/w drug load is used to prepare the 30-mg and 60-mg tablets. The content of the 30-mg strength tablet is proportionally similar to the content of the 60-mg strength tablet ⬛⬛⬛⬛⬛ (b) (4) (Table 2). The only difference in their composition is the Opadry® Green used in the tablet coating. The 30-mg strength tablet has a green color, whereas the 60-mg strength tablet has a light green color.

Table 2. Composition of Daclatasvir Dihydrochloride Film-Coated Tablet, 30 mg Composition of Daclatasvir Dihydrochloride Film-Coated Tablets, 60 mg (Reference) and 30 mg (Test)

		Quantity per dosage unit (% w/w)	
Component	Function	Reference Batch 1L66791 60 mg	Test Batch 1J67783 30 mg
Daclatasvir Dihydrochloride	Active	22.0[a]	22.0[a]
Anhydrous Lactose			(b) (4)
Microcrystalline Cellulose			
Croscarmellose Sodium			
Magnesium Stearate			
Silicon Dioxide			
Opadry Green[b]			

[a] The amount is expressed in terms of the dihydrochloride salt at 100% purity. The corrected amount may vary depending on the "as is" purity of the BMS-790052-05 batch used.
[b] Slight color difference to differentiate between the two strengths.

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2. *Is there any information on BCS classification? What claim did the applicant make based on BCS classification? What data are available to support this claim?*

According to the Applicant, DCV is classified as a Biopharmaceutical Classification System (BCS) Class II compound (low solubility/high permeability). The proposed dose of DCV is 60 mg once a day for patients with chronic hepatitis C infection. According to the BCS classification criteria, DCV is classified as low solubility since the dose/solubility ratio is > ███████████ (b) (4)

The in vitro apparent permeability of DCV in the parallel artificial membrane permeability assay (PAMPA) was high with a permeability coefficient ████ (b) (4) ████ , which is comparable to compounds that are well absorbed in humans. In Caco-2 cells, DCV exhibited an efflux ratio of >24, which according to the Applicant this suggest that DCV is likely to be a substrate of the efflux transporter P-glycoprotein (P-gp). Despite being a P-gp substrate, DCV was well absorbed with an absolute BA of 67% observed in humans.

B) DISSOLUTION INFORMATION
B1) Dissolution Method

3. *What is the proposed dissolution method?*

The dissolution method proposed as a quality control tool for DCV IR Tablets is summarized below:

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium
II	(b) (4) rpm	1000 mL	37°C	50 mM potassium phosphate buffer at pH 6.8 with 0.75% Brij 35

4. *What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?*

Dissolution Method Development

(b) (4)

███

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D) DISSOLUTION APPLICATIONS
D.1 BIOWAIVERS

11. *Is there a request for waiver of in vivo BE data (Biowaiver)? What is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s?*

The purposed of the waiver was to support the approval of the 30 mg strength since it was not tested in clinical trials and there is no information on the its PK. The following information/data was submitted to support the biowaiver:

- **Formal biowaiver request**: The formal request can be found at \\cdsesub1\evsprod\NDA206843\0001\m3\32-body-data\32r-reg-info

- **Formulation composition:** The 60-mg tablets (reference) and the 30-mg tablets (test) are manufactured using   (b) (4)   therefore, the composition of the ingredients in the core of both strengths   (b) (4)   as presented in Tables 2 above. The   (b) (4)   between the two dose strengths are the tablet weight, color   (b) (4)

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- **Dissolution profile comparisons in four different media (pH ▮(b)(4)▮ and proposed QC medium).**

Dissolution testing was performed for the Reference tablets (1 x 60 mg) and Test tablets (2 x 30 mg) in the four media listed in Table 3. The dissolution results and the similarity factor in all media are summarized in Table 4.

Table 3. Dissolution Parameters

Apparatus	USP Apparatus 2 (Paddle) at ▮(b)(4)▮ (75 rpm for Method 14081[a])
Medium volume	▮(b)(4)▮ (1000 mL for Method 14081)
Temperature	37 ± 0.5 °C
Dissolution time	▮(b)(4)▮ min
Time points	▮(b)(4)▮ min
Medium	1) ▮(b)(4)▮
	2)
	3)
	4) potassium phosphate buffer, pH 6.8 with 0.75% Brij 35 (Method 14081)

[a] Method intended for QC testing to release commercial product. Additional time point (▮(b)(4)▮ minute) was added to ensure enough time points with %Dissolved ▮(b)(4)▮ % to enable similarity (f2) calculation

Table 4. Summary of Dissolution Similarities Established between Daclatasvir Dihydrochloride 1 x 60 mg (Reference) Tablet and 2 x 30 mg (Test) Tablets in the Four Media (n=12)

(b)(4)

Reviewer's Comments

The data shown above (Table 4) show that the 30 mg and 60 mg tablets meet the similarity criteria at all pH values; however, it is noted that the dissolution was conducted comparing 2x 30 mg tablets vs. one 60 mg tablet. Therefore, an IR letter was

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submitted to the Applicant to perform the analysis using 1x 30 mg tablets vs. one 60 mg tablet.

On a submission dated June 08. 2014, the Applicant provided a response to this request which can be summarized as follows:

A relative bioavailability study was conducted in vivo which demonstrated bioequivalence of a single 60 mg Phase 3/commercial tablet relative to two 30 mg Phase 2 tablets. The 30-mg and 60-mg Phase 3/commercial tablets are manufactured from the (b) (4) **. The** (b) (4) **between the two dose strengths are the tablet weight, color** (b) (4) **. Thus, in vivo BE of the lower strength (30 mg) can be waived based on dissolution tests and an in vivo study on the highest strength (60 mg) per the FDA guidances.**

The rational to compare dissolution profiles of two 30-mg tablets to one 60-mg tablet are:

1) **If an in vivo BE was conducted, it would have used two 30-mg tablets vs. one 60-mg tablet. Therefore, for the in vitro dissolution study, the same comparison was performed;**

2) **The solubility of daclatasvir dihydrochloride is pH dependent. Sink conditions do not exist in two of the three recommended media (pH 4.5 and 6.8). Thus, the amount dissolved would be solubility limited, resulting in dissolution differences between different strengths.**

Reviewer's Comments
The rationale for using 2x30 mg tablets in the dissolution studies is acceptable given that the 30mg tablets were shown to be BE to the 60 mg tablets. Therefore, the biowaiver for the BA/BE requirements for the 30 mg tablets is granted.

- *Is there any IVIVC information submitted? What is the regulatory application of the IVIVC in the submission? What data is provided to support the acceptability of the IVIVC?*

There were no IVIVC models included.

- *Is there any in vitro alcohol dose-dumping information submitted? What data are provided to support the Applicant's claim (e.g. lack of dose-dumping in the presence of alcohol)?*

Not applicable.

D.2 SURROGATES IN LIEU OF DISSOLUTION

- *Are there any manufacturing parameters (e.g. disintegration, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data is available to support this claim?*

No. In laboratory dissolution testing is being implemented.

D.3 DISSOLUTION AND QBD

- *If the application contains QbD elements, is dissolution identified as a CQA for defining design space?*

This NDA does not claim the presence of a QbD approach; however, some elements of Quality by Design and Quality Risk Management were applied to the development of the drug product. According to the Applicant, quality risk assessments and design of experiments (DOE) were performed to increase understanding of the robustness of the proposed commercial formulation. A summary of the critical quality attributes identified for DCV Tablets is shown in Table 5.

Table 5. Critical Quality Attributes Established for the Daclatasvir Dihydrochloride Film-Coated Tablets

Drug Product Quality Attributes	Proposed Target
Appearance[a]	Color, shape, and markings to comply with product description
Assay (% label)	100%
Content uniformity	Meets harmonized pharmacopeial specification for uniformity of dosage units
Dissolution	(b) (4) % (Q) in 30 minutes

a The appearance of the tablets must be acceptable such that the patient will comply with the dosing regimen.

10. Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution? What is the risk assessment been performed to evaluate the criticality of dissolution?

On a response to an IR letter on 06/25/14 the Applicant stated that the effect of drug substance particle size and process parameters such as hardness and (b) (4) and their impact on dissolution were evaluated during development. The results from these studies indicated that there are no critical process parameter (CPPs) identified that could have a direct impact on the critical quality attributes (including dissolution) for daclatasvir dihydrochloride tablets. In addition, based on the long-term stability there was no change in the dissolution performance under the conditions studied. Therefore, the risk mitigation approach for dissolution is acceptable (Table 6).

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Table 6. NDA Risk Assessment Table

From Biopharmaceutics Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation approach	Risk Evaluation	Lifecycle Consideration /Comments
Dissolution	None identified	M	• An adequate, discriminating dissolution method was developed.	Acceptable	• The NDA's dissolution method and acceptance criteria were found acceptable.

a. Drug Substance Particle size

During formulation development studies, the effect of DS particle size on dissolution was evaluated by manufacturing the batches using large and small particle sizes, (D [90] = ____ (b) (4)) at target ____ (b) (4) process parameters. Dissolution profiles from these batches were compared, and the extent of drug release was similar (> (b) (4) (Q) at 30 minutes) in both cases.

The capability of the drug product process was further verified at scale during manufacture of batches for long-term stability studies, which contained materials at the edge of the proposed particle size range. The batches had complete dissolution for both the 30-mg and 60-mg drug product. The data provided confirm that there is no influence, within the specification range, of D90 ____ (b) (4) on dissolution.

Reviewer's Comments

On a response to an IR letter received on 07/22/14 (refer to \\cdsesub1\evsprod\NDA206843\0018\m1\us) the Applicant submitted the drug substance PSD values for all the batches tested in pivotal clinical trials. The D90 ranged from (b) (4) ____ . The proposed D90 specification is supported by the dissolution data where a batch with a particle size of ____ (b) (4) met the dissolution acceptance criterion.

b. Impact of Tablet Hardness and Film Coating Amount on Dissolution

Dissolution testing was conducted on tablets manufactured at the upper end of the selected hardness and ____ (b) (4) (____ (b) (4) ____) and compared to tablets manufactured at the target conditions (____ (b) (4) ____). The dissolution test results presented (dissolution at 30 min > (b) (4) % indicate that there was no significant difference in the dissolution profiles between the two sets of tablets (Figure 9) (refer to \\cdsesub1\evsprod\NDA206843\0018\m1\us for more details).
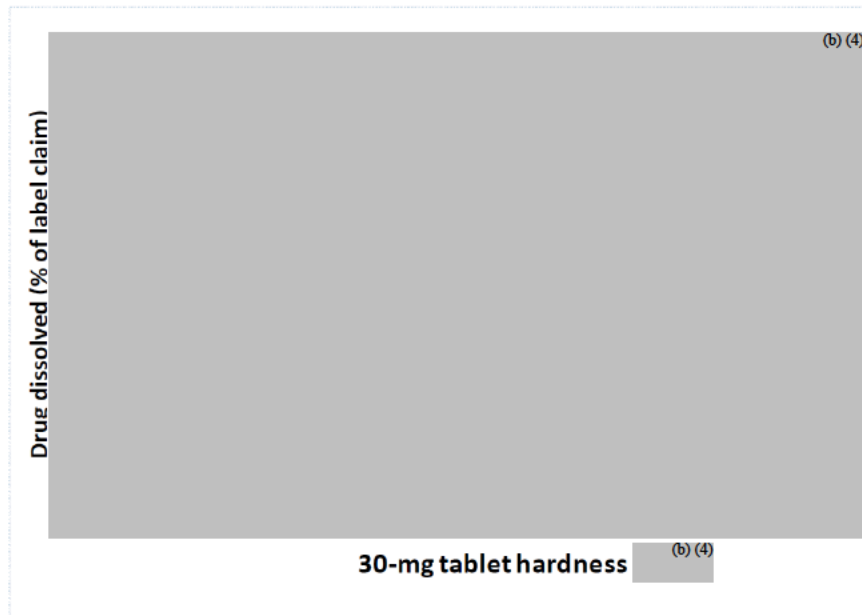
Figure 9. Dissolution at 30 minutes of Daclatasvir Dihydrochloride 30-mg Tablets as a Function of Tablet Hardness.

Reviewer's Comments
The proposed specifications for tablet weight gain   (b) (4) for the 30 mg and 60 mg strength, respectively); hardness   ((b) (4)   for the 30 mg and 60 mg strength, respectively); and drug substance particle size (D90   (b) (4)   ) are supported by the dissolution data.

20.   *What biopharmaceutics information is available to support the clinical relevance of the proposed design space?*

There is no design space being proposed.

21.   *Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?*

No dissolution models were proposed.

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OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDAs: 206843/206844	Submission Date: March 29, 2014
Brand Names	To be determined
Generic Names	Daclatasvir (NDA 206843)
	Asunaprevir (NDA 206844)
Reviewers	Stanley Au, Pharm.D., BCPS
	Yongheng (Eric) Zhang, Ph.D.
Pharmacometrics Reviewer	Fang Li, Ph.D.
Genomics and Targeted Therapy Reviewer	Jeffrey Kraft, Ph.D.
Pharmacometrics Team Leader	Jeffry A. Florian, Ph.D. (acting)
Genomics and Targeted Therapy Associate Director	Michael A. Pacanowski, Pharm.D., MPH
Clinical Pharmacology Team Leader	Shirley K. Seo, Ph.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products (DAVP)
Applicant	Bristol Myers Squibb
Formulation; strength(s) to-be-marketed	Daclatasvir oral tablets, 30 mg and 60 mg
	Asunaprevir ████████ (b) (4)
Proposed Indication	Treatment of chronic hepatitis C infection
Review Type	505 (b)(1) New Drug Application, priority review

1   Executive Summary

Two separate New Drug Applications (NDAs) were submitted by the applicant, Bristol Myers Squibb, for asunaprevir or BMS-650032 (NDA 206844) and daclatasvir or BMS-790052 (NDA 206843). The two separate NDAs were incorporated into a combined Clinical Pharmacology review because the pivotal trials evaluated the combination of asunaprevir and daclatasvir with or without pegylated interferon alfa and ribavirin.

Asunaprevir and daclatasvir (also known as ASV and DCV, respectively) were evaluated for the treatment of chronic hepatitis C infection. Asunaprevir inhibits the NS3/4A serine protease complex and daclatasvir inhibits the NS5A portion of the hepatitis C virus.

The applicant is proposing the following dosage regimens administered with or without food:
-Asunaprevir in combination with daclatasvir (also known as Dual therapy) in subjects with hepatitis C genotype 1b virus:
Asunaprevir   (b) (4)

-Asunaprevir   (b) (4)

The clinical pharmacology studies and trials that were submitted in support of the two NDAs included in vitro studies, trials to evaluate the effect of asunaprevir or daclatasvir on the QT interval (thorough QT trials), food effect trials, hepatic impairment trials, renal impairment trials, mass balance trials, and multiple drug-drug interaction trials in healthy subjects.   The drug-drug interaction trials included trials where asunaprevir and daclatasvir were evaluated as single entities or administered in combination with each other. In addition, asunaprevir or daclatasvir population pharmacokinetic models were developed that included pharmacokinetic data from Phase 2 or Phase 3 trials.

1.1   Recommendation

The Office of Clinical Pharmacology (OCP) has reviewed the information in the two NDAs and the information provided supports the approval of the applications.

1.2   Postmarketing Commitments or Requirements

There are no postmarketing commitments or requirements for either NDA.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

1.3.1 Exposure-response (efficacy) analysis

Exposure-response analyses for efficacy or safety were provided by the applicant for the Dual therapy. The applicant did not submit exposure-response analyses for efficacy or safety for the Quad therapy and the review team determined that it was not necessary to submit the analyses for review. A detailed discussion of the asunaprevir or daclatasvir exposure-response analyses for efficacy is provided in the Pharmacometrics review (section 4).

No major differences were identified across the asunaprevir or daclatasvir exposure range in evaluating the exposure-response relationship for efficacy when the overall information from the Phase 3 trials was analyzed. A lower sustained virologic response rate was observed in subjects with Y93H or L31F/I/M/V baseline NS5A polymorphisms. A consistent daclatasvir exposure-response relationship was not observed for this subpopulation.

1.3.2 Exposure-safety analyses

The exposure-safety analyses evaluated whether there was a potential relationship between predicted asunaprevir or daclatasvir exposure and liver function related laboratory abnormalities. During the drug development program, higher asunaprevir exposure was observed in subjects with clinically relevant liver function related laboratory abnormalities. This was not observed for daclatasvir. Only a limited number of Grade 3 or higher liver function related laboratory abnormalities were observed with the proposed asunaprevir or daclatasvir dosage regimens.

During the NDA review, a potential safety issue was identified in subjects with pyrexia and increased eosinophils with or with liver function abnormalities. The issue was identified in the AI447026 trial that enrolled only Japanese subjects. The exposure-safety analysis evaluated only the data from the Phase 3 trials that studied the Dual therapy to avoid the potential confounding effects on the adverse events of interest from pegylated interferon alfa and ribavirin. Based on the analyses, neither asunaprevir nor daclatasvir exposure in these subjects appear to play a major role in contributing to the reported adverse events of interest.

1.3.3 Pharmacokinetics

Information on the pharmacokinetics of asunaprevir or daclatasvir from the multiple dosing trials in hepatitis C infected subjects is displayed in Table 1 and Table 2, respectively. The results of the population PK analysis for the Phase 3 trials are displayed in section 2.

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Table 1-Asunaprevir pharmacokinetic parameters in subjects with multiple dosing

Table 2-Daclatasvir pharmacokinetic parameters in subjects with multiple dosing of daclatasvir dosage regimens ranging from 1 mg once daily to 100 mg once daily from the AI444004 trial

Treatment	Study Day	Cmax (ng/mL) Geo. Mean [N] (CV)	Cmin (ng/mL) Geo. Mean [N] (CV)	Tmax (h) Median [N] (Min-Max)	AUC(TAU) (ng•h/mL) Geo. Mean [N] (CV)	T-HALF (h) Mean [N] (SD)
TRT A	1	15.731[4] (48)	1.212[4] (105)	2.000[4] (1.00-3.00)	111.8[4] (54)	NA NA
	14	10.430[4] (76)	1.234[4] (95)	1.250[4] (1.00-2.00)	92.0[4] (80)	11.68[4] (2.214)
TRT B	1	159.665[4] (41)	15.141[4] (49)	1.000[4] (1.00-2.00)	1113.6[4] (38)	NA NA
	14	154.196[4] (49)	23.674[4] (53)	1.250[4] (1.00-1.50)	1332.1[4] (46)	14.31[4] (3.848)
TRT C	1	483.365[4] (25)	41.114[4] (34)	1.000[4] (0.50-1.00)	3528.6[4] (19)	NA NA
	14	555.878[4] (38)	61.635[4] (42)	1.000[4] (1.00-1.50)	4391.3[4] (27)	12.99[4] (2.039)
TRT D	1	1409.202[4] (13)	129.822[4] (25)	1.500[4] (1.50-3.00)	10691.5[4] (20)	NA NA
	14	1726.383[4] (21)	254.602[4] (42)	1.000[4] (1.00-2.00)	15120.9[4] (35)	12.81[4] (1.233)
TRT E	1	563.569[4] (26)	171.330[4] (53)	2.500[4] (1.50-3.00)	3307.2[4][a] (36)	NA NA
	14	831.792[4] (37)	206.941[4] (74)	1.750[4] (1.00-2.00)	5431.6[4] (35)	13.04[4] (3.654)
TRT F	1	1960.732[4] (21)	174.642[4] (21)	1.500[4] (1.00-1.50)	15136.1[4] (19)	NA NA
	14	1853.925[4] (26)	287.852[4] (37)	1.750[4] (1.00-2.00)	17592.8[4] (15)	15.19[4] (3.411)

Treatments: A=1mg QD, B=10mg QD, C=30mg QD, D=60mg QD, E=30mg BID, F=100mg QD

[a] AUC(TAU) = AUC over 12 hour dosing interval for Treatment E

Statistical analyses were not conducted evaluating whether daclatasvir or asunaprevir exposure is similar when comparing healthy subjects to hepatitis C infected subjects. However, in general it appears that exposures are similar when comparing the data across trials between the two groups for daclatasvir. (b) (4)

1.3.4 Absorption

The absolute bioavailability of asunaprevir (b) (4) and daclatasvir 60 mg tablets is 67%.

The solubility of daclatasvir is pH-dependent. However, in the drug-drug interaction

trials with medications that alter gastric pH, such as H$_2$ antagonists (e.g. famotidine) and proton pump inhibitors (PPIs) [e.g. omeprazole], no clinically relevant changes in daclatasvir AUC were observed when these medications were evaluated with daclatasvir.

Based on the in vitro information, both asunaprevir and daclatasvir are P-gp substrates. With concomitant use of cyclosporine, increased daclatasvir exposure was observed but a dose adjustment is not necessary. A corresponding trial with concomitant use of a P-gp inhibitor was not conducted for asunaprevir.

Asunaprevir and daclatasvir exposure were both altered in the presence of food. A food effect was observed on daclatasvir or asunaprevir exposure when administered with a high fat meal. When a single dose of asunaprevir (b) (4)

When a single dose of daclatasvir 60 mg was administered with a high fat meal, the daclatasvir C$_{max}$, AUC$_{(0-t)}$ and AUC$_{(0-inf)}$ were decreased by 28%, 24% and 23%, respectively, when compared with a single dose of daclatasvir 60 mg administered under fasted conditions. The 90% confidence intervals for daclatasvir C$_{max}$, AUC$_{(0-t)}$ and AUC$_{(0-inf)}$ were all not within the standard "no effect" 90% confidence interval limits of 80%-125%. The specific 90% confidence intervals were 66% to 79% for C$_{max}$, 72% to 80% for AUC$_{(0-t)}$ and 73% to 80% for AUC$_{(0-inf)}$. Based on the exposure-efficacy or exposure-safety information, the recommendation to administer daclatasvir (b) (4) with or without food is acceptable.

1.3.5   Distribution

The protein binding of (b) (4) daclatasvir is approximately 98% or greater in human species and appears to be concentration independent based on the in vitro studies. Based on the data from the absolute bioavailability trials, the volume of distribution for daclatasvir is 47.1 liters (b) (4).

1.3.6   Metabolism

In plasma, daclatasvir parent drug was the major contributor to total radioactivity. (b) (4)

The in vitro study results indicate that CYP3A is the primary cytochrome P450 enzyme system responsible for daclatasvir (b) (4) metabolism and in a drug-drug interaction trial, (b) (4) daclatasvir exposure were both increased with concomitant use of ketoconazole ((b) (4) daclatasvir AUC$_{[0-inf]}$ increased by 200%).

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1.3.7 Excretion

Based on the results of the mass balance trials, in the feces, for daclatasvir, the majority of the dose was eliminated through the fecal route (88%) with 7% eliminated renally (b) (4)

For daclatasvir, approximately half of the total dose in feces was identified as daclatasvir parent drug (53%) and virtually the entire total dose in urine (6%) was identified as daclatasvir parent drug (b) (4).

1.3.8 Intrinsic factors

Hepatic impairment

(b) (4)

Based on the available information from the daclatasvir hepatic impairment trial and the daclatasvir exposure-response analysis, dosage adjustments are not necessary to compensate for the changes in total daclatasvir exposure. The following results were obtained when compared to the corresponding matched control group: 1) Child Pugh A: C_{max} and $AUC_{(0\text{-inf})}$ decreased by 45.5% and 42.7%, respectively, 2) Child Pugh B: C_{max} and $AUC_{(0\text{-inf})}$ decreased by 45.2% and 37.6%, respectively, and 3) Child Pugh C: C_{max} and $AUC_{(0\text{-inf})}$ decreased by 54.6% and 36.2%, respectively.

Renal impairment

Dosage adjustments are not necessary to compensate for the changes in (b) (4) daclatasvir exposure with renal impairment.

Population pharmacokinetic analysis

Covariates were evaluated as part of the population pharmacokinetic analysis for (b) (4) daclatasvir, including age, gender, body weight, race, ALT, AST, and creatinine clearance (CrCL). The covariates had minimal or no influence on (b) (4) daclatasvir exposure and dosage adjustments are not necessary because of a lack of an exposure-response relationship for either efficacy or safety.

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Pharmacogenomics

The disposition of asunaprevir   (b) (4)

1.3.9   **Drug-drug interactions**

Both asunaprevir and daclatasvir are mainly metabolized by CYP3A.   (b) (4)

Clinically relevant changes in midazolam exposure were not observed with concomitant use of daclatasvir in a drug-drug interaction trial.

The in vitro results indicate that asunaprevir   (b) (4)

Based on the in vitro study results, daclatasvir is a P-gp substrate but not an OATP1B1 or OATP1B3 substrate and does not appear to be a BCRP substrate, though BCRP inhibitors were not evaluated in the in vitro study. The in vitro studies also indicate that daclatasvir potentially inhibits P-gp, BCRP, OATP1B1 and OATP1B3. Inhibitory effects on digoxin exposure, a P-gp substrate, and rosuvastatin (OATP and BCRP substrate), were observed in drug-drug interaction trials with daclatasvir or asunaprevir plus daclatasvir.

The applicant is proposing the following dosing recommendations to address potential drug interaction issues:

1) Daclatasvir (in the absence of concomitant use of asunaprevir):
-strong CYP3A inhibitors: decrease daclatasvir dose to 30 mg once daily: 200% increase in daclatasvir $AUC_{(0-inf)}$ with ketoconazole coadministration.
-moderate CYP3A inducers: increase daclatasvir dose to 90 mg once daily: 32% decrease in dose-normalized daclatasvir $AUC_{(0-tau)}$ with efavirenz coadministration.

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2) Contraindicate use of certain medications in combination with DCV:
-strong CYP 3A inducers: 79% decrease in daclatasvir $AUC_{(0-inf)}$ with rifampin coadministration.

3) [redacted] (b) (4)

[redacted] (b) (4)

The proposed contraindications are acceptable. [redacted] (b) (4)

[redacted]

No specific exposure-response or exposure-safety issues were identified for daclatasvir. For strong CYP3A inhibition, the proposed dosage adjustment for daclatasvir would be expected to mitigate but not completely compensate for the changes in daclatasvir exposure due to drug-drug interactions. However, considering that only a 30 mg tablet will be available for dosage adjustments, the proposed dosage adjustment is reasonable if supported by concerns regarding safety. While specific examples of strong CYP3A inhibitors or moderate CYP 3A inducers may be included, it is not anticipated that an all-encompassing list will be included in the proposed daclatasvir prescribing information.

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2 Question based review (QBR)

2.1 General Attributes of the Drug

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology review?

The structures are provided in Figure 1 below.

Figure 1-Asunaprevir and daclatasvir structural formulas
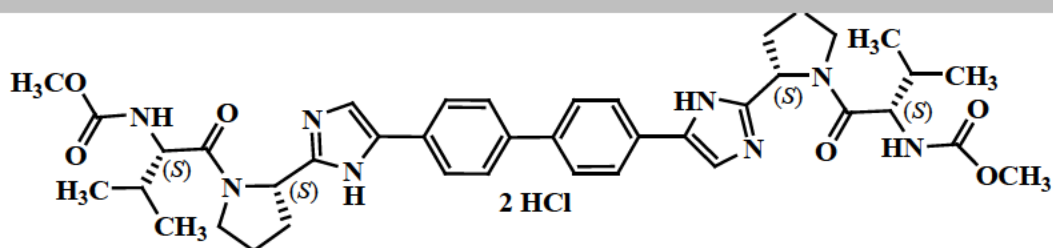
Table 1 lists the active and inactive ingredients for the proposed to-be-marketed daclatasvir tablets.

Table 1-Active and inactive ingredients for the proposed to-be-marketed asunaprevir (b) (4) **and daclatasvir 60 mg tablets**

(b) (4)

B) Daclatasvir-60 mg tablets

Component	Quality Standard	Function	Quantity per Tablet (%w/w)	Quantity per Tablet (mg)
(b) (4) TABLET				
Daclatasvir Dihydrochloride (BMS-790052-05)[a]	In-house[b]	Active	22.0	66.00
Anhydrous Lactose[c]	NF/Ph.Eur./JP			(b) (4)
Microcrystalline Cellulose	NF/Ph.Eur./JP			
Croscarmellose Sodium	NF/Ph.Eur./JP			
Silicon Dioxide	NF/Ph.Eur.[d]/JPE			
Magnesium Stearate	NF/Ph.Eur./JP			
(b) (4)				
FILM COAT				
Opadry® Green[e]	In-house[f]			
(b) (4)	USP/Ph.Eur.			
Total Tablet Weight				315.00

[a] The amount of daclatasvir dihydrochloride shown is based on the theoretical assay "as is" of (b) (4) % with respect to daclatasvir free base. Adjustments will be made based upon actual assay "as is" of the drug substance batch that will be used for drug product manufacture.

[b] In-house requirements for daclatasvir dihydrochloride are listed in Testing Standard Specification ID 00011698, which is provided in Section 3.2.S.4.1, *Specification*.

[c] (b) (4)

[d]

[e]

[f]

[g]

Clinical Pharmacology reviewer note: a (b) (4) *30 mg daclatasvir tablet is also proposed to be commercially marketed in the U.S.*

2.1.2   What is the proposed mechanism of action and therapeutic indication(s)?

Asunaprevir (b) (4)

2.1.3   What are the proposed dosage(s) and route(s) of administration?

The proposed dosage regimens that are to be administered with or without food are as follows:

-Asunaprevir in combination with daclatasvir (also known as Dual therapy) in subjects with hepatitis C genotype 1b virus:
Asunaprevir (b) (4)

-Asunaprevir (b) (4)

2.2   General Clinical Pharmacology

2.2.1   What are the design features of the clinical studies used to support dosing or claims?

Two Phase 3 trials (AI447026 and AI447028) were used to support the indication for asunaprevir in combination with daclatasvir (Dual therapy).   A third trial (AI447029) was used to support the indication for asunaprevir in combination with daclatasvir plus pegylated interferon alfa and ribavirin (Quad therapy).

The primary endpoint for the trials was based on achievement of undetectable HCV viral load 12 weeks after the end of treatment, referred to as sustained virologic response or SVR12. Information regarding the applicant's results of the Phase 3 trials is provided below.

Table 2-Applicant's SVR12 results for Dual therapy

AI447026		
SVR12	Prior partial or null responders	Interferon intolerant or ineligible
	N=87	N=135
	n (%)	n (%)
Yes	70 (81%)	119 (88%)

AI447028			
SVR12	Treatment naive	Prior partial or null responders	Interferon intolerant or ineligible
	N=203	N=205	N=235
	n (%)	n (%)	n (%)
Yes	184 (91%)	169 (82%)	194(83%)

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Table 3-Applicant's relapse results for Dual therapy

AI447026		
Relapse	Prior partial or null responders	Interferon intolerant or ineligible
	n (%)	n (%)
Yes	6/76 (8%)	10/129 (8%)

AI447028			
Relapse	Treatment naive	Prior partial or null responders	Interferon intolerant or ineligible
	n (%)	n (%)	n (%)
Yes	5/189 (3%)	7/174 (4%)	12/204 (6%)

Denominator is subjects with undetectable HCV RNA at end of treatment

Table 4-Applicant's SVR12 results for Quad therapy

AI447029		
SVR12	Genotype 1	Genotype 4
	N=354	N=44
	n (%)	n (%)
Yes	330 (93%)	44 (100%)

Table 5-Applicant's relapse results for Quad therapy

AI447029		
Relapse	Genotype 1	Genotype 4
	n (%)	n (%)
Yes	8/337 (2%)	0/43 (0%)

2.2.2   What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics [PD]) and how are they measured in clinical pharmacology and clinical studies?

Please see the response in 2.2.1. The SVR12 has been demonstrated to be a valid surrogate to establish the efficacy of medications for the treatment of chronic hepatitis C infection.

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2.2.3   Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure-response relationships?

The relevant analytes were measured in plasma including using validated LC/MS/MS analytical methods. The analytes that were measured were asunaprevir, daclatasvir, and concomitant medications of interest in the drug-drug interaction trials.

2.2.4   Exposure-response

2.2.4.1   What are the characteristics of the exposure-response relationships (dose response, concentration-response) for efficacy?

No major differences were identified across the asunaprevir or daclatasvir exposure range in evaluating the exposure-response relationship for efficacy (see Figure 2).

Figure 2-Exposure-response analyses for asunaprevir or daclatasvir exposure versus SVR 12 (Pooled data from AI447026 and AI447028)
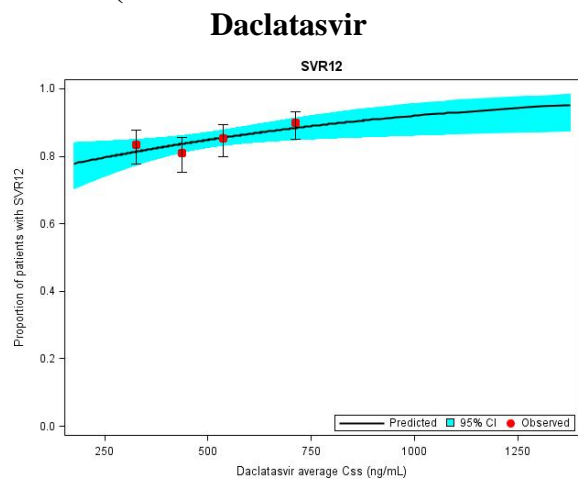
Daclatasvir

(b) (4)

Note: The points are observed quartile mean. The shaded areas are model-estimated 95% CI based on a logistic analysis.

A lower SVR12 rate was observed in subjects with Y93H or L31F/I/M/V baseline NS5A polymorphisms. A consistent daclatasvir exposure-response relationship was not observed for the two subpopulations (see Figure 3).

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Figure 3-Exposure-response analyses for daclatasvir exposure versus SVR12 with Y93H or L31F/I/M/V baseline NS5A polymorphisms
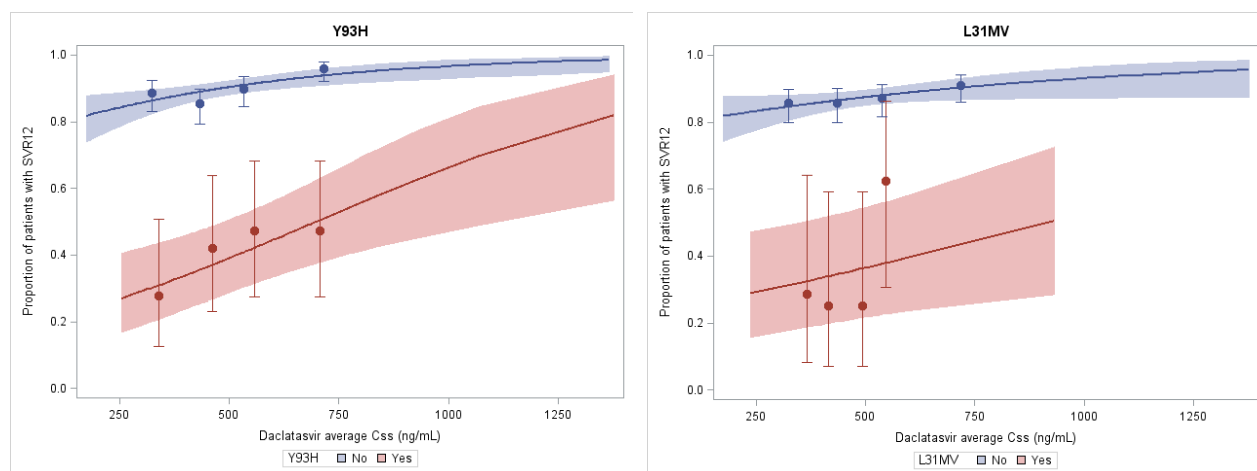
2.2.4.2   What are the characteristics of the exposure-response relationships (dose response, concentration-response) for safety?

Higher asunaprevir exposure was observed in subjects with clinically relevant liver function related laboratory abnormalities. This was not observed for daclatasvir. Only a limited number of Grade 3 or higher liver function-related laboratory abnormalities were observed with the proposed asunaprevir or daclatasvir dosage regimens.

A potential safety issue was identified in subjects with pyrexia and increased eosinophils with or with liver function abnormalities from the AI447026 trial that enrolled only Japanese subjects. Based on the available information, asunaprevir or daclatasvir exposure in these subjects does not appear to play a major role in contributing to the reported adverse events of interest.

2.2.4.3   Does this drug prolong the QT or QTc interval?

Asunaprevir

(b) (4)

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Daclatasvir

A total of 56 subjects received daclatasvir 60 mg, daclatasvir 180 mg, placebo and moxifloxacin 400 mg. No significant QTc prolongation effects of daclatasvir doses of 60 mg and 180 mg were detected in the TQT trial. The largest upper bounds of the 2-sided 90% CI for the mean differences between daclatasvir 60 mg and placebo, and between daclatasvir 180 mg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, indicating that assay sensitivity was established.

Table 6-Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for daclatasvir (60 mg and 180 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
BMS-790052 60 mg	16	1.1	(-0.8, 3.0)
BMS-790052 180 mg	16	1.5	(-0.4, 3.3)
Moxifloxacin 400 mg*	3	10.8	(9.3, 12.3)

Note: daclatasvir is BMS-790052
Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 8.7 ms.

 No exposure-response relationship was evident between ΔΔQTcF and daclatasvir concentrations.

2.2.4.4   Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

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The dose and dosing regimen selected by the applicant is supported by the exposure-response or exposure-safety relationship for asunaprevir and daclatasvir which indicate the absence of any exposure related virologic response or safety issues for the Phase 3 trials.

Asunaprevir

(b) (4)

Daclatasvir

During the end of Phase 2 review, the Phase 2 trial results indicated that similar antiviral activity was achieved when the following dosing daclatasvir regimens: 10 mg, 20 mg, or 60 mg once daily with pegylated interferon alfa and ribavirin.

Overall, the combined safety and efficacy analyses indicated that 60 mg was an appropriate daclatasvir dose to evaluate in the Phase 3 trials. Additionally, no exposure-response relationships between safety events and daclatasvir exposure were identified during Phase 2 suggesting that doses of 60 mg would not lead to an increase in adverse events compared to lower daclatasvir doses.

2.2.5   What are the PK characteristics of the drug and its major metabolite?

2.2.5.1   What are the multiple dose PK parameters?

PK parameters of DCV and ASV after multiple doses in Phase 3 studies were estimated in the population PK analyses and summarized in the table below.

Table 8-Population Pharmacokinetic Estimates of DCV and ASV for Pooled Data from Phase 3 trials

Parameters	DCV 60 mg QD (N=862)	(b) (4)
AUC_{0-tau} (ng.h/mL)		
geometric mean	12019.3	
90% CI	(11798, 12245)	
C_{trough} (ng/mL)		
geometric mean	206.5	
90% CI	(202.5, 210.7)	

2.2.5.2   How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Statistical comparisons have not been made regarding whether daclatasvir or asunaprevir exposure is similar when comparing healthy to hepatitis C infected subjects. However, in general it appears that exposures are similar when comparing the two groups for daclatasvir across trials.   (b) (4)

No asunaprevir or daclatasvir metabolites in plasma were routinely measured in clinical trials.

2.2.5.3   What are the characteristics of drug absorption?

The absolute bioavailability of   (b) (4)
daclatasvir 60 mg tablets is 67%.

Based on the in vitro information, both asunaprevir and daclatasvir are P-gp substrates. With concomitant use of cyclosporine, increased daclatasvir exposure was observed (daclatasvir $AUC_{(0-tau)}$ increased by 40%), but a dose adjustment is not necessary based on the absence of anticipated safety issues. A corresponding trial with concomitant use of a P-gp inhibitor was not conducted for asunaprevir.

Asunaprevir and daclatasvir exposure were both altered in the presence of food (see 2.5.3). The proposed asunaprevir or daclatasvir U.S. prescribing information both

recommend administration of the respective medication with or with food. This recommendation is acceptable for asunaprevir or daclatasvir.

2.2.5.4   What are the characteristics of drug distribution?

The protein binding of ⬛⬛⬛ (b) (4) daclatasvir is approximately 98% or greater in human species and appears to be concentration independent based on the in vitro studies.

2.2.5.5   Does the mass balance trial suggest renal or hepatic as the major route of elimination?

⬛⬛⬛ (b) (4) daclatasvir are primarily hepatically eliminated.

2.2.5.6   What are the characteristics of drug metabolism?

In plasma, daclatasvir parent drug was the major contributor to total radioactivity. ⬛⬛⬛ (b) (4) ⬛⬛⬛ No asunaprevir or daclatasvir metabolites in plasma were routinely measured in clinical trials.

Figure 4-Proposed metabolic pathways for asunaprevir

Figure 5-Proposed metabolic pathways for daclatasvir

2.2.5.7   What are the characteristics of drug excretion?
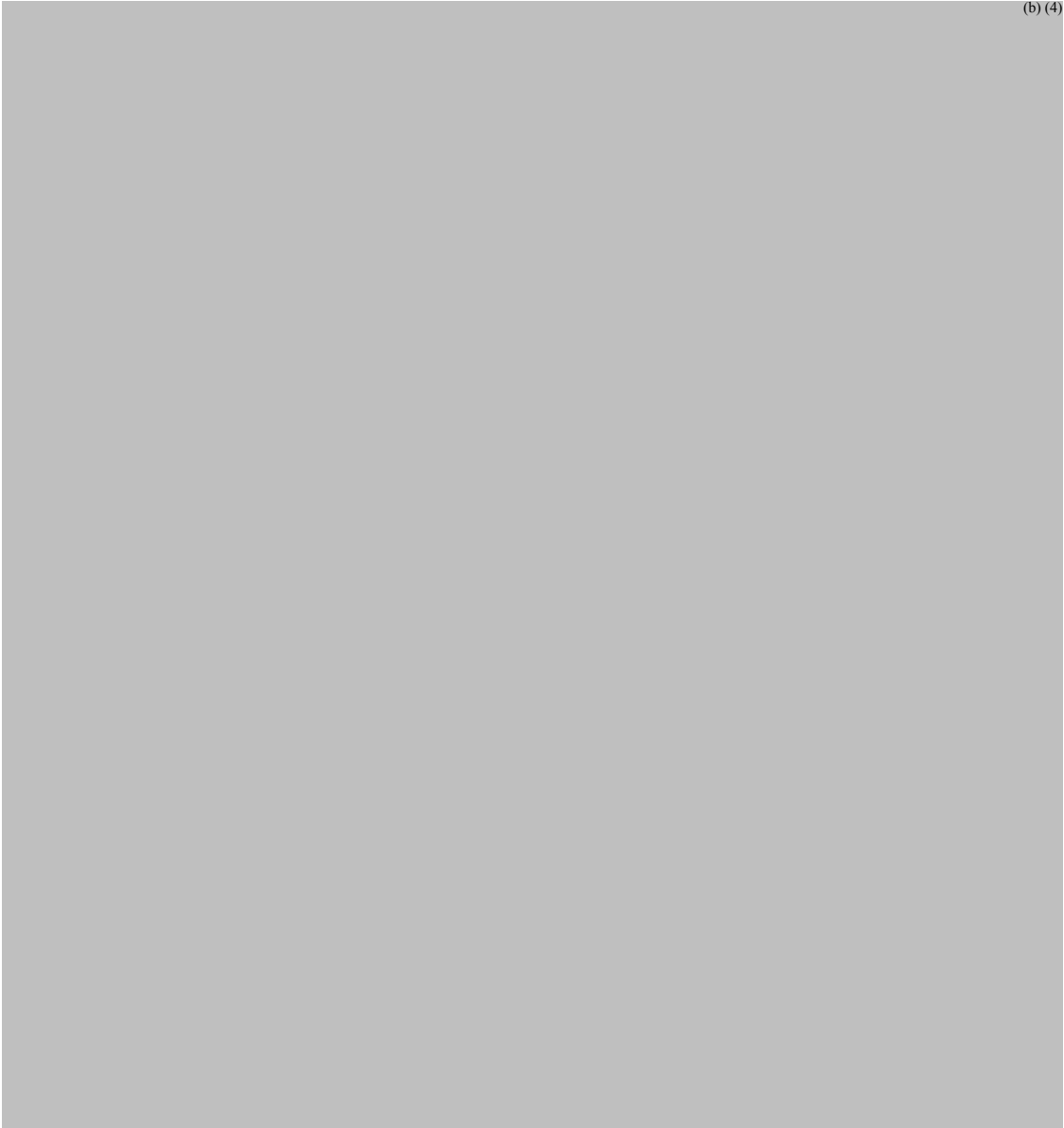
For asunaprevir

            For daclatasvir, the majority of the dose was eliminated through the fecal route (the cumulative amount recovered expressed as the percentage of the dose was 88%) and the cumulative amount recovered expressed as the percentage of the dose was 7% eliminated renally.

Based on the results of the mass balance trials, for asunaprevir, and for daclatasvir, approximately half of the total dose in feces was identified as daclatasvir parent drug (53%) and virtually the entire total dose in urine (6%) was identified as daclatasvir parent drug.

Table 9-Information on asunaprevir and asunaprevir metabolites in feces

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Table 10-Information on daclatasvir and daclatasvir metabolites identified in urine and feces

	Percentage distribution of radioactivity and percentage of dose	
	Urine (0-72 h for human)	Feces (0-144 h for human)
Parent	96.4 (6.4)	60.3 (52.5)
M1	ND	ND
M2	2.8 (0.2)	17.5 (15.2)
M4	0.8 (0.1)	4.6 (4.0)
M7	ND	ND
M9	ND	ND
M11	ND	ND
M20	ND	3.9 (3.4)
M27	ND	ND
M6	ND	1.2 (1.0)
M12	ND	ND
M13	ND	2.2 (1.9)
M15	ND	1.0 (0.9)
M16	ND	1.2 (1.0)
M17	ND	ND
M21	ND	2.7 (2.4)
M24	ND	ND
Total	100	94.6

2.2.5.8   Based on the PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The asunaprevir   (b) (4)

Based on the daclatasvir multiple dosing data in hepatitis C infected subjects, greater than dose proportional increases in $AUC_{(0\text{-tau})}$, C_{max} and C_{min} were observed on Day 14 over 1 to 100 mg once daily, however the analysis was not powered to evaluate dose proportionality. An additional daclatasvir linearity analysis is included in the Pharmacometrics review.

2.2.5.9   How do the PK parameters change with time following chronic dosing?

Based on the multiple dosing trial in hepatitis C infected subjects, there were no significant changes in daclatasvir exposure with multiple dosing over 14 days. ^{(b) (4)}

2.2.5.10   What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Asunaprevir

^{(b) (4)}

Daclatasvir

Based on the population PK analysis, the inter-individual variability, expressed as percent coefficient of variation (%CV), was modest for apparent oral clearance (CL/F, CV 35.1%) and apparent volume of distribution (Vc/F, CV 29.5%). The inter-individual variability (%CV) for the population PK $AUC_{(0-\tau)}$ was approximately 37.6%.

There were no major causes of variability identified. The population pharmacokinetic analysis that was conducted using data from chronic hepatitis C infected subjects enrolled in the Phase 3 trials determined that covariates including body weight, race, age less than 65 years old, and gender only demonstrated a minimal or no influence on asunaprevir or daclatasvir exposure.

2.3   Intrinsic Factors

2.3.1   What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, & organ dysfunction) influence exposure &/or response and what is the impact of any differences in exposure on the PDs? What dosage regimen adjustments, if any, are recommended for each of these subgroups?

The covariates that were evaluated had minimal or no influence on asunaprevir or daclatasvir exposure and dosage adjustments are not necessary because of a lack of an exposure-response relationship for either efficacy or safety. For asunaprevir and daclatasvir, a population PK analysis was conducted to investigate the potential effects of selected covariates, including age, gender, body weight, race, and creatinine clearance (CrCL).

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2.3.2   Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

Based on the results from the population PK analysis that was conducted that included data from hepatitis C infected subjects enrolled in the Phase 3 trials, no dosage adjustments are necessary for the covariates discussed below (for the specific groups where data are available).

2.3.2.1   Elderly

Age appeared to have minimal effect on asunaprevir or daclatasvir exposure. Based on results of the population PK analyses, the asunaprevir $^{(b)(4)}$

. The daclatasvir $AUC_{SS(0-24)}$ in subjects < 65 years old (n=184) was 11.9 ± 4.5 µg*h/mL and in subjects >= 65 years old (n=307) the daclatasvir $AUC_{SS(0-24)}$ was 13.6 ± 4.7 µg*h/mL.

2.3.2.2   Pediatrics

The safety and effectiveness of asunaprevir $^{(b)(4)}$

2.3.2.3   Gender

In population PK analyses, the asunaprevir $^{(b)(4)}$ $^{(b)(4)}$

The daclatasvir $AUC_{ss(0-24)}$ in female subjects (n=982) was 14.0 ± 4.7 µg*h/mL and in male subjects (n=1167), the daclatasvir $AUC_{ss(0-24)}$ was 10.5 ± 3.7µg*h/mL.

2.3.2.4   Race

The population PK analysis indicated that there was no clinically significant effect of race (whites, blacks and Asians) on asunaprevir or daclatasvir exposure.

The effect of race on asunaprevir or daclatasvir exposure was assessed in population PK analyses. The asunaprevir $^{(b)(4)}$ $^{(b)(4)}$

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The daclatasvir AUC$_{ss\,(0-24)}$ were as follows: whites, (n=1440, 11.9 ± 4.6 µg*h/mL), , Japanese subjects (n=339, 12.6 ± 4.0 µg*h/mL), other Asians (n=178, 11.8 ± 4.3 µg*h/mL), and blacks (n=156, 12.9 ± 5.0 µg*h/mL).

2.3.2.5   Renal impairment

The renal impairment trial for asunaprevir   (b) (4)

Population PK analysis showed no significant relationship between asunaprevir and daclatasvir exposure and renal function. The steady state AUC   (b) (4) of asunaprevir in
                                                                                    (b) (4)
                                                      (b) (4) The steady state AUC$_{ss(0\_24)}$ of daclatasvir in subjects with CrCL<50, 50<=CrCL<80 and CrCL>=80 were 15.2±5.4 µg*h/mL (n=22), 13.7±4.7 µg*h/mL(n=328), and 11.8±4.4 µg*h/mL (n=1799), respectively.

For daclatasvir, two different methods were used to analyze the data: a regression analysis and a statistical analysis using the observed data. The applicant is proposing to include the regression analysis data for all the renal impairment groups with the exception of the end stage renal disease subjects that were receiving dialysis. Using a regression analysis, the following changes in daclatasvir exposure were derived when compared to subjects with normal renal function using Cockcroft-Gault as the measurement of renal function: 1) 15 mL/min: C_{max} and AUC$_{(0-inf)}$ increased by 15% and 79.6%, respectively, 2) 30 mL/min: C_{max} and AUC$_{(0-inf)}$ increased by 11.8% and 59.8%, respectively, and c) 60 mL/min: C_{max} and AUC$_{(0-inf)}$ increased by 5.8% and 26.4%, respectively. Using a statistical analysis approach, for end stage renal disease subjects, C_{max} decreased by 2.5% and AUC$_{(0-inf)}$ increased by 26.9%. Based on the daclatasvir exposure-response or exposure-safety information, dosage adjustments are not necessary to compensate for the changes in daclatasvir exposure.

2.3.2.6   Hepatic impairment

For asunaprevir,   (b) (4)

When a single dose of daclatasvir 30 mg was administered, the following changes in daclatasvir exposure were observed when the following hepatic impairment groups were comapred to the corresponding matched control group: 1) Child Pugh A: C_{max} and $AUC_{(0-inf)}$ decreased by 45.5% and 42.7%, respectively, 2) Child Pugh B: C_{max} and $AUC_{(0-inf)}$ decreased by 45.2% and 37.6%, respectively, and 3) Child Pugh C: C_{max} and $AUC_{(0-inf)}$ decreased by 54.6% and 36.2%, respectively. An increased free fraction was observed for hepatically impaired subjects in Child Pugh categories A, B and C compared to the corresponding matched control group at each measured time point. Based on the available information from this trial and the daclatasvir exposure-response analysis, dosage adjustments are not necessary to compensate for the changes in total daclatasvir exposure.

2.3.2.7   What pregnancy and lactation use information is there in the application?

There were no trials evaluating the use of asunaprevir or daclatasvir in pregnant or lactating women that were included in the NDA submissions.

2.4   Extrinsic Factors

2.4.1   What extrinsic factors influence dose-exposure and/or response, and what is the impact of any differences in exposure on response?

In the current NDA submission, two extrinsic factors were evaluated: the effect of food on asunaprevir or daclatasvir exposure and drug-drug interactions. Both factors can potentially alter asunaprevir or daclatasvir exposure. The effect of food is discussed in 2.5.3.

The drug-drug interaction trials are discussed in 1.3.9, including information regarding recommendations for managing clinically relevant drug-drug interactions.

2.4.2   Drug-drug interactions

2.4.2.1   Is there an in vitro basis to suspect in vivo drug-drug interactions?

The conclusions below are based, where applicable, on an evaluation of the IC_{50} values evaluating the effect on the relevant CYP enzymes or transporters as well as criteria for interpreting the results based on the information in the FDA's February 2012 guidance document: Drug Interaction Studies -Study Design, Data Analysis, Implications for Dosing, and Labeling.

Cytochrome P450 enzymes

(b) (4)

Daclatasvir

For daclatasvir's effects on other medications, the in vitro information indicated a potential for CYP3A inhibition and induction. Daclatasvir is also a CYP3A substrate.

Transporters

(b) (4)

Daclatasvir

For daclatasvir's effects on transporters, the in vitro information indicated a potential for P-gp, BCRP, OATP1B1 and OATP1B3 inhibition. Daclatasvir is also a P-gp substrate.

2.4.2.2   Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

The in vitro study results indicate that CYP3A is the primary cytochrome P450 enzyme system responsible for asunaprevir or daclatasvir metabolism.

The influence of genetics on asunaprevir or daclatasvir metabolism was not evaluated as part of the NDA submission. (b) (4)

2.4.2.3   Is the drug an inhibitor and/or an inducer of CYP enzymes?

Based on the available data, the major CYP mediated interaction of clinical relevance is potential asunaprevir (b) (4)
.

2.4.2.4   Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Please see the response for 2.4.2.1.

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2.4.2.5   Are there other metabolic/transporter pathways that may be important?

Based on the information provided in the current NDA submissions, no additional CYP enzyme metabolism pathways and transporters are relevant that have not been discussed in this section.

2.4.2.6   Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

The concomitant use of asunaprevir and daclatasvir were evaluated in a drug-drug interaction trial. No efficacy or safety issues related to changes in asunaprevir or daclatasvir exposure due to potential drug-drug interaction issues were identified in clinical trials with concurrent use of these medications. Similarly, while a drug-drug interaction trial was not conducted for asunaprevir coadministered with daclatasvir plus pegylated interferon alpha and ribavirin, no efficacy or safety issues were identified in clinical trials with concurrent use of these medications.

2.4.2.7   What other co-medications are likely to be administered to the target patient population?

Based on the potential for a drug-drug interaction with asunaprevir or daclatasvir, the applicant has sufficiently evaluated the appropriate representative medications likely to be administered to chronic hepatitis C infected patients.

2.4.2.8   Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Please see section 1.3.9 for a list of potential drug-drug interactions that warrant either a contraindication or a dosage adjustment.

2.4.2.9   Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

There are no pharmacodynamic drug-drug interactions for asunaprevir and daclatasvir.

2.4.2.10   Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

There are no unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding.

2.4.3   What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

No issues related to dose, dosing regimens, or administration are unresolved or that represent significant omissions.

2.5   General Biopharmaceutics

2.5.1   Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

According to the applicant,   ^{(b) (4)} BCS Class 2 compounds based on the solubility data and the PAMPA permeability model.

2.5.2   What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

According to the biopharmaceutics reviewer, no major differences exist between the to-be-marketed formulations of asunaprevir and daclatasvir and the formulations that were administered in the two Phase 3 trials.

2.5.2.1   What data support or do not support a waiver of in vivo BE data?

A biowaiver of in vivo BE data for the daclatasvir 30 mg tablet was requested. Please see the biopharmaceutics review for further information.

2.5.3   What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Asunaprevir

(b) (4)

Daclatasvir

For the daclatasvir Phase 3 tablets, when a single dose of daclatasvir 60 mg was administered with a high fat meal, the daclatasvir C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were decreased by 28%, 24% and 23%, respectively, when compared with a single dose of daclatasvir 60 mg administered under fasted conditions. The 90% confidence intervals for daclatasvir C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were all not within the standard "no effect" 90% confidence interval limits of 80%-125%. The specific 90% confidence intervals were 66% to 79% for C_{max}, 72% to 80% for $AUC_{(0-t)}$ and 73% to 80% for $AUC_{(0-inf)}$. A food effect was observed on daclatasvir exposure when administered with high fat meals with the daclatasvir Phase 3 tablets Based on the daclatasvir exposure-response information, the recommendation to administer daclatasvir with or without food is acceptable.

2.5.4   When would a fed BE study be appropriate and was one conducted?

This question is not applicable to the asunaprevir or daclatasvir NDA submissions.

2.5.5   How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

Please refer to the asunaprevir or daclatasvir biopharmaceutics review for information regarding dissolution conditions and specifications.

2.5.6   What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

There are no in vivo BA and BE issues that need to be addressed for the asunaprevir or daclatasvir NDA submissions. Please refer to the asunaprevir or daclatasvir biopharmaceutics review for information regarding the review of the in vitro dissolution data for asunaprevir or daclatasvir.

2.6   Analytical section

2.6.1   How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Asunaprevir or daclatasvir plasma samples and whole blood or plasma samples for concomitant medications were analyzed using LC/MS/MS analytical methods.

Which metabolites have been selected for analysis and why?

2.6.2   Which metabolites have been selected for analysis and why?

There were no metabolites that were routinely analyzed to further characterize the exposure, exposure-response for efficacy, or exposure-safety of asunaprevir or

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daclatasvir.

2.6.3   For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

For asunaprevir or daclatasvir, total plasma concentrations were determined with specific exceptions (e.g. hepatic or renal impairment trials). The plasma protein binding of asunaprevir or daclatasvir is concentration independent according to the in vitro data. Analysis of free or pharmacologically active concentrations is not expected to provide additional information to further characterize the exposure, exposure-response, or exposure-safety of asunaprevir or daclatasvir.

2.6.4   What bioanalytical methods are used to assess concentrations?

Please see the individual trial reviews in section 4 for information regarding the bioanalysis of asunaprevir, daclatasvir or concomitant medications in the clinical trials.

3 Labeling Recommendations

The applicant's proposed language and the clinical pharmacology reviewer's preliminary proposed modifications for the asunaprevir or daclatasvir U.S. prescribing information are displayed below.

Asunaprevir

(b) (4)

31 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Daclatasvir

Section 4

Applicant proposed language	Proposed reviewer changes
Table 2	*Clinical pharmacology reviewer comment: For the examples of the strong CYP3A inducers, the specific medications were edited to be consistent with the list of strong CYP3A inducers that are included in the draft February 2102 guidance-Drug Interaction Studies-Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations or the information in the respective U.S prescribing information.*

Applicant proposed language — Table 2

Mechanism of Interaction	Clinical Comment	Drugs that are Contraindicated with <TRADENAME-DCV>[a]
Strong induction of CYP3A4 by coadministered drug	May lead to loss of virologic response to <TRADENAME-DCV>	*Anticonvulsants* phenytoin, carbamazepine, (b) (4) *Antimycobacterial agents* rifampin, (b) (4) (b) (4) *Herbal products* St. John's wort (*Hypericum perforatum*)

[a] This table is not a comprehensive list of all drugs that strongly induce CYP3A4

Proposed reviewer changes — table

Mechanism of Interaction	Clinical Comment	Drugs that are Contraindicated with <TRADENAME-DCV>[a]
Strong induction of CYP3A4 by coadministered drug	May lead to loss of virologic response to <TRADENAME-DCV>	*Anticonvulsants* phenytoin, carbamazepine, *Antimycobacterial agents* rifampin *Herbal products* St. John's wort (*Hypericum perforatum*)

[a] This table is not a comprehensive list of all drugs that strongly induce CYP3A4

Section 7

Applicant proposed language	Proposed reviewer changes
Table 6 (b) (4) [redacted] ᵇ These interactions have been studied [*see Clinical Pharmacology (12.3, Table 6 and Table 7)*].	*Clinical pharmacology reviewer comment: The separate entries for* [redacted] (b) (4) *should be deleted and a separate table included for strong CYP3A inhibitors or moderate CYP3A inducers.*

Strong CYP3A inhibitors Examples: clarithromycin, conivaptan, itraconazole, ketoconazole, nefazodone, posaconazole,, telaprevir, telithromycin, voriconazole , and certain HIV protease inhibitors (e.g. indinavir, nelfinavir, ritonavir, saquinavir).	↑ Daclatasvir	The dose of <TRADENAME-DCV> should be reduced to 30 mg once daily when coadministered with strong inhibitors of CYP3A.
Moderate CYP3A inducers Examples: Bosentan, efavirenz, modafinil, nafcillin	↓ Daclatasvir	The dose of <TRADENAME-DCV> should be increased to 90 mg once daily when coadministered with moderate inducers of CYP3A.

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(b) (4)

Applicant proposed language	Proposed reviewer changes
<u>Table 6</u> **Cardiovascular agents** Antiarrhythmic: Digoxin ↑ Digoxin[b] (b) (4) [b] These interactions have been studied [*see Clinical Pharmacology (12.3, Table 6 and Table 7)*].	Clinical pharmacology reviewer comment: In the U.S prescribing information for digoxin, for drug-drug interactions resulting in an increase in digoxin concentrations greater than 50%, the recommendation states: *Measure serum digoxin concentrations before initiating concomitant drugs. Reduce digoxin concentrations by decreasing dose by approximately 30-50% or by modifying the dosing frequency and continue monitoring.*

Proposed reviewer changes table:

Cardiovascular agents		
Antiarrhythmic: Digoxin	↑ Digoxin[b]	**<u>Patients already receiving daclatasvir initiating digoxin:</u>** Initiate treatment using the lowest appropriate digoxin dose. Monitor digoxin concentrations; adjust digoxin doses if necessary and continue monitoring. **<u>Patients already receiving digoxin prior to initiating daclatasvir:</u>** Measure serum digoxin concentrations before initiating daclatasvir. Reduce digoxin concentrations by decreasing dose by approximately 30-50% or by modifying the dosing frequency and continue monitoring.

[b]These interactions have been studied [see Clinical Pharmacology (12.3, Table 6 and Table 7)].

Applicant proposed language	Proposed reviewer changes
Section 7.4-Other Drugs Based on the results of drug interaction studies [*see Clinical Pharmacology (12.3)*], no dose adjustment is recommended when <TRADENAME-DCV> is given wit [REDACTED] (b) (4) [REDACTED]	*Clinical pharmacology reviewer comment:* [REDACTED] (b) (4) [REDACTED] *The wording for the information in section 7.4 was modified to account for the possibility that dosage adjustments may not be possible with certain medications. The wording regarding potential interactions with* [REDACTED] (b) (4) *sofosbuvir, peginterferon alfa, or ribavirin was also edited.* Table 6 [REDACTED] (b) (4) b These interactions have been studied [*see Clinical Pharmacology (12.3, Table 6 and Table 7)*]. Based on the results of drug interaction studies [*see Clinical Pharmacology (12.3)*], no clinically relevant changes in exposure were observed for daclatasvir or the following concomitant medications: cyclosporine, escitalopram, famotidine, methadone, midazolam, omeprazole, simeprevir, tacrolimus, or tenofovir. No clinically relevant interaction is anticipated for daclatasvir or the following concomitant medications: [REDACTED] (b) (4) atazanavir/ritonavir, sofosbuvir, peginterferon alfa, or ribavirin.

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Section 12.3-Pharmacokinetics

Applicant proposed language	Proposed reviewer changes
(b) (4)	*Clinical Pharmacology Reviewer note: The geometric mean population PK parameters for DCV should be included.*
(b) (4)	(b) (4)

Applicant proposed language	Proposed reviewer changes
Absorption and Bioavailability ████████████████ (b) (4) following multiple oral doses (b) (4) peak plasma concentrations occur (b) (4) 2 hours. ████████ ████████████████████████████. *In vitro* studies with human Caco-2 cells indicated that daclatasvir is a substrate of P-gp. The absolute bioavailability of the tablet formulation is 67%.	*Clinical Pharmacology Reviewer note: The information below in the first paragraph was modified to reflect the information from the multiple dosing trial in hepatitis C infected subjects.* **Absorption and Bioavailability** When daclatasvir was administered as a tablet following multiple oral doses in Hepatitis C infected subjects ranging from 1 mg to 100 mg once daily, with multiple dosing, peak plasma concentrations occurred between 1 and 1.75 hours and the daclatasvir C_{max}, AUC, and C_{min} increased in a greater than dose-proportional manner. At the 60 mg dose, no clinically relevant differences in daclatasvir exposure were observed between healthy and HCV-infected subjects. *In vitro* studies with human Caco-2 cells indicated that daclatasvir is a substrate of P-gp. The absolute bioavailability of the tablet formulation is 67%.

Applicant proposed changes	Proposed reviewer changes
Effect of Food on Oral Absorption In healthy subjects, administration of a daclatasvir 60 mg tablet after a high-fat meal (approximately (b) (4) kcal, (b) (4)) decreased daclatasvir C_{max} and AUC by 28% and 23%, respectively, compared with (b) (4) fas (b) (4) conditions. Administration of a daclatasvir 60 mg tablet after a (b) (4) meal (approximately 27 (b) kcal, (b) (4) [*see Dosage and Administration (2)*].	**Effect of Food on Oral Absorption** In healthy subjects, administration of a daclatasvir 60 mg tablet after a high-fat meal (approximately 950 kcal, approximately 50% from fat) decreased daclatasvir C_{max} and AUC by 28% and 23%, respectively, compared with administration under fasting conditions. Administration of a daclatasvir 60 mg tablet after a light meal (approximately 275 kcal, approximately 15% from fat) did not reduce daclatasvir exposure [*see Dosage and Administration (2)*].

Applicant proposed changes	Proposed reviewer changes
Metabolism (b) (4) daclatasvir is a substrate of CYP3A, with CYP3A4 the major CYP isoform responsible for the metabolism. (b) (4)	**Metabolism** *In vitro* studies demonstrate that daclatasvir is a substrate of CYP3A, with CYP3A4 the major CYP isoform contributing to daclatasvir's metabolism based on the mass balance and in vitro information. In plasma, the distribution of radioactivity was predominately attributed to parent drug (97% or greater).

Applicant proposed changes	Proposed reviewer changes
Elimination Following single-dose oral administration of ^{14}C-daclatasvir in healthy subjects, 88% of total radioactivity was recovered in feces (53% as unchanged (b) (4)) and 6.6% was excreted in the urine (primarily as unchanged (b) (4)). Following multiple-dose administration of daclatasvir in HCV-infected subjects, the terminal elimination half-life of daclatasvir ranged from 12 to 15 hours. In subjects who received daclatasvir 60 mg tablet orally followed by 100 µg [^{13}C,^{15}N]-daclatasvir intravenous dose, the total clearance was 4.24 L/h.	**Elimination** Following single-dose oral administration of ^{14}C-daclatasvir in healthy subjects, 88% of total radioactivity was recovered in feces (53% of the dose as unchanged daclatasvir) and 6.6% was excreted in the urine (primarily as unchanged drug). Following multiple-dose administration of daclatasvir in HCV-infected subjects ranging from 1 mg to 100 mg once daily, the terminal elimination half-life of daclatasvir ranged from approximately 12 to 15 hours. In subjects who received daclatasvir 60 mg tablet orally followed by 100 µg [^{13}C,^{15}N]-daclatasvir intravenous dose, the total clearance was 4.24 L/h.

Applicant proposed changes	Proposed reviewer changes
Specific Populations *Renal Impairment* (b) (4) Daclatasvir is highly protein bound to plasma proteins and is unlikely to be removed by dialysis.	**Specific Populations** *Renal Impairment* (b) (4) Daclatasvir is highly protein bound to plasma proteins, and is unlikely to be removed by dialysis.

Applicant proposed changes	Proposed reviewer changes
Specific Populations *Hepatic Impairment* (b) (4)	**Specific Populations** *Hepatic Impairment* The pharmacokinetics of daclatasvir following a 30 mg single dose were studied in non–HCV-infected subjects with mild (Child-Pugh A), moderate (Child-Pugh B), and severe (Child-Pugh C) hepatic impairment compared with the corresponding matched control group. In Child Pugh A subjects, C_{max} and $AUC_{(0-inf)}$ were decreased by (b) (4) % and (b) (4) %, respectively. In Child Pugh B subjects, C_{max} and $AUC_{(0-inf)}$ were decreased by 45.2% and 37.6%, respectively. In Child Pugh C subjects, C_{max} and $AUC_{(0-inf)}$ were decreased by (b) (4) % and (b) (4) %, respectively [*see Use in Specific Populations (8.7)*].

Applicant proposed changes	Proposed reviewer changes
Specific Populations *Gender* Population pharmacokinetic analysis (b) (4)	**Specific Populations** *Gender* Based on the population pharmacokinetic analysis of data from clinical trials the magnitude of the effect for gender on daclatasvir exposure is not clinically relevant.

75

Applicant proposed changes	Proposed reviewer changes
Specific Populations *Race* Population pharmacokinetic analysis ^{(b) (4)}	**Specific Populations** *Race* Based on the population pharmacokinetic analysis of data from clinical trials the magnitude of the effect for race on daclatasvir exposure is not clinically relevant.

Drug Interactions

Daclatasvir is a substrate of CYP3A4.   (b) (4)

Drug Interactions

<u>CYP enymes</u>
Daclatasvir is a substrate of CYP3A. *In vitro*, daclatasvir did not inhibit (IC_{50} >40 µM) CYP enzymes 1A2, 2B6, 2C8, 2C9, 2C19, or 2D6. Daclatasvir did not have a clinically relevant effect on the pharmacokinetics of midazolam, a sensitive CYP3A substrate.

<u>Transporters</u>
Daclatasvir is a substrate of P-gp. However, cyclosporine, which inhibits multiple transporters including P-gp, did not have a clinically relevant effect on the pharmacokinetics of daclatasvir.

Daclatasvir, *in vitro*, did not inhibit OCT2 and did not have a clinically relevant effect on the pharmacokinetics of tenofovir, an OAT1/OAT3 substrate. Daclatasvir demonstrated inhibitory effects on digoxin (a P-gp substrate) and rosuvastatin (an OATP1B1, OATP1B3, and BCRP substrate) in drug-drug interaction trials.

Drug interaction studies were conducted with daclatasvir and other drugs likely to be coadministered or drugs commonly used as probes to evaluate potential drug-drug interactions. The effects of daclatasvir on the C_{max}, AUC, and C_{min} of the coadministered drug are summarized in Table 6, and the effects of the coadministered drug on the C_{max}, AUC, and C_{min} of daclatasvir are summarized in Table 7. For information regarding clinical recommendations, see *Contraindications (4)* and *Drug Interactions (7.3)*. Drug interaction studies were conducted in healthy adults unless otherwise noted.

Applicant proposed changes	Proposed reviewer changes
Table 6:-Effect of <TRADENAME-DCV> on the Pharmacokinetics of Concomitant Drugs	*Clinical pharmacology reviewer note: the Cmin should be defined as a footnote:*

Concomitant Drug	Co administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min} [g]

[g] The C_{min} was defined either as the C_{tau} or the Ct_{rough} daclatasvir concentration value.

Applicant proposed changes	Proposed reviewer changes
Table 6:-Effect of <TRADENAME-DCV> on the Pharmacokinetics of Concomitant Drugs	*Clinical pharmacology reviewer note: The data for asunaprevir should be deleted because it assumes that the differences in asunaprevir exposure are dose proportional. Based on the available information, the changes in asunaprevir exposure do not appear to be dose proportional. A statement regarding the potential interaction for asunaprevir plus daclatasvir is included in section 7.*

Concomitant Drug	Co administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}

(b) (4)

Applicant proposed changes	Proposed reviewer changes

Table 6:-Effect of \<TRADENAME-DCV> on the Pharmacokinetics of Concomitant Drugs

Concomitant Drug	Co administered Drug Dose	\<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}
					(b) (4)

Table 6:-Effect of \<TRADENAME-DCV> on the Pharmacokinetics of Concomitant Drugs

Concomitant Drug	Co administered Drug Dose	\<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}
					(b) (4)
Cyclosporine	400 mg single dose	60 mg QD			

Applicant proposed changes	Proposed reviewer changes

Table 6:-Effect of <TRADENAME-DCV> on the Pharmacokinetics of Concomitant Drugs

Concomitant Drug	Co administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}

(b) (4)

Table 6:-Effect of <TRADENAME-DCV> on the Pharmacokinetics of Concomitant Drugs

Concomitant Drug	Co administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}

(b) (4)

Applicant proposed changes	Proposed reviewer changes
Table 6:-Effect of <TRADENAME-DCV> on the Pharmacokinetics of Concomitant Drugs	*Clinical pharmacology reviewer note: The bolded drug-drug interaction data can be deleted because the low exposure oral contractive comparison is not critical to management of a potential drug-drug interaction.* Table 6:-Effect of <TRADENAME-DCV> on the Pharmacokinetics of Concomitant Drugs

Table 6:-Effect of <TRADENAME-DCV> on the Pharmacokinetics of Concomitant Drugs

Concomitant Drug	Co administered Drug Dose	<TRADE -NAME- DCV> Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}
					(b) (4)

Table 6:-Effect of <TRADENAME-DCV> on the Pharmacokinetics of Concomitant Drugs

Concomitant Drug	Co administered Drug Dose	<TRADE -NAME- DCV> Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}
					(b) (4)

Table 6:-Effect of <TRADENAME-DCV> on the Pharmacokinetics of Concomitant Drugs

Concomitant Drug	Co Administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}
Methadone	40-120 mg QD individualized dose[d]	60 mg QD	(b) (4)		

[d] Evaluated in _____ (b) (4) adults on stable methadone maintenance therapy.

Clinical pharmacology reviewer note: the total and _____ (b) (4) *PK data should also be added. In addition, the following note should be added* (b) (4)

Table 6:-Effect of <TRADENAME-DCV> on the Pharmacokinetics of Concomitant Drugs

Concomitant Drug	Co administered Drug Dose	<TRADE -NAME- DCV> Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min} (b) (4)

Clinical pharmacology reviewer note: The drug-drug interaction data does not need to be included. A statement regarding the potential interaction (b) (4)
for p

Table 6:-Effect of <TRADENAME-DCV> on the Pharmacokinetics of Concomitant Drugs

Concomitant Drug	Co administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}
					(b) (4)

Clinical pharmacology reviewer note: In the absence of method validation data for _____ (b) (4), the drug-drug interaction data should not be included in Table 6. A statement regarding the potential interaction for _____ (b) (4) _____

Table 7:Effect of Coadministered Drugs on <TRADENAME-DCV> Pharmacokinetics

Concomitant Drug	Co administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}
					(b) (4)

Clinical pharmacology reviewer note: (b) (4)

Table 7:Effect of Coadministered Drugs on <TRADENAME-DCV> Pharmacokinetics

Concomitant Drug	Co administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}
Atazanavir/ ritonavir	300 mg/100 mg QD	20 mg QD			(b) (4)

(b) (4)

Clinical pharmacology reviewer note: The data for daclatasvir should be deleted because it assumes that the differences in daclatasvir exposure are dose proportional. Based on the available information, the changes in daclatasvir exposure do not appear to be dose proportional. Information regarding the potential interaction for atazanavir/ritonavir plus daclatasvir is included in section 7.

Table 7:Effect of Coadministered Drugs on <TRADENAME-DCV> Pharmacokinetics

Concomitant Drug	Co administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}
Efavirenz	600 mg QD	60 mg QD (b) (4) (b) (4) 120 mg OD (b) (4)			(b) (4)

(b) (4)

Clinical pharmacology reviewer note: The data for daclatasvir should be deleted because it assumes that the differences in daclatasvir exposure are dose proportional. Based on the available information, the changes in daclatasvir exposure do not appear to be dose proportional. Information regarding the potential interaction for efavirenz plus daclatasvir is included in section 7.

Table 7:Effect of Coadministered Drugs on <TRADENAME-DCV> Pharmacokinetics

Concomitant Drug	Co administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}
Famotidine	40 mg single dose	60 mg single dose	0.56 (0.46, 0 (b)(4))	0.82 (0.70, 0.96)	0.89 (0.75, 1.06)

Table 7:Effect of Coadministered Drugs on the Pharmacokinetics of <TRADENAME-DCV>

Concomitant Drug	Co administered Drug Dose	<TRADE-NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}
Famotidine	40 mg single dose	60 mg single dose	0.56 (0.46, 0.67)	0.82 (0.70, 0.96)	0.89 (0.75, 1.06)

Table 7:Effect of Coadministered Drugs on <TRADENAME-DCV> Pharmacokinetics

Concomitant Drug	Co administered Drug Dose	<TRADE -NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}

Clinical pharmacology reviewer note: The drug-drug interaction data does not need to be included. A statement regarding the potential interaction

(b) (4)

Table 7:Effect of Coadministered Drugs on <TRADENAME-DCV> Pharmacokinetics

Concomitant Drug	Co administered Drug Dose	<TRADE -NAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}

Clinical pharmacology reviewer note: The drug-drug interaction data does not need to be included. A statement regarding the potential interaction

(b) (4)

Patient prescribing information

Applicant proposed changes	Proposed reviewer changes
(b) (4)	

Applicant proposed changes	Proposed reviewer changes
	(b) (4)

4   Appendices

4.1 Individual Trial Reviews

Trial Reviews	Page Numbers
Absolute/Relative bioavailability trials	92
Drug-drug interaction trials	129
Food effect trials	332
Hepatic impairment trials	339
Mass balance trials	356
Multiple dosing trials	375
Renal impairment trials	390
In vitro studies	411

Absolute and relative bioavailability trials-asunaprevir

Trial Number	Title	Page Number
(b) (4)		94
		99
		99

Absolute and relative bioavailability trials-daclatasvir

Trial Number	Title	Page Number
AI444044	Study of the Absolute Oral Bioavailability of BMS-790052 in Healthy Subjects	108
AI444009	Bioavailability of BMS-790052 (b) (4) Tablet and (b) (4) Tablet Relative to BMS-790052 Capsule and Effect of a High Fat Meal and Famotidine on the Pharmacokinetics of BMS-790052 in Healthy Subjects	113
AI444039	Bioavailability of BMS-790052 Phase 3 (b) (4) Tablet Relative to Phase 2 (b) (4) Tablet and the Effect of a High Fat Meal and Light Meal on the	122

| | Pharmacokinetics of BMS-790052 when Administered as the Phase 3 (b) (4) Tablet in Healthy Subjects | |

1. Title

Final Clinical Study Report for Study AI444044 Study of the Absolute Oral Bioavailability of BMS-790052 in Healthy Subjects

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at one site from April 18, 2012 (trial initiation) to May 10, 2012 (trial completion).

3. Objectives

The objectives of the trial included evaluating the absolute bioavailability of daclatasvir.

4. Trial Design

AI444044 was an open label clinical trial that enrolled healthy subjects 18 to 49 years old. Information on the trial design is displayed in Figure 1.

Figure 1-AI444044 trial design

Screening within 21 days of Day 1	Admit to clinical facility	Dosing on Day 1 60 mg dose of BMS-790052 60 mg orally, followed 1 hour later by a 100 µg dose of $[^{13}C, ^{15}N]$-BMS-790052 intravenously	Discharge
21 Day screening period	Day -1	Day 1	Day 4

5. Excluded Medications, Restrictions or Exceptions

Unless otherwise approved, prescription medications or nonprescription acid modifying medications were not permitted within 4 weeks and nonprescription medications, including herbal products, were not permitted within 2 weeks prior to medication administration. In general, prescription and nonprescription medications, including herbal products, were not permitted during the trial.

6. Dosage and Administration

The trial design, including the dose that was administered, is specified in Figure 1. The single 60 mg daclatasvir oral dose was administered under fasted conditions after fasting for 10 hours. For daclatasvir, the applicant is proposing to administer the medication with or without food.

7. Rationale for Doses Used in the Trial

The daclatasvir single dose of 60 mg is consistent with the proposed dosage regimen of 60 mg once daily. The 100 microgram stable labeled daclatasvir dose was selected based on recommendations regarding microdosing.

8. Drugs Used in the Trial

Information regarding the daclatasvir formulations that were administered in the trial is displayed in Table 1.

Table 1-Information on the daclatasvir formulations administered in the AI444044 trial

Drug Product	Route of Administration	Product ID Number	Product Batch Number
BMS-790052, 60 mg	Oral	790052-K060-028	1D65922
[^{13}C, ^{15}N]BMS-790052, 100 µg	IV	790052-NX05-001	2A76030

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood samples that were obtained included daclatasvir blood samples at predose and up to 72 hours postdose.

Bioanalysis

The method and bioanalysis of daclatasvir are acceptable. Daclatasvir plasma samples were analyzed using a validated LC/MS/MS method in EDTA anticoagulated plasma by BMS (930057408). The blood samples for analysis of daclatasvir appear to have been collected in tubes containing EDTA.

For the AI444044 plasma samples that were analyzed for daclatasvir, the lower limit of quantification for daclatasvir was 2 ng/mL and the upper limit of quantification was 500 ng/mL for the non stable labeled daclatasvir analyte and the lower limit of quantification for daclatasvir was 0.02 ng/mL and the upper limit of quantification was 5 ng/mL for the stable labeled daclatasvir analalyte. There were no precision or accuracy issues identified for daclatasvir based on the bioanalytical report. For the AI444044 trial, for the non stable labeled daclatasvir analyte, precision and accuracy were evaluated using plasma daclatasvir quality control (QC) samples at 5 ng/mL, 35 ng/mL, 250 ng/mL and 380 ng/mL. The corresponding daclatasvir inter-run accuracy values were 5.2% for 5 ng/mL, 3.1% for 35 ng/mL, 3.4% for 250 ng/mL and 2.6% for 380 ng/mL. The daclatasvir inter-run precision values were 2.7% for 5 ng/mL, 2.3% for 35 ng/mL, 1.7% for 250 ng/mL

and 1.6% for 380 ng/mL. For the stable labeled daclatasvir analyte, precision and accuracy were evaluated using plasma daclatasvir quality control (QC) samples at 0.05 ng/mL, 0.35 ng/mL, 2.5 ng/mL and 3.8 ng/mL. The corresponding daclatasvir inter-run accuracy values were 2.4% for 0.05 ng/mL, -1.1% for 0.35 ng/mL, 2.1% for 2.5 ng/mL and 2.4% for 3.8 ng/mL. The daclatasvir inter-run precision values were 3.7% for 0.05 ng/mL, 1.7% for 0.35 ng/mL, 1.7% for 2.5 ng/mL and 1.4% for 3.8 ng/mL.

For the AI444044 trial, in response to an information request, the applicant stated that the daclatasvir plasma samples were stored at the trial site at -20°C for up to 15 days and the bioanalytical laboratory at -20°C for up to 27 days. For the 930057408 method, the generated long term stability data for daclatasvir included stability data in EDTA anticoagulated plasma at -20°C for 154 days. For the AI444044 trial, the generated long term stability data appears to cover the duration of long term stability data necessary for daclatasvir.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for daclatasvir. For the noncompartmental analysis, daclatasvir plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, and $AUC_{(0-inf)}$ for both the non stable labeled daclatasvir analyte and the stable labeled daclatasvir analyte.

Statistical Analysis

The absolute bioavailability for daclatasvir was calculated using the following equation:

$$F = \frac{[AUC(INF)]_{po}/dose_{po}}{[AUC(INF)]_{IV}/dose_{IV}}$$

10. Results

10.1 Subject Demographics

Table 2-AI444044 subject demographics

```
-----------------------------------------------------------------------
                                             Total
                                             N=8
-----------------------------------------------------------------------

AGE (YRS)
   N                                                8
   MEAN                                          33.8
   MEDIAN                                        36.0
   MIN, MAX                                   19 , 47
   STANDARD DEVIATION                           12.16

AGE CATEGORIZATION (%)
   < 65                                      8 (100.0)
   >= 65                                     0

GENDER (%)
   MALE                                      7 ( 87.5)
   FEMALE                                    1 ( 12.5)

RACE (%)
   WHITE                                     7 ( 87.5)
   BLACK OR AFRICAN AMERICAN                 1 ( 12.5)

ETHNICITY (%)
   HISPANIC/LATINO                           0
   NOT HISPANIC/LATINO                       8 (100.0)

-----------------------------------------------------------------------
```

10.2 Concomitant Medications

No concomitant medications were administered in the trial.

10.3 Pharmacokinetic and Statistical Analysis

Table 3-Single dosing daclatasvir pharmacokinetic parameters with 60 mg oral dosing and 100 microgram intravenous dosing

Analyte (N = 8)	AUC(INF) (ng.h/mL) Geo. Mean (CV%)	AUC(0-T) (ng.h/mL) Geo. Mean (CV%)	CMAX (ng/mL) Geo. Mean (CV%)	T-HALF (h) Mean (SD)	TMAX (h) Median (MIN,MAX)	CL (L/h) Geo. Mean (CV%)	Vss (L) Mean (SD)	F (%) Geo. Mean (CV%)
BMS-790052	9486	9396	928	11.9	1.38	NA	NA	67.0
	(33)	(33)	(41)	(2.12)	(1.13, 2.02)			(20)
$[^{13}C,^{15}N]$BMS-790052	23.6	23.0	6.57	9.51	0.133	4.24	47.1	NA
	(24)	(24)	(26)	(1.93)	(0.133, 0.167)	(21)	(9.78)	

Treatments: A = BMS-790052 Phase 2 ▓▓▓(b) (4) tablets, 2×30 mg, fasted; B = BMS-790052 Phase 3 ▓▓▓(b) (4) tablet, 1×60 mg, fasted; C = BMS-790052 Phase 3 ▓▓▓(b) (4) tablet, 1×60 mg, with high-fat meal; D = BMS-790052 Phase 3 ▓▓▓(b) (4) tablet, 1×60 mg, with light meal

Table 4-Statistical analyses for daclatasvir

BMS-790052 Pharmacokinetic Parameter	Point Estimate	90% CI
F (%)	67.0	(56.2, 79.8)

10.4 Safety Analysis

No deaths, serious adverse events or adverse events resulting in discontinuation were reported for the trial.

11. Discussion and Conclusions

Based on the results from the AI444044 trial, the absolute bioavailability of daclatasvir is 67%.

<u>AI444009 trial</u>

1. Title

Bioavailability of Daclatasvir (BMS-790052) [   ] (b) (4) Tablet and [   ] (b) (4) [   ] (b) (4) Tablet Relative to BMS-790052 Capsule and Effect of a High Fat Meal and Famotidine on the Pharmacokinetics of BMS-790052 in Healthy Subjects.

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at Orlando clinical research center, Orlando, FL by BMS from November 10, 2008 to January 23, 2009.

3. Objectives

The primary objective was to assess the bioavailability of BMS-790052 as 6x10 mg (b) (4) [   ] tablets and 6x10 mg [   ] (b) (4) tablets relative to the 6x10 mg reference capsules in healthy subjects.

The secondary objectives were:
- To assess the effect of a high fat meal on the PK of BMS-790052 when administered as the [   ] (b) (4) tablet. (*Not reviewed here*)
- To assess the effect of famotidine on the PK of BMS-790052 when administered as the [   ] (b) (4) tablet.
- To assess the bioavailability of BMS-790052 as 6x10 mg [   ] (b) (4) tablets relative to 6x10 mg [   ] (b) (4) tablets.
- To assess the safety and tolerability of BMS-790052

4. Trial Design

The study was an open label randomized, 5-period, 5-treatment, crossover study in healthy subjects (**Figure 1**). Eighteen subjects were enrolled and randomized according to one of six randomly assigned treatment sequences (**Figure 2**). The subjects were admitted to the clinical facility the day before dosing (Day -1) in Period 1 and confined to the clinical facility for the duration of the study. All subjects received a single oral dose of BMS-790052 in each period with a 4-day washout between each dose. In Periods 1, 2 and 3, each subject was randomized to receive one of six sequences either Treatment A (reference capsules), Treatment B ([   ] (b) (4) tablets), or Treatment C ([   ] (b) (4) [   ] (b) (4) tablets) in the morning, after at least a 10 h fast. All subjects received Treatment D ([   ] (b) (4) tablets with a high-fat meal) in Period 4 and Treatment E ([   ] (b) (4) tablets 2 hours post administration of 40 mg famotidine under fasted condition) in Period 5.

Figure 1: Study Design Schematic
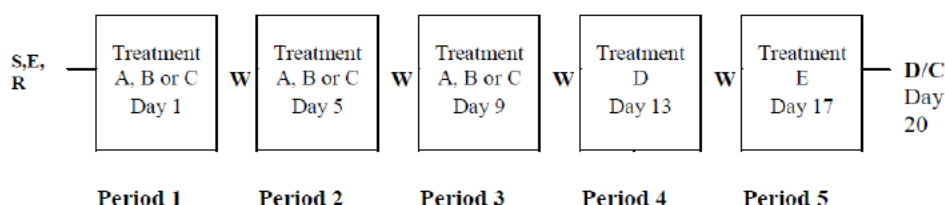
S: Screening	Treatment A: BMS-790052 reference capsule, 6x10 mg, fasted
E: Enrollment	Treatment B: BMS-790052 Tablet 1, 6x10 mg (b) (4) fasted
R: Randomization	Treatment C: BMS-790052 Tablet 2, 6x10 mg (b) (4) fasted
W: a 4-day Washout	Treatment D: BMS-790052 Tablet 1, 6x10 mg with high-fat meal
D/C: Discharge	Treatment E: BMS-790052 Tablet 1, 6x10 mg with 40 mg famotidine, fasted

5. Excluded Medications, Restrictions or Exceptions

Two subjects received concomitant medications with analgesics as treatment for AEs of headache and migraine. One subject reported taking multivitamin tablets at screening. No other concomitant medications (prescription, over-the-counter or herbal) were administered during study. All concomitant therapies were recorded on the CRF.

6. Rationale for Doses Used in the Trial

The study was designed to evaluate formulation-related effects on DCV bioavailability. The DCV formulations used in the study (i.e., ., 6×10 mg capsules; 6×10 (b) (4) tablets; 6×10 mg (b) (4) tablets) is different from the DCV 60 mg tablet formulation proposed for marketing.

Generic famotidine was administered in accordance with the complete prescribing information in the package insert.

7. Drugs Used in the Trial

BMS-790052-05 was supplied by BMS. Generic famotidine was sourced as a marketed product by the investigator.

Table 1-Information on the medications administered in the trial

Drug Product	Formulation	Product Identification Number	Product Batch Number	Label Batch Number
BMS-790052-05, 10 mg	Capsule	790052-R010-005	8F41843	8J44941
BMS-790052-05, 10 mg	Film-coated tablet	790052-K010-009	8J43343	8J44946
BMS-790052-05, 10 mg [a]	Film-coated tablet	790052-K010-015	8J43325	8J44952

[a] Label indicated (b) (4) formulation

8. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Table 2 - PK sampling schedule

Study Day [a]	Time (Relative To Dosing) Hour	PK Blood Sample
1, 5, 9, 13, 17	0 (predose) [b]	X
	0.5	X
	1	X
	1.5	X
	2	X
	3	X
	4	X
	6	X
	8	X
	12	X
	16	X
2, 6, 10, 14, 18	24	X
3, 7, 11, 15, 19	48	X
4, 8, 12, 16, 20	72	X

[a] Procedures are the same for Period 1 to Period 5.

[b] Predose samples will be obtained prior to BMS-790052 administration on Days 1, 5, 9, 13, and 17.

Bioanalytical method for DCV

The method and bioanalysis of DCV is acceptable.

Analyte	BMS-790052		
Internal Standard	BMS-790052-^{13}C$_{10}$ (added to all samples except Blanks)		
Regression, Weighting	Linear 1/x^2		
LLOQ	0.500 ng/mL		
ULOQ	500 ng/mL		
Calibration Standard Concentrations	0.500, 1.00, 5.00, 25.0, 50.0, 100, 250, 450, and 500 ng/mL		
Analytical QC Concentrations	1.50, 20.0, 200, and 400 ng/mL		
Dilution QC Concentration	5000 ng/mL		
Dilution Factor	20 (5000 ng/mL)		
Performance of Analytical QCs	Precision (%CV)		Accuracy (%Bias)
(Low through High)	3.4% to 8.5%		-5.8% to 0.5%

Pharmacokinetic Assessments

Noncompartmental analysis was performed for DCV. The PK parameters assessed include t_{max}, C_{max}, C_{24h}, $AUC_{(0-t)}$, $AUC_{(inf)}$, and T-HALF.

Statistical Analysis

To assess the bioavailability of the ⬚⬚⬚ (b) (4) tablet and the ⬚⬚⬚ (b) (4) tablet relative to the reference capsule, ratios of geometric means and the corresponding 90% confidence intervals (CIs) for BMS-790052 C_{max}, C_{24}, $AUC_{(0-T)}$, and $AUC_{(INF)}$ were estimated. In addition, the effect of famotidine on the pharmacokinetics of BMS-790052 were estimated by ratios of geometric means and the corresponding 90% CIs for BMS-790052 C_{max}, C_{24}, $AUC_{(0-T)}$, and $AUC_{(INF)}$. The capsule dosed under fasted conditions was used as the reference when estimating the relative bioavailability for the two tablet formulations. The ⬚⬚⬚ (b) (4) tablet, dosed alone under fasted conditions, was used as the reference when estimating bioavailability versus the ⬚⬚⬚ (b) (4) tablet. Although not specified in the study protocol, when the 90% CIs for any of the planned and unplanned analyses was completely contained within the bounds (0.80, 1.25), the test and reference products were concluded to have "similar bioavailability".

9. Results

9.1 Subject Demographics and Disposition

Eighteen subjects were enrolled and received study medication. All of them completed the study as planned. Subject disposition is summarized by treatment in **Table 3**.

Table 3-Subject Demographics

```
-----------------------------------------------------------------
                                         All Subjects
                                           N = 18
-----------------------------------------------------------------
AGE
  N                                            18
  MEAN                                         38.9
  MEDIAN                                       38.5
  MIN , MAX                          23 ,      48
  STANDARD DEVIATION                            5.50

AGE CATEGORIZATION (%)
  < 65                                    18   (100.0)

GENDER (%)
  MALE                                    15   ( 83.3)
  FEMALE                                   3   ( 16.7)

RACE (%)
  WHITE                                   16   ( 88.9)
  BLACK/AFRICAN AMERICAN                   1   (  5.6)
  AMERICAN INDIAN/ALASKA NATIVE            1   (  5.6)

ETHNICITY (%)
  HISPANIC/LATINO                         10   ( 55.6)
  NOT HISPANIC/LATINO                      8   ( 44.4)
```

9.2 Concomitant Medications

The concomitant medications that were administered in the trial are not expected to significantly alter the conclusions of the trial.

9.3 Pharmacokinetic and Statistical Analysis

Tablets vs. Capsule

Mean plasma concentration-time profiles for the two tablets versus capsule in linear are in **Figure 2**.

Figure 2 - Mean (+SD) Plasma Concentration-Time Profiles for BMS-790052 Following Administration to Healthy Subjects of 6x10 mg Reference Capsules, 6x10 mg ▒▒▒▒▒▒ (b) (4) Tablets (Tablet 1), and 6x10 mg ▒▒▒▒▒▒ (b) (4) Tablets (Tablet 2) - Linear Scale

BMS-790052 StudyDay=1

TREATMENT CODES:
TRT A = BMS-790052 reference capsule, 6x10 mg, fasted
TRT B = BMS-790052 Tablet 1, 6x10 mg ▒▒▒ (b) (4) fasted
TRT C = BMS-790052 Tablet 2, 6x10 mg ▒▒▒ (b) (4) fasted
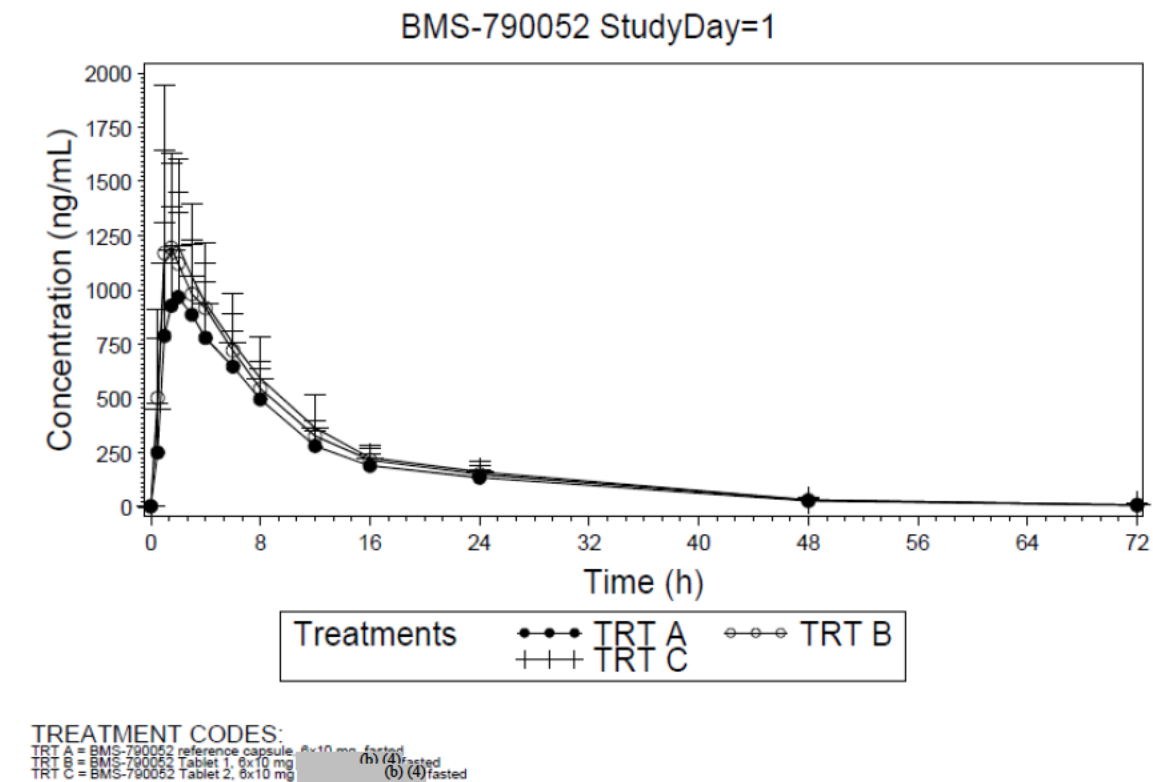
The results of assessment of bioavailability of BMS-790052 as 6x10 mg ▒▒▒▒▒ (b) (4) tablets and 6x10 mg ▒▒▒▒▒ (b) (4) tablets relative to the 6x10 mg reference capsules in healthy subjects, corresponding to analyses of Treatment B vs. A and Treatment C vs. Treatment A is presented in **Table 4**. Since the 90% CIs for Treatment B versus A and Treatment C versus A were not completely within the (0.80, 1.25) bounds, Tablets 1 and 2 do not have similar bioavailability to the reference capsule.

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Table 4- Results of Statistical Analysis of BMS-790052 C_{max}, $AUC_{(INF)}$, $AUC_{(0-T)}$, and C24, Tablet 1 and Tablet 2 versus Capsule

Treatment and Comparison	CMAX (ng/mL) Geo.Mean,(CV)	AUC(0-T) (ng.h/mL) Geo.Mean,(CV)	AUC(INF) (ng.h/mL) Geo.Mean,(CV)	C24 (ng/mL) Geo.Mean,(CV)
A	1012.9 (40)	10918.3 (27)	11065.3 (27)	131.1 (27)
B	1385.7 (41)	12805.7 (22)	12980.0 (22)	146.5 (26)
C	1341.3 (28)	13362.5 (26)	13543.2 (26)	155.0 (29)
	GMR (90% CI)	GMR (90% CI)	GMR (90% CI)	GMR (90% CI)
B vs A	1.368 (1.189,1.574)	1.173 (1.068,1.288)	1.173 (1.068,1.288)	1.117 (1.012,1.234)
C vs A	1.324 (1.145,1.531)	1.224 (1.110,1.350)	1.224 (1.110,1.350)	1.182 (1.060,1.319)

Treatments: A=BMS-790052 reference capsule, 6x10 mg, fasted

B=BMS-790052 Tablet 1, 6x10 mg ███████ (b) (4) fasted

C=BMS-790052 Tablet 2, 6x10 mg ███████ (b) (4) fasted

Effect of Famotidine

Mean plasma concentration-time profiles for ███████ (b) (4) tablets fasting compared to that following famotidine in linear scale are presented in **Figure 3**.

Figure 3 - Mean (+SD) Plasma Concentration-Time Profiles for BMS-790052 Following Administration of 6x10 mg ███████ (b) (4) Tablets (Tablet 1) and with 40 mg Famotidine to Healthy Subjects - Linear Scale

TREATMENT CODES:
TRT B = BMS-790052 Tablet 1, 6x10 mg ████ (b) (4) fasted
TRT E = BMS-790052 Tablet 1 with 40 mg famotidine, fasted
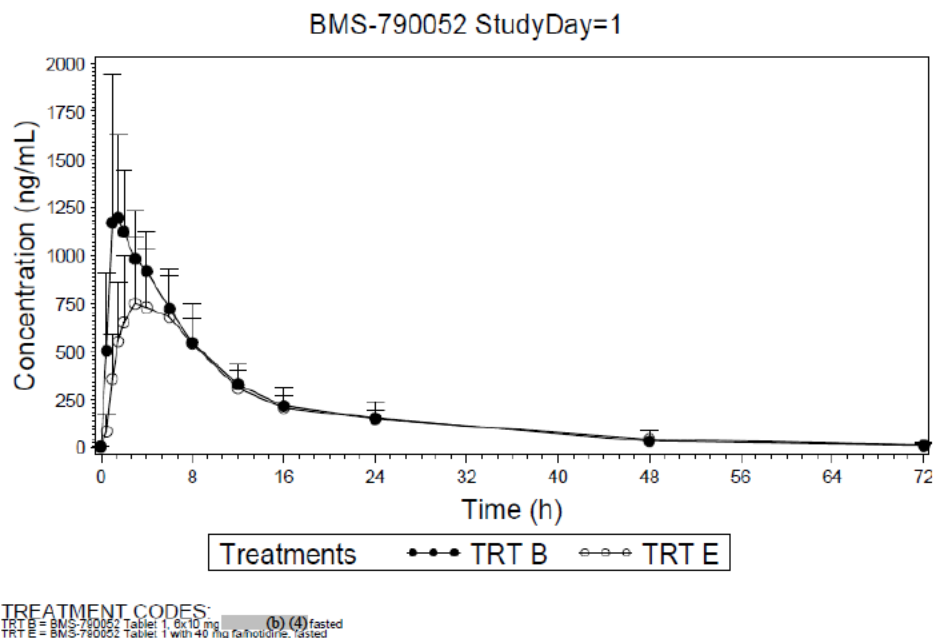
Analysis **in Table 5** shows that none of the 90% CIs for Cmax, AUC(0-T), and AUC(INF) were wholly contained within the (0.80, 1.25) bounds leading to the conclusion that Tablet 1 administered with 40 mg famotidine in a fasted state did not have similar bioavailability to Tablet 1 administered alone.

Table 5- Results of Statistical Analysis of BMS-790052 C_{max}, AUC$_{(INF)}$, AUC$_{(0-T)}$, and C24, Effect of Famotidine 40 mg on the ▓▓▓▓ (b) (4) **Tablet**

Treatment and Comparison	Cmax (ng/mL) Geo.Mean,(CV)	AUC(0-T) (ng.h/mL) Geo.Mean,(CV)	AUC(INF) (ng.h/mL) Geo.Mean,(CV)	C24 (ng/mL) Geo.Mean,(CV)
B	1385.7 (41)	12805.7 (22)	12980.0 (22)	146.5 (26)
E	772.3 (36)	10433.7 (44)	10618.2 (45)	130.9 (60)
	GMR (90% CI)	GMR (90% CI)	GMR (90% CI)	GMR (90% CI)
E vs B	0.557 (0.461,0.674)	0.815 (0.695,0.956)	0.818 (0.698,0.959)	0.893 (0.750,1.064)

Treatments: B=BMS-790052 Tablet 1, 6x10 mg ▓▓▓▓ (b) (4) fasted
E=BMS-790052 Tablet 1 with 40 mg famotidine, fasted

BA of ▓▓▓▓ (b) (4) Tablet vs. BA of the ▓▓▓▓ (b) (4) Tablet

The results of the comparison of the pharmacokinetics of the ▓▓▓▓ (b) (4) form of the BMS-790052 tablet relative to the ▓▓▓▓ (b) (4) form of the BMS-790052 tablet is shown in **Table 6**. The data indicates no difference in terms of bioavailability between the ▓▓▓▓ (b) (4) and ▓▓▓▓ (b) (4) forms of the BMS-790052 tablet.

Table 6- Results of Statistical Analysis of BMS-790052 C_{max}, AUC$_{(INF)}$, AUC$_{(0-T)}$, and C24, Comparison of the ▓▓▓▓ (b) (4) **Tablet to the** ▓▓▓▓ (b) (4) **Tablet**

Treatment and Comparison	CMAX (ng/mL) Geo.Mean,(CV)	AUC(0-T) (ng.h/mL) Geo.Mean,(CV)	AUC(INF) (ng.h/mL) Geo.Mean,(CV)	C24 (ng/mL) Geo.Mean,(CV)
B	1385.7 (41)	12805.7 (22)	12980.0 (22)	146.5 (26)
C	1341.3 (28)	13362.5 (26)	13543.2 (26)	155.0 (29)
	GMR (90% CI)	GMR (90% CI)	GMR (90% CI)	GMR (90% CI)
C vs B	0.968 (0.878,1.067)	1.043 (0.978,1.113)	1.043 (0.978,1.113)	1.058 (0.967,1.158)

Treatments: B=BMS-790052 Tablet 1, 6x10 mg ▓▓▓▓ (b) (4) fasted
C=BMS-790052 Tablet 2, 6x10 mg ▓▓▓▓ (b) (4) fasted

9.5 Safety Analysis

There were no deaths, SAEs, or treatment discontinuations due to AEs. Sixteen AEs were reported for 9 (50%) subjects. All AEs were assessed by the investigator as unrelated to study drug. The most frequently reported AEs were vomiting, cough, abdominal pain, and headache; each occurring in 2 (11.1%) subjects. There were no clinically relevant mean changes over time in any laboratory parameter. There were no evidence of clinically meaningful effects on ECGs and vital sign measurements.

10. Sponsor's Conclusions

- Increased bioavailability as measured by C_{max} (32% to 37%), $AUC_{(0-T)}$ [17% to 22%], $AUC_{(INF)}$ [17% to 22%] was observed with both _____ (b) (4) and _____ (b) (4) _____ tablets compared with capsule formulation.
- Administration with 40 mg famotidine had the effect of reducing the bioavailability of the _____ (b) (4) tablet as measured by C_{max} (44%), $AUC_{(0-T)}$ [18%], $AUC_{(INF)}$ [18%].
- The exposures of _____ (b) (4) and _____ (b) (4) tablets had similar bioavailability with 90% CIs of all PK parameters within the 0.8 and 1.25 limits.
- Compared with the capsule formulation in the fasted state, administration with 40 mg famotidine reduced C_{max} by 24% and AUC by 4% of the _____ (b) (4) tablet.
- BMS-790052 was safe and generally well tolerated when administered as a 60 mg dose tablets under fasting condition, or with famotidine.

11. Reviewer's Assessment

The AI444009 trial adequately assessed the bioavailability of BMS-790052 (b) (4) _____ tablet and _____ (b) (4) tablet relative to BMS-790052 capsule and effect of Famotidine on the PK of BMS-790052 in healthy subjects. The sponsor's conclusions are valid.

On the proposed label, the ratio of Cmax should be read as "0.56 (0.46, 0.67)" instead of "0.56 (0.46, (b) (4)

Table 7: Effect of Coadministered Drugs on <TRADENAME-DCV>Pharmacokinetics

Concomitant Drug	Coadministered Drug Dose	<TRADENAME-DCV> Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}
Famotidine	40 mg single dose	60 mg single dose	0.56 (0.46, 0. (b) (4))	0.82 (0.70, 0.96)	0.89 (0.75, 1.06)

<u>AI444039</u>

1. Title

Bioavailability of BMS-790052 Phase 3 [   ] (b) (4) Tablet Relative to Phase 2 [   ] (b) (4) Tablet and the Effect of a High Fat Meal and Light Meal on the Pharmacokinetics of BMS-790052 when Administered as the Phase 3 (b) (4) [   ] Tablet in Healthy Subjects

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at one site from May 16, 2011 (trial initiation) to June 29, 2011 (trial completion).

3. Objectives

The objectives of the trial included evaluating the effect of food on the bioavailability of the Phase 3 daclatasvir tablets and the bioavailability of the daclatasvir Phase 3 tablets compared to the Phase 2 tablets.

4. Trial Design

AI444039 was an open label clinical trial that enrolled healthy subjects 18 to 49 years old. Information on the trial design is displayed in Figure 1.

Figure 1-AI444039 trial design

	A	-W-	D	-W-	B	-W-	C	
S, E	D	-W-	C	-W-	A	-W-	B	
— R	C	-W-	B	-W-	D	-W-	A	
	B	-W-	A	-W-	C	-W-	D	— D

Period 1	Period 2	Period 3	Period 4	Day
Day 1	Day 1	Day 1	Day 1	17
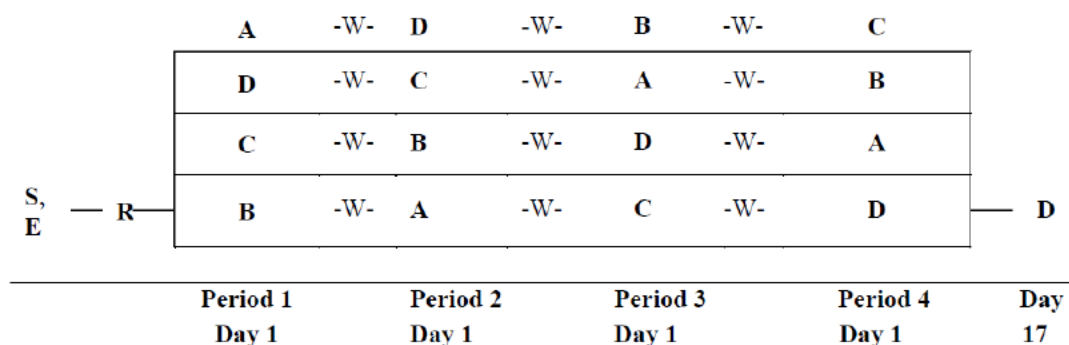
S = Screening; E=Enrollment; R = Randomization; W = 4-day Washout; D = Study Discharge
Treatment A: BMS-790052 phase 2 [   ] (b) (4) tablets, 2x30 mg, fasted
Treatment B: BMS-790052 phase 3 [   ] tablet 1x60 mg, fasted
Treatment C: BMS-790052 phase 3 [   ] tablet 1x60 mg tablet with high-fat meal
Treatment D: BMS-790052 phase 3 [   ] tablet 1x60 mg tablet with light-fat meal

5. Excluded Medications, Restrictions or Exceptions

Unless otherwise approved, prescription medications or nonprescription acid modifying

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medications were not permitted within 4 weeks and nonprescription medications, including herbal products, were not permitted within 2 weeks prior to medication administration. In general, prescription and nonprescription medications, including herbal products, were not permitted during the trial.

6. Dosage and Administration

The trial arms, including the doses that were administered and information regarding whether daclatasvir was administered under fed or fasted conditions, are specified in Figure 1. Subjects were required to fast for 10 hours before dosing in all treatment arms, and in treatments C and D, daclatasvir was administered 30 minutes after the start of the meal. For daclatasvir, the applicant is proposing to administer the medication with or without food. The four day washout period appears to be adequate for daclatasvir. Information regarding the light and high fat meals that were administered is provided in Table 1 A and 1B.

Table 1A-Example of the light meal administered in the AI444039 trial

Food Item	Calories (kcal)	Fat (g)	Carbohydrates (g)	Protein (g)
2 slices white bread toasted	129	1.8	24.0	4.0
1 teaspoon low fat margarine	21	2.3	trace	trace
1 tablespoon jam/preserves	56	trace	13.8	trace
5 fluid ounces of skim milk	71	0.36	9.8	6.9
Total Grams (g)	-	4.5	47.6	10.9
Total calories (kcal)	277	41	190	44
% of Total Calories	100	15	69	16

Table 1B-Example of the high fat meal administered in the AI444039 trial

Food Item	Calories (kcal)	Fat (g)	Carbohydrates (g)	Protein (g)
2 eggs fried	185	14.1	1.3	12.5
2 slices of white bread toasted	129	1.8	24.0	4.0
1 tablespoon butter	102	11.5	trace	0.1
1 tablespoon jam	56	trace	13.8	trace
3 strips of bacon fried	126	9.6	0.4	9.1
4 ounces of hash brown potatoes	207	9.8	27.4	2.3
8 fluid ounces (237 mL) of whole milk	146	7.9	11.0	7.9
Total Grams (g)	-	54.7	77.9	35.9
Total Calories (kcal)	951	492	312	144
% of Total Calories	100	52	33	15

7. Rationale for Doses Used in the Trial

The daclatasvir single dose of 60 mg is consistent with the proposed dosage regimen of 60 mg once daily.

8. Drugs Used in the Trial

Information regarding the daclatasvir formulations that were administered in the trial is displayed in Table 2.

Table 2-Information on the daclatasvir formulation administered in the AI444039 trial

Drug Product	Formulation	Product ID Number	Product Batch Number	Label Batch Number
BMS-790052, 30 mg	Film-coated tablet	790052-K030-019	9H43474	9C55376
BMS-790052, 60 mg	Film-coated tablet	790052-K060-028	1D65922	1D65922

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood samples that were obtained included daclatasvir blood samples at predose and up to 72 hours postdose.

Bioanalysis

The method and bioanalysis of daclatasvir are acceptable. Daclatasvir plasma samples were analyzed using a validated LC/MS/MS method in K_2EDTA anticoagulated plasma by [(b) (4)] (TNJM1113.00). The blood samples for analysis of daclatasvir appear to have been collected in tubes containing K_2EDTA.

For the AI444039 plasma samples that were analyzed for daclatasvir, the lower limit of quantification for daclatasvir was 2 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for daclatasvir based on the bioanalytical report. For the AI444039 trial, precision and accuracy were evaluated using plasma daclatasvir quality control (QC) samples at 6 ng/mL, 60 ng/mL, 800 ng/mL and 1600 ng/mL. The corresponding daclatasvir inter-run accuracy values were 5.3% for 6 ng/mL, 1.5% for 60 ng/mL, 1.8% for 800 ng/mL and 1.9% for 1600 ng/mL. The daclatasvir inter-run precision values were 11.4% for 6 ng/mL, 3% for 60 ng/mL, 2.7% for 800 ng/mL and 3.3% for 1600 ng/mL. In addition, for the daclatasvir dilution QC samples at 10000 ng/mL, the inter-run accuracy and precision were -4.3% and 1.4%, respectively.

Of the samples selected for incurred sample reanalysis for daclatasvir (total number less than 150), all samples were within 20% using the percentage values of the repeat and original concentrations. However, it is not clear whether the total number of daclatasvir samples that were reanalyzed represents 7% of the total number of samples that were initially analyzed.

For the AI444039 trial, in response to an information request, the applicant stated that the daclatasvir plasma samples were stored at the trial site at -20°C for up to 20 days and the bioanalytical laboratory at -20°C for up to 27 days. For the TNJM1113.00 method, the generated long term stability data for daclatasvir included stability data in K_2EDTA anticoagulated plasma at -20°C and-70°C for 93 days. For the AI444039 trial, the generated long term stability data appears to cover the duration of long term stability data necessary for daclatasvir.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for daclatasvir. For the noncompartmental analysis, daclatasvir plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, and $AUC_{(0-inf)}$.

Statistical Analysis

For the food effect analysis, statistical analyses were conducted and 90% confidence intervals were derived comparing daclatasvir administered with high fat or light meals (test arm) compared to daclatasvir administered under fasted conditions (reference arm). For the bioavailability comparison, statistical analyses were conducted and 90% confidence intervals were derived comparing daclatasvir Phase 3 tablets (test arm) to daclatasvir Phase 2 tablets (reference arm) with 90% confidence interval limits of 80% to 125% as the acceptance criteria for comparability in daclatasvir exposure.

10. Results

10.1 Subject Demographics

Table 3-AI444039 subject demographics

```
                                   All Subjects
Characteristic                       (N=23 )
----------------------------------------------------------

AGE (YEARS)
     N                                 23
     MEAN                              31.9
     MEDIAN                            30.0
     MIN, MAX                     20, 47
     STANDARD DEVIATION                 9.02

AGE CATEGORIZATION (%)
     <65                            23 (100.0)

GENDER (%)
     MALE                          14 ( 60.9)
     FEMALE                         9 ( 39.1)

RACE (%)
     WHITE                         12 ( 52.2)
     BLACK/AFRICAN AMERICAN        11 ( 47.8)

ETHNICITY (%)
     HISPANIC/LATINO                9 ( 39.1)
     NOT HISPANIC/LATINO           14 ( 60.9)
```

10.2 Concomitant Medications

The concomitant medications that were administered in the trial included acetaminophen and amoxicillin. The conclusions of the trial are not expected to be significantly altered by the concomitant medications that were administered in the trial.

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10.3 Pharmacokinetic and Statistical Analysis

Table 4-Single dosing daclatasvir pharmacokinetic parameters and statistical analyses with daclatasvir 60 mg Phase 3 tablets under fed and fasted conditions

Treatment and Comparison	Cmax (ng/mL) Adjusted Geo. Mean (90% CI)	AUC(0-72h) (ng/mL) Adjusted Geo. Mean (90% CI)	AUC(INF) (ng•h/mL) Adjusted Geo. Mean (90% CI)
B	1490 (1342, 1655)	15397 (13642, 17377)	15707 (13878, 17777)
C	1075 (969, 1193)	11692 (10360, 13196)	12040 (10641, 13624)
D	1450 (1308, 1609)	15346 (13602, 17314)	15664 (13844, 17724)
	Ratio of Adjusted Geometric Means (90% CI)		
C vs. B	0.722 (0.662, 0.786)	0.759 (0.724, 0.797)	0.767 (0.731, 0.804)
D vs. B	0.973 (0.893, 1.061)	0.997 (0.950, 1.046)	0.997 (0.951, 1.046)
C vs. D	0.741 (0.681, 0.807)	0.762 (0.726, 0.799)	0.769 (0.733, 0.806)

Treatments: A = BMS-790052 Phase 2 (b) (4) tablets, 2×30 mg, fasted; B = BMS-790052 Phase 3 (b) (4) tablet, 1×60 mg, fasted; C = BMS-790052 Phase 3 (b) (4) tablet, 1×60 mg, with high-fat meal; D = BMS-790052 Phase 3 (b) (4) tablet, 1×60 mg, with light meal

Table 5-Single dosing daclatasvir pharmacokinetic parameters and statistical analyses comparing daclatasvir Phase 2 and Phase 3 tablets

Treatment and Comparison	Cmax (ng/mL) Adjusted Geo. Mean (90% CI)	AUC(0-72h) (ng/mL) Adjusted Geo. Mean (90% CI)	AUC(INF) (ng•h/mL) Adjusted Geo. Mean (90% CI)
A	1489 (1341, 1654)	15432 (13673, 17417)	15781 (13943, 17861)
B	1490 (1342, 1655)	15397 (13642, 17377)	15707 (13878, 17777)
	Ratio of Adjusted Geometric Means (90% CI)		
B vs. A	1.001 (0.918, 1.091)	0.998 (0.951, 1.047)	0.995 (0.949, 1.044)

Treatments: A = BMS-790052 Phase 2 (b) (4) tablets, 2×30 mg, fasted; B = BMS-790052 Phase 3 (b) (4) tablet, 1×60 mg, fasted.

10.4 Safety Analysis

No deaths or serious adverse events were reported for the trial. There was one adverse event resulting in discontinuation.

11. Discussion and Conclusions

Based on the results from the AI444039 trial, the following conclusions can be made.

- For the daclatasvir Phase 3 tablets, when a single dose of daclatasvir 60 mg was administered with a high fat meal, the daclatasvir C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were decreased by 28%, 24% and 23%, respectively, when compared with a single dose of daclatasvir 60 mg administered under fasted conditions. The 90% confidence intervals for daclatasvir C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were all not within the standard "no effect" 90% confidence interval limits of 80%-125%.
- For the daclatasvir Phase 3 tablets, when a single dose of daclatasvir 60 mg was administered with a light meal, the daclatasvir C_{max} was decreased by 3%, and $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were both decreased by less than 1% when compared with a single dose of daclatasvir 60 mg administered under fasted conditions. The 90% confidence intervals for daclatasvir C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were all within the standard "no effect" 90% confidence interval limits of 80%-125%.
- For the daclatasvir Phase 3 tablets, when a single dose of daclatasvir 60 mg was administered with a high fat meal, the daclatasvir C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were decreased by 26%, 24% and 23%, respectively, when compared with a single dose of daclatasvir 60 mg administered with light meals. The 90% confidence intervals for daclatasvir C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were all not within the standard "no effect" 90% confidence interval limits of 80%-125%.
- Under fasted conditions, when a single dose of daclatasvir 60 mg was administered as a 60 mg Phase 3 tablet, the daclatasvir C_{max} was unchanged and the $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were both decreased by less than 1%, when compared with a single dose of daclatasvir 60 mg administered as two 30 mg Phase 2 tablets. The 90% confidence intervals for daclatasvir C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were all within the standard "no effect" 90% confidence interval limits of 80%-125%.

A food effect was observed on daclatasvir exposure when administered with high fat meals that was not observed with light meals with a single daclatasvir 60 mg dose using the Phase 3 tablets. Comparable daclatasvir exposure was not observed with high fat meals compared to light meals (the 90% confidence interval limits for C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were not within 80% to 125%) with a single daclatasvir 60 mg dose using the Phase 3 tablets. Under fasted conditions, for a single daclatasvir 60 mg dose, comparable daclatasvir exposure was observed when comparing daclatasvir Phase 3 tablets to Phase 2 tablets (the 90% confidence interval limits for C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were within 80% to 125%).

Based on the information from the AI444039 trial and the daclatasvir exposure-response information, the recommendation to administer daclatasvir with or without food is acceptable.

Drug-drug interaction trials-asunaprevir

Trial Number	Title	Page Number
(b) (4)		135
		141
		147
		153
		161
		173

in Healthy Subjects (b) (4)	
	180
	190
	200
	209

Drug-drug interaction trials-daclatasvir

Trial Number	Title	Page Number
AI44005	Study to Evaluate the Effect of the CYP3A4 Inhibitor Ketoconazole on the Pharmacokinetics of BMS-790052 in Healthy Subjects	216
AI444008	Study to Evaluate the Effect of BMS-790052 on the Pharmacokinetics of the CYP3A4 Probe Midazolam Administered Orally in Healthy Subjects	222
AI444009	Bioavailability of BMS-790052 (b) (4) and (b) (4) Tablet Relative to BMS-790052 Capsule and Effect of a High Fat Meal and Famotidine on the Pharmacokinetics of BMS-790052 in Healthy Subjects	113
AI444012	Study to Evaluate the Effect of Rifampin on the Pharmacokinetics of BMS-790052 in Healthy Subjects	227
AI444014	A Phase 2a Study of BMS-790052 in Combination with Peginterferon Alfa-2a (Pegasys®) and Ribavirin (Copegus®) in Treatment Naive Subjects with Chronic Hepatitis C Virus Genotype 1 Infection	233
AI444020	The Effect of the Co-administration of BMS-790052 on the Pharmacokinetics of a Combined Oral Contraceptive Containing Ethinyl Estradiol and	237

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	Norgestimate (Ortho Tri-Cyclen®) in Healthy Female Subjects	
AI444024	The Effect of the Coadministration of a Proton Pump Inhibitor (Omeprazole) on the Pharmacokinetics of BMS-790052 in Healthy Subjects	246
AI444027	Open-Label Multiple-Dose Study to Assess the Effect of BMS-790052 on the Pharmacokinetics of Digoxin in Healthy Subjects	253
AI444032	A One-Way Drug-Drug Interaction Study To Assess The Effect Of Ritonavir-Boosted Atazanavir On The Pharmacokinetics, Safety And Tolerability Of BMS-790052 In Healthy Subjects	258
AI444033	An Open-Label Two-Way Drug-Drug Interaction Study To Assess The Effect Of Tenofovir On The Pharmacokinetics Of BMS-790052 And The Effect Of BMS-790052 On The Pharmacokinetics Of Tenofovir In Healthy Subjects	266
AI444034	A One-Way Drug-Drug Interaction Study To Assess The Effect Of Efavirenz On The Pharmacokinetics, Safety And Tolerability Of BMS-790052 In Healthy Subjects	273
AI444054	A Phase 1 Open-label, Single-sequence Study to Evaluate the Effect of Concomitant	283

	Administration of Multiple Doses of Daclatasvir (BMS-790052) on the Single-dose Pharmacokinetics of Rosuvastatin in Healthy Subjects	
AI444064	A Phase 1, Open-Label, Drug-Drug Interaction Study between Methadone and Daclatasvir, and between Buprenorphine/ Naloxone and Daclatasvir	289
AI444065	Open-label, Single-sequence Study to Evaluate the Pharmacokinetic Interaction Between Multiple Doses of Daclatasvir (BMS-790052) and a Single Dose of Cyclosporine or Tacrolimus in Healthy Subjects	299
AI444084	An Open-Label Two-Way Drug-Drug Interaction Study to Assess the Effect of Daclatasvir on the Pharmacokinetics of Escitalopram and the Effect of Escitalopram on the Pharmacokinetics of Daclatasvir in Healthy Subjects	308
AI447009	Open-label, Randomized, Multiple Dose, Drug-drug Interaction Study to Assess the Pharmacokinetics and Safety of BMS-790052 and BMS-650032 Co-administered in Healthy Subjects	315
TMC435HPC1005	A Phase I, 2-panel, open-label, randomized, crossover trial in healthy subjects to	322

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	investigate the pharmacokinetic interaction between TMC435 and the NS5A inhibitor BMS-790052.	

81 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

AI444005

1. Title

Study To Evaluate The Effect Of The CYP3A4 Inhibitor Ketoconazole On The Pharmacokinetics Of BMS-790052 In Healthy Subjects

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at one site (MDS Pharma) from March 12, 2009 (trial initiation) to April 5, 2009 (trial completion).

3. Objectives

The primary objective of the trial was to evaluate the potential drug-drug interaction between daclatasvir and ketoconazole.

4. Trial Design

AI444005 was an open label clinical trial that enrolled healthy subjects 18 to 49 years old. Information on the trial design is displayed in Figure 1.

Figure 1-AI444005 trial design
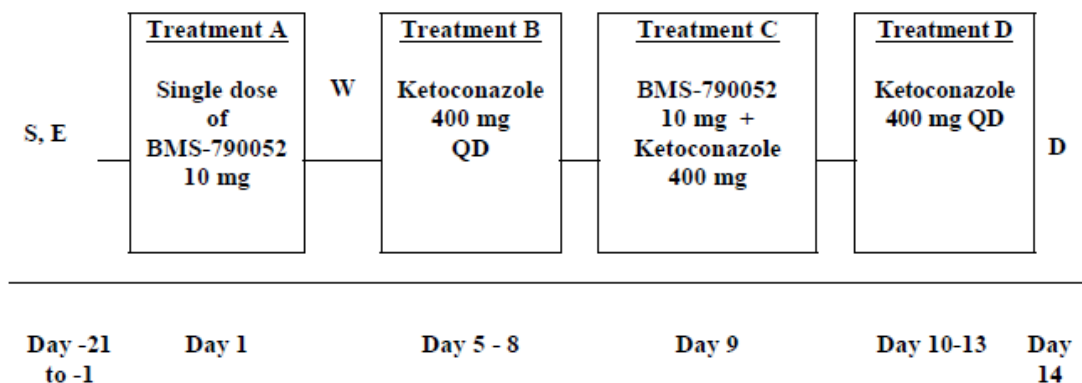
S = Screening; E = Enrollment; W = Washout; D = Study Discharge, QD = once daily

5. Excluded Medications, Restrictions or Exceptions

Unless otherwise approved, prescription medications or nonprescription acid modifying medications were not permitted within 2 weeks and nonprescription medications, including herbal products, were also not permitted within 2 weeks prior to medication administration. In general, prescription and nonprescription medications, including herbal products, were not permitted during the trial.

6. Dosage and Administration

The trial arms, including the dosage regimens that were administered, are specified in Figure 1. On days 1 and 9, after fasting for 10 hours, doses were administered under fasted conditions. The U.S prescribing information (USPI) for ketoconazole does not provide specific dosing recommendations with regards to food or meals. For daclatasvir, the applicant is proposing to administer the medication with or without food.

7. Rationale for Doses Used in the Trial

The daclatasvir single dose of 10 mg for daclatasvir was selected to account for a potential drug-drug interaction. The ketoconazole dosage regimen of 400 mg once daily is a recommended maintenance dosage regimen in adults.

8. Drugs Used in the Trial

Daclatasvir was provided as 10 mg hard gelatin capsules (batch number 8K42126). There were no specific details provided regarding the ketoconazole formulation that was administered.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

According to the trial report the blood samples that were obtained included daclatasvir blood samples beginning on day 1 at predose and up to 96 hours postdose and on day 9 at predose and up to 120 hours postdose.

Bioanalysis

The method and bioanalysis of daclatasvir are acceptable. Daclatasvir plasma samples were analyzed using a validated LC/MS/MS method in EDTA anticoagulated plasma by   (b) (4) (TNJM07177.00). The blood samples for analysis of daclatasvir appear to have been collected in tubes containing EDTA.

For the AI444005 plasma samples that were analyzed for daclatasvir, the lower limit of quantification for daclatasvir was 0.05 ng/mL and the upper limit of quantification was 50 ng/mL. There were no precision or accuracy issues identified for daclatasvir based on the bioanalytical report. For the AI444005 trial, precision and accuracy were evaluated using plasma daclatasvir quality control (QC) samples at 0.150 ng/mL, 2 ng/mL, 20 ng/mL, and 40 ng/mL. The corresponding daclatasvir inter-run accuracy values were 2.7% for 0.150 ng/mL, -0.5% for 2 ng/mL, 2% for 20 ng/mL, and -0.3% for 40 ng/mL. The daclatasvir inter-run precision values were 8.2% for 0.150 ng/mL, 4% for 2 ng/mL, 5.9% for 20 ng/mL, and 5.5% for 40 ng/mL. In addition, for the daclatasvir dilution QC

samples at 200 ng/mL, the inter-run accuracy and precision were 0% and 5.4%, respectively.

Of the samples selected for incurred sample reanalysis for daclatasvir (total number less than 30), all samples were within 20% using the percentage values of the repeat and original concentrations. However, it is not clear whether the total number of daclatasvir samples that were reanalyzed represents 7% of the total number of samples that were initially analyzed.

For the AI444005 trial, in response to an information request, the applicant stated that the daclatasvir plasma samples were stored at the trial site at -20°C for up to 36 days, and the bioanalytical laboratory at -20°C for up to 9 days. For daclatasvir, the generated long term stability data included stability data in EDTA anticoagulated plasma at -20°C for 387 days and -70°C for 7 days (of note, long term stability for the 0.15 ng/mL QC failed at 70°C for 14 days).   For the AI444005 trial, the generated long term stability data appears to covers the duration of long term stability data necessary for daclatasvir.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for daclatasvir. For the noncompartmental analysis, daclatasvir plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, and $AUC_{(0-inf)}$.

Statistical Analysis

Statistical analyses were conducted and 90% confidence intervals were derived comparing ketoconazole coadministered with daclatasvir (test arm) compared to daclatasvir administered alone (reference arm).

10. Results

10.1 Subject Demographics

Table 1-AI444005 subject demographics

Characteristics	All Subjects
Age, years	
Mean (SD)	36 (11)
Range	21, 47
Gender, n (%)	
Male	13 (92.9)
Female	1 (7.1)
Race, n (%)	
White	13 (92.9)
Black/African American	1 (7.1)
Ethnicity, n (%)	
Hispanic	10 (71.4)
Non-Hispanic	4 (28.6)
Weight, kg	
Mean (SD)	78.8 (16.0)
Range	46.9, 105.2
Height, cm	
Mean (SD)	172 (8)
Range	159, 189
Body Mass Index, kg/m^2	
Mean (SD)	26.4 (3.7)
Range	18.6, 31.9

10.2 Concomitant Medications

No concomitant medications were administered in the trial.

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10.3 Pharmacokinetic and Statistical Analysis

Table 2-Single dosing daclatasvir pharmacokinetic parameters with daclatasvir 10 mg or ketoconazole 400 mg once daily combined with daclatasvir 10 mg

Treatment	Cmax (ng/mL) Geo.Mean (CV)	AUC(0-T) (ng*h/mL) Geo.Mean (CV)	AUC(INF) (ng*h/mL) Geo.Mean (CV)	Tmax (h) Median (Min, Max)	T-HALF (h) Mean (SD)	CL/F (mL/min) Geo.Mean (CV)
BMS-790052 10 mg (Trt A)	183.5	1932.7	1942.3	1.50	13.82	85.8
[N=14]	(36)	(29)	(29)	(1.0-4.0)	(2.484)	(24)
BMS-790052 10 mg + KETO 400 mg QD (Trt C)	288.8	5710.3	5843.5	1.50	22.49	28.5
[N=13]	(14)	(18)	(18)	(1.0-2.0)	(3.540)	(17)

KETO=ketoconazole; Trt=treatment

Table 3-Statistical analyses for daclatasvir

Treatment and Comparison	Cmax (ng/mL) Adjusted Geo. Mean	AUC(0-T) (ng.h/mL) Adjusted Geo. Mean	AUC(INF) (ng.h/mL) Adjusted Geo. Mean
BMS-790052 10 mg (Trt A)	183.49	1932.75	1942.30
BMS-790052 10 mg + KETO 400 mg QD (Trt C)	288.32	5690.25	5823.96
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
BMS-790052 10 mg + KETO 400 mg QD vs. BMS-790052 10 mg (Trt C / Trt A)	1.571 (1.311,1.883)	2.944 (2.570,3.373)	2.998 (2.616,3.437)

Treatments (TRT): A=digoxin 0.125 mg QD; B=BMS-790052 60 mg QD + digoxin 0.125 mg QD
KETO=ketoconazole; Trt=treatment; GMR=ratios of adjusted geometric means

10.4 Safety Analysis

No deaths, serious adverse events or adverse events resulting in discontinuation were reported for the trial.

11. Discussion and Conclusions

Based on the results from the AI444005 trial, the following conclusions can be made.

- When ketoconazole 400 mg once daily was coadministered with a single dose of daclatasvir 10 mg, the daclatasvir C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were increased by 57%, 194% and 200%, respectively, when compared with a single dose of daclatasvir 10 mg. The 90% confidence intervals for daclatasvir C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were all not within the standard "no effect" 90% confidence interval limits of 80%-125%.

The applicant is proposing a dose adjustment with concomitant use of strong CYP3A inhibitors and daclatasvir when daclatasvir   (b) (4). The applicant is proposing to include the following recommendation in the daclatasvir U.S. prescribing information: The dose of DCV should be reduced to 30 mg once daily when coadministered with ketoconazole or other strong inhibitors of CYP3A4.

For strong CYP3A inhibition, the proposed dosage adjustment for daclatasvir would be expected to mitigate but not completely compensate for the changes in daclatasvir exposure due to drug-drug interactions. However, considering that only a 30 mg tablet will be available for dosage adjustments, the proposed dosage adjustment is reasonable if supported by concerns regarding safety.

AI444008

1. Title

Study to Evaluate the Effect of BMS-790052 on the Pharmacokinetics of the CYP3A4 Probe Midazolam Administered Orally in Healthy Subjects

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at PPD from October 29, 2008 (trial initiation) to December 1, 2008 (trial completion).

3. Objectives

The primary objective of the trial was to evaluate the potential drug-drug interaction between daclatasvir and midazolam.

4. Trial Design

AI444008 was an open label clinical trial that enrolled healthy subjects 18 to 49 years old. Information on the trial design is displayed in Figure 1.

Figure 1-AI444008 trial design
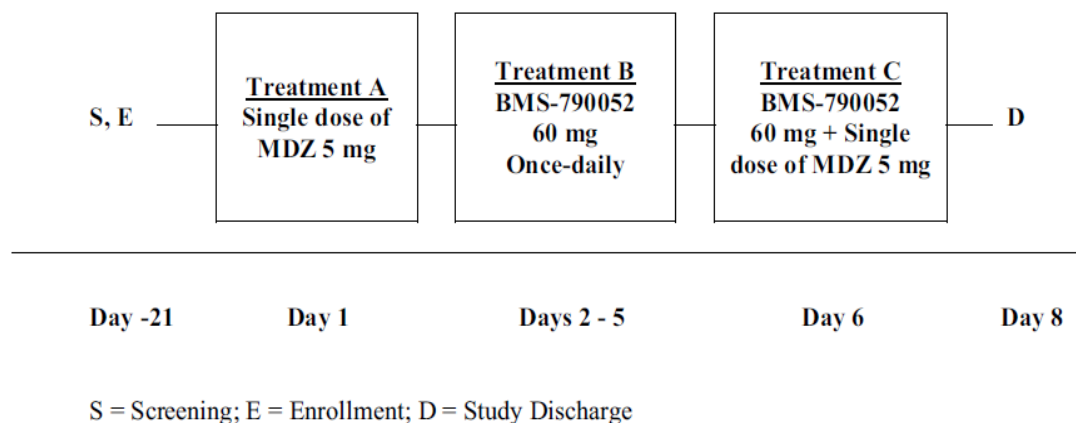
S = Screening; E = Enrollment; D = Study Discharge

5. Excluded Medications, Restrictions or Exceptions

Unless otherwise approved, prescription medications were not permitted within 4 weeks and prescription or nonprescription acid modifying medications, nonprescription medications, including herbal products, were not permitted within 2 weeks prior to medication administration. In general, prescription and nonprescription medications, including herbal products, were not permitted during the trial.

6. Dosage and Administration

The trial arms, including the dosage regimens that were administered, are specified in Figure 1. After fasting for a minimum of 10 hours on dosing days, doses were administered under fasted conditions. The U.S prescribing information (USPI) for midazolam does not provide specific dosing recommendations with regards to food or meals. For daclatasvir, the applicant is proposing to administer the medication with or without food.

7. Rationale for Doses Used in the Trial

The dosage regimen of 60 mg once daily for daclatasvir is the proposed recommended dosage regimen. There are no recommended midazolam dosage regimens for adults using the midazolam oral syrup in the U.S. prescribing information for the oral syrup.

8. Drugs Used in the Trial

Daclatasvir was provided as 10 mg capsules (batch number 8F4183). Midazolam was provided by the investigator as a 2 mg/mL oral syrup (lot number 856963A).

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood samples that were obtained included daclatasvir blood samples beginning on day 6 at predose and up to 24 hours postdose and midazolam blood samples beginning on days 1 and 6 at predose and up to 24 hours postdose.

Bioanalysis

The method and bioanalysis of daclatasvir and midazolam are acceptable. Daclatasvir plasma samples were analyzed using a validated LC/MS/MS method in EDTA anticoagulated plasma by ⬛⬛⬛⬛ (b) (4) (TNJM08199) and midazolam plasma samples were also analyzed using a validated LC/MS/MS method by ⬛⬛⬛⬛ (b) (4). The blood samples for analysis of daclatasvir and midazolam appears to have been collected in tubes containing EDTA.

For the AI444008 plasma samples that were analyzed for daclatasvir, the lower limit of quantification for daclatasvir was 0.5 ng/mL and the upper limit of quantification was 500 ng/mL. There were no precision or accuracy issues identified for daclatasvir based on the bioanalytical report. For the AI444008 trial, precision and accuracy were evaluated using plasma daclatasvir quality control (QC) samples at 1.5 ng/mL, 20 ng/mL, 200 ng/mL, and 400 ng/mL. The corresponding daclatasvir inter-run accuracy values were 1.3% for 1.5 ng/mL, 4.5% for 20 ng/mL, 1% for 200 ng/mL, and -3.8% for 400 ng/mL. The daclatasvir inter-run precision values were 12.8% for 1.5 ng/mL, 6.1% for

20 ng/mL, 5.1% for 200 ng/mL, and 3.6% for 400 ng/mL. In addition, for the daclatasvir dilution QC samples at 5000 ng/mL, the inter-run accuracy and precision were -9.4% and 2.8%, respectively.

For the midazolam AI444008 plasma samples, the lower limit of quantification was 0.1 ng/mL and the upper limit of quantification was 50 ng/mL. There were no precision or accuracy issues identified for midazolam based on the bioanalytical report. For the AI444008 trial, precision and accuracy were evaluated using plasma midazolam quality control (QC) samples at 0.3 ng/mL, 3 ng/mL, 20 ng/mL, and 40 ng/mL. The corresponding midazolam inter-run accuracy values were 2% for 0.3 ng/mL, 3.3% for 3 ng/mL, 3.5% for 20 ng/mL, and -0.3% for 40 ng/mL. The midazolam inter-run precision values were 9.2% for 0.3 ng/mL, 4.7% for 3 ng/mL, 4.1% for 20 ng/mL, and 5.9% for 40 ng/mL.

For the AI444008 trial, in response to an information request, the applicant stated that the daclatasvir plasma samples were stored at the trial site at -20°C for up to 10 days, at the central laboratory at -20°C for up to 43 days and the bioanalytical laboratory at -20°C for up to 69 days and midazolam plasma samples were stored at the trial site at -80°C for up to 13 days, at the central laboratory at -80°C for up to 43 days and the bioanalytical laboratory at -70°C for up to 19 days. For the TNJM08199 method, the generated long term stability data for daclatasvir included stability data in EDTA anticoagulated plasma at -20°C for 1081 days (of note, the long term stability experiment at -20°C for 1039 days failed at 1.5 ng/mL). For midazolam, the generated long term stability data included stability data in EDTA anticoagulated plasma at -20°C and -70°C for 269 days and at 20°C for 655 days (there was also failed long term stability data in EDTA anticoagulated plasma at -20°C and -70°C that was generated for 270 days).   The generated long term stability data appears to covers the duration of long term stability data necessary for the AI444008 trial for midazolam and for daclatasvir.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for midazolam and daclatasvir. For the noncompartmental analysis, the plasma pharmacokinetic parameters that were calculated included t_{max}, C_{max}, and $AUC_{(0\text{-tau})}$ for daclatasvir and t_{max}, C_{max}, and $AUC_{(0\text{-inf})}$ for midazolam.

Statistical Analysis

Statistical analyses were conducted and 90% confidence intervals were derived comparing midazolam coadministered with daclatasvir (test arm) compared to midazolam administered alone (reference arm).

10. Results

10.1 Subject Demographics

Table 1-AI444008 subject demographics

```
--------------------------------------------------------------
                                   BMS-790052 60 MG + MIDAZOLAM
                                            N = 18
--------------------------------------------------------------
AGE
   N                                          18
   MEAN                                        29.6
   MEDIAN                                      27.0
   MIN , MAX                          20 ,     44
   STANDARD DEVIATION                           7.87

AGE CATEGORIZATION (%)
   < 65                                18   (100.0)

GENDER (%)
   MALE                                17   ( 94.4)
   FEMALE                               1   (  5.6)

RACE (%)
   WHITE                               14   ( 77.8)
   BLACK/AFRICAN AMERICAN               4   ( 22.2)

ETHNICITY (%)
   HISPANIC/LATINO                      4   ( 22.2)
   NOT HISPANIC/LATINO                 14   ( 77.8)
```

10.2 Concomitant Medications

The only concomitant medication administered in the trial was ibuprofen in one subject. The conclusions of the trial are not expected to be significantly altered by the concomitant medication that was administered in the trial.

10.3 Pharmacokinetic and Statistical Analysis

Table 2-Single dosing midazolam pharmacokinetic parameters with midazolam 0.5 mg or midazolam 0.5 mg single dose combined with daclatasvir 60 mg once daily

Treatment	Cmax (ng/mL) Geo. Mean [N] (CV)	AUC(0-T) (ng*h/mL) Geo. Mean [N] (CV)	AUC(INF) (ng*h/mL) Geo. Mean [N] (CV)	Tmax (h) Median [N] (Min, Max)	T-HALF (h) Mean [N] (SD)	CLT/F (mL/min) Geo. Mean [N] (CV)
A	20.6 [18] (32)	54.1 [18] (38)	56.2 [18] (38)	0.50 [18] (0.5 - 1.0)	5.05 [18] (1.764)	1483.6 [18] (38)
C	19.4 [16] (31)	46.2 [16] (32)	47.8 [16] (32)	0.53 [16] (0.5 - 1.0)	4.40 [16] (2.005)	1742.9 [16] (33)

Treatments A: MDZ 5 mg; Treatment C: MDZ 5 mg + BMS-790052 60 mg

Abbreviations: CV = coefficient of variation; Geo. Mean = geometric mean; h = hour; MDZ = midazolam; N = number of subjects; SD = standard deviation

Table 3-Statistical analyses for midazolam

Treatment and Comparison	Cmax (ng/mL) Adjusted Geo. Mean	AUC(INF) (ng*h/mL) Adjusted Geo. Mean	AUC(0-T) (ng*h/mL) Adjusted Geo. Mean
TRT A:	20.6	56.2	54.1
TRT C:	19.7	49.0	47.3
	GMR (90% CI)	GMR (90% CI)	GMR (90% CI)
TRT C vs. TRT A C/A	0.954 (0.879,1.035)	0.873 (0.828,0.921)	0.874 (0.826,0.925)

Treatment A: MDZ 5 mg; Treatment C: MDZ 5 mg + BMS-790052 60 mg
Abbreviations: CI = confidence interval; Geo. Mean = geometric mean; GMR: geometric mean ratio; TRT = treatment

Table 4-Multiple dosing daclatasvir pharmacokinetic parameters with midazolam 0.5 mg single dose combined with daclatasvir 60 mg once daily

Treatment	Cmax (ng/mL) Geo. Mean [N] (CV)	AUC(TAU) (ng*h/mL) Geo. Mean [N] (CV)	Tmax (h) Median [N] (Min, Max)
C	1288.3 [16] (25)	13161.0 [16] (27)	2.00 [16] (1.0, 4.0)

Abbreviations: CV = coefficient of variation; h = hour; Max = maximum; Min = minimum; N = number of subjects

10.4 Safety Analysis

No deaths or serious adverse events were reported for the trial. Two subjects discontinued from the trial due to adverse events of vivid dreams.

11. Discussion and Conclusions

Based on the results from the AI444008 trial, the following conclusions can be made.

- When a single dose of midazolam 5 mg was coadministered with daclatasvir 60 mg once daily, the midazolam C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$ were decreased by 5%, 13% and 13%, respectively, when compared with a single dose of midazolam 5 mg. The 90% confidence intervals for midazolam C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$ were all within the standard "no effect" 90% confidence interval limits of 80%-125%.

No clinically relevant changes in midazolam exposure were observed with concurrent use of daclatasvir.

<u>AI444012</u>

1. Title

Study To Evaluate The Effect Of Rifampin On The Pharmacokinetics Of BMS-790052 In Healthy Subjects

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at one site (Inje University, Korea) from November 5, 2009 (trial initiation) to November 28, 2009 (trial completion).

3. Objectives

The primary objective of the trial was to evaluate the potential drug-drug interaction between daclatasvir and rifampin.

4. Trial Design

AI444012 was an open label clinical trial that enrolled healthy subjects 18 to 49 years old. Information on the trial design is displayed in Figure 1.

Figure 1-AI444012 trial design

S,E	**Treatment A** Single dose of 60 mg BMS-790052 (AM)	W	**Treatment B** 600 mg Rifampin (QD[a]) (PM)	**Treatment C**		Discharge
				Single dose of 60 mg BMS-790052 (AM) 600 mg Rifampin (PM)	600 mg Rifampin (PM)	
D -21	D 1	D 2-3	D 3-9	D 10	D 11	D 12

S=Screening; E=Enrollment; W=Washout of approximately 60 hours; D=Study Days

[a] QD = once daily

5. Excluded Medications, Restrictions or Exceptions

Unless otherwise approved, prescription medications were not permitted within 4 weeks and nonprescription medications, including herbal products, and prescription or nonprescription acid modifying medications were not permitted within 2 weeks prior to medication administration. In general, prescription and nonprescription medications, including herbal products, were not permitted during the trial.

6. Dosage and Administration

The trial arms, including the dosage regimens that were administered, are specified in Figure 1. For treatments A and C, after fasting for a minimum of 10 hours, daclatasvir doses were administered under fasted conditions. The rifampin doses were administered a minimum of 2 hours after dinner and it appears there was an additional 2 hours of fasting postdose. The U.S. prescribing information (USPI) for rifampim states that oral rifampin should be administered one hour before or two hours after a meal. For daclatasvir, the applicant is proposing to administer the medication with or without food.

7. Rationale for Doses Used in the Trial

The daclatasvir single dose of 60 mg is consistent with the proposed dosage regimen of 60 mg once daily. The rifampin dosage regimen of 600 mg once daily is a recommended dosage regimen in adults.

8. Drugs Used in the Trial

Information regarding the daclatasvir formulation that was administered in the trial is displayed in Table 1.

Table 1-Information on the daclatasvir formulation administered in the AI444012 trial

Unit	Formulation	Product ID Number	Product Batch Number	Label Batch Number
BMS-790052 Tablet	30 mg	790052-K030-019	9C55376	9H43474

The rifampin formulation was obtained by the clinical trial site. The applicant states in the Summary of Clinical Pharmacology information for daclatasvir that the rifampin formulation was manufactured by   (b) (4) and the applicant concluded that that there were no discrepancies in the reported rifampin concentrations when compared to information in the rifampin U.S. prescribing information.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood samples that were obtained included daclatasvir blood samples beginning on days 1 and 10 at predose and up to 48 hours postdose.

Bioanalysis

The method and bioanalysis of daclatasvir are acceptable. Daclatasvir plasma samples were analyzed using a validated LC/MS/MS method in EDTA anticoagulated plasma by ▨▨▨▨▨ (b) (4) (TNJM08199.00 and TNJM08199.01). The blood samples for analysis of daclatasvir appear to have been collected in tubes containing K_2EDTA.

For the AI444012 plasma samples that were analyzed for daclatasvir, the lower limit of quantification for daclatasvir was 0.5 ng/mL and the upper limit of quantification was 500 ng/mL. There were no precision or accuracy issues identified for daclatasvir based on the bioanalytical report. For the AI444012 trial, precision and accuracy were evaluated using plasma daclatasvir quality control (QC) samples at 1.5 ng/mL, 20 ng/mL, 200 ng/mL, and 400 ng/mL. The corresponding daclatasvir inter-run accuracy values were 4.7% for 1.5 ng/mL, -1% for 20 ng/mL, -1% for 200 ng/mL, and -2% for 400 ng/mL. The daclatasvir inter-run precision values were 8.5% for 1.5 ng/mL, 4.9% for 20 ng/mL, 3.8% for 200 ng/mL, and 3.9% for 400 ng/mL. In addition, for the daclatasvir dilution QC samples at 5000 ng/mL, the inter-run accuracy and precision were -11.2% and 5.9%, respectively.

Of the samples selected for incurred sample reanalysis for daclatasvir (total number less than 40), all samples were within 20% using the percentage values of the repeat and original concentrations. However, it is not clear whether the total number of daclatasvir samples that were reanalyzed represents 7% of the total number of samples that were initially analyzed.

For the AI444012 trial, in response to an information request, the applicant stated that the daclatasvir plasma samples were stored at the trial site at -20°C for up to 25 days, at the central laboratory at -20°C for up to 59 days and the bioanalytical laboratory at -20°C for up to 19 days. For the TNJM08199 (and TNJM08199.01) method, the generated long term stability data for daclatasvir included stability data in EDTA anticoagulated plasma at -20°C for 1081 days (of note, the long term stability experiment at -20°C for 1039 days failed at 1.5 ng/mL). For the AI444012 trial, the generated long term stability data appears to covers the duration of long term stability data necessary for daclatasvir.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for daclatasvir. For the noncompartmental analysis, daclatasvir plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, and $AUC_{(0-inf)}$.

Statistical Analysis

Statistical analyses were conducted and 90% confidence intervals were derived comparing rifampin coadministered with daclatasvir (test arm) compared to daclatasvir administered alone (reference arm).

10. Results

10.1 Subject Demographics

Table 2-AI444012 subject demographics

```
----------------------------------------------------
                                     All Subjects
                                        N = 14
----------------------------------------------------
AGE
   N                                        14
   MEAN                                     25.1
   MEDIAN                                   25.0
   MIN , MAX                         21 ,   28
   Q1 , Q3                         24.0 ,   26.0
   STANDARD DEVIATION                       1.86

AGE CATEGORIZATION (%)
   < 65                                 14   (100.0)
   NOT REPORTED                          0

GENDER (%)
   MALE                                 14   (100.0)
   NOT REPORTED                          0

RACE (%)
   ASIAN                                14   (100.0)
   NOT REPORTED                          0
```

10.2 Concomitant Medications

No concomitant medications were administered in the trial.

10.3 Pharmacokinetic and Statistical Analysis

Table 3-Single dosing daclatasvir pharmacokinetic parameters with daclatasvir 60 mg or rifampin 600 mg once daily combined with daclatasvir 60 mg

Treatment (N=14)	Cmax (ng/mL) Geo. Mean (CV)	AUC(0-T) (ng•h/mL) Geo. Mean (CV)	AUC(INF) (ng•h/mL) Geo. Mean (CV)	Tmax (h) Median (Min-Max)	T-HALF (h) Mean (SD)	CLT/F (mL/min) Geo. Mean (CV)
TRT A: BMS-790052 60 mg	1216.5 (20)	11337.0 (20)	11594.4 (21)	1.00 (1.00-3.00)	8.59 (0.940)	86.2 (21)
TRT C: BMS-790052 60 mg + Rifampin 600 mg QD	532.8 (20)	2452.7 (20)	2459.7 (20)	1.00 (0.50-2.00)	4.47 (0.464)	406.6 (20)

Table 4-Statistical analyses for daclatasvir

Treatment and Comparison	Cmax (ng/mL) Geo.Mean	AUC(0-T) (ng•h/mL) Geo.Mean	AUC(INF) (ng•h/mL) Geo.Mean
TRT A: BMS-790052 60 mg	1216.50	11337.03	11594.39
TRT C: BMS-790052 60 mg + Rifampin 600 mg QD	532.76	2452.65	2459.70
	GMR (90% CI)	GMR (90% CI)	GMR (90% CI)
TRT C vs. TRT A C/A	0.438 (0.399,0.481)	0.216 (0.197,0.237)	0.212 (0.193,0.233)

10.4 Safety Analysis

No deaths, serious adverse events or adverse events resulting in discontinuation were reported for the trial.

11. Discussion and Conclusions

Based on the results from the AI444012 trial, the following conclusions can be made.

- When rifampin 600 mg once daily was coadministered with a single dose of daclatasvir 60 mg, the daclatasvir C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were decreased by 56%, 78% and 79%, respectively, when compared with a single dose of daclatasvir 60 mg. The 90% confidence intervals for daclatasvir C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were all not within the standard "no effect" 90% confidence interval limits of 80%-125%.

The applicant is proposing to contraindicate concomitant use of strong CYP3A inducers with daclatasvir. Based on the changes in daclatasvir exposure that were observed in the AI444012 trial, the contraindication is appropriate.

<u>AI444014</u>

Reviewer note: only a brief review of the information relevant to the ribavirin or daclatasvir pharmacokinetic information is discussed below.

1. Title

A Phase 2a Study of BMS-790052 in Combination with Peginterferon Alfa-2a (Pegasys) and Ribavirin (Copegus) in Treatment Naïve Subjects with Chronic Hepatitis C Virus Genotype 1 Infection

2. Summary Information

<u>Ribavirin</u>

Pharmacokinetic data was generated for ribavirin with or without various dosage regimens of daclatasvir.

Bioanalytical

Only the bioanalytical information for ribavirin is discussed in detail in this review. The proposed U.S. prescribing information for daclatasvir does not include information regarding the magnitude of change in daclatasvir exposure with concomitant use of pegylated interferon and ribavirin from the AI444014 trial.

The method and bioanalysis of ribavirin are acceptable. Ribavirin plasma samples were analyzed using a validated LC/MS/MS method in K_2EDTA anticoagulated plasma by PPD. The blood samples for analysis of ribavirin appear to have been collected in tubes containing K_2EDTA.

For the AI444014 plasma samples that were analyzed for ribavirin, the lower limit of quantification for ribavirin was 5 ng/mL and the upper limit of quantification was 5000 ng/mL. There were no precision or accuracy issues identified for ribavirin based on the bioanalytical report. For the AI444014 trial, precision and accuracy were evaluated using plasma ribavirin quality control (QC) samples at 15 ng/mL, 40 ng/mL, 150 ng/mL, 600 ng/mL and 3800 ng/mL. The corresponding ribavirin inter-run accuracy values were 2.36% for 15 ng/mL, -1.72% for 40 ng/mL, 1.9% for 150 ng/mL, 3.76% for 600 ng/mL and 1.51% for 3800 ng/mL. The ribavirin inter-run precision values were 2.17% for 15 ng/mL, 7.59% for 40 ng/mL, 2.32% for 150 ng/mL, 1.94% for 600 ng/mL and 4.18% for 3800 ng/mL. In addition, for the ribavirin dilution QC samples at 10000 ng/mL, the inter-run accuracy and precision were 1.35% and 6.01%, respectively.

For the AI444014 trial, in response to an information request, the applicant stated that the ribavirin plasma samples were stored at the trial site at -20°C for up to 2 days, at the central laboratory at -70°C for up to 42 days and the bioanalytical laboratory at -20°C for up to 18 days. For ribavirin, the generated long term stability data included stability data

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in K$_2$EDTA anticoagulated plasma at -20°C and -70°C for 453 days. The generated long term stability data appears to covers the duration of ribavirin long term stability data necessary for the AI444014 trial.

Table 1-Multiple dosing ribavirin pharmacokinetic parameters with pegylated interferon and ribavirin or pegylated interferon and ribavirin combined with various daclatasvir dosage regimens

Treatment	Cmax (ng/mL) Geometric Mean (%CV)	Tmax (h) Median (Min-Max)	C0 (ng/mL) Geometric Mean (%CV)	C12 (ng/mL) Geometric Mean (%CV)	AUC(0-12) (ng.h/mL) Geometric Mean (%CV)
A (N = 9)	3135 (16)	2.00 (0.00-12.12)	2721 (21)	2534 (14)	32689 (12)
B (N =10)	2582 (36)	2.00 (0.00-8.00)	1873 (45)	1803 (40)	24067 (32)
C (N = 11)	3191 (21)	2.00 (1.00-12.08)	2414 (30)	2556 (25)	31803 (27)
D (N =10)	2945 (25)	1.50 (1.00-12.00)	2358 (25)	2482 (27)	30787 (27)

Treatments: A = Placebo + pegIFNα/RBV; B = BMS-790052 3 mg + pegIFNα/RBV; C = BMS-790052 10 mg + pegIFNα/RBV; D = BMS=790052 60 mg + pegIFNα/RBV.

Abbreviations: AUC(0-12) = plasma concentration 12 hours post observed dose; C0 = trough plasma concentration pre-observed dose; C12 = area under the concentration-time curve in 1 dosing interval, from time zero to 12 hours post observed dose; Cmax = maximum observed concentration; CV = coefficient of variation; Tmax = Time of maximum observed concentration.

Note: Subjects administered pegylated interferon 180 µg subcutaneously weekly plus ribavirin 400 mg (<75 kg) or 600 mg (>75 kg) in the morning and 600 mg in the evening with food.

Table 2-Statistical analyses for ribavirin

Treatment and Comparisons	Cmax (ng/mL)	AUC(0-12) (ng.h/mL)	C12 (ng/mL)
	Adjusted Geometric Mean (%CV)		
A	3135 (16)	32689 (12)	2534 (14)
B	2582 (36)	24067 (32)	1803 (40)
C	3191 (21)	31803 (27)	2556 (25)
D	2945 (25)	30787 (27)	2482 (27)
	Adjusted Geometric Mean Ratio (90% CI)		
B vs A	0.824 (0.631, 1.075)	0.736 (0.564, 0.962)	0.712 (0.527, 0.962)
C vs A	1.018 (0.879, 1.179)	0.973 (0.824, 1.148)	1.009 (0.859, 1.185)
D vs A	0.939 (0.794, 1.112)	0.942 (0.797, 1.113)	0.980 (0.823, 1.166)

Treatments: A = Placebo + pegIFNα/RBV; B = BMS-790052 3 mg + pegIFNα/RBV; C = BMS-790052 10 mg + pegIFNα/RBV; D = BMS-790052 60 mg + pegIFNα/RBV.

Abbreviations: AUC(0-12) = plasma concentration 12 hours post observed dose; C12 = area under the concentration-time curve in 1 dosing interval, from time zero to 12 hours post observed dose; Cmax = maximum observed concentration; CI = confidence interval; CV = coefficient of variation.

Daclatasvir

Table 3-Multiple dosing daclatasvir pharmacokinetic parameters with pegylated interferon and ribavirin or pegylated interferon and ribavirin combined with various daclatasvir dosage regimens

Treatment	Cmax (ng/mL) Geometric Mean (%CV)	Tmax (Hours) Median (Min-Max)	C0 (ng/mL) Geometric Mean (%CV)	C24 (ng/mL) Geometric Mean (%CV)	AUC(0-24) (ng.h/mL) Geometric Mean (%CV)	T-HALF (Hours) Mean (SD)
B (N = 10)	62.4 (55)	1.00 (1.00-4.00)	8.03 (105)	9.81 (83)	582 (55)	12.3 (6.443)
C (N =11)	166 (49)	1.87 (1.00-2.08)	22.9 (68)	23.0 (67)	1533 (50)	10.5 (3.464)
D (N = 10)	1534 (58)	1.08 (1.00-4.00)	255 (84)	232 (83)	14122 (70)	10.5 (1.773)

Treatments: B = BMS-790052 3 mg + pegINFα/RBV; C = BMS-790052 10 mg + pegINFα/RBV; D = BMS=790052 60 mg + pegINFα/RBV.

Abbreviations: AUC(0-24) = Area under the concentration-time curve in 1 dosing interval, from time zero to 24 hours post observed dose; C0 = Trough plasma concentration pre-observed dose; C24 = Plasma concentration 24 hours post observed dose; Cmax = Maximum observed concentration; CV = coefficient of variation; SD = standard deviation; T-HALF = Terminal elimination half-life; Tmax = Time of maximum observed concentration.

3. Discussion and Conclusions

Based on the results from the AI444014 trial, the following conclusions can be made.

- When pegylated interferon and ribavirin were coadministered with daclatasvir 60 mg once daily, the ribavirin C_{max}, $AUC_{(0-tau)}$, and C_{12h} were decreased by 6%, 6% and 2%, respectively, when compared with pegylated interferon and ribavirin pegylated interferon and ribavirin administered alone. The 90% confidence intervals for the ribavirin $AUC_{(0-tau)}$, and C_{12h} were both within the standard "no effect" 90% confidence interval limits of 80%-125% but the ribavirin C_{max}, was not within 80%-125%.

No ribavirin dose adjustment is necessary when pegylated interferon and ribavirin are coadministered with daclatasvir 60 mg once daily based on the available efficacy data with concomitant use of these medications.

The trial did not provide a direct comparison of the daclatasvir exposure in the presence and absence of pegylated interferon and ribavirin. The daclatasvir exposure from the AI444014 trial with 60 mg once daily dosing plus pegylated interferon and ribavirin appear to be consistent with the daclatasvir exposure from the AI444004 trial with 60 mg once daily dosing in hepatitis C infected, genotype 1 subjects, however the number of subjects from AI444004 was limited (n=4).

<u>AI444020</u>

1. Title

The Effect of the Co-administration of BMS-790052 on the Pharmacokinetics of a Combined Oral Contraceptive Containing Ethinyl Estradiol and Norgestimate (Ortho Tri-Cyclen®) in Healthy Female Subjects

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at various sites from October 26, 2009 (trial initiation) to February, 8, 2010 (trial completion).

3. Objectives

The primary objective of the trial was to evaluate the potential drug-drug interaction between daclatasvir and a combined oral contraceptive: ethinyl estradiol and norgestimate (Ortho Tri-Cyclen).

4. Trial Design

AI444020 was an open label clinical trial that enrolled healthy female subjects 18 to 45 years old. Information on the trial design is displayed in Figure 1.

Figure 1-AI444020 trial design
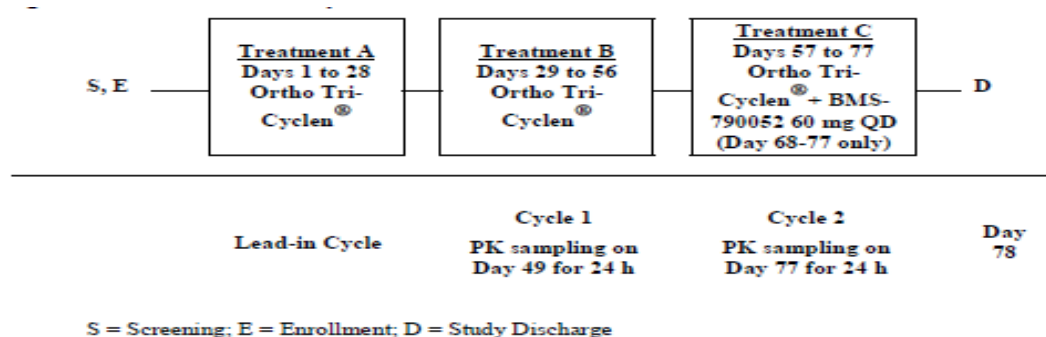
S = Screening; E = Enrollment; D = Study Discharge

5. Excluded Medications, Restrictions or Exceptions

Prescription medications or nonprescription acid modifying medications were not permitted within 4 weeks (unless otherwise approved) and nonprescription medications, including herbal products, were not permitted within 2 weeks prior to medication administration. The use of approved oral contraceptives was noted as an exception. In general, prescription and nonprescription medications, including herbal products, were not permitted during the trial.

6. Dosage and Administration

The trial arms are specified in Figure 1. The ethinyl estradiol and norgestimate contraceptive product (Ortho Tri-Cyclen) contains .035 mg of ethinyl estradiol combined with one of the following strengths of norgestimate: 0.18 mg (week 1), 0.215 mg (week 2) and 0.25 mg (week 3), with each of the different combinations of ethinyl estradiol and norgestimate administered daily for seven days followed by seven daily doses of inactive tablets. On days when pharmacokinetic samples were drawn in cycle 1 and during concomitant administration of Ortho Tri-Cyclen and daclatasvir in cycle 2, after fasting for a minimum of 10 hours, doses were administered under fasted conditions. The U.S. prescribing information (USPI) for Ortho Tri-Cyclen does not provide specific dosing recommendations with regards to food or meals. For daclatasvir, the applicant is proposing to administer the medication with or without food.

7. Rationale for Doses Used in the Trial

The dosage regimen of 60 mg once daily for daclatasvir is the proposed recommended dosage regimen. The ethinyl estradiol and norgestimate doses are consistent with the information in the Ortho Tri-Cyclen U.S. prescribing information.

8. Drugs Used in the Trial

Information regarding the daclatasvir formulation that was administered in the trial is displayed in Table 1. There were no specific details provided regarding the ethinyl estradiol and norgestimate (Ortho Tri-Cyclen) formulation that was administered.

Table 1-Information on the daclatasvir formulation administered in the AI444020 trial

Drug Product	Route	Dose	Product Identification Number	Batch Product Number	Batch Label Number
BMS-790052-05, 30 mg	Oral	2 x 30 mg	790052-K030-019	9C55376	9H43474

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood samples that were obtained included ethinyl estradiol blood samples and blood samples to measure norgestimate metabolites (e.g. norelgestromin, norgestrel) beginning on days 49 and 77 at predose and up to 24 hours postdose.

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Bioanalysis

The method and bioanalysis of ethinyl estradiol, norelgestromin, and norgestrel are acceptable. Two separate methods were used: one for ethinyl estradiol and norgestrel and a second method for norelgestromin. Ethinyl estradiol, norelgestromin, and norgestrel plasma samples were analyzed using validated LC/MS/MS methods by (b) (4). Both methods were validated in plasma containing potassium oxalate and sodium fluoride. The blood samples for analysis of ethinyl estradiol, norelgestromin, and norgestrel appears to have been collected in tubes containing potassium oxalate and sodium fluoride.

For the AI444020 plasma samples that were analyzed for ethinyl estradiol, the lower limit of quantification for ethinyl estradiol was 2 pg/mL and the upper limit of quantification was 500 pg/mL. The ethinyl estradiol concentrations for the calibration curve standards and quality control (QC) samples that were evaluated during the method validation did not exactly match the ethinyl estradiol concentrations for the calibration curve standards and QC samples that were evaluated during the AI444020 bioanalysis, however the reported ethinyl estradiol concentration data is acceptable based on the available bioanalytical information. There were no precision or accuracy issues identified for ethinyl estradiol based on the bioanalytical report. For the AI444020 trial, precision and accuracy were evaluated using plasma ethinyl estradiol QC samples at 5 pg/mL, 10 pg/mL, 30 pg/mL, 100 pg/mL and 400 pg/mL. The corresponding ethinyl estradiol inter-run accuracy values were -6.5% for 5 pg/mL, -4.7% for 10 pg/mL, -4.79% for 30 pg/mL, -5.71% for 100 pg/mL and -4.61% for 400 pg/mL. The ethinyl estradiol inter-run precision values were 5.26% for 5 pg/mL, 4.87% for 10 pg/mL, 2.91% for 30 pg/mL, 4.57% for 100 pg/mL and 4.06% for 400 pg/mL.

For norelgestromin, the lower limit of quantification was 0.02 ng/mL and the upper limit of quantification was 10 ng/mL. The norelgestromin concentrations for the calibration curve standards and QC samples that were evaluated during the method validation did not exactly match the norelgestromin concentrations for the calibration curve standards and QC samples that were evaluated during the AI444020 bioanalysis, however the reported norelgestromin concentration data is acceptable based on the available bioanalytical information. There were no precision or accuracy issues identified for norelgestromin based on the bioanalytical report. For the AI444020 trial, precision and accuracy were evaluated using plasma norelgestromin QC samples at 0.05 ng/mL, 0.13 ng/mL, 0.45 ng/mL, 1.5 ng/mL and 7.6 ng/mL. The corresponding norelgestromin inter-run accuracy values were 2.49% for 0.05 ng/mL, 2.62% for 0.13 ng/mL, 3.22% for 0.45 ng/mL, 2.3% for 1.5 ng/mL and 3.01% for 7.6 ng/mL. The norelgestromin inter-run precision values were 4.31% for 0.05 ng/mL, 3.31% for 0.13 ng/mL, 3.01% for 0.45 ng/mL, 2.03% for 1.5 ng/mL and 2.44% for 7.6 ng/mL.

For norgestrel, the lower limit of quantification was 50 pg/mL and the upper limit of quantification was 25000 pg/mL. The norgestrel concentrations for the calibration curve standards and QC samples that were evaluated during the method validation did not exactly match the norgestrel concentrations for the calibration curve standards and QC

samples that were evaluated during the AI444020 bioanalysis, however the reported norgestrel concentration data is acceptable based on the available bioanalytical information, . There were no precision or accuracy issues identified for norgestrel based on the bioanalytical report. For the AI444020 trial, precision and accuracy were evaluated using plasma norgestrel QC samples at 125 pg/mL, 300 pg/mL, 1200 pg/mL, 4000 pg/mL and 20000 pg/mL. The corresponding norelgestrel inter-run accuracy values were 4.85% for 125 pg/mL, -2% for 300 pg/mL, 2.13% for 1200 pg/mL, 1.01% for 4000 pg/mL and 1.47% for 20000 pg/mL. The norelgestrel inter-run precision values were 11.6% for 125 pg/mL, 6.43% for 300 pg/mL, 3.79% for 1200 pg/mL, 4.51% for 4000 pg/mL and 3.95% for 20000 pg/mL.

For the AI444020 trial, in response to an information request, the applicant stated that the ethinyl estradiol plasma samples were stored at the trial site at -70°C for up to 35 days, at the central laboratory at -70°C for up to 48 days and the bioanalytical laboratory at -70°C for up to 9 days, norgestrel plasma samples were stored at the trial site at -70°C for up to 35 days, at the central laboratory at -70°C for up to 48 days and the bioanalytical laboratory at -70°C for up to 17 days and the norelgestromin plasma samples were stored at the trial site at -70°C for up to 35 days, at the central laboratory at -70°C for up to 48 days and the bioanalytical laboratory at -70°C for up to 24 days. The generated long term stability data for ethinyl estradiol included stability data in plasma containing potassium oxalate and sodium fluoride at -20°C for 323 days and at-70°C for 811 days. For norelgestromin, the generated long term stability data included stability in plasma containing potassium oxalate and sodium fluoride at-70°C for 515 days. The generated long term stability data for norgestrel included stability data in plasma containing potassium oxalate and sodium fluoride at -20°C for 328 days and at-70°C for 811 days. For the AI444020 trial, the generated long term stability data appears to covers the duration of long term stability data necessary for ethinyl estradiol, norgestrel and norelgestromin.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for ethinyl estradiol, norelgestromin, and norgestrel. For the noncompartmental analysis, ethinyl estradiol, norelgestromin, and norgestrel plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, and $AUC_{(0-tau)}$.

Statistical Analysis

Statistical analyses were conducted that included the following comparisons and 90% confidence intervals were derived for ethinyl estradiol, norelgestromin or norgestrel with concomitant use of ethinyl estradiol and norgestimate (Ortho Tri-Cyclen) with daclatasvir (test arms) compared to ethinyl estradiol and norgestimate (Ortho Tri-Cyclen) administered alone (reference arm).

10. Results

10.1 Subject Demographics

Table 2-AI444020 subject demographics

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-------------------------------------------------
                                  All Subjects
                                     N = 20
-------------------------------------------------
AGE
   N                                       20
   MEAN                                    29.8
   MEDIAN                                  31.0
   MIN , MAX                       18 ,    44
   Q1 , Q3                       22.5 ,    35.0
   STANDARD DEVIATION                       7.36

AGE CATEGORIZATION (%)
   <=45                             20    (100.0)
   NOT REPORTED                      0

GENDER (%)
   FEMALE                           20    (100.0)
   NOT REPORTED                      0

RACE (%)
   WHITE                            20    (100.0)
   NOT REPORTED                      0
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10.2 Concomitant Medications

The concomitant medications that were administered in the trial included acetaminophen. The conclusions of the trial are not expected to be significantly altered by the concomitant medications that were administered in the trial.

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10.3 Pharmacokinetic and Statistical Analysis

Ethinyl estradiol

Table 3-Multiple dosing ethinyl estradiol pharmacokinetic parameters with ethinyl estradiol and norgestimate (Ortho Tri-Cyclen) or with ethinyl estradiol and norgestimate (Ortho Tri-Cyclen) combined with daclatasvir 60 mg once daily

Treatment	Cmax (pg/mL) Geo.Mean (CV)	AUC(TAU) (pg*h/mL) Geo.Mean (CV)	Tmax (h) Median (Min, Max)
B Ortho Tri-Cyclen® Day 49	118.53	959.37	1.5
(N = 20)	(34)	(38)	(1 - 2)
C Ortho Tri-Cyclen® + BMS-790052 60 mg QD Day 77	134.70	994.40	1.5
(N = 18)	(30)	(35)	(1 - 2)

Treatment B: Ortho Tri-Cyclen® on Day 49; Treatment C: Ortho Tri-Cyclen® + BMS-790052 60 mg QD on Day 77

Table 4-Statistical analyses for ethinyl estradiol

Treatment and Comparison	Cmax (pg/mL) Adjusted Geometric Mean	AUC(TAU) (pg•h/mL) Adjusted Geometric Mean
B Ortho Tri-Cyclen® Day 49	118.53	959.37
C Ortho Tri-Cyclen® + BMS-790052 60 mg QD Day 77	131.03	968.03
	Adjusted GMR(90% CI)	Adjusted GMR(90% CI)
C vs. B	1.105 (1.023,1.195)	1.009 (0.951,1.070)

Treatment B: Ortho Tri-Cyclen® on Day 49

Treatment C: Ortho Tri-Cyclen® + BMS-790052 60 mg QD on Day 77

Norelgestromin

Table 5-Multiple dosing norelgestromin pharmacokinetic parameters with ethinyl estradiol and norgestimate (Ortho Tri-Cyclen) or with ethinyl estradiol and norgestimate (Ortho Tri-Cyclen) combined with daclatasvir 60 mg once daily

Treatment	Cmax (ng/mL) Geo.Mean (CV)	AUC(TAU) (ng*h/mL) Geo.Mean (CV)	Tmax (h) Median (Min, Max)
B Ortho Tri-Cyclen® Day 49	1.99	15.38	1.3
(N = 20)	(20)	(24)	(1 - 3)
C Ortho Tri-Cyclen® + BMS-790052 60 mg QD Day 77	2.10	16.84	1.5
(N = 18)	(20)	(20)	(1 - 2)

Treatment B: Ortho Tri-Cyclen® on Day 49
Treatment C: Ortho Tri-Cyclen® + BMS-790052 60 mg QD on Day 77

Table 6- Statistical analyses for norelgestromin

Treatment and Comparison	Cmax (ng/mL) Adjusted Geometric Mean	AUC(TAU) (ng•h/mL) Adjusted Geometric Mean
B Ortho Tri-Cyclen® Day 49	1.99	15.38
C Ortho Tri-Cyclen® + BMS-790052 60 mg QD Day 77	2.11	17.15
	Adjusted GMR(90% CI)	Adjusted GMR(90% CI)
C vs. B	1.059 (0.988,1.135)	1.115 (1.063,1.171)

Treatment B: Ortho Tri-Cyclen® on Day 49
Treatment C: Ortho Tri-Cyclen® + BMS-790052 60 mg QD on Day 77

Norgestrel

Table 7- Multiple dosing norgestrel pharmacokinetic parameters with ethinyl estradiol and norgestimate (Ortho Tri-Cyclen) or with ethinyl estradiol and norgestimate (Ortho Tri-Cyclen) combined with daclatasvir 60 mg once daily

Treatment	Cmax (pg/mL) Geo.Mean (CV)	AUC(TAU) (pg*h/mL) Geo.Mean (CV)	Tmax (h) Median (Min, Max)
B Ortho Tri-Cyclen® Day 49	2674.69	47258.35	1.8
(N = 20)	(32)	(38)	(1 - 3)
C Ortho Tri-Cyclen® + BMS-790052 60 mg QD Day 77	2815.98	51760.43	2.0
(N = 18)	(32)	(35)	(1 - 8)

Treatment B: Ortho Tri-Cyclen® on Day 49

Treatment C: Ortho Tri-Cyclen® + BMS-790052 60 mg QD on Day 77

Table 8- Statistical analyses for norgestrel

Treatment and Comparison	Cmax (pg/mL) Adjusted Geometric Mean	AUC(TAU) (pg•h/mL) Adjusted Geometric Mean
B Ortho Tri-Cyclen® Day 49	2674.69	47258.35
C Ortho Tri-Cyclen® + BMS-790052 60 mg QD Day 77	2864.03	52958.98
	Adjusted GMR(90% CI)	Adjusted GMR(90% CI)
C vs. B	1.071 (0.988,1.160)	1.121 (1.018,1.234)

Treatment B: Ortho Tri-Cyclen® on Day 49

Treatment C: Ortho Tri-Cyclen® + BMS-790052 60 mg QD on Day 77

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10.4 Safety Analysis

No deaths or serious adverse events were reported for the trial. There was one adverse events leading to discontinuation in a subject that did not receive daclatasvir.

11. Discussion and Conclusions

Based on the results from the AI444020 trial, the following conclusions can be made.

- Ethinyl estradiol: When daclatasvir 60 mg once daily was coadministered with ethinyl estradiol and norgestimate (Ortho Tri-Cyclen), the ethinyl estradiol C_{max} and the $AUC_{(0-tau)}$ were increased by 11% and 1%, respectively, when compared with ethinyl estradiol and norgestimate (Ortho Tri-Cyclen) administered alone. The 90% confidence intervals for ethinyl estradiol C_{max} and $AUC_{(0-tau)}$ were both within the standard "no effect" 90% confidence interval limits of 80%-125%.
- Norelgestromin: When daclatasvir 60 mg once daily was coadministered with ethinyl estradiol and norgestimate (Ortho Tri-Cyclen), the norelgestromin C_{max} and the $AUC_{(0-tau)}$ were increased by 6% and 12%, respectively, when compared with ethinyl estradiol and norgestimate (Ortho Tri-Cyclen) administered alone. The 90% confidence intervals for norelgestromin C_{max} and $AUC_{(0-tau)}$ were both within the standard "no effect" 90% confidence interval limits of 80%-125%.
- Norgestrel: When daclatasvir 60 mg once daily was coadministered with ethinyl estradiol and norgestimate (Ortho Tri-Cyclen), the norgestrel C_{max} and the $AUC_{(0-tau)}$ were increased by 7% and 12%, respectively, when compared with ethinyl estradiol and norgestimate (Ortho Tri-Cyclen) administered alone. The 90% confidence intervals for norgestrel C_{max} and $AUC_{(0-tau)}$ were both within the standard "no effect" 90% confidence interval limits of 80%-125%.

No clinically relevant changes in ethinyl estradiol, norelgestromin or norgestrel exposure were observed with concurrent use of daclatasvir.

1. Title

The Effect of the Coadministration of a Proton Pump Inhibitor (Omeprazole) on the Pharmacokinetics of BMS-790052 in Healthy Subjects

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted by Bristol-Myers Squibb from October 7, 2011 to November 18, 2010.

3. Objectives

The primary objective was to assess the effect of omeprazole on the single-dose PK of BMS-790052 at steady state in healthy subjects.

The secondary objective was to assess the safety and tolerability of BMS-790052 when administered alone and with omeprazole in healthy subjects.

4. Trial Design

This was a randomized, open-label study in healthy subjects. All subjects were screened within 21 days prior to dosing on Day 1. Eligible subjects were randomized to receive BMS-790052 20 mg (Sequence 1) or BMS-790052 60 mg (Sequence 2). Subjects were admitted to the clinical research facility on Day -1 and were confined to the clinical research facility until discharge on Day 10. On Day 1, subjects received a single oral dose of BMS-790052 20 mg (Treatment A) or 60 mg (Treatment B). Following a 48-hour washout, subjects received QD oral doses of omeprazole 40 mg from Day 3 to Day 7 (Treatment C), concurrent single doses of omeprazole 40 mg and BMS-790052 20 mg (Treatment D) or 60 mg (Treatment E) on Day 8, and a single dose of omeprazole 40 mg on Day 9 (Treatment F). The dose of BMS-790052 a subject received on Day 8 was the same as the dose he/she received on Day 1.

Figure 1: Study Design Schematic
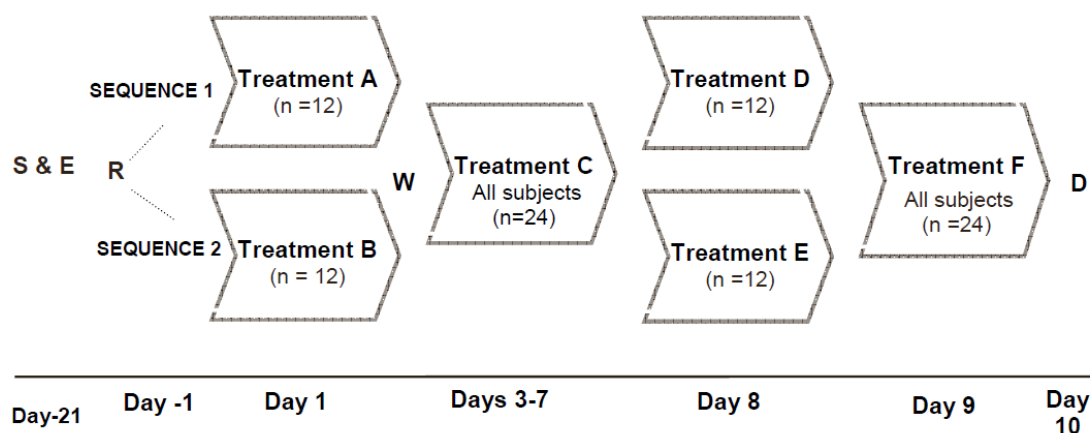
S = Screening; E = Enrollment; R = Randomization; W = 48-hour Washout; D = Discharge

Treatment A = Single dose of BMS-790052 20 mg

Treatment B = Single dose of BMS-790052 60 mg

Treatment C = Omeprazole 40 mg once-daily

Treatment D = Single dose of BMS-790052 20 mg with single dose of omeprazole 40 mg

Treatment E = Single dose of BMS-790052 60 mg with single dose of omeprazole 40 mg

Treatment F = Single dose of omeprazole 40 mg

5. Excluded Medications, Restrictions or Exceptions

No concomitant medications (prescription, over-the-counter or herbal) were administered during study unless they were prescribed by the investigator for treatment of specific clinical events. Any concomitant therapies must be recorded on the CRF.

6. Rationale for Doses Used in the Trial

Omeprazole was administered at the highest approved dose regimen, 40 mg QD. Omeprazole's inhibitory effect on acid secretion increases with repeated QD dosing, reaching maximal effect after 4 days. In this study, BMS-790052 was administered simultaneously with omeprazole on the morning of Day 8, after 6 days of dosing with omeprazole alone, to ensure that the maximal PD effect of omeprazole was achieved prior to concomitant dosing. BMS-790052 was administered at the lowest dose (20 mg) and the highest dose (60 mg) evaluated in a Phase 2b study in the HCV population. The dosage regimen of BMS-790052 (i.e. DCV 60 mg) is consistent with the recommended DCV dosage regimen in the proposed DCV U.S. prescribing information.

BMS-790052 has a solubility of 0.11 mg/mL at pH 5, the gastric pH that was anticipated to be reached (or exceeded) after steady-state administration of omeprazole 40 mg QD. At this gastric pH, the maximum dose of BMS-790052 that can be dissolved when administered with 240 mL of water is approximately 26 mg. Therefore, at steady-state, omeprazole 40 mg QD was expected to decrease BMS-790052 exposure when coadministered with a dose of 60 mg BMS-790052, but to have minimal effect when

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coadministered with a dose of BMS-790052 20 mg.

7. Drugs Used in the Trial

- BMS-790052 was supplied by BMS as plain, round, biconvex, bevel-edged, film-coated white tablets containing either 10 mg (Product batch number 8J43343) or 30 mg (Product batch number 9C55376) of drug substance as the free base, BMS-**790052-05.**
- Omeprazole 40 mg delayed-release capsules were sourced by the clinical site from a single commercial lot.

8. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Table 1 - PK sampling schedule for DCV

Study Day	Time (Event) Hour	Time (Relative to Dosing) Hour:Min	PK Blood Sample for BMS-790052
1 and 8	0 (pre-dose)	00:00	X
1 and 8	0.5	00:30	X
1 and 8	1	01:00	X
1 and 8	1.5	01:30	X
1 and 8	2	02:00	X
1 and 8	4	04:00	X
1 and 8	6	06:00	X
1 and 8	8	08:00	X
1 and 8	12	12:00	X
2 and 9	0	24:00	X
2 and 9	12	36:00	X
3 and 10	0	48:00	X

Bioanalytical method for DCV

The method and bioanalysis of DCV is acceptable.

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Analyte	BMS-790052	
Internal Standard	BMS-790052-$^{13}C_{10}$ (added to all samples except Blanks)	
Regression, Weighting	Linear $1/x^2$	
LLOQ	0.500 ng/mL	
ULOQ	500 ng/mL	
Calibration Standard Concentrations	0.500, 1.00, 5.00, 25.0, 50.0, 100, 250, 450, and 500 ng/mL	
Analytical QC Concentrations	1.50, 20.0, 200, and 400 ng/mL	
Dilution QC Concentration	5000 ng/mL	
Dilution Factor	20	
Performance of Analytical QCs	Precision (%CV)[a]	Accuracy (%Bias)[a]
(Low through High)	2.9% to 4.8%	-4.0% to -0.8%

a: Excludes Dilution QCs.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for DCV. The PK parameters assessed include t_{max}, C_{max}, C_{24h}, AUC_{0-T}, and AUC_{INF}, and T-half.

Statistical Analysis

To assess the effects of omeprazole on BMS-790052, point estimates and 90% confidence intervals for the ratios of the geometric means for BMS-790052 Cmax, AUC(0-T), and AUC(INF), with and without omeprazole were constructed. BMS-790052 alone will be used as the reference in the comparisons. Similar analyses will be conducted for BMS-790052 C24.

9. Results

9.1 Subject Demographics and Disposition

Of the 24 subjects (12 subjects per treatment sequence) who were treated in the study, 22 subjects (11 per treatment sequence) completed the study as planned. Two (2) subjects withdrew consent following family emergencies. (**Table 2**).

Table 2-Subject Demographics

	Sequence 1 Trt A/C/D/F	Sequence 2 Trt B/C/E/F	Overall
Age in years			
Mean (SD)	34 (7)	33 (10)	34 (8)
Min, Max	24, 45	22, 49	22, 49
Gender, n (%)			
Male	11 (91.7)	8 (66.7)	19 (79.2)
Female	1 (8.3)	4 (33.3)	5 (20.8)
Race, n (%)			
White	3 (25.0)	4 (33.3)	7 (29.2)
Black/African American	7 (58.3)	7 (58.3)	14 (58.3)
Other	2 (16.7)	1 (8.3)	3 (12.5)
BMI in kg/m^2			
Mean (SD)	26.5 (2.6)	26.8 (3.2)	26.7 (2.9)
Min, Max	22.4, 31.4	21.8, 31.8	21.8, 31.8

Treatments (Trt): A = BMS-790052 20 mg; B = BMS-790052 60 mg; D = BMS-790052 20 mg + omeprazole 40 mg; E = BMS-790052 60 mg + omeprazole 40 mg

9.2 Concomitant Medications

The concomitant medications that were administered in the trial are not expected to significantly alter the conclusions of the trial.

9.3 Pharmacokinetic and Statistical Analysis

Effect of omeprazole on the PK of BMS-790052 (DCV)

Mean BMS-790052 plasma concentrations versus time plots for each treatment are provided **Figure 2.**

Figure 2 - Mean Plasma Concentration-Time Profiles for BMS-790052 by Treatment in Healthy Subjects (Linear Scale)
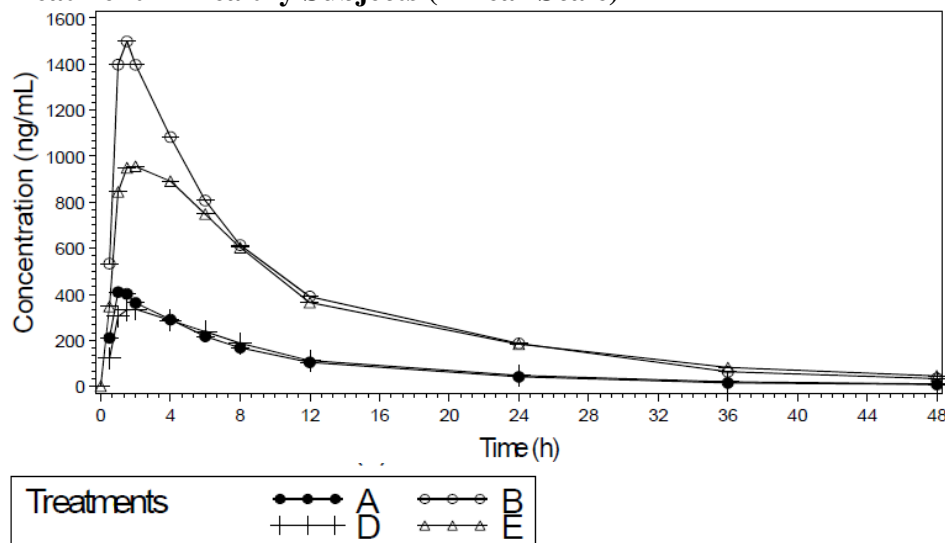
Treatments: A = BMS-790052 20 mg (N=12); B = BMS-790052 60 mg (N=12); D = BMS-790052 20 mg + omeprazole 40 mg (N=11); E = BMS-790052 60 mg + omeprazole 40 mg (N=11).

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Results of the statistical analysis of the effect of omeprazole on BMS-790052 exposure when coadministered with BMS-790052 20 mg and 60 mg are summarized in **Table 3** and **Table 4**.

Table 3- Effect of Omeprazole on PK Parameters of BMS-790052 20 mg

Treatment and Comparison	Cmax (ng/mL) Geo. Mean (%CV)	AUC(0-T) (ng•h/mL) Geo. Mean (%CV)	AUC(INF) (ng•h/mL) Geo. Mean (%CV)	C24 (ng/mL) Geo.Mean (%CV)
A	427.6 (23)	3908.2 (23)	3931.9 (24)	41.8(31)
D	340.8 (41)	3853.2 (35)	4016.1 (34)	44.7(36)
	GMR (90% CI)	**GMR (90% CI)**	**GMR (90% CI)**	**GMR (90% CI)**
D vs. A	0.800 (0.633,1.012)	1.004 (0.869,1.161)	1.021 (0.888,1.175)	1.113 (0.989,1.254)

Table 4- Effect of Omeprazole on PK Parameters of BMS-790052 60 mg

Treatment and Comparison	Cmax (ng/mL) Geo. Mean (%CV)	AUC(0-T) (ng•h/mL) Geo. Mean (%CV)	AUC(INF) (ng•h/mL) Geo. Mean (%CV)	C24 (ng/mL) Geo.Mean (%CV)
B	1419.2(46)	13504.4(50)	13904.4(50)	159.7(57)
E	974.2(57)	11944.0(51)	12594.7(53)	160.4(58)
	GMR (90% CI)	**GMR (90% CI)**	**GMR (90% CI)**	**GMR (90% CI)**
E vs. B	0.643 (0.536,0.771)	0.821 (0.716,0.941)	0.840 (0.732,0.963)	0.915 (0.795,1.054)

9.5 Safety Analysis

A total of 13 treatment-emergent AEs were reported by 5 (21%) subjects during the study. Each of these 5 subjects reported AEs during treatment with omeprazole 40 mg QD alone, most commonly constipation (3 [12.5%] subjects). One subject reported AEs during treatment with BMS-790052 60 mg alone (somnolence) and in combination with omeprazole (increased alkaline phosphatase, rhinorrhoea). No AEs were reported during treatment with BMS-790052 20 mg alone or in combination with omeprazole. All AEs were assessed by the investigator as mild in intensity and unrelated to treatment and resolved prior to study completion. There were no deaths, serious adverse events, or treatment discontinuations due to AEs.

10. Sponsor's Conclusions

Disorders of gastric acid secretion are prevalent within the HCV population. Thus, it is anticipated that BMS-790052 will frequently be coadministered with acid-suppressing medications. The most common therapeutic approach involves administration of a proton

pump inhibitor (PPI) to reduce gastric acid secretion. Administration of a PPI suppresses gastric acid secretion, resulting in increased gastric pH. BMS-790052 has pH-dependent solubility, as demonstrated by nonclinical data where the solubility of the ___ (b) (4) di-hydrochloride salt was decreased from 20 mg/mL at pH 2.0 to 0.11 mg/mL and 0.015 mg/mL at pH 5.0 and 7.0, respectively. This study was conducted to assess the effect of omeprazole 40 mg QD, a commonly administered PPI, on BMS-790052 exposures when coadministered with single oral doses of 20 mg and 60 mg BMS-790052. Omeprazole was dosed for 6 days in order to ensure steady state and maximum PD effect was achieved prior to coadministration with BMS-790052.

- Coadministration of BMS-790052 20 mg with omeprazole 40 mg resulted in an approximate 20% decrease in BMS-790052 Cmax, while BMS-790052 AUC(INF) was unaffected.
- Coadministration of BMS-790052 60 mg with omeprazole 40 mg resulted in approximate 36% and 16% decreases in BMS-790052 Cmax and AUC(INF), respectively.
- Single oral doses of BMS-790052 20 mg and 60 mg, administered alone and with omeprazole, were generally safe and well tolerated by the healthy subjects in this study.

11. Reviewer's Assessment

The AI444034 trial adequately assessed the effect of omeprazole on the single-dose PK of BMS-790052 at steady state in healthy subjects. The larger impact on BMS-790052 exposures observed at the higher dose of 60 mg compared to 20 mg was expected. Reduced solubility (due to increased gastric pH) is expected to have a larger impact at higher doses as less drug (as a percentage of the administered dose) is in solution and thus available for absorption into systemic circulation. The sponsor's conclusions are valid and no DCV dose adjustment is needed when coadministered with omeprazole 40 mg ___ (b) (4)

1. Title

Open-Label Multiple-Dose Study to Assess the Effect of BMS-790052 on the Pharmacokinetics of Digoxin in Healthy Subjects

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at PPD from October 7, 2010 (trial initiation) to November 18, 2010 (trial completion).

3. Objectives

The primary objective of the trial was to evaluate the potential drug-drug interaction between daclatasvir and digoxin.

4. Trial Design

AI444027 was an open label clinical trial that enrolled healthy subjects 18 to 40 years old. Information on the trial design is displayed in Figure 1.

Figure 1-AI444027 trial design
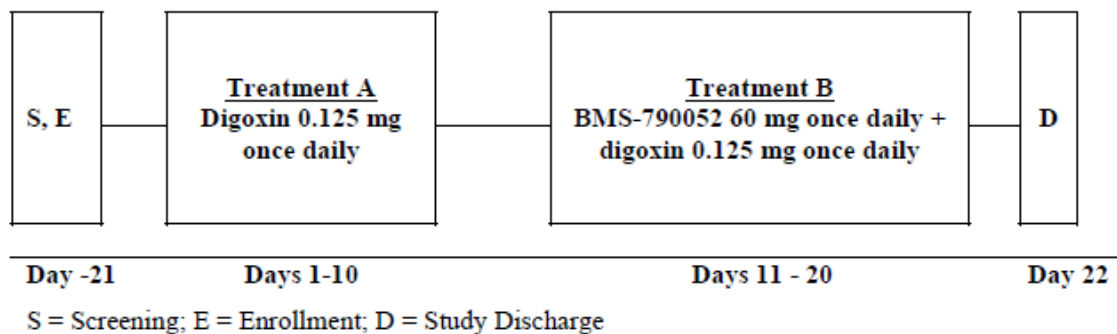
S = Screening; E = Enrollment; D = Study Discharge

5. Excluded Medications, Restrictions or Exceptions

Prescription medications or nonprescription acid modifying medications were not permitted within 4 weeks (unless otherwise approved) and nonprescription medications, including herbal products, were not permitted within 2 weeks prior to medication administration. In general, prescription and nonprescription medications, including herbal products, were not permitted during the trial.

6. Dosage and Administration

The trial arms, including the dosage regimens that were administered, are specified in Figure 1. On days 10 and 20, after fasting for a minimum of 10 hours, doses were

administered under fasted conditions. The U.S prescribing information (USPI) for digoxin does not provide specific dosing recommendations with regards to food or meals. For daclatasvir, the applicant is proposing to administer the medication with or without food.

7. Rationale for Doses Used in the Trial

The dosage regimen of 60 mg once daily for daclatasvir is the proposed recommended dosage regimen. The digoxin dosage regimen of 0.125 mg once daily is within the range of recommended maintenance dosage regimens in adults.

8. Drugs Used in the Trial

Daclatasvir was provided as 30 mg tablets (batch number 9C553756). There were no specific details provided regarding the digoxin formulation that was administered.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood samples that were obtained included digoxin blood samples beginning on days 10 and 20 at predose and up to 24 hours postdose.

Bioanalysis

The method and bioanalysis of digoxin are acceptable. Digoxin plasma samples were analyzed using a validated LC/MS/MS method in K_2EDTA anticoagulated plasma by (b) (4). Of note, during the method validation, a digoxin response that exceeded 20% was observed in samples containing digoxin d_3 (the internal standard) and is not anticipated to have a major impact assuming the effects are relatively constant. The blood samples for analysis of digoxin appear to have been collected in tubes containing K_2EDTA.

For the AI444027 plasma samples that were analyzed for digoxin, the lower limit of quantification for digoxin was 0.01 ng/mL and the upper limit of quantification was 10 ng/mL. There were no precision or accuracy issues identified for digoxin based on the bioanalytical report. For the AI444027 trial, precision and accuracy were evaluated using plasma digoxin quality control (QC) samples at 0.025 ng/mL, 0.075 ng/mL, 0.3 ng/mL, 1.25 ng/mL and 7.5 ng/mL. The corresponding digoxin inter-run accuracy values were 0.0548% for 0.025 ng/mL, 1.13% for 0.075 ng/mL, 2.93% for 0.3 ng/mL, 1.32% for 1.25 ng/mL and -5.14% for 7.5 ng/mL. The digoxin inter-run precision values were 8.11% for 0.025 ng/mL, 2.76% for 0.075 ng/mL, 3.26% for 0.3 ng/mL, 1.77% for 1.25 ng/mL and 4.3% for 7.5 ng/mL.

For the AI444027 trial, in response to an information request, the applicant stated that the digoxin plasma samples were stored at the trial site at -20°C for up to 9 days and the

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bioanalytical laboratory at -20°C for up to 56 days. For digoxin, the generated long term stability data included stability data in K_2EDTA anticoagulated plasma at -20°C and -70°C for 286 days. For the AI444027 trial, the generated long term stability data appears to covers the duration of long term stability data necessary for digoxin.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for digoxin. For the noncompartmental analysis, digoxin plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, and $AUC_{(0-tau)}$.

Statistical Analysis

Statistical analyses were conducted and 90% confidence intervals were derived comparing digoxin coadministered with daclatasvir (test arm) compared to digoxin administered alone (reference arm).

10. Results

10.1 Subject Demographics

Table 1-AI444027 subject demographics

```
----------------------------------------------------
                                    All Subjects
                                       N = 17
----------------------------------------------------
AGE
  N                                       17
  MEAN                                    28.9
  MEDIAN                                  30.0
  MIN , MAX                        21 ,    35
  STANDARD DEVIATION                       4.83

AGE CATEGORIZATION (%)
  < 65                                17  (100.0)

GENDER (%)
  MALE                               15  ( 88.2)
  FEMALE                              2  ( 11.8)

RACE (%)
  WHITE                              11  ( 64.7)
  BLACK/AFRICAN AMERICAN              4  ( 23.5)
  ASIAN                               2  ( 11.8)

ETHNICITY (%)
  HISPANIC/LATINO                     4  ( 23.5)
  NOT HISPANIC/LATINO                13  ( 76.5)
```

10.2 Concomitant Medications

The concomitant medications that were administered in the trial were cetirizine (one subject) and a multivitamin (one subject). The conclusions of the trial are not expected to be significantly altered by the concomitant medications that were administered in the trial.

10.3 Pharmacokinetic and Statistical Analysis

Table 2-Multiple dosing digoxin pharmacokinetic parameters with digoxin 0.125 mg once daily or digoxin 0.125 mg once daily combined with daclatasvir 60 mg once daily

Treatment	Cmax (pg/mL) Geo. Mean [N] (%CV)	AUC(TAU) (pg•h/mL) Geo. Mean [N] (CV)	Tmax (h) Median [N] (Min - Max)	Cmin (pg/mL) Geo. Mean [N] (%CV)	UR (%) Median [N] (Min - Max)	CLR (mL/min) Geo. Mean [N] (%CV)
TRT A	703.5 [15] (26)	7510.15 [15] (22)	1.00 [15] (0.5-1.5)	253.4 [15] (28)	52.780 [15] (35.36-75.89)	147.07 [15] (19)
TRT B	1163.0 [15] (19)	9541.29 [15] (15)	0.50 [15] (0.5-1.1)	299.0 [15] (17)	67.586 [15] (34.56-84.28)	137.53 [15] (19)

Treatments (TRT): A=digoxin 0.125 mg QD; B=BMS-790052 60 mg QD + digoxin 0.125 mg QD

Table 3-Statistical analyses for digoxin

Treatment and Comparison	Cmax (pg/mL) Geo. Mean (CV)	AUC(TAU) (pg•h/mL) Geo. Mean (CV)	Cmin (pg/mL) Geo. Mean (CV)
TRT A	703.5 (26)	7510.15 (22)	253.4 (28)
TRT B	1163.0 (19)	9541.29 (15)	299.0 (17)
	Ratio of Adjusted Geometric Means (90% CI)		
TRT B vs TRT A	1.653 (1.521,1.797)	1.270 (1.203,1.342)	1.180 (1.087,1.280)

Treatments (TRT): A=digoxin 0.125 mg QD; B=BMS-790052 60 mg QD + digoxin 0.125 mg QD

Reviewer note: the C_{min} was defined as the plasma trough concentration 24 hours postdose.

10.4 Safety Analysis

No deaths or serious adverse events were reported for the trial. One adverse event leading to discontinuation was reported: uriticaria which was treated with cetirizine that resolved within 3 days.

11. Discussion and Conclusions

Based on the results from the AI444027 trial, the following conclusions can be made.

- When digoxin 0.125 mg once daily was coadministered with daclatasvir 60 mg once daily, the digoxin C_{max}, $AUC_{(0\text{-}tau)}$ and C_{min} were increased by 65%, 27% and 18%, respectively, when compared with digoxin 0.125 mg once daily. The 90% confidence intervals for digoxin C_{max}, $AUC_{(0\text{-}tau)}$ and C_{min} were all not within the standard "no effect" 90% confidence interval limits of 80%-125%.

In the U.S prescribing information for digoxin, for drug-drug interactions resulting in an increase in digoxin concentrations greater than 50%, the recommendation states the following prior to starting an interacting concomitant medication:

Measure serum digoxin concentrations before initiating concomitant drugs. Reduce digoxin concentrations by decreasing dose by approximately 30-50% or by modifying the dosing frequency and continue monitoring.

A recommendation will be sent to the applicant recommending revising the clinical comment in section 7 of the proposed U.S. prescribing information for the daclatasvir-digoxin drug-drug interaction to include this information to be consistent with the recommendation in the U.S. prescribing information for digoxin.

AI444032

1. Title

A One-Way Drug-Drug Interaction Study To Assess The Effect Of Ritonavir-Boosted Atazanavir On The Pharmacokinetics, Safety And Tolerability Of BMS-790052 In Healthy Subjects

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at one site from March 1, 2011 (first screening) to April 13, 2011 (last follow up).

3. Objectives

The primary objective of the trial was to evaluate the potential drug-drug interaction between daclatasvir and atazanavir/ritonavir.

4. Trial Design

AI444032 was an open label clinical trial that enrolled healthy subjects 18 to 49 years old. Information on the trial design is displayed in Figure 1.

Figure 1-AI444032 trial design
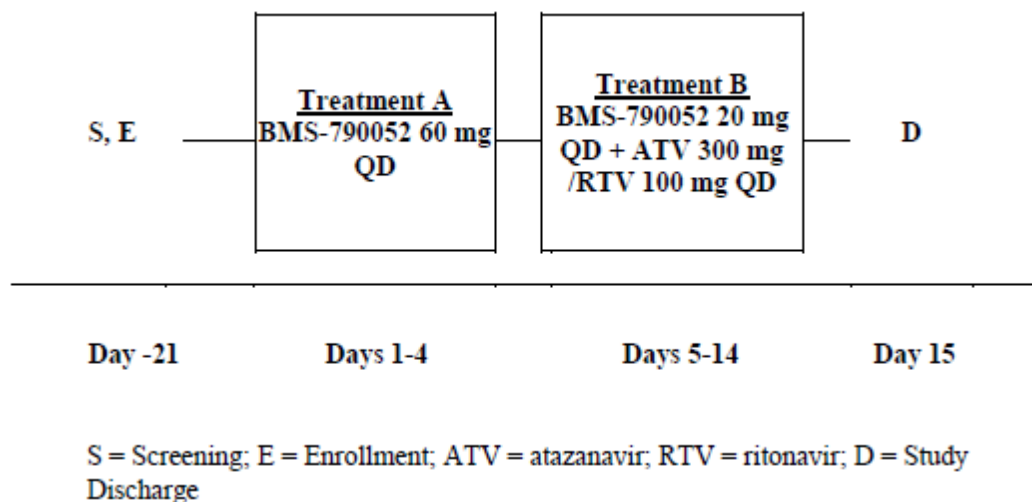
S = Screening; E = Enrollment; ATV = atazanavir; RTV = ritonavir; D = Study Discharge

5. Excluded Medications, Restrictions or Exceptions

Unless otherwise approved, prescription medications or nonprescription acid modifying medications were not permitted within 4 weeks and nonprescription medications, including herbal products, were not permitted within 2 weeks prior to medication

administration. In general, prescription and nonprescription medications, including herbal products, were not permitted during the trial.

6. Dosage and Administration

The trial arms, including the dosage regimens that were administered, are specified in Figure 1. On days 4, 10, and 14, after fasting for 10 hours, doses were administered under fed conditions. According to the atazanavir U.S prescribing information (USPI), atazanavir is to be administered with food. For daclatasvir, the applicant is proposing to administer the medication with or without food.

7. Rationale for Doses Used in the Trial

The dosage regimen of 60 mg once daily for daclatasvir is the proposed recommended dosage regimen. In treatment B, the daclatasvir dosage regimen was changed to 20 mg once daily to account for a potential drug-drug interaction. The atazanavir/ritonavir dosage regimen of 300 mg/100 mg once daily is the recommended dosage regimen for the treatment of HIV infection.

8. Drugs Used in the Trial

Information regarding the medications that were administered in the trial is displayed in Table 1.

Table 1-Information on the medications administered in the AI444032 trial

Active compound	: BMS-790052
Strength	: 10 and 30 mg
Dosage form	: film coated tablets
Batch number	: 0L58850 (10 mg) and 0L58822 (30 mg)
Expiration date	: 31 March 2012
Manufacturer	: BMS
Active compound	: Atazanavir (Reyataz®)
Strength	: 300 mg
Dosage form	: capsules
Batch number	: OK63435
Expiration date	: May 2012
Manufacturer	: BMS

Active compound	: Ritonavir (Norvir®)
Strength	: 100 mg
Dosage form	: tablets
Batch number	: 935628D
Expiration date	: May 2012
Manufacturer	: Abbott

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood samples that were obtained included daclatasvir blood samples beginning on days 4 and 14 at predose and up to 24 hours postdose and atazanavir blood samples were obtained starting on day 14 at predose and up to 24 hours postdose.

Bioanalysis

Note: The bioanalytical information for atazanavir was not reviewed because the applicant is not proposing to include atazanavir pharmacokinetic data in the daclatasvir U.S. prescribing information. The atazanavir pharmacokinetic data is included in this trial review for information purposes only.

The method and bioanalysis of daclatasvir was acceptable. Daclatasvir plasma samples were analyzed using a validated LC/MS/MS method in EDTA anticoagulated plasma by _____ (b) (4) (TNJM08199.02). The blood samples for analysis of daclatasvir appear to have been collected in tubes containing K_2EDTA as an anticoagulant.

For the AI444032 plasma samples that were analyzed for daclatasvir, the lower limit of quantification for daclatasvir was 0.5 ng/mL and the upper limit of quantification was 500 ng/mL. There were no precision or accuracy issues identified for daclatasvir based on the bioanalytical report. For the AI444032 trial, precision and accuracy were evaluated using plasma daclatasvir quality control (QC) samples at 1.5 ng/mL, 20 ng/mL, 202 ng/mL (the bioanalytical report notes that this should have been prepared at 200 ng/mL), and 400 ng/mL. There were also dilution QCs prepared at 5000 ng/mL. The corresponding daclatasvir inter-run accuracy values were -4% for 1.5 ng/mL, -7.5% for 20 ng/mL, -5.4% for 202 ng/mL, and -4% for 400 ng/mL. The daclatasvir inter-run precision values were 5.1% for 1.5 ng/mL, 3.9% for 20 ng/mL, 2.9% for 202 ng/mL, and 3.3% for 400 ng/mL. In addition, for the daclatasvir dilution QC samples at 5000 ng/mL, the inter-run accuracy and precision were -11.6% and 3.2%, respectively.

Of the samples selected for incurred sample reanalysis for daclatasvir (total number less than 50), only one sample was not within 20% using the percentage values of the repeat and original concentrations. However, it is not clear whether the total number of

daclatasvir samples that were reanalyzed represents 7% of the total number of samples that were initially analyzed.

For the AI444032 trial, in response to an information request, the applicant stated that the daclatasvir plasma samples were stored at the trial site at -20°C for up to 16 days and the bioanalytical laboratory at -20°C for up to 8 days. For the TNJM08199.02 method, the generated long term stability data for daclatasvir included stability data in EDTA anticoagulated plasma at -20°C for 1081 days (of note, the long term stability experiment at -20°C for 1039 days failed at 1.5 ng/mL). For the AI444032 trial, the generated long term stability data appears to covers the duration of long term stability data necessary for daclatasvir.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for daclatasvir and atazanavir. For the noncompartmental analysis, daclatasvir and atazanavir plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, and $AUC_{(0-tau)}$.

Statistical Analysis

Statistical analyses were conducted and 90% confidence intervals were derived comparing atazanavir/ritonavir coadministered with daclatasvir (test arm) compared to daclatasvir administered alone (reference arm). The analysis was also performed with the test arm dose normalized to daclatasvir 60 mg.

10. Results

10.1 Subject Demographics

Table 2-AI444032 subject demographics

		N = 14
Age (yr)	Mean (SD)	25.2 (7.87)
	Range	18 - 43
Gender (N; %)	Male	11; 79%
	Female	3; 21%
Height (cm)	Mean (SD)	180.7 (11.53)
	Range	160 - 195
Weight (kg)	Mean (SD)	77.76 (15.045)
	Range	48.2 – 109.7
BMI (kg/m^2)	Mean (SD)	23.68 (3.250)
	Range	18.8 – 29.5

10.2 Concomitant Medications

The concomitant medications administered in the trial included acetaminophen. The conclusions of the trial are not expected to be significantly altered by the concomitant medications that were administered in the trial.

10.3 Pharmacokinetic and Statistical Analysis

Daclatasvir

Table 3-Multiple dosing daclatasvir pharmacokinetic parameters with daclatasvir 60 mg once daily or atazanavir/ritonavir 300 mg/100 mg once daily combined with daclatasvir 20 mg once daily (or dose normalized to 60 mg)

Treatment	Cmax (ng/mL) geo.mean [N] (CV)	Tmax (h) median [N] (min-max)	AUC(TAU) (ng.h/mL) geo.mean [N] (CV)	C24 (ng/mL) geo.mean [N] (CV)
Treatment A (BMS-790052)	973 [14] (36%)	2.00 [14] (1.00-4.00)	9495 [14] (36%)	147 [14] (48%)
Treatment B (BMS-790052 + ritonavir-boosted atazanavir)	438 [14] (31%)	2.03 [14] (1.00-6.00)	6640 [14] (31%)	179 [14] (36%)
Dose normalized to 60-mg dose				
Treatment A (BMS-790052)	973 [14] (36%)	-	9495 [14] (36%)	147 [14] (48%)
Treatment B (BMS-790052 + ritonavir-boosted atazanavir)	1314 [14] (31%)	-	19920 [14] (31%)	536 [14] (36%)

Table 4-Statistical analyses for daclatasvir

	Geometric LS means			
PK Parameter	Treatment B (Test)	Treatment A (Reference)	Ratio Test/Reference	90% CI
Cmax (ng/mL)	438	973	0.4502	(0.4134, 0.4901)
AUC(TAU) (h.ng/mL)	6640	9495	0.6993	(0.6505, 0.7518)
C24 (ng/mL)	179	147	1.2181	(1.0833, 1.3698)
Dose normalized to 60-mg dose				
Cmax/D (ng/mL)	1314	973	1.3505	(1.2403, 1.4704)
AUC(TAU)/D (h.ng/mL)	19920	9495	2.0980	(1.9515, 2.2555)
C24/D (ng/mL)	536	147	3.6544	(3.2498, 4.1093)

Note: the dose normalized daclatasvir pharmacokinetic parameters and statistical analysis assumes that daclatasvir exposure is dose proportional from 20 to 60 mg.

Atazanavir

Table 5-Multiple dosing atazanavir pharmacokinetic parameters with atazanavir/ritonavir 300 mg/100 mg once daily combined with daclatasvir 20 mg once daily or historical data

Treatment	Cmax (ng/mL) geo.mean [N] (CV)	AUC(TAU) (ng.h/mL) geo.mean [N] (CV)	C24 (ng/mL) geo.mean [N] (CV)
Treatment B (BMS-790052 + ritonavir-boosted atazanavir)	4942 [14] (27%)	52817 [14] (32%)	978 [14] (45%)
Ritonavir-boosted atazanavir alone, historical data[1]	5734 [27] (21%)	56575 [27] (26%)	1213 [27] (44%)
Ritonavir-boosted atazanavir alone, historical data[2]	5331 [19] (27%)	50851 [19] (33%)	979 [19] (61%)

[1] Data were obtained following 10 days of 300 mg atazanavir + 100 mg ritonavir treatment as described in the CSR of study AI424288.[1]

[2] Data were obtained following 10 days of 300 mg atazanavir + 100 mg ritonavir treatment as described in the CSR of study AI424139.[2]

10.4 Safety Analysis

No deaths, serious adverse events or adverse events resulting in discontinuation were reported for the trial.

11. Discussion and Conclusions

Based on the results from the AI444032 trial, the following conclusions can be made.

- When daclatasvir 20 mg once daily was coadministered with atazanavir/ritonavir 300 mg/100 mg once daily, the dose normalized daclatasvir C_{max}, $AUC_{(0-tau)}$ and C_{24h} were increased by 35%, 110% and 265%, respectively, when compared with daclatasvir 60 mg once daily. The 90% confidence intervals for daclatasvir C_{max}, $AUC_{(0-tau)}$ and C_{24h} were all not within the standard "no effect" 90% confidence interval limits of 80%-125%.
- There does not appear to be any significant differences in atazanavir exposure when daclatasvir 20 mg once daily was coadministered with atazanavir/ritonavir 300 mg/100 mg once daily based on comparisons to historical data.

However, it is important to note that based on the analysis that was conducted during the NDA review, dose proportionality was not observed for daclatasvir.

The applicant is proposing a dose adjustment with concomitant use of strong CYP3A inhibitors and daclatasvir   (b) (4). The applicant is proposing to include the following recommendation in the daclatasvir U.S. prescribing information: The dose of DCV should be reduced to 30 mg once daily when coadministered with atazanavir/ritonavir or other strong inhibitors of CYP3A4.

Atazanavir is a moderate CYP3A inhibitor. It is not clear whether atazanavir when combined with ritonavir is a strong CYP 3A inhibitor. For strong CYP3A inhibition, the proposed dosage adjustment for daclatasvir would be expected to mitigate but not completely compensate for the changes in daclatasvir exposure due to drug-drug interactions. However, considering that only a 30 mg tablet will be available for dosage adjustments, the proposed dosage adjustment is reasonable if supported by concerns regarding safety. A similar rationale would be applicable to a potential drug-drug interaction between atazanavir/ritonavir and daclatasvir.

<u>AI444033</u>

1. Title

An Open-Label Two-Way Drug-Drug Interaction Study To Assess The Effect Of Tenofovir On The Pharmacokinetics Of BMS-790052 And The Effect Of BMS-790052 On The Pharmacokinetics Of Tenofovir In Healthy Subjects

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at one site from January 27, 2011 (first screening) to March 22, 2011 (last follow up).

3. Objectives

The primary objective of the trial was to evaluate the potential drug-drug interaction between daclatasvir and tenofovir.

4. Trial Design

AI444033 was an open label clinical trial that enrolled healthy subjects 18 to 49 years old. Information on the trial design is displayed in Figure 1.

Figure 1-AI444033 trial design

S = Screening; E = Enrollment; Treatment A; multiple doses of BMS-790052 60 mg QD; Treatment B: multiple doses of tenofovir 300 mg QD; Treatment C: multiple doses of BMS-790052 60 mg QD and tenofovir 300 mg QD administrated simultaneously ; D = Study Discharge

Treatment sequences were A-B-C; A-C-B; B-A-C; B-C-A; C-A-B or C-B-A.
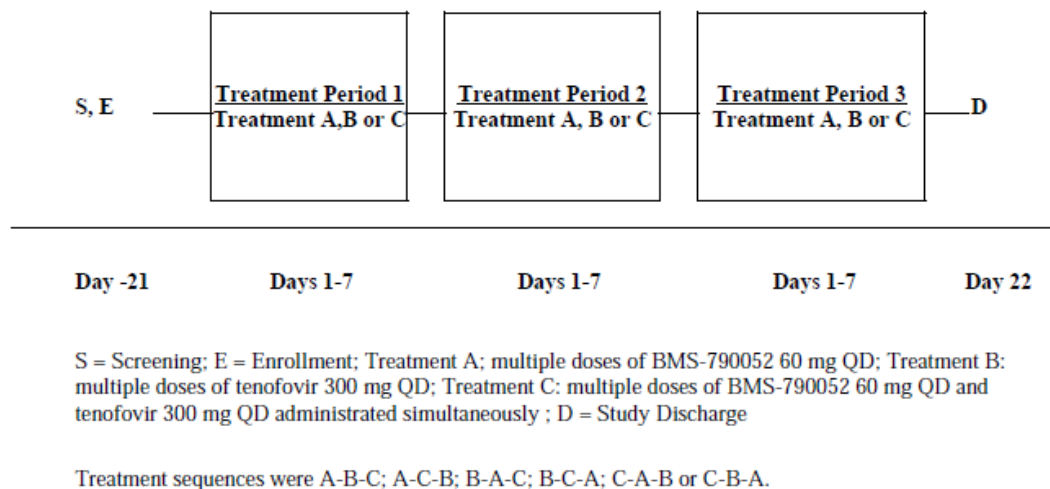
Note: there was no washout between periods.

5. Excluded Medications, Restrictions or Exceptions

Unless otherwise approved, prescription medications or nonprescription acid modifying medications were not permitted within 4 weeks and nonprescription medications,

including herbal products, were not permitted within 2 weeks prior to medication administration. In general, prescription and nonprescription medications, including herbal products, were not permitted during the trial.

6. Dosage and Administration

The trial arms, including the dosage regimens that were administered, are specified in Figure 1. On day 7 for each treatment period, after fasting for 10 hours, doses were administered under fed conditions. According to the tenofovir U.S prescribing information (USPI), tenofovir can be administered with or without food. For daclatasvir, the applicant is proposing to administer the medication with or without food.

7. Rationale for Doses Used in the Trial

The dosage regimen of 60 mg once daily for daclatasvir is the proposed recommended dosage regimen. The tenofovir dosage regimen of 300 mg once daily is the recommended dosage regimen for the treatment of HIV or hepatitis B infection.

8. Drugs Used in the Trial

Information regarding the medications that were administered in the trial is displayed in Table 1.

Table 1-Information on the medications administered in the AI444033 trial

Active compound	: BMS-790052
Strength	: 30 mg
Dosage form	: film coated tablets
Batch number	: 0L58822
Expiration date	: 31 March 2012
Manufacturer	: BMS
Active compound	: Tenofovir (Viread®)
Strength	: 300 mg
Dosage form	: film coated tablets
Batch number	: FDB086D
Expiration date	: August 2013
Manufacturer	: Gilead Sciences Limited

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood samples that were obtained included daclatasvir blood samples beginning on day 7 (treatments A and C) at predose and up to 24 hours postdose and tenofovir blood samples were obtained starting on day 7 (treatments B and C) at predose and up to 24 hours postdose.

Bioanalysis

The method and bioanalysis of daclatasvir and tenofovir are acceptable. Daclatasvir plasma samples were analyzed using a validated LC/MS/MS method in EDTA anticoagulated plasma by _____ (b) (4) (TNJM08199.02) and tenofovir plasma samples were analyzed using a validated LC/MS/MS method in K_2EDTA anticoagulated plasma by _____ (b) (4). The blood samples for analysis of daclatasvir and tenofovir appears to have been collected in tubes containing K_2EDTA as an anticoagulant.

For the AI444033 plasma samples that were analyzed for daclatasvir, the lower limit of quantification for daclatasvir was 0.5 ng/mL and the upper limit of quantification was 500 ng/mL. There were no precision or accuracy issues identified for daclatasvir based on the bioanalytical report. For the AI444033 trial, precision and accuracy were evaluated using plasma daclatasvir quality control (QC) samples at 1.5 ng/mL, 20 ng/mL, 200 ng/mL, and 400 ng/mL. The corresponding daclatasvir inter-run accuracy values were -2.7% for 1.5 ng/mL, -4% for 20 ng/mL, -3% for 200 ng/mL, and -1.8% for 400 ng/mL. The daclatasvir inter-run precision values were 4.6% for 1.5 ng/mL, 1.9% for 20 ng/mL, 1.8% for 200 ng/mL, and 4.7% for 400 ng/mL. In addition, for the daclatasvir dilution QC samples at 5000 ng/mL, the inter-run accuracy and precision were -3.6% and 12.1%, respectively.

For tenofovir, the lower limit of quantification was 1 ng/mL and the upper limit of quantification was 500 ng/mL. There were no precision or accuracy issues identified for tenofovir based on the bioanalytical report. For the AI444033 trial, precision and accuracy were evaluated using tenofovir QC samples at 3 ng/mL, 20 ng/mL, 200 ng/mL, and 400 ng/mL. The 20 ng/mL tenofovir QC was not evaluated as part of the method validation. The corresponding tenofovir inter-run accuracy values were 1.7% for 3 ng/mL, 4% for 20 ng/mL, 2.5% for 200 ng/mL, and 1.8% for 400 ng/mL. The tenofovir inter-run precision values were 2.2% for 3 ng/mL,.4.8% for 20 ng/mL, 2.1% for 200 ng/mL, and 1.8% for 400 ng/mL.

Of the samples selected for incurred sample reanalysis for daclatasvir (approximately 50 in total), all samples were within 20% using the percentage values of the repeat and original concentrations. Of the samples selected for incurred sample reanalysis for tenofovir (approximately 50 in total), all samples were within 20% using the percentage values of the repeat and original concentrations. However, it is not clear whether the total number of daclatasvir or tenofovir samples that were reanalyzed represents 7% of the total number of samples that were initially analyzed.

For the AI444033 trial, in response to an information request, the applicant stated that the daclatasvir plasma samples were stored at the trial site at -20°C for up to 31 days and the bioanalytical laboratory at -20°C for up to 7 days and the tenofovir plasma samples were stored at the trial site at -20°C for up to 31 days and the bioanalytical laboratory at -20°C for up to 6 days. For the TNJM08199.02 method, the generated long term stability data for daclatasvir included stability data in EDTA anticoagulated plasma at -20°C for 1081 days (of note, the long term stability experiment at -20°C for 1039 days failed at 1.5

ng/mL). The generated long term stability data for tenofovir included stability data in K_2EDTA anticoagulated plasma at -70°C for 239 days and stability data in EDTA anticoagulated plasma at -20°C for 96 days using a different tenofovir method (study number TSLS04-032). For the AI444033 trial, the generated long term stability data appears to covers the duration of long term stability data necessary for daclatasvir and for tenofovir at-20°C if the different methods do not impact long term tenofovir stability.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for daclatasvir and tenofovir. For the noncompartmental analysis, daclatasvir and tenofovir plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, and $AUC_{(0-tau)}$.

Statistical Analysis

Statistical analyses were conducted that included the following comparisons and 90% confidence intervals were derived: a) tenofovir coadministered with daclatasvir (test arm) compared to tenofovir administered alone (reference arm), and b) daclatasvir coadministered with tenofovir (test arm) compared to daclatasvir administered alone (reference arm).

10. Results

10.1 Subject Demographics

Table 2-AI444033 subject demographics

		N = 21
Age (yr)	Mean (SD)	31.6 (9.12)
	Range	20 - 49
Gender (N; %)	Male	20; 95%
	Female	1; 5%
Height (cm)	Mean (SD)	181.5 (10.37)
	Range	159 - 201
Weight (kg)	Mean (SD)	79.73 (14.292)
	Range	55.7 - 114.9
BMI (kg/m^2)	Mean (SD)	24.04 (2.543)
	Range	20.1 - 28.4

10.2 Concomitant Medications

The concomitant medications administered in the trial included acetaminophen. The conclusions of the trial are not expected to be significantly altered by the concomitant medications that were administered in the trial.

10.3 Pharmacokinetic and Statistical Analysis

Tenofovir

Table 3-Multiple dosing tenofovir pharmacokinetic parameters with tenofovir 300 mg once daily or tenofovir 300 mg once daily combined with daclatasvir 60 mg once daily

Treatment	Cmax (ng/mL) geo.mean[N] (CV)	Tmax (h) median [N] (min-max)	AUC(TAU) (ng.h/mL) geo.mean [N] (CV)	C24 (ng/mL) geo.mean [N] (CV)
Treatment B (Tenofovir)	248 [20] (27%)	2.00 [20] (1.00 – 4.00)	2385 [20] (20%)	49.1 [20] (26%)
Treatment C (Tenofovir + BMS-790052)	237 [20] (35%)	2.00 [20] (1.00 - 4.03)	2647 [20] (24%)	58.0 [20] (27%)

Table 4-Statistical analyses for tenofovir

PK Parameter	Geometric LS means		Ratio Test/Reference	90% CI	
	Treatment B (Reference)	Treatment C (Test)		Lower	Upper
Primary					
Cmax (ng/mL)	245	234	0.9521	0.8897 - 1.0188
AUC(TAU) (ng.h/mL)	2361	2601	1.1018	1.0521 - 1.1539
Secondary					
C24 (ng/mL)	48.6	56.9	1.1706	1.1031 - 1.2422

Daclatasvir

Table 5-Multiple dosing daclatasvir pharmacokinetic parameters with daclatasvir 60 mg once daily or tenofovir 300 mg once daily combined with daclatasvir 60 mg once daily

Treatment	Cmax (ng/mL) geo.mean[N] (CV)	Tmax (h) median [N] (min-max)	AUC(TAU) (ng.h/mL) geo.mean [N] (CV)	C24 (ng/mL) geo.mean [N] (CV)
Treatment A (BMS-790052)	1065 [20] (29%)	2.01 [20] (1.00 – 4.02)	10592 [20] (34%)	177 [20] (52%)
Treatment C (BMS-790052 + Tenofovir)	1128 [20] (24%)	4.00 [20] (1.00 - 4.03)	11697 [20] (24%)	203 [20] (37%)

Table 6-Statistical analyses for daclatasvir

| PK Parameter | Geometric LS means | | | 90% CI | |
	Treatment A (Reference)	Treatment C (Test)	Ratio Test/Reference	Lower	Upper
Primary					
Cmax (ng/mL)	1059	1121	1.0586	0.9765 -	1.1475
AUC(TAU) (ng.h/mL)	10570	11672	1.1043	1.0056 -	1.2126
Secondary					
C24 (ng/mL)	177	204	1.1485	1.0159 -	1.2985

10.4 Safety Analysis

No deaths or serious adverse events were reported for the trial. One subject discontinued from the trial due to adverse events.

11. Discussion and Conclusions

Based on the results from the AI444033 trial, the following conclusions can be made.

- When daclatasvir 60 mg once daily was coadministered with tenofovir 300 mg once daily, the tenofovir C_{max} was decreased by 5% and the $AUC_{(0-tau)}$ and C_{24h} were increased by 10% and 17%, respectively, when compared with tenofovir 300 mg once daily. The 90% confidence intervals for tenofovir $C_{max,}$ $AUC_{(0-tau)}$, and C_{24h} were all within the standard "no effect" 90% confidence interval limits of 80%-125%.
- When daclatasvir 60 mg once daily was coadministered with tenofovir 300 mg once daily, the daclatasvir C_{max}, $AUC_{(0-tau)}$ and C_{24h} were increased by 6%, 10% and 15%, respectively, when compared with daclatasvir 60 mg once daily. The 90% confidence intervals for daclatasvir C_{max} and the $AUC_{(0-tau)}$ were both within the standard "no effect" 90% confidence interval limits of 80%-125% but daclatasvir C_{24h} was not within the standard "no effect" 90% confidence interval limits of 80%-125%.

A dose adjustment for daclatasvir is not necessary with concomitant use of tenofovir based on the information from the AI444033 trial and the absence of anticipated safety issues from the daclatasvir exposure-safety information.

<u>AI444034 trial</u>

1. Title

A one-way drug-drug interaction study to assess the effect of efavirenz on the PK, safety and tolerability of BMS-790052 in healthy subjects

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted by Bristol-Myers Squibb from February 17, 2011 to April 27, 2011.

3. Objectives

The primary objective was to assess the effect of multiple oral doses of 600 mg efavirenz once daily (QD) on the PK of daclatasvir (BMS-790052) at steady state in healthy subjects.

The secondary objective was to assess the safety of multiple oral doses of BMS-790052 given alone and together with multiple doses of efavirenz.

4. Trial Design

The study was an open-label, three-treatment, single-sequence, multiple-dose, one-way interaction study in healthy subjects. Subjects were screened and enrolled up to 21 days prior to Day 1. Subjects were admitted to the clinical facility one day prior to dosing (Day -1). All subjects received 3 treatments, A, B and C, sequentially (**Figure 1**).

- Treatment A: Multiple doses of BMS-790052 60 mg (2 x 30-mg tablets), orally, QD, administered after a light breakfast in the morning on Days 1 to 4.
- Treatment B: Multiple doses of efavirenz 600 mg, orally, QD, administered in the evening at bed time on Days 5 to 13 together with BMS-790052 60 mg (2 x 30-mg tablets), orally, QD, administered after a light breakfast in the morning on Days 5 to 13.
- Treatment C: Multiple doses of efavirenz 600 mg, orally, QD, administered in the evening at bed time on Days 14 to 18 together with BMS-790052 120 mg (4 x 30-mg tablets), orally, QD, administered after a light breakfast in the morning on Days 14 to 18.

Figure 1: Study Design Schematic

	Treatment A	Treatment B	Treatment C	
S,E	BMS-790052 60 mg QD	BMS-790052 60 mg QD + Efavirenz 600 mg QD	BMS-790052 120 mg QD + Efavirenz 600 mg QD	D
Day -21	Day 1-4	Day 5-13	Day 14-18	Day 20
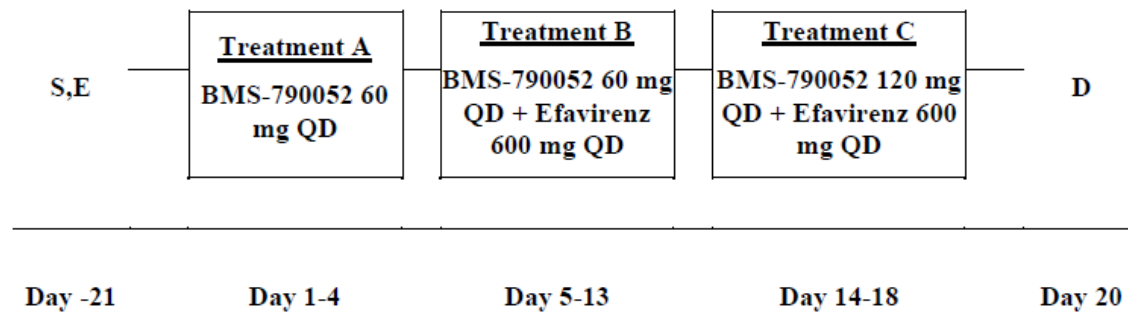
S = Screening; E = Enrollment; D = Study Discharge; BMS-790052 was administered in the morning; efavirenz was administered in the evening.

5. Excluded Medications, Restrictions or Exceptions

No concomitant medications (prescription, over-the-counter or herbal) are to be administered during study unless they are prescribed by the investigator for treatment of specific clinical events. Any concomitant therapies must be recorded on the CRF.

6. Rationale for Doses Used in the Trial

The dosage regimen of BMS-790052 (i.e. DCV 60 mg) is consistent with the recommended DCV dosage regimen in the proposed DCV U.S. prescribing information. The dose of 600 mg efavirenz is the dose in the efavirenz U.S. prescribing information. During the last 5 days of co-administration with efavirenz, a higher dose of 120 mg BMS-790052 was selected as the potential existed for a 50% decrease in BMS-790052 exposure.

7. Drugs Used in the Trial

- BMS-790052-05 supplied by BMS: 30 mg film coated tablets; Batch # 0L58822.
- Efavirenz obtained by the pharmacy of PRA: 600 mg film coated tablets; Batch # NN32040

8. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Table 1 - PK sampling schedule for DCV and efavirenz

Study Day	Time (Event) Hour	Time (Relative To Dosing) Hour: Min	PK Blood Sample for BMS-790052	PK Blood Sample for Efavirenz[a]
4	0 (pre-dose)	00:00	X	
	0.5 h	00:30	X	
	1 h	01:00	X	
	1.5 h	01:30	X	
	2 h	02:00	X	
	4 h	04:00	X	
	6 h	06:00	X	
	8 h	08:00	X	
	12 h	12:00	X	
	16 h	16:00	X	
5	24 h (pre-dose)	24:00	X	
7	0 (pre-dose)	00:00	X	X
9	0 (pre-dose)	00:00	X	X
11	0 (pre-dose)	00:00	X	X
13	0 (pre-dose)	00:00	X	X
15	0 (pre-dose)			X
18	0 (pre-dose)	00:00	X	X
	0.5 h	00:30	X	
	1 h	01:00	X	
	1.5 h	01:30	X	
	2 h	02:00	X	
	4 h	04:00	X	
	6 h	06:00	X	
	8 h	08:00	X	
	12 h	12:00	X	
	16 h	16:00	X	
19	24 h	24:00	X	

[a] Please note that blood sample time points for efavirenz were relative to efavirenz dosing (in the evening)

Bioanalytical method for DCV and efavirenz

The method and bioanalysis of DCV is acceptable.

Analyte	BMS-790052	
Internal Standard	BMS-790052-$^{13}C_{10}$ (added to all samples except Blanks)	
Regression, Weighting	Linear $1/x^2$	
LLOQ	0.500 ng/mL	
ULOQ	500 ng/mL	
Calibration Standard Concentrations	0.500, 1.00, 5.00, 25.0, 50.0, 100, 250, 450, and 500 ng/mL	
Analytical QC Concentrations	1.50, 20.0, 200, and 400 ng/mL	
Dilution QC Concentration	5000 ng/mL	
Dilution Factor	20	
Performance of Analytical QCs (see Table 6)	Precision (%CV)[a, b]	Accuracy (%Bias)[a, b]
(Low through High)	1.3% to 8.8% (1.3% to 22.5%)	-9.4% to -1.3% (-9.4% to 4.7%)

The method and bioanalysis of efavirenz are acceptable. Efavirenz plasma samples were analyzed using a validated LC/MS/MS method in K_2EDTA plasma by ▒▒▒▒▒▒▒▒ (b) (4) ▒▒▒▒▒▒▒▒.

The lower limit of quantification for efavirenz was 10.0 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for efavirenz based on the bioanalytical report. The precision and accuracy were evaluated using plasma efavirenz QC samples at five concentration levels: 30.0 ng/mL, 160 ng/mL, 800 ng/mL, 1600 ng/mL, and 20,000 ng/mL (diluted to 1000 ng/mL).

Analyte interference evaluation showed that human plasma blanks fortified with DCV (4000 ng/mL) had no interference on the quantification of efavirenz.

Twenty four study samples (~ 20% of the total efavirenz plasma samples) were selected for incurred sample reanalysis for efavirenz, all samples were within 10% (Note: two third samples within 20% considered acceptable) using the percentage values of the repeat and original concentrations.

All samples were analyzed within the 260 days demonstrated long-term storage stability in human plasma containing K_2EDTA at -20 °C or colder.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for DCV. The PK parameters assessed include t_{max}, C_{max}, C_{24h}, AUC_{Tau}, and AUC_{Tau}/D.

Statistical Analysis

Statistical analysis was conducted on the PK parameters of BMS-790052 with and without dose normalization. To assess the effect of concomitant administration of efavirenz on the PK of BMS-790052, point estimates and 90% confidence intervals (CIs) for the ratios of the geometric means for non-dose-normalized BMS-790052 C_{max}, AUC_{Tau} and C_{24} parameters were constructed when BMS-790052 was administered with (Treatment C) and without (Treatment A) efavirenz. BMS-790052 60 mg (Treatment A) was used as the reference in the comparisons. Similar analyses were conducted for dose-normalized BMS-790052 C_{max}/D, AUC_{Tau}/D and C_{24}/D parameters.

9. Results

9.1 Subject Demographics and Disposition

A total of 42 subjects were screened, and 17 of these subjects were included in the study. A total of 15 subjects completed the study (**Table 2**).

Table 2-Subject Demographics

		N = 17
Age (yr)	Mean (SD)	33.9 (10.32)
	Range	18 - 48
Gender (N; %)	Male	16; 94%
	Female	1; 6%
Height (cm)	Mean (SD)	176.0 (9.29)
	Range	161 - 192
Weight (kg)	Mean (SD)	81.29 (12.938)
	Range	58.7 - 109.4
BMI (kg/m^2)	Mean (SD)	26.19 (3.332)
	Range	18.8 - 30.8

9.2 Concomitant Medications

The concomitant medications that were administered in the trial are not expected to significantly alter the conclusions of the trial.

9.3 Pharmacokinetic and Statistical Analysis

Effect of efavirenz on the PK of BMS-790052 (DCV)

Arithmetic mean ± SD BMS-790052 plasma concentration-time profiles (linear and semi-logarithmic) are given in **Figure 2.**

Figure 2 - Arithmetic Mean ± SD Concentration-Time Profiles (Linear and Semi-Logarithmic) for BMS-790052 in Plasma Following 4 Days of BMS-790052 60 mg QD Treatment (Treatment A) or 5 Days of BMS-790052 120 mg QD + Efavirenz 600 mg QD Treatment (Treatment C)
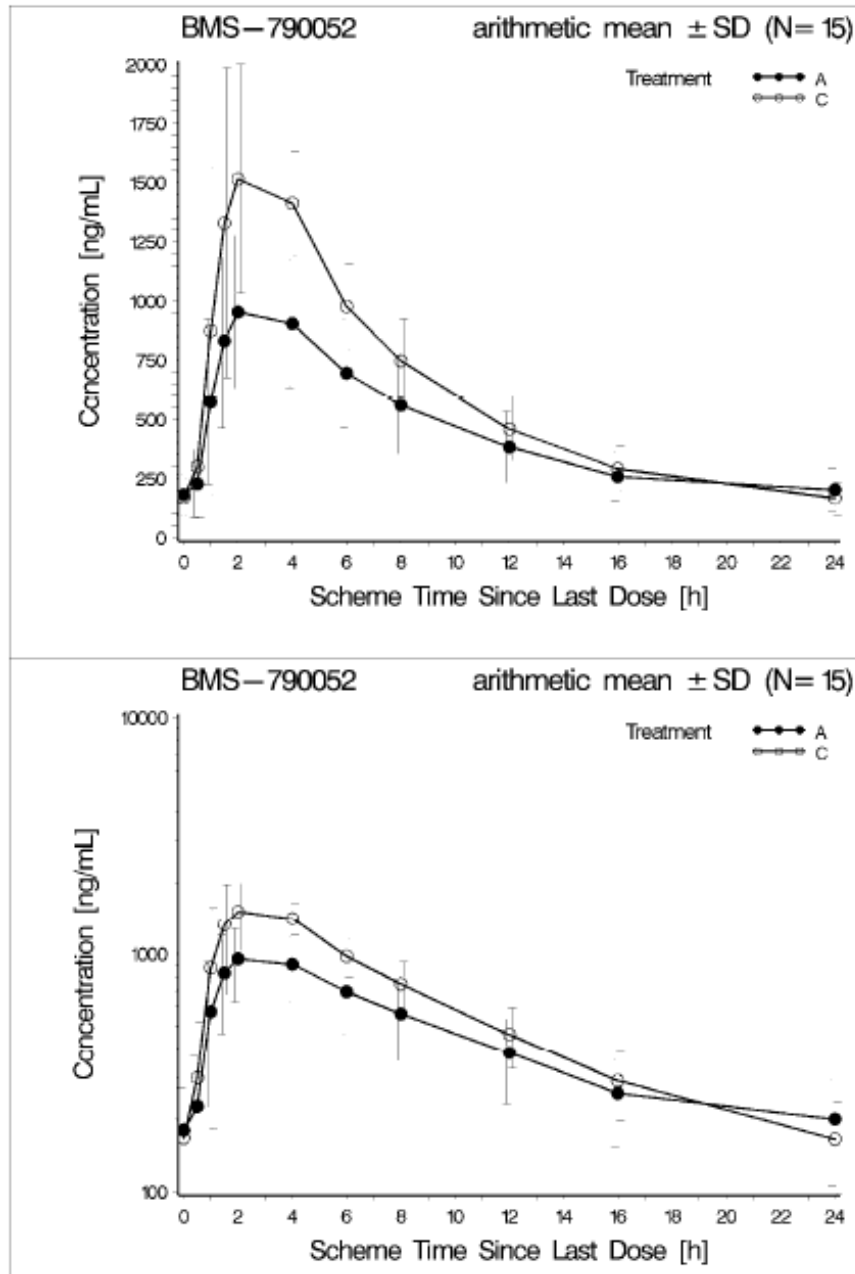
A summary of statistical analysis results of the effect of efavirenz on the steady state PK of BMS-790052 is shown in **Table 3**.

Table 3-Summary of Statistical Analysis Results of the Effect of Efavirenz on the Steady State PK of BMS-790052

| PK Parameter | Geometric LS means | | | |
	Treatment C (Test)	Treatment A (Reference)	Ratio Test/Reference	90% CI
Cmax (ng/mL)	1655	993	1.6675	(1.5117, 1.8393)
AUC(TAU) (ng.h/mL)	14068	10278	1.3687	(1.2064, 1.5530)
C24 (ng/mL)	153	185	0.8280	(0.6883, 0.9959)
	Dose normalized to 60-mg dose			
Cmax/D (ng/mL)	828	993	0.8337	(0.7559, 0.9196)
AUC(TAU)/D (ng.h/mL)	7034	10278	0.6844	(0.6032, 0.7765)
C24/D (ng/mL)	76.7	185	0.4140	(0.3442, 0.4979)

Table 4 shows the predicted BMS-790052 PK parameters if a 90-mg BMS-790052 dose would be co-administered with efavirenz assuming dose proportionality of BMS790052 in the 60-120 mg range. These predictions indicate that a 90-mg BMS-790052 dose co-administered with efavirenz is expected to give an AUC(TAU) similar to that of a 60-mg BMS-790052 dose administered alone.

Table 4- Summary of Statistical Analysis Results of Predicted BMS-790052 Plasma PK Parameters Following 5 Days of 90 mg BMS-790052 QD + 600 mg Efavirenz QD Treatment

| PK Parameter | Geometric LS means | | | |
	'Predicted'[1] Treatment C (Test)	Treatment A (Reference)	Ratio Test/Reference	90% CI
Cmax (ng/mL)	1241	993	1.2506	(1.1338, 1.3795)
AUC(TAU) (ng.h/mL)	10551	10278	1.0266	(0.9048, 1.1647)
C24 (ng/mL)[1]	115	185	0.6210	(0.5163, 0.7469)

[1] Assuming a 90-mg dose had been given (based on 120-mg results) and based on the linear PK profile of BMS-790052.

Additionally, as shown in **Figure 3**, BMS-790052 trough concentrations (C24) showed a decline during treatment with 60 mg BMS-790052 in the presence of 600 mg efavirenz (Treatment B). The plot does not indicate that maximal induction of CYP3A4 by efavirenz was reached at the start of Treatment C (i.e. on Day 14; 120 mg BMS-790052

in combination with efavirenz). The two similar (dose-normalized) trough levels (C24) on Days 18 and 19 suggest that steady state had been reached for 120 mg BMS-790052 in the presence of efavirenz at that time.

Figure 3: Geometric Mean C24 levels of BMS-790052 Following 60 mg BMS-790052 + 600 mg Efavirenz QD Treatment (Treatment B –Day 5-13)
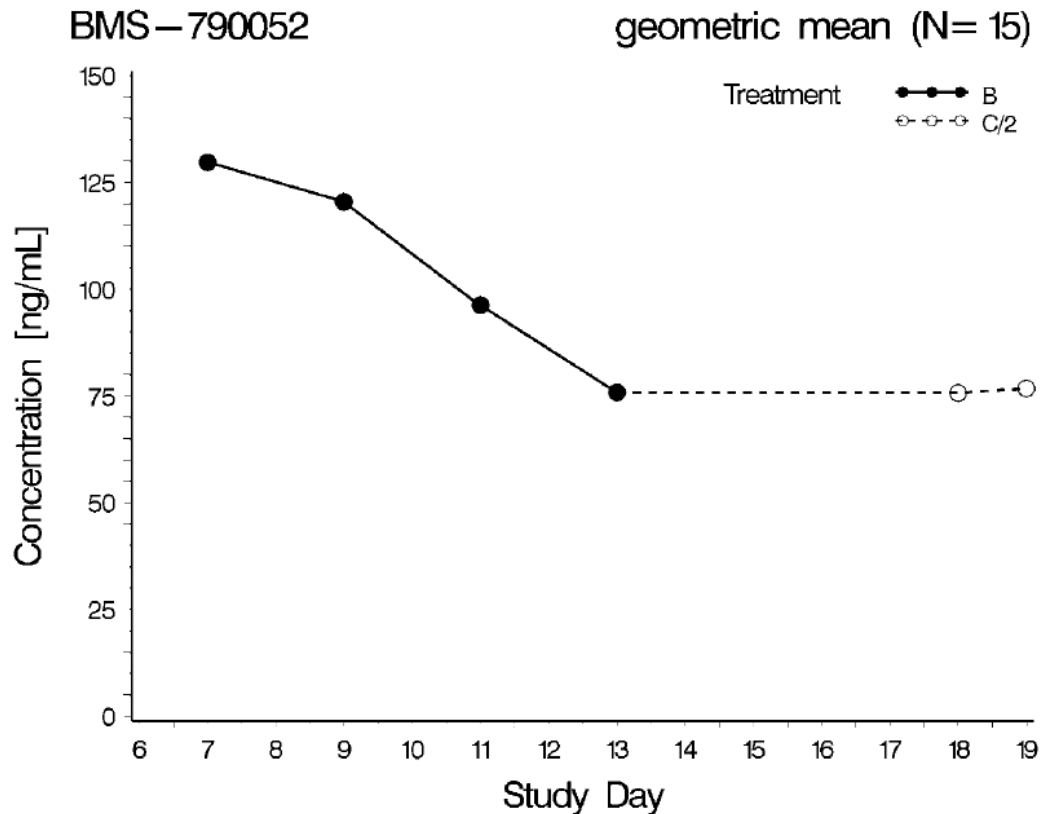
Note: the dashed line represents the trough concentrations during Treatment C (120 mg BMS-790052 + 600 mg efavirenz) divided by two

<u>Efavirenz Trough Concentrations</u>
Geometric mean efavirenz trough concentration-time profiles in plasma (linear) are presented in **Figure 4**. Efavirenz trough concentrations showed an increase during Treatment B from Day 7 until Day 13 and thereafter these trough concentrations did not change during Treatment C on Days 15 and 18 indicating that the higher dose of BMS-790052 in Treatment C did not decrease efavirenz exposure.

Figure 4: Geometric Mean Plasma Trough Concentrations of Efavirenz Following 9 Days of BMS-790052 60 mg + Efavirenz 600 mg QD Treatment (Treatment B; Day 5-13) and 5 Days of BMS-790052 120 mg QD + Efavirenz 600 mg QD Treatment (Treatment C; Day 14-18)
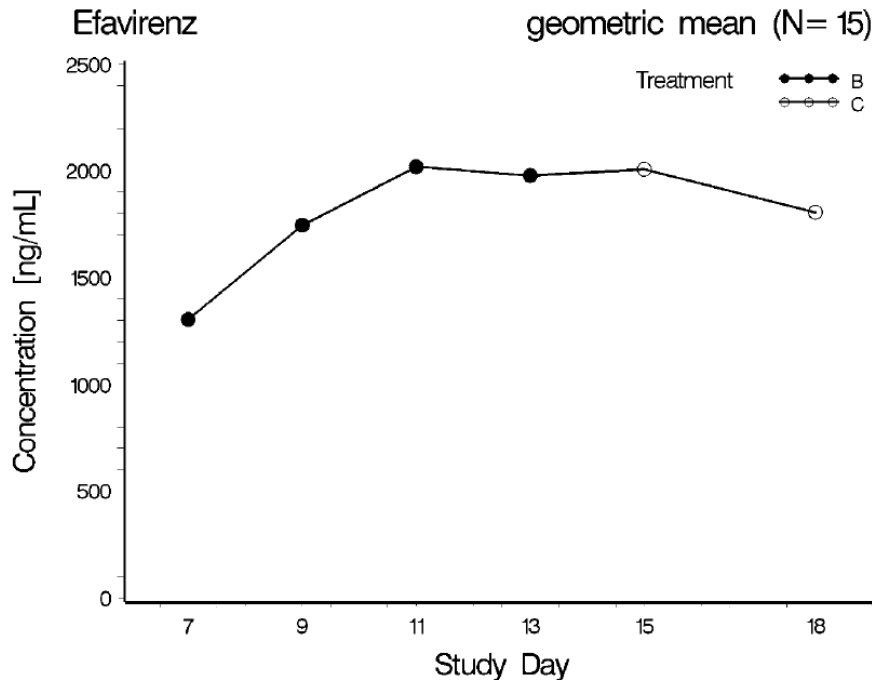
9.5 Safety Analysis

Administration of multiple oral doses of BMS-790052 and efavirenz was generally safe and well-tolerated in the 17 healthy male and female subjects exposed. A total of 16 subjects (94.1%) experienced TEAEs in this study. The most frequently TEAEs that were reported by the subjects were headache, dizziness, insomnia, diarrhoea, fatigue, flushing, paraesthesia and skin irritation. The majority of the TEAEs were considered to be related to the study medication. Sixteen subjects (94.1%) reported treatment-related TEAEs and these treatment-related TEAEs were mainly nervous system disorders with the highest incidence seen for headache, and psychiatric disorders with the highest incidence seen for insomnia. These treatment-related nervous system disorders and psychiatric disorders were reported in relatively large numbers during Treatment B, but in smaller numbers during Treatment C. These TEAEs are typical for efavirenz treatment.

10. Sponsor's Conclusions

Patients receiving treatment with BMS-790052 will frequently receive treatment with efavirenz, a preferred non-nucleoside reverse transcriptase inhibitor as part of the initial HAART regimen for treatment of HIV infection. Efavirenz is a moderate-to-strong CYP3A4 inducer. Therefore, it was necessary to evaluate to what extent co-administration of BMS-790052 and efavirenz altered the PK of DCV (BMS-790052).

- Co-administration of BMS-790052 120 mg with efavirenz 600 mg resulted in BMS-790052 exposure that was higher than administration of BMS-790052 60 mg alone.
- Dose-normalized Cmax, AUC_{TAU}, and C24 of BMS-790052 (to 60 mg) were decreased by 17%, 32%, and 59%, respectively, during co-administration with 600 mg efavirenz.
- Co-administration of BMS-790052 90 mg with efavirenz 600 mg is predicted to give an exposure (AUC_{TAU}) similar to 60 mg BMS-790052 administered alone. The predicted BMS-790052 PK parameters if a 90-mg BMS-790052 dose would be co-administered with efavirenz showed an increase of 25% for the Cmax and a decrease of 38% for the C24.
- Administration of multiple oral doses of BMS-790052 when given alone was generally safe and well-tolerated in a group of 17 healthy male and female subjects.
- Administration of multiple oral doses of BMS-790052 when given in combination with efavirenz showed an AE pattern that was consistent with efavirenz treatment without increased severity of AEs when given with BMS-790052.
- Co-administration of BMS-790052 120 mg (as compared to the 60 mg dose) with efavirenz 600 mg did not decrease efavirenz exposure as assessed by trough concentrations.

11. Reviewer's Assessment

The AI444034 trial adequately assessed the effect of coadministration of multiple (QD) oral doses of efavirenz 600 mg (CYP3A4 inducer) on the PK of daclatasvir at steady state in healthy subjects. Overall, the sponsor's conclusions are valid and the proposed DCV dose adjustment from 60 mg to 90 mg when coadministered with moderate CYP3A4 inducer including efavirenz is acceptable. However, it is important to note that based on the analysis that was conducted during the NDA review, dose proportionality was not observed for daclatasvir.

<u>AI444054</u>

1. Title

A Phase 1 Open-label, Single-sequence Study to Evaluate the Effect of Concomitant Administration of Multiple Doses of Daclatasvir (BMS-790052) on the Single-dose Pharmacokinetics of Rosuvastatin in Healthy Subjects

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at one site (Healthcare Discoveries) from May 15, 2012 (trial initiation) to June 28, 2012 (trial completion).

3. Objectives

The primary objective of the trial was to evaluate the potential drug-drug interaction between daclatasvir and rosuvastatin.

4. Trial Design

AI444054 was an open label clinical trial that enrolled healthy subjects 18 to 49 years old. Information on the trial design is displayed in Figure 1.

Figure 1-AI444054 trial design

Screening / Admission to CPU	Treatment A Single dose rosuvastatin, 10 mg orally	Treatment B QD dose daclatasvir, 60 mg orally	Treatment C Single oral dose rosuvastatin (10 mg) in combination with daclatasvir (60 mg) (Day 10), then QD dosing of daclatasvir 60 mg orally (Days 11, 12, and 13)	Discharge
Days -21 to -1 →	Day 1 →	Days 5 to 9 →	Days 10 to 13 →	Day 14

5. Excluded Medications, Restrictions or Exceptions

Unless otherwise approved, prescription or nonprescription acid modifying medications were not permitted within 4 weeks and prescription and nonprescription medications, including herbal products, were not permitted within 2 weeks prior to medication administration. In general, prescription and nonprescription medications, including herbal products, were not permitted during the trial.

6. Dosage and Administration

The trial arms, including the dosage regimens that were administered, are specified in Figure 1. After fasting for a minimum of 10 hours on dosing days, doses were

administered under fasted conditions. The U.S prescribing information (USPI) for rosuvastatin states that the medication can be administered with or without food.   For daclatasvir, the applicant is proposing to administer the medication with or without food.

7. Rationale for Doses Used in the Trial

The dosage regimen of 60 mg once daily for daclatasvir is the proposed recommended dosage regimen. The rosuvastatin single dose of 10 mg is consistent with the range of recommended dosage regimens in adults.

8. Drugs Used in the Trial

Information regarding the daclatasvir formulation that was administered in the trial is displayed in Table 1. There were no specific details provided regarding the rosuvastatin formulation that was administered.

Table 1-Information on the daclatasvir formulation administered in the AI444054 trial

Product Description and Dosage Form (Batch # 1G66277)	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Quantity) /Label Type	Appearance	Storage Conditions (per label)
Daclatasvir (BMS-790052-05) Film coated tablet	60 mg (as the free base)	33 tablets per bottle / open label	n/a	A plain, green, biconvex, pentagonal film coated tablet	15°C-25°C (59°F-77°F). Store in a tightly closed container.

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood samples that were obtained included rosuvastatin blood samples beginning on days 1 and 10 at predose and up to 96 hours postdose.

Bioanalysis

The method and bioanalysis of rosuvastatin are acceptable. Rosuvastatin plasma samples were analyzed using a validated LC/MS/MS method in K_3EDTA anticoagulated plasma by PPD. The blood samples for analysis of rosuvastatin appear to have been collected in tubes containing K_2EDTA.

For the AI444054 plasma samples that were analyzed for rosuvastatin, the lower limit of quantification for rosuvastatin was 0.1 ng/mL and the upper limit of quantification was 100 ng/mL. Based on the response to an information request, the lower limit of quantification (LLOQ) in runs 9 and 10 were raised to 0.2 ng/mL subsequent to the rejection of the 0.1 ng/mL LLOQ in both runs. There were no precision or accuracy issues identified for rosuvastatin based on the bioanalytical report. For the AI444054

trial, precision and accuracy were evaluated using plasma rosuvastatin quality control (QC) samples at 0.3 ng/mL, 0.8 ng/mL, 3.2 ng/mL, 12 ng/mL and 75 ng/mL. The corresponding rosuvastatin inter-run accuracy values were 0.964% for 0.3 ng/mL, -1.8% for 0.8 ng/mL, -1.98% for 3.2 ng/mL, -0.446% for 12 ng/mL and 0.377% for 75 ng/mL. The rosuvastatin inter-run precision values were 9.37% for 0.3 ng/mL, 5.64% for 0.8 ng/mL, 5.57% for 3.2 ng/mL, 4.43% for 12 ng/mL and 5.11% for 75 ng/mL.

For the AI444054 trial, in response to an information request, the applicant stated that the rosuvastatin plasma samples were stored at the trial site at -70°C for up to 24 days and the bioanalytical laboratory at -70°C for up to 41 days. For rosuvastatin, the generated long term stability data included stability data in K_3EDTA anticoagulated plasma at -70°C for 86 days and in K_2EDTA anticoagulated plasma at -20°C and -70°C for 485 days using a different method (393). For the AI444054 trial, the generated long term stability data appears to covers the duration of long term stability data necessary for rosuvastatin.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for rosuvastatin. For the noncompartmental analysis, the plasma pharmacokinetic parameters that were calculated included t_{max}, C_{max}, and $AUC_{(0-inf)}$ for rosuvastatin.

Statistical Analysis

Statistical analyses were conducted and 90% confidence intervals were derived comparing rosuvastatin coadministered with daclatasvir (test arm) compared to rosuvastatin administered alone (reference arm).

10. Results

10.1 Subject Demographics

Table 2-AI444054 subject demographics

Assessment Variable	Total (N=22)
Age (years)	22
Mean (SD)	34.0 (8.30)
Median	33.0
Range (min, max)	19, 47
Sex, n (%)	
Male	13 (59.1)
Female	9 (40.9)
Ethnicity, n (%)	
Hispanic / Latino	15 (68.2)
Not Hispanic / Latino	7 (31.8)
Race, n (%)	
White	21 (95.5)
Black / African American	1 (4.5)
Height (cm)	
Mean (SD)	167.37 (10.790)
Median	168.85
Range (min, max)	146.3, 183.7
Weight (kg)	
Mean (SD)	75.35 (13.620)
Median	76.20
Range (min, max)	55.4, 95.5
BMI (kg/m^2)	
Mean (SD)	26.75 (2.928)
Median	26.50
Range (min, max)	20.1, 31.5

N = number of subjects; SD = standard deviation; n = number of nonmissing observations; % = percentage of subjects (n/N X 100); BMI = body mass index

10.2 Concomitant Medications

The concomitant medications administered in the trial included magnesium hydroxide and various laxatives. The conclusions of the trial are not expected to be significantly altered by the concomitant medications that were administered in the trial.

10.3 Pharmacokinetic and Statistical Analysis

Table 3-Single dosing rosuvastatin pharmacokinetic parameters with rosuvastatin 10 mg or rosuvastatin 10 mg once daily combined with daclatasvir 60 mg once daily

Treatment	Cmax (ng/mL) GM [n] (CV%)	AUC(0-T) (ng.h/mL) GM [n] (CV%)	AUC(INF) (ng.h/mL) GM [n] (CV%)	Tmax (h) median [n] (min-max)	T-HALF (h) mean [n] (SD)	CLT/F (L/h) GM [n] (CV%)
A	6.64 [22] (59)	65.8 [22] (51)	70.3 [22] (49)	4.00 [22] (1.50-8.00)	15.2 [22] (8.37)	183 [22] (61)
C	12.2 [21] (35)	98.0 [21] (36)	103 [21] (37)	3.00 [21] (1.50-4.00)	18.9 [21] (21.6)	109 [21] (33)

Treatment A = Single dose 10-mg rosuvastatin (Day 1), Treatment B = QD dose 60-mg daclatasvir (Days 5 to 9), Treatment C = Single dose 10-mg rosuvastatin in combination with 60-mg daclatasvir (Day 10); then QD dose 60 mg daclatasvir (Days 11, 12, 13).

n = number of nonmissing observations.

Table 4-Statistical analyses for rosuvastatin

Treatment and Comparison	Cmax (ng/mL) Adjusted GM	AUC(0-T) (ng.h/mL) Adjusted GM	AUC(INF) (ng.h/mL) Adjusted GM
A	5.80	57.9	62.6
C	11.8	94.1	98.8
	Ratio of Adjusted GM (90% CI)		
C vs A	2.04 (1.83, 2.26)	1.63 (1.47, 1.80)	1.58 (1.44, 1.74)

10.4 Safety Analysis

No deaths or serious adverse events were reported for the trial. One subject discontinued from the trial due to adverse events.

11. Discussion and Conclusions

Based on the results from the AI444054 trial, the following conclusions can be made.

- When a single dose of rosuvastatin 10 mg was coadministered with daclatasvir 60 mg once daily, the rosuvastatin C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$ were increased by 104%, 63% and 58%, respectively, when compared with a single dose of rosuvastatin 10 mg. The 90% confidence intervals for rosuvastatin C_{max}, $AUC_{(0-t)}$, and $AUC_{(0-inf)}$ were all not within the standard "no effect" 90% confidence interval limits of 80%-125%.

The changes in rosuvastatin exposure are similar to the changes in rosuvastatin exposure that are included in the rosuvastatin U.S. prescribing information (USPI) for darunavir/ritonavir, where rosuvastatin C_{max} and AUC were increased by 140% and 50%, respectively and eltrombopag, where rosuvastatin C_{max} and AUC were increased by 100% and 60%, respectively (in the eltrombopag USPI, the C_{max} and $AUC_{(0-inf)}$ were increased by 103% and 55%, respectively). There are no specific recommendations regarding concomitant use of either of these medications with rosuvastatin in the rosuvastatin U.S. prescribing information, other than stating that caution should be used with concomitant use of rosuvastatin and protease inhibitors that are combined with ritonavir.

The applicant is proposing to include the following recommendation in the daclatasvir U.S. prescribing information: Caution should be used when daclatasvir is coadministered with rosuvastatin or other substrates of OATP 1B1, OATP 1B3, or BCRP. The recommendation is consistent with the information in the rosuvastatin U.S. prescribing information.

AI444064 trial

1. Title

A Phase 1, Open-Label, Drug-Drug Interaction Study between Methadone and Daclatasvir (Part 1), and between Buprenorphine/Naloxone and Daclatasvir (Part 2). [*Note: The sponsor stated that Part 2 will be reported separately due to potential slow enrollment. Only Part 1 was reviewed here*]

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial (Part 1) was conducted at Anaheim Clinical Trials, Anaheim, CA and Yale University School of Medicine, New Haven, CT by Bristol-Myers Squibb from December 5, 2012 to April 26, 2013.

3. Objectives

The primary objective of the Part 1 of the trial was to assess the effect of steady-state daclatasvir (DCV; BMS-790052) on the PK of methadone. The secondary objectives for Part 1 were to characterize the PK of DCV coadministered with methadone and to assess the effect of steady-state DCV on the pharmacodynamics (PD) of methadone utilizing the Clinical Opiate Withdrawal Scale (COWS), Subjective Opiate Withdrawal Scale (SOWS), Objective Opiate Withdrawal Scale (OOWS) and Opiate Overdose Assessment (OOA).

4. Trial Design

The study was an open label clinical trial that enrolled patients on a stable dose of methadone QD (**Figure 1**). Total 38 subjects were enrolled. Of these, 14 subjects entered Part 1 and all completed the study.

Figure 1: Study Design Schematic

Part 1	Methadone 40-120 mg QD	Methadone 40-120 mg QD + DCV 60 mg QD	Methadone 40-120 mg QD + DCV 60 mg QD	Study Discharge
	Day 1 Methadone PK (24h)	Days 2-8	Day 9 Methadone + DCV PK (24h)	Day 10

5. Excluded Medications, Restrictions or Exceptions

No concomitant medications (prescription, over-the-counter or herbal) were administered during study unless they were prescribed by the investigator for treatment of specific clinical events. Any concomitant therapies must be recorded on the CRF.

6. Rationale for Doses Used in the Trial

The dosage regimen of DCV 60 mg is consistent with the recommended DCV dosage regimen in the DCV U.S. prescribing information.

7. Drugs Used in the Trial

Information regarding DCV administered in the trial is displayed in **Table 1**. Methadone was purchased as commercially available product by the clinical site.

Table 1-Information on the medications administered in the trial

Product Description and Dosage Form	Potency	Product Identification Number	Product Batch Number
DCV (BMS-790052-05) Film coated tablet	60 mg (as the free base)	790052-K060-028	2D72563

8. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Table 2 - PK sampling schedule

Study Day[a]	Time (Event) Hour	Time (Relative To Dosing) Hour: Min	PK Blood Sample for Methadone or Buprenorphine / naloxone	PK Blood Sample for Daclatasvir
1	0 (predose)	00:00 (predose)	X	
	0.5	00:30	X	
	1	01:00	X	
	1.5	01:30	X	
	2	02:00	X	
	3	03:00	X	
	4	04:00	X	
	6	06:00	X	
	8	08:00	X	
	10	10:00	X	
	12	12:00	X	
	16	16:00	X	
2	0	24:00	X	
9	0 (predose)	00:00 (predose)	X	X
	0.5	00:30	X	X
	1	01:00	X	X
	1.5	01:30	X	X
	2	02:00	X	X
	3	03:00	X	
	4	04:00	X	X
	6	06:00	X	X
	8	08:00	X	X
	10	10:00	X	
	12	12:00	X	X
	16	16:00	X	X
10	0	24:00	X	X

Bioanalytical method for methadone enatiomers

The method and bioanalysis of methadone enatiomers are acceptable. Methadone plasma samples were analyzed using a validated LC/MS/MS method in tripotassium EDTA plasma by [   ] (b) (4)

The lower limit of quantification for both (R)- and (S)- methadone was 5.00 ng/mL and the upper limit of quantification was 1000 ng/mL. There were no precision or accuracy issues identified for methadone enatiomers based on the bioanalytical report. The precision and accuracy were evaluated using plasma (R)- and (S)- methadone QC samples at five concentration levels: 10 ng/mL, 25 ng/mL, 70 ng/mL, 200 ng/mL, and 750 ng/mL.

Analyte interference evaluation showed that human plasma blanks fortified with DCV (4000 ng/mL) had no interference on the quantification of (R)- and (S)- methadone.

Approximately 10% of the study samples were selected for incurred sample reanalysis for (R)- and (S)- methadone, all samples were within 15% (Note: within 20% considered acceptable) using the percentage values of the repeat and original concentrations.

All samples were analyzed within the 365 days demonstrated long-term storage stability in human plasma containing tripotassium EDTA at -20 °C or colder.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for (R)-, (S)- methadone , and DCV. The PK parameters assessed include t_{max}, C_{max}, C_{24h}, and $AUC_{(tau)}$.

Statistical Analysis

To assess the effect of steady-state DCV on the dose-normalized (to 40 mg) PK ($AUC_{(tau)}$, Cmax, and C24) of R-methadone, S-methadone, and total methadone after multiple doses administration of methadone with or without coadministration of DCV, a general linear mixed effect model with treatment as fixed effect variable and subject as repeated measures were fitted to the log transformed PK parameters for use in estimation of effects and construction of CIs. A 90% CI for the $AUC_{(tau)}$, Cmax and C24 ratio of the geometric means (GMR, [methadone+DCV]/methadone) was computed from the above model after back-transformation. If the 90% CIs of the GMRs ([methadone+DCV]/methadone) for $AUC_{(tau)}$ and Cmax for both R-methadone and S-methadone fell within the pre-specified bound [0.70, 1.43], it was concluded that the coadministration of DCV did not affect the PK of methadone.

The steady-state PK parameters of DCV were summarized by parts using descriptive statistics. Summary statistics were provided for Tmax.

9. Results

9.1 Subject Demographics and Disposition

The treated subjects were mostly male (71.4%) and white (92.9%) with a mean BMI of 24.7 kg/m2 and a mean age of 29.6 years (**Table 3**).

Table 3 Subject demographics

	Total N=14
Age (years)	
Mean	29.6
Min, Max	19, 39
Race (%)	
White	13 (92.9)
Chinese	1 (7.1)
Gender (%)	
Male	10 (71.4)
Female	4 (28.6)
Mean Weight (kg)	73.05
Mean BMI (kg/m^2)	24.70

9.2 Concomitant Medications

The concomitant medications that were administered in the trial are not expected to significantly alter the conclusions of the trial.

9.3 Pharmacokinetic and Statistical Analysis

(R)- Methadone

Mean plasma concentration-time profile for dose-normalized (to 40 mg) R-methadone is presented in **Figure 2**.

Figure 2 - Plot of Mean (+SD) Dose-normalized (to 40mg) R-Methadone Plasma Concentration Profile vs. Time

TREATMENT CODES:
A = Methadone 40-120 mg QD
B = Methadone 40-120 mg QD + Daclatasvir 60 mg QD
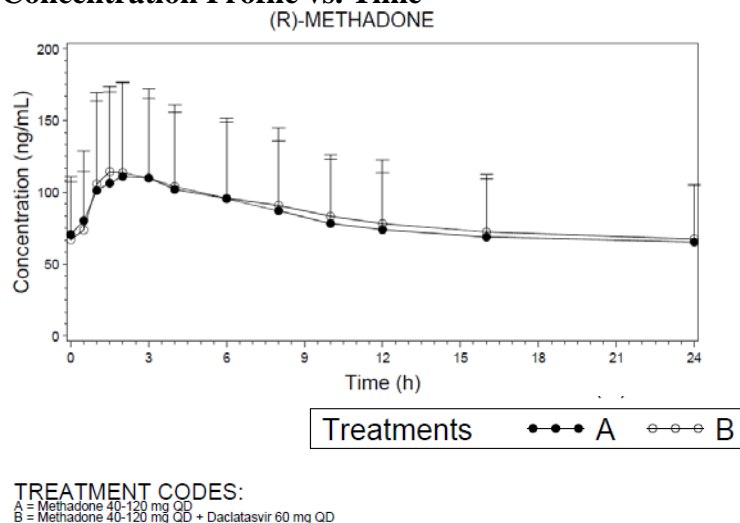
Statistical analyses of dose-normalized R-methadone Cmax, C24, and AUC$_{(tau)}$ are presented in **Table 4**.

Table 4 -Statistical Analysis of Dose-normalized (to 40 mg) R-Methadone PK Parameters

Treatment and Comparison	Cmax (ng/mL) Adj. Geo. Mean	AUC(TAU) (ng.h/mL) Adj. Geo. Mean	C24 (ng/mL) Adj. Geo. Mean
A	96.56	1569.79	52.49
B	103.61	1699.59	56.72
	GMR (90% CI)	GMR (90% CI)	GMR (90% CI)
B vs A	1.073 (0.973,1.184)	1.083 (0.943,1.243)	1.080 (0.927,1.259)

Treatment Code: A: Methadone 40-120mg QD on Day 1, B: Methadone 40-120mg QD and Daclatasvir 60mg QD on Day 2-9.

(S)- Methadone

Mean plasma concentration-time profile for dose-normalized (to 40 mg) S-methadone is presented in **Figure 3**.

Figure 3 - Plot of Mean (+SD) Dose-normalized (to 40mg) S-Methadone Plasma Concentration Profile vs. Time
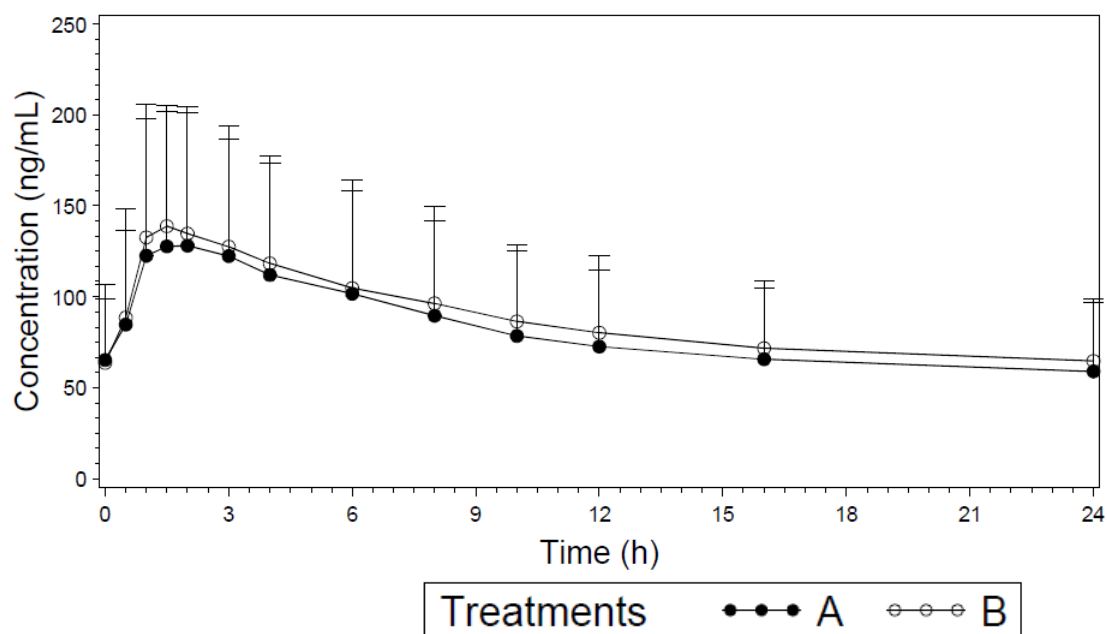
TREATMENT CODES:
A = Methadone 40-120 mg QD
B = Methadone 40-120 mg QD + Daclatasvir 60 mg QD

Statistical analyses of dose-normalized S-methadone Cmax, C24, and AUC$_{(tau)}$ are presented in **Table 5**.

Table 5 -Statistical Analysis of Dose-normalized (to 40 mg) S-Methadone PK Parameters

Treatment and Comparison	Cmax (ng/mL) Adj. Geo. Mean	AUC(TAU) (ng.h/mL) Adj. Geo. Mean	C24 (ng/mL) Adj. Geo. Mean
A	114.97	1619.94	47.46
B	127.64	1834.11	55.23
	GMR (90% CI)	GMR (90% CI)	GMR (90% CI)
B vs A	1.110 (0.999,1.234)	1.132 (0.990,1.295)	1.164 (0.997,1.359)

Treatment Code: A: Methadone 40-120mg QD on Day 1, B: Methadone 40-120mg QD and Daclatasvir 60mg QD on Day 2-9

Total Methadone

Mean plasma concentration-time profile for dose-normalized (to 40 mg) total methadone is presented in **Figure 4**.

Figure 4 - Plot of Mean (+SD) Dose-normalized (to 40mg) Total Methadone Plasma Concentration Profile vs. Time
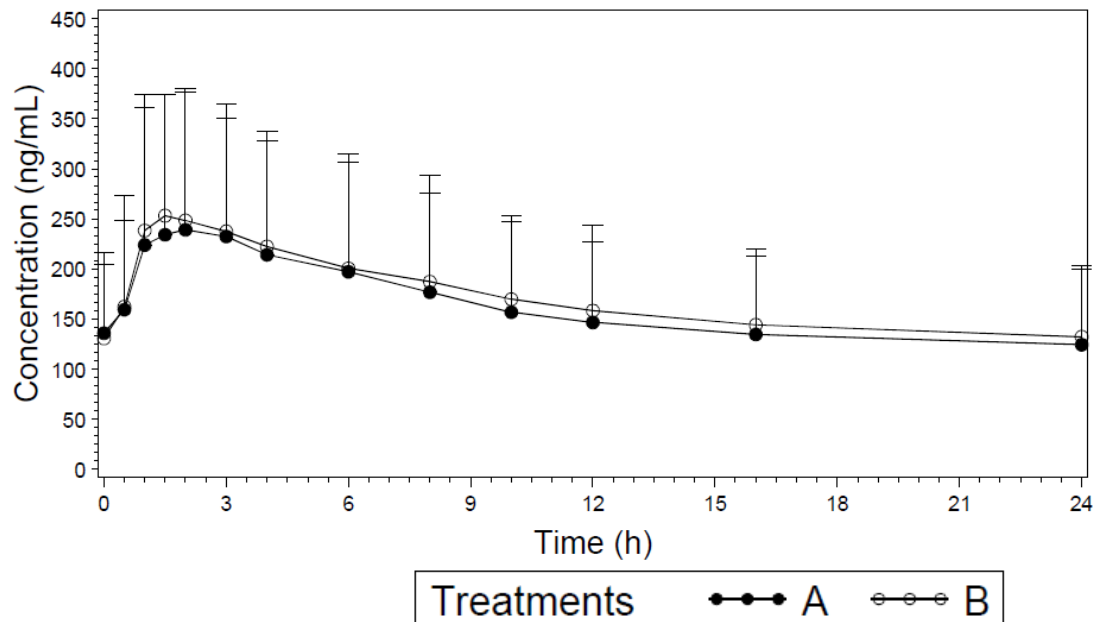
TREATMENT CODES:
A = Methadone 40-120 mg QD
B = Methadone 40-120 mg QD + Daclatasvir 60 mg QD

Statistical analyses of dose-normalized total-methadone Cmax, C24, and AUC(tau) are presented in **Table 6**.

Table 6 -Statistical Analysis of Dose-normalized (to 40 mg) Total Methadone PK Parameters

Treatment and Comparison	Cmax (ng/mL) Adj. Geo. Mean	AUC(TAU) (ng.h/mL) Adj. Geo. Mean	C24 (ng/mL) Adj. Geo. Mean
A	211.46	3212.62	101.06
B	231.21	3549.12	112.78
	GMR (90% CI)	GMR (90% CI)	GMR (90% CI)
B vs A	1.093 (0.988,1.210)	1.105 (0.968,1.261)	1.116 (0.962,1.294)

Treatment Code: A: Methadone 40-120mg QD on Day 1, B: Methadone 40-120mg QD and Daclatasvir 60mg QD on Day 2-9

Daclatasvir (DCV)

Mean plasma concentration-time profile for DCV is presented in **Figure 5**.

Figure 5 - Plot of Mean (+SD) DCV Plasma Concentration Profile vs. Time
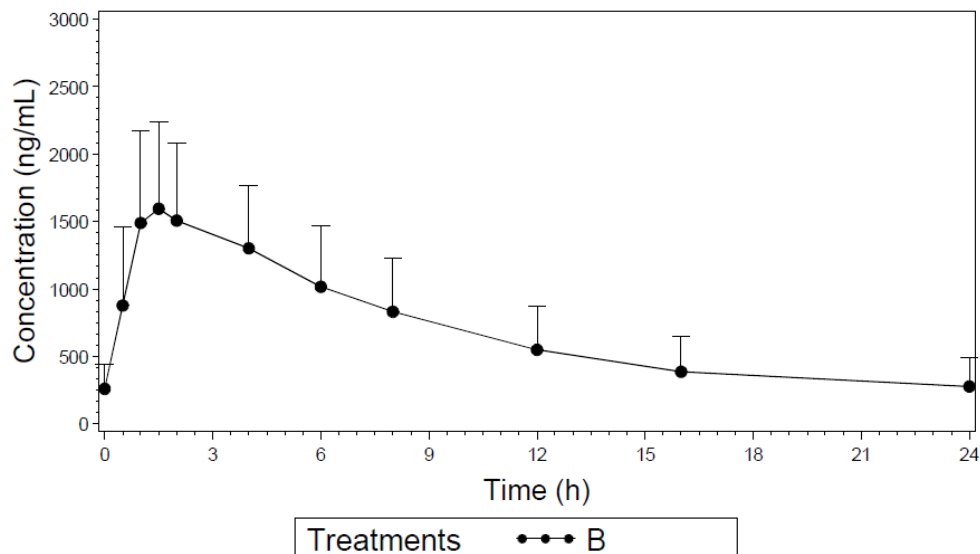
TREATMENT CODES:
B = Methadone 40-120 mg QD + Daclatasvir 60 mg QD

Steady state PK parameters of DCV 60 mg QD following steady state co-administration of methadone 40 - 120 mg QD were numerically similar to historical reference values obtained in healthy subjects(**Table 7**).

Table 7- Comparison of Historical Daclatasvir Pharmacokinetic Parameters

	Formulation	Cmax (ng/mL) Geo. Mean [N] (CV%)	Tmax (h) Median [N] (Min, Max)	AUC(TAU) (ng.h/mL) Geo. Mean [N] (CV%)	Cmin/C24 (ng/mL) Geo. Mean [N] (CV%)
AI444004[a]	Capsule	1726.383[4] (21)	1.000[4] (1.00-2.00)	15120.9[4] (35)	254.602[4] (42)
Integrated Analysis[b]	Capsule	1582.03 [6] (37)	1.50 [6] (1.5, 3.0)	15666.45 [6] (47)	295.83 [6] (67)
Integrated Analysis[c]	Tablet	1548.93 [43] (29)	1.00 [43] (1.0, 4.0)	13203.13 [15] (29)	230.95 [43] (48)
AI444064[d]	Tablet	1620 [14] (35)	1.25 [14] (0.9, 4.0)	14935 [14] (49)	215 [14] (77)

Source: Clinical Study Report AI444004[12], Summary of Clinical Pharmacology Studies[13], and Table S.9.1.4.2

[a] AI444004 - Day 14 in healthy subjects

[b] Summary of Clinical Pharmacology Studies - Day 5 in healthy subjects (AI444003, AI444005, AI444007, AI444009)

[c] Summary of Clinical Pharmacology Studies - Day 5 in healthy subjects (AI444009, AI444012, AI444023, AI444024, AI444039, AI444044, AI444065, AI444084)

[d] AI444064 - Day 9

9.4 PD results

Opiate withdrawal as assessed by the COW, SOW, and OOW scale, and opiate toxicity as assessed by OOA were not observed in Part 1 of this study.

9.5 Safety Analysis

Overall, 6 (42.9%) subjects had AEs in Part1 of this study. The most frequently AEs, occurring in 2 or more subjects, were nausea and pruritus. Most of the AEs were considered mild in intensity by the Investigator. Three subjects had 4 AEs (hand dermatitis, pruritus, abdominal distension and flatulence) that were considered mild and related to study drug by the Investigator and resolved without treatment. One AE of pruritus that was considered mild and unrelated to study drug was unresolved at study discharge.

10. Sponsor's Conclusions

- The 90% CI of the geometric mean ratios of the exposure of R-methadone and S-methadone (Cmax and AUC) when given with and without DCV were within the pre-defined criteria (0.70 to 1.43) indicating that coadministration of DCV did not have a clinically significant effect on the PK of methadone.
- Daclatasvir PK, when coadministered with methadone, was numerically similar to what has been observed historically in healthy subjects receiving multiple oral doses of DCV 60 mg.
- Coadministration of DCV and methadone did not result in opiate withdrawal as assessed by the COW, SOW, and OOW scales or opiate toxicity as assessed by OOA. Based on the results from the trial, the following conclusions can be made.

11. Reviewer's Assessment

The AI444064 trial (Part 1) adequately evaluated the drug-drug interaction potential when methadone and daclatasvir are coadministered. The sponsor's conclusions are valid.

<u>AI444065</u>

1. Title

Open-label, Single-sequence Study to Evaluate the Pharmacokinetic Interaction Between Multiple Doses of Daclatasvir (BMS-790052) and a Single Dose of Cyclosporine or Tacrolimus in Healthy Subjects

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at ICON from July 27, 2012 (first enrollment) to October 16, 2012 (last contact).

3. Objectives

The primary objective of the trial was to evaluate the potential drug-drug interaction between daclatasvir and cyclosporine and daclatasvir and tacrolimus.

4. Trial Design

AI444065 was an open label clinical trial that enrolled healthy subjects 18 to 49 years old. Information on the trial design is displayed in Figure 1.

Figure 1-AI444065 trial design

Abbreviations: CPU = clinical pharmacology unit; QD = once daily; S = screening.

5. Excluded Medications, Restrictions or Exceptions

Unless otherwise approved, prescription or nonprescription acid modifying medications were not permitted within 4 weeks and prescription and nonprescription medications, including herbal products, were not permitted within 2 weeks prior to medication administration. In general, prescription and nonprescription medications, including herbal products, were not permitted during the trial.

6. Dosage and Administration

The trial arms, including the dosage regimens that were administered, are specified in Figure 1. After fasting for a minimum of 10 hours before dosing, doses were administered under fasted conditions. According to the respective U.S prescribing information (USPI), for cyclosporine, the USPI states that the medication should be administered consistently with regards to meals and similarly for tacrolimus, the USPI states that the medication should be administered consistently with regards to food. For daclatasvir, the applicant is proposing to administer the medication with or without food.

7. Rationale for Doses Used in the Trial

The dosage regimen of 60 mg once daily for daclatasvir is the proposed recommended dosage regimen. No specific rationale was provided for the tacrolimus or cyclosporine doses that were evaluated other than stating that both doses were anticipated to result in plasma concentrations. A variety of dosage regimens exist for both medications: tacrolimus regimens include initial dosage regimens ranging from 0.075 mg/kg/day to 0.2 mg/kg/day in adults and cyclosporine regimens include initial dosage regimens ranging from 7 mg/kg/day to 9 mg/kg/day in adults.

8. Drugs Used in the Trial

Information regarding the medications that were administered in the trial is displayed in Table 1.

Table 1-Information on the medications administered in the AI444065 trial

Drug Name	Strength	Batch/Lot No
Daclatasvir (BMS-790052) Film-coated tablet	60 mg	2D72563
Cyclosporine capsules[a]	100 mg	F4150
Tacrolimus capsules[®]	5 mg	043001

a.   Cyclosporine was supplied as Neoral[®], Novartis Pharmaceuticals Corporation, East Hanover, New Jersey

b.   Tacrolimus was supplied as Prograf[®] Capsules, 5 mg, Astellas Pharma US, Northbrook, IL

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

In group 1, the blood samples that were obtained included cyclosporine blood samples beginning on days 1 and 9 at predose and up to 72 hours postdose and daclatasvir blood samples were obtained starting on days 8 and 9 at predose and up to 24 hours postdose.

In group 2, the blood samples that were obtained included tacrolimus blood samples

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beginning on days 1 and 13 at predose and up to 168 hours postdose and daclatasvir blood samples were obtained starting on days 12 and 13 at predose and up to 24 hours postdose.

Bioanalysis

The method and bioanalysis of daclatasvir, tacrolimus and cyclosporine are acceptable. Daclatasvir plasma samples were analyzed using a validated LC/MS/MS method in EDTA anticoagulated plasma by ⬛⬛⬛⬛ (b) (4) (TNJM11132.01) and cyclosporine and tacrolimus whole blood samples were analyzed using a validated LC/MS/MS method by ⬛⬛⬛⬛ (b) (4), respectively. The cyclosporine method was validated in K_2EDTA anticoagulated whole blood and the tacrolimus method was validated in K_3EDTA anticoagulated whole blood. The blood samples for analysis of daclatasvir, cyclosporine, and tacrolimus appear to have been collected in tubes containing K_2EDTA as an anticoagulant.

For the AI444065 plasma samples that were analyzed for daclatasvir, the lower limit of quantification for daclatasvir was 2 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for daclatasvir based on the bioanalytical report. For the AI444065 trial, precision and accuracy were evaluated using plasma daclatasvir quality control (QC) samples at 6 ng/mL, 80 ng/mL, 800 ng/mL, and 1600 ng/mL. The corresponding daclatasvir inter-run accuracy values were 0% for 6 ng/mL, 1.9% for 80 ng/mL, -1.5% for 800 ng/mL, and -1.9% for 1600 ng/mL. The daclatasvir inter-run precision values were 5.4% for 6 ng/mL, 4% for 80 ng/mL, 4% for 800 ng/mL, and 4.5% for 1600 ng/mL. In addition, for the daclatasvir dilution QC samples at 10000 ng/mL, the inter-run accuracy and precision were -0.1% and 3.8%, respectively.

For tacrolimus, the lower limit of quantification was 0.25 ng/mL and the upper limit of quantification was 100 ng/mL. There were no precision or accuracy issues identified for tacrolimus based on the bioanalytical report. For the AI444065 trial, precision and accuracy were evaluated using whole blood tacrolimus QC samples at 0.6 ng/mL, 1.5 ng/mL, 5 ng/mL, 16 ng/mL and 75 ng/mL. The corresponding tacrolimus inter-run accuracy values were 1.58% for 0.6 ng/mL, -2.22% for 1.5 ng/mL, -13.1% for 5 ng/mL, -7.97% for 16 ng/mL and -5.44% for 75 ng/mL. The tacrolimus inter-run precision values were 9.07% for 0.6 ng/mL, 7.13% for 1.5 ng/mL, 5.81% for 5 ng/mL, 6.2% for 16 ng/mL and 6.86% for 75 ng/mL.

The AI444065 bioanalytical report for cyclosporine was submitted in response to an information request. For cyclosporine, the lower limit of quantification was 0.1 ng/mL and the upper limit of quantification was 100 ng/mL. There were no precision or accuracy issues identified for cyclosporine based on the bioanalytical report. For the AI444065 trial, precision and accuracy were evaluated using whole blood cyclosporine QC samples at 0.3 ng/mL, 40 ng/mL, and 80 ng/mL. The corresponding cyclosporine inter-run accuracy values were 1.6% for 0.3 ng/mL, -9.92% for 40 ng/mL, and 1.4% for 80 ng/mL. The cyclosporine inter-run precision values were 8.39% for 0.3 ng/mL, 6.24% for 40 ng/mL, and 6.60% for 80 ng/mL. In addition, for the cyclosporine dilution QC

samples at 200 ng/mL, the inter-run accuracy and precision were 1.10% and 5.51%, respectively.

For the AI444065 trial, in response to an information request, the applicant stated that the daclatasvir plasma samples were stored at the trial site at -20°C for up to 7 days and the bioanalytical laboratory at -20°C for up to 3 days, tacrolimus whole blood samples were stored at the trial site at -20°C for up to 19 days and the bioanalytical laboratory at -20°C for up to 9 days and cyclosporine whole blood samples were stored at the trial site at -20°C for up to 13 days and the bioanalytical laboratory at -20°C for up to 23 days. For the TNJM11132.01 method, the generated long term stability data for daclatasvir included stability data in K_2EDTA anticoagulated plasma at -20°C for 686 days and at -80°C for 658 days. For tacrolimus, the generated long term stability data included stability data at -20°C in K_2EDTA anticoagulated whole blood for 150 days. The generated long term stability data for cyclosporine included stability data in K_2EDTA anticoagulated whole blood at -20°C and -70°C for 182 days. For the AI444065, the generated long term stability data appears to covers the duration of long term stability data necessary for daclatasvir, cyclosporine and tacrolimus.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for daclatasvir, tacrolimus and cyclosporine. For the noncompartmental analysis, daclatasvir plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, and $AUC_{(0-tau)}$ and tacrolimus and cyclosporine whole blood pharmacokinetic parameters were calculated, including t_{max}, C_{max}, and $AUC_{(0-inf)}$.

Statistical Analysis

Statistical analyses were conducted that included the following comparisons and 90% confidence intervals were derived: a) cyclosporine or tacrolimus coadministered with daclatasvir (test arms) compared to cyclosporine or tacrolimus administered alone (reference arms), and b) daclatasvir coadministered with cyclosporine or tacrolimus (test arms) compared to daclatasvir administered alone (reference arms).

10. Results

10.1 Subject Demographics

Table 2-AI444065 subject demographics

Assessment Variable	Group 1 N = 14	Group 2 N = 14
Age, years		
Mean (SD)	34.8 (7.14)	34.5 (8.65)
Min, Max	25, 46	21, 46
Sex, n (%)		
Male	12 (85.7)	10 (71.4)
Female	2 (14.3)	4 (28.6)
Ethnicity, n (%)		
Hispanic/Latino	2 (14.3)	1 (7.1)
Not Hispanic/Latino	12 (85.7)	13 (92.9)
Race, n (%)		
White	6 (42.9)	10 (71.4)
Black/African American	7 (50.0)	4 (28.6)
Other	1 (7.1)	0 (0.0)
Height, cm [a]		
Mean (SD)	173.57 (9.525)	174.43 (7.521)
Min, Max	157.0, 191.0	162.0, 187.0
Weight, kg [b]		
Mean (SD)	86.18 (13.633)	80.12 (13.530)
Min, Max	64.9, 111.3	62.3, 105.9
BMI, kg/m^2 [b]		
Mean (SD)	28.49 (2.735)	26.29 (3.668)
Min, Max	21.9, 31.7	18.8, 31.4

Abbreviations: BMI = body mass index; max = maximum; min = minimum; n = non-missing observations; N = number of subjects; SD = standard deviation.
a. Measurement at screening.
b. Measurement on Day −1.

10.2 Concomitant Medications

No concomitant medications were administered in the trial.

10.3 Pharmacokinetic and Statistical Analysis

Cyclosporine

Table 3-Single dosing cyclosporine pharmacokinetic parameters with cyclosporine 400 mg or cyclosporine 400 mg combined with daclatasvir 60 mg once daily

Treatment	Cmax (ng/mL) GM [n] (CV%)	Tmax (h) Median [n] (Min-Max)	AUC(0-T) (ng.h/mL) GM [n] (CV%)	AUC(INF) (ng.h/mL) GM [n] (CV%)	T-HALF (h) Mean [n] (SD)	CLT/F (L/h) GM [n] (CV%)
A	1504 [14] (20)	1.50 [14] (1.00-2.02)	7825 [14] (21)	8198 [14] (21)	23.3 [14] (3.28)	48.8 [14] (23)
C	1447 [14] (20)	1.50 [14] (1.00-2.02)	7989 [14] (24)	8405 [14] (24)	21.2 [14] (5.36)	47.6 [14] (25)

Abbreviations: CV% = coefficient of variation; GM = geometric mean; Max = maximum; Min = minimum; n = number of non-missing observations; QD = once daily; SD = standard deviation.
Treatment A = single dose cyclosporine 400 mg QD on Day 1. Treatment C = single dose cyclosporine 400 mg QD in combination with daclatasvir 60 mg QD on Day 9 then daclatasvir 60 mg QD on Days 10 to 11.

Table 4-Statistical analyses for cyclosporine

Analyte	Treatment and Comparison	Cmax (ng/mL) Adjusted GM [n]	AUC(0-T) (ng.h/mL) Adjusted GM [n]	AUC(INF) (ng.h/mL) Adjusted GM [n]
Cyclosporine	A	1504 [14]	7825 [14]	8198 [14]
	C	1447 [14]	7989 [14]	8405 [14]
		Ratio of Adjusted GM (90% CI)		
	C vs. A	0.962 (0.908, 1.02)	1.02 (0.963, 1.08)	1.03 (0.966, 1.09)

Abbreviations: CI = confidence interval; GM = geometric mean; n = number of non-missing observations; QD = once daily.
The statistical model includes treatment as a fixed effect and measurements within subject as repeated measures.
Treatment A = single dose cyclosporine 400 mg QD on Day 1. Treatment C = Single dose cyclosporine 400 mg QD in combination with daclatasvir 60 mg QD on Day 9 then daclatasvir 60 mg QD on Days 10 to 11.

Tacrolimus

Table 5- Single dosing tacrolimus pharmacokinetic parameters with tacrolimus 5 mg or tacrolimus 5 mg combined with daclatasvir 60 mg once daily

Treatment	Cmax (ng/mL) GM [n (CV%)	Tmax (h) Median [n] (Min-Max)	AUC(0-T) (ng.h/mL) GM [n] (CV%)	AUC(INF) (ng.h/mL) GM [n] (CV%)	T-HALF (h) Mean [n] (SD)	CLT/F (L/h) GM [n] (CV%)
D	22.8 [14] (28)	1.50 [14] (1.00-2.00)	225 [14] (46)	246 [14] (44)	40.4 [14] (8.75)	20.3 [14] (72)
F	24.0 [14] (40)	1.50 [14] (0.55-2.00)	224 [14] (59)	245 [14] (56)	38.9 [14] (6.49)	20.4 [14] (76)

Abbreviations: CV% = coefficient of variation; GM = geometric mean; Min = minimum; Max = maximum; n = number of non-missing observations; QC = once daily; SD = standard deviation.
Treatment D = single dose tacrolimus 5 mg QD on Day 1. Treatment F = single dose tacrolimus 5 mg QD in combination with daclatasvir 60 mg QD on Day 13 then daclatasvir 60 mg QD on Days 14 to 19.

Table 6-Statistical analyses for tacrolimus

Analyte	Treatment and Comparison	Cmax (ng/mL) Adjusted GM [n]	AUC(0-T) (ng.h/mL) Adjusted GM [n]	AUC(INF) (ng.h/mL) Adjusted GM [n]
Tacrolimus	D	22.8 [14]	225 [14]	246 [14]
	F	24.0 [14]	224 [14]	245 [14]
		Ratio of Adjusted GM (90% CI)		
	F vs. D	1.05 (0.904, 1.23)	0.997 (0.868, 1.15)	0.996 (0.877, 1.13)

Abbreviations: CI = confidence interval; GM = geometric mean; n = number of non-missing observations; QD = once daily.
The statistical model includes treatment as a fixed effect and measurements within subject as repeated measures.
Treatment D = single dose tacrolimus 5 mg QD on Day 1. Treatment F = single dose tacrolimus 5 mg QD in combination with daclatasvir 60 mg QD on Day 13 then daclatasvir 60 mg QD on Days 14 to 19.

Daclatasvir

Cyclosporine-daclatasvir

Table 7-Multiple dosing daclatasvir pharmacokinetic parameters with cyclosporine 400 mg or cyclosporine 400 mg combined with daclatasvir 60 mg once daily

Treatment	Cmax (ng/mL) GM [n] (CV%)	Tmax (h) Median [n] (Min-Max)	AUC(TAU) (ng.h/mL) GM [n] (CV%)	C24 (ng/mL) GM [n] (CV%)
B	1690 [14] (31)	1.00 [14] (1.00-4.00)	16092 [14] (32)	306 [14] (44)
C	1756 [14] (25)	2.00 [14] (1.50-4.00)	22587 [14] (24)	475 [14] (30)

Abbreviations: CV% = coefficient of variation; GM = geometric mean; Min = minimum; Max = maximum; n = number of non-missing observations; QD = once daily.
Treatment B = daclatasvir 60 mg QD on Days 4 to 8. Treatment C = single dose cyclosporine 400 mg QD in combination with daclatasvir 60 mg QD on Day 9 then daclatasvir 60 mg QD on Days 10 to 11.

Table 8-Statistical analyses for daclatasvir

Analyte	Treatment and Comparison	Cmax (ng/mL) Adjusted GM [n]	AUC(TAU) (ng.h/mL) Adjusted GM [n]	C24 (ng/mL) Adjusted GM [n]
Daclatasvir	B	1690 [14]	16092 [14]	306 [14]
	C	1756 [14]	22587 [14]	475 [14]
		Ratio of Adjusted GM (90% CI)		
	C vs. B	1.04 (0.936, 1.15)	1.40 (1.29, 1.53)	1.56 (1.41, 1.71)

Abbreviations: CI = confidence interval; GM = geometric mean; n = number of non-missing observations; QD = once daily.
The statistical model includes treatment as a fixed effect and measurements within subject as repeated measures.
Treatment B = daclatasvir 60 mg QD on Days 4 to 8. Treatment C = single dose cyclosporine 400 mg QD in combination with daclatasvir 60 mg QD on Day 9 then daclatasvir 60 mg QD on Days 10 to 11.

Tacrolimus-daclatasvir

Table 9-Multiple dosing daclatasvir pharmacokinetic parameters with tacrolimus 5 mg or tacrolimus 5 mg combined with daclatasvir 60 mg once daily

Treatment	Cmax (ng/mL) GM [n] (CV%)	Tmax (h) Median [n] (Min-Max)	AUC(TAU) (ng.h/mL) GM [n] (CV%)	C24 (ng/mL) GM [n] (CV%)
E	1489 [14] (20)	1.00 [14] (1.00-1.50)	13786 [14] (28)	205 [14] (43)
F	1578 [14] (27)	1.00 [14] (0.55-1.50)	14439 [14] (30)	226 [14] (33)

Abbreviations: CV% = coefficient of variation; GM = geometric mean; Min = minimum; Max = maximum; n = number of non-missing observations; QD = once daily.
Treatment E = daclatasvir 60 mg QD on Days 8 to 12. Treatment F = single dose tacrolimus 5 mg QD in combination with daclatasvir 60 mg QD on Day 13 then daclatasvir 60 mg QD on Days 14 to 19.

Table 10-Statistical analyses for daclatasvir

Analyte	Treatment and Comparison	Cmax (ng/mL) Adjusted GM [n]	AUC(TAU) (ng.h/mL) Adjusted GM [n]	C24 (ng/mL) Adjusted GM [n]
Daclatasvir	E	1489 [14]	13786 [14]	205 [14]
	F	1587 [14]	14439 [14]	226 [14]
		Ratio of Adjusted GM (90% CI)		
	F vs. E	1.07 (1.02, 1.12)	1.05 (1.03, 1.07)	1.10 (1.03, 1.19)

Abbreviations: CI = confidence interval; GM = geometric mean; n = number of non-missing observations; QD = once daily.
The statistical model includes treatment as a fixed effect and measurements within subject as repeated measures. Treatment E = daclatasvir 60 mg QD on Days 8 to 12. Treatment F = single dose tacrolimus 5 mg QD in combination with daclatasvir 60 mg QD on Day 13 then daclatasvir 60 mg QD on Days 14 to 19.

10.4 Safety Analysis

No deaths, serious adverse events or adverse events leading to discontinuation were reported for the trial.

11. Discussion and Conclusions

Based on the results from the AI444065 trial, the following conclusions can be made.

- Cyclosporine: When daclatasvir 60 mg once daily was coadministered with a single dose of cyclosporine 400 mg, the cyclosporine C_{max} was decreased by 4% and the $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were increased by 2% and 3%, respectively, when compared with cyclosporine 400 mg. The 90% confidence intervals for cyclosporine C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were all within the standard "no effect" 90% confidence interval limits of 80%-125%.

- Tacrolimus: When daclatasvir 60 mg once daily was coadministered with a single dose of tacrolimus 5 mg, the tacrolimus C_{max} was increased by 5% and the $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were both decreased by less than 1%, when compared with tacrolimus 5 mg. The 90% confidence intervals for tacrolimus C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were all within the standard "no effect" 90% confidence interval limits of 80%-125%.

- Daclatasvir (with concomitant use of cyclosporine): When daclatasvir 60 mg once daily was coadministered with a single dose of cyclosporine 400 mg, the daclatasvir C_{max}, $AUC_{(0-tau)}$ and C_{24h} were increased by 4%, 40% and 56%, respectively, when compared with daclatasvir 60 mg once daily. Only the 90% confidence interval for daclatasvir C_{max} was within the standard "no effect" 90% confidence interval limits of 80%-125%.

- Daclatasvir (with concomitant use of tacrolimus): When daclatasvir 60 mg once daily was coadministered with a single dose of tacrolimus 5 mg, the daclatasvir C_{max}, $AUC_{(0-tau)}$ and C_{24h} were increased by 7%, 5% and 10%, respectively, when compared with daclatasvir 60 mg once daily. The 90% confidence intervals for daclatasvir C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-inf)}$ were all within the standard "no effect" 90% confidence interval limits of 80%-125%.

No clinically relevant changes in cyclosporine or tacrolimus exposure were observed with concurrent use of daclatasvir and no clinically relevant changes in daclatasvir exposure were observed with concurrent use of tacrolimus. A dose adjustment for daclatasvir is not necessary when coadministered with cyclosporine based on the information from the AI444065 trial and the absence of anticipated safety issues from the daclatasvir exposure-safety information.

AI444084

1. Title

An Open-Label Two-Way Drug-Drug Interaction Study to Assess the Effect of Daclatasvir on the Pharmacokinetics of Escitalopram and the Effect of Escitalopram on the Pharmacokinetics of Daclatasvir in Healthy Subjects

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at ICON from January 21, 2013 (trial initiation) to March 14, 2013 (trial completion).

3. Objectives

The primary objective of the trial was to evaluate the potential drug-drug interaction between daclatasvir and escitalopram.

4. Trial Design

AI444084 was an open label clinical trial that enrolled healthy subjects 25 to 55 years old. Information on the trial design is displayed in Figure 1.

Figure 1-AI444084 trial design

S, E	Daclatasvir 60 mg QD	4-day Washout	Escitalopram 10 mg QD	Escitalopram 10 mg QD + Daclatasvir 60 mg QD	Clinic Furlough[a]	Study Discharge[b]
	Treatment A		Treatment B	Treatment C		
Days -21 to -1	Day 1-Day 5	Days 6-9	Days 10-16	Days 17-23	Day 25	Day 30 ±2 days
	24-h PK sampling on D5		24-h PK sampling on D16	24-h (Daclatasvir) and 24-h (Escitalopram) PK sampling on D23		

[a] Subjects will be furloughed from the clinical facility following the completion of safety assessments

[b] Subjects will return to the clinical facility for the study discharge visit during Day 30±2. Subjects will be discharged from the clinical facility following the completion of safety assessments

5. Excluded Medications, Restrictions or Exceptions

Unless otherwise approved, prescription medications or nonprescription acid modifying medications were not permitted within 2 weeks and nonprescription medications, including herbal products, were not permitted within 4 weeks prior to medication administration. In general, prescription and nonprescription medications, including

herbal products, were not permitted during the trial.

6. Dosage and Administration

The trial arms, including the dosage regimens that were administered, are specified in Figure 1. After fasting for a minimum of 10 hours on days 1 to 5, days 10 to 16, and days 17 to 23, doses were administered under fasted conditions. According to the escitalopram U.S prescribing information (USPI), escitalopram can be administered with or without food. For daclatasvir, the applicant is proposing to administer the medication with or without food.

7. Rationale for Doses Used in the Trial

The dosage regimen of 60 mg once daily for daclatasvir is the proposed recommended dosage regimen. The escitalopram dosage regimen of 10 mg once daily is within the range of recommended dosage regimens in adults.

8. Drugs Used in the Trial

Information regarding the daclatasvir formulation that was administered in the trial is displayed in Table 1. There were no specific details provided regarding the escitalopram formulation that was administered.

Table 1-Information on the daclatasvir formulation administered in the AI444084 trial

Product Description and Dosage Form	Potency	Product Identification Number	Product Batch Number
Daclatasvir* (BMS-790052-05) Film coated tablet	60 mg (as the free base)	790052-K060-028	2G72986

*Phase 3 Formulation

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood samples that were obtained included daclatasvir blood samples beginning on days 5 and 23 at predose and up to 24 hours postdose and escitalopram blood samples were obtained starting on days 16 and 23 at predose and up to 24 hours postdose.

Bioanalysis

The method and bioanalysis of daclatasvir and citalopram are acceptable. Daclatasvir plasma samples were analyzed using a validated LC/MS/MS method in EDTA

anticoagulated plasma by [blank] (b) (4) (TNJM11132.01). However, the escitalopram blood samples were not analyzed using a validated method to measure escitalopram plasma concentrations. Instead, a citalopram validated LC/MS/MS method in sodium heparin anticoagulated plasma was used by [blank] (b) (4) to measure escitalopram plasma concentrations (escitalopram is the S-isomer of citalopram). For the AI444084 trial, escitalopram calibration curve standards and citalopram quality control (QC) samples were evaluated. The potential for interconversion of the S-isomer of citalopram to the R-isomer of citalopram does not appear to a major issue, and the use of the citalopram method is acceptable. The blood samples for analysis of daclatasvir and the blood samples from subjects that were administered escitalopram appears to have been collected in tubes containing K_2EDTA and sodium heparin as an anticoagulant, respectively.

For the AI444084 plasma samples that were analyzed for daclatasvir, the lower limit of quantification for daclatasvir was 2 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for daclatasvir based on the bioanalytical report. For the AI444084 trial, precision and accuracy were evaluated using plasma daclatasvir QC samples at 6 ng/mL, 80 ng/mL, 800 ng/mL, and 1600 ng/mL. The corresponding daclatasvir inter-run accuracy values were 3.7% for 6 ng/mL, 1.6% for 80 ng/mL, -0.8% for 800 ng/mL, and 1.9% for 1600 ng/mL. The daclatasvir inter-run precision values were 5.9% for 6 ng/mL, 2.3% for 80 ng/mL, 4% for 800 ng/mL, and 4.2% for 1600 ng/mL. In addition, for the daclatasvir dilution QC samples at 10000 ng/mL, the inter-run accuracy and precision were -6.6% and 2.9%, respectively.

For blood samples from subjects that were administered escitalopram that were analyzed using a citalopram method, the lower limit of quantification was 1 ng/mL and the upper limit of quantification was 500 ng/mL. There were no precision or accuracy issues identified for citalopram based on the bioanalytical report. For the AI444084 trial, precision and accuracy were evaluated using citalopram QC samples at 2.5 ng/mL, 6 ng/mL, 22.5 ng/mL, 75 ng/mL and 375 ng/mL. The corresponding citalopram inter-run accuracy values were 2.04% for 2.5 ng/mL, 2.27% for 6 ng/mL, 2.24% for 22.5 ng/mL, 2.19% for 75 ng/mL and -1.30% for 375 ng/mL. The citalopram inter-run precision values were 6.45% for 2.5 ng/mL, 3.06% for 6 ng/mL, 5.44% for 22.5 ng/mL, 2.87% for 75 ng/mL and 4.82% for 375 ng/mL.

Of the samples selected for incurred sample reanalysis for daclatasvir (approximately 50 in total), all samples were within 20% using the percentage values of the repeat and original concentrations. However, it is not clear whether the total number of daclatasvir samples that were reanalyzed represents 7% of the total number of samples that were initially analyzed.

For the AI444084 trial, in response to an information request, the applicant stated that the daclatasvir plasma samples were stored at the trial site at -20°C for up to 6 days, at the central laboratory at -20°C for up to 33 days and the bioanalytical laboratory at -20°C for up to 8 days and escitalopram plasma samples were stored at the trial site at -20°C for up to 6 days, at the central laboratory at -20°C for up to 21 days and the bioanalytical

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laboratory at -20°C for up to 30 days. For the TNJM11132.01 method, the generated long term stability data for daclatasvir included stability data in K_2EDTA anticoagulated plasma at -20°C for 686 days and at -80°C for 658 days. For escitalopram, no specific long term stability data was generated. The long term stability data that was generated for citalopram included stability data at -20°C in sodium heparin anticogulated plasma for 948 days. For the AI444084 trial, the generated long term stability data appears to covers the duration of long term stability data necessary for daclatasvir and escitalopram.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for daclatasvir and escitalopram. For the noncompartmental analysis, daclatasvir and escitalopram plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, and $AUC_{(0\text{-}tau)}$.

Statistical Analysis

Statistical analyses were conducted that included the following comparisons and 90% confidence intervals were derived: a) escitalopram when coadministered with daclatasvir (test arm) compared to escitalopram administered alone (reference arm), and b) daclatasvir when coadministered with escitalopram (test arm) compared to daclatasvir administered alone (reference arm). The applicant proposed "no effect" bounds of 75% to 150% for daclatasvir and 70% to 170% for escitalopram. The trial report states that the rationales for the proposed limits were based on the escitalopram literature and the pharmacokinetic and pharmacodyamic daclatasvir information.

10. Results

10.1 Subject Demographics

Table 2-AI444084 subject demographics

	Total N = 15
Age (years)	
Median	34.0
Min, Max	27, 49
Race (%)	
White	7 (46.7)
Black	7 (46.7)
Other	1 (6.7)
Gender (%)	
Male	13 (86.7)
Female	2 (13.3)
Mean Height (cm)	176.76
Mean Weight (kg)	83.99
Mean BMI (kg/cm^2)	26.86

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10.2 Concomitant Medications

No concomitant medications were administered in the trial.

10.3 Pharmacokinetic and Statistical Analysis

Escitalopram

Reviewer note: as mentioned in section 9 (Bioanalysis), the actual reported concentration data was for citalopram not escitalopram.

Table 3-Multiple dosing pharmacokinetic parameters for subjects receiving escitalopram 10 mg once daily or escitalopram 10 mg once daily combined with daclatasvir 60 mg once daily

Parameter Statistic	Treatment	
	B	C
Cmax (ng/mL) Geo.Mean [N] (%CV)	22.1 [15] (26)	22.1 [15] (34)
Tmax (h) Median [N] (Min - Max)	4.50 [15] (3.00 - 8.00)	4.50 [15] (3.00 - 6.00)
AUC(TAU) (ng.h/mL) Geo.Mean [N] (%CV)	353 [15] (35)	370 [15] (40)
C24 (ng/mL) Geo.Mean [N] (%CV)	11.0 [15] (45)	12.1 [15] (49)

Treatment: A=Daclatasvir 60 mg QD on Days 1 to 5, B=Escitalopram 10 mg QD on Days 10 to 16, C=Escitalopram 10 mg QD + Daclatasvir 60 mg QD on Days 17 to 23

Table 4-Statistical analyses for subjects receiving escitalopram 10 mg once daily or escitalopram 10 mg once daily combined with daclatasvir 60 mg once daily

TREATMENT AND COMPARISON	Cmax (ng/mL) Adj.GEO.MEAN	AUC(TAU) (ng.h/mL) Adj.GEO.MEAN	C24 (ng/mL) Adj.GEO.MEAN
B	22.136	352.726	11.020
C	22.066	370.456	12.070
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
C vs B	0.997(0.921,1.079)	1.050(1.018,1.083)	1.095(1.039,1.155)

Treatment Codes: B=Escitalopram 10 mg QD on Days 10 to 16, C=Escitalopram 10 mg QD + Daclatasvir 60 mg QD on Days 17 to 23

Daclatasvir

Table 5-Multiple dosing daclatasvir pharmacokinetic parameters with escitalopram 10 mg once daily or escitalopram 10 mg once daily combined with daclatasvir 60 mg once daily

Parameter Statistic	Treatment	
	A	C
Cmax (ng/mL) Geo.Mean [N] (%CV)	1481 [15] (33)	1682 [15] (25)
Tmax (h) Median [N] (Min - Max)	1.50 [15] (1.00 - 3.00)	1.50 [15] (1.00 - 2.00)
AUC(TAU) (ng.h/mL) Geo.Mean [N] (%CV)	13203 [15] (29)	14847 [15] (26)
C24 (ng/mL) Geo.Mean [N] (%CV)	199 [15] (38)	244 [15] (36)

Treatment: A=Daclatasvir 60 mg QD on Days 1 to 5, B=Escitalopram 10 mg QD on Days 10 to 16, C=Escitalopram 10 mg QD + Daclatasvir 60 mg QD on Days 17 to 23

Table 6-Statistical analyses for daclatasvir

TREATMENT AND COMPARISON	Cmax (ng/mL) Adj.GEO.MEAN	AUC(TAU) (ng.h/mL) Adj.GEO.MEAN	C24 (ng/mL) Adj.GEO.MEAN
A	1481.388	13203.13	199.164
C	1681.710	14846.78	244.193
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
C vs A	1.135(0.977,1.319)	1.124(1.006,1.257)	1.226(1.087,1.383)

Treatment Codes: A=Daclatasvir 60 mg QD on Days 1 to 5,
C=Escitalopram 10 mg QD + Daclatasvir 60 mg QD on Days 17 to 23

10.4 Safety Analysis

No deaths, serious adverse events or adverse events leading to discontinuation were reported for the trial.

11. Discussion and Conclusions

Based on the results from the AI444084 trial, the following conclusions can be made.

- Escitalopram: When escitalopram 10 mg once daily was coadministered with daclatasvir 60 mg once daily, the C_{max} was decreased by less than 1% and the $AUC_{(0-tau)}$ and C_{24h} were increased by 5% and 10%, respectively, when compared with escitalopram 10 mg once daily. The 90% confidence intervals for escitalopram C_{max}, $AUC_{(0-tau)}$ and C_{24h} were all within the standard "no effect" 90% confidence interval limits of 80%-125% or the applicant's proposed limits of 70% to 170%.

- Daclatasvir :When daclatasvir 60 mg once daily was coadministered with escitalopram 10 mg once daily, the daclatasvir C_{max}, $AUC_{(0-tau)}$ and C_{24h} were increased by 14%, 12% and 23%, respectively, when compared with daclatasvir 60 mg once daily. The 90% confidence interval for daclatasvir C_{max}, $AUC_{(0-tau)}$, and C_{24h} were not within the standard "no effect" 90% confidence interval limits of 80%-125% but were within the applicant's proposed limits of 75% to 150%.

No clinically relevant changes in escitalopram exposure were observed with concurrent use of daclatasvir. A dose adjustment for daclatasvir is not necessary when coadministered with escitalopram based on the information from the AI444084 trial and the absence of anticipated safety issues from the daclatasvir exposure-safety information.

AI447009

1. Title

Open-label, Randomized, Multiple Dose, Drug-drug Interaction Study to Assess the Pharmacokinetics and Safety of BMS-790052 and BMS-650032 Co-administered in Healthy Subjects

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at PPD from May 18, 2009 (trial initiation) to July 1, 2009 (trial completion).

3. Objectives

The primary objective of the trial was to evaluate the potential drug-drug interaction between daclatasvir (BMS-790052) and asunaprevir (BMS-650032).

4. Trial Design

AI447009 was an open label clinical trial that enrolled healthy subjects 18 to 49 years old. Information on the trial design is displayed in Figure 1.

Figure 1-AI447009 trial design
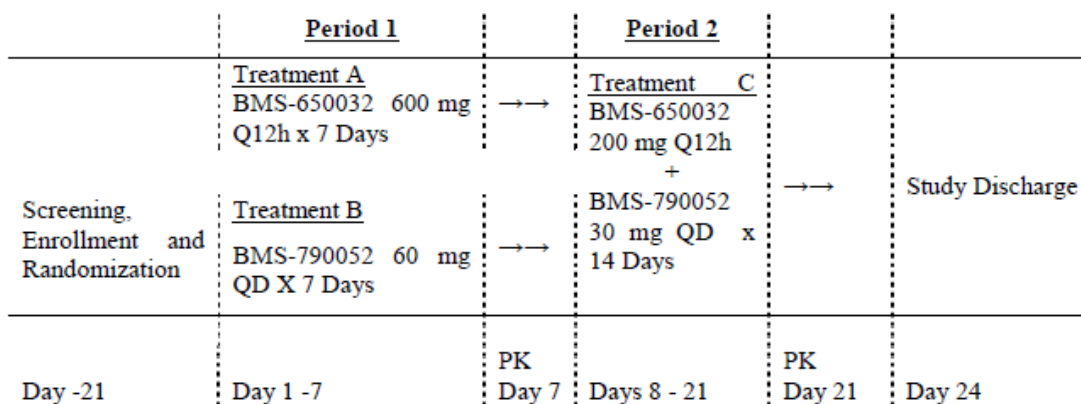
5. Excluded Medications, Restrictions or Exceptions

Unless otherwise approved, according to the trial protocol, prescription medications (except acid modifying medications) were not permitted within 4 weeks and nonprescription medications, including herbal products, and prescription and nonprescription acid modifying medications were not permitted within 1 week prior to medication administration. In general, prescription and nonprescription medications, including herbal products, were not permitted during the trial.

6. Dosage and Administration

The trial arms, including the dosage regimens that were administered, are specified in Figure 1. The morning doses were administered under fasted conditions and the evening dose was administered two hours after a meal.

7. Rationale for Doses Used in the Trial

The dosage regimens of 600 mg twice daily and 60 mg once daily for asunaprevir and daclatasvir, respectively, administered alone were selected because both regimens were the highest proposed dosage regimens. The dosage regimens of 200 mg twice daily and 30 mg once daily for asunaprevir and daclatasvir, respectively, with concomitant use were selected because they were expected to provide exposures that did not exceed the exposures with each of the medications administered alone.

8. Drugs Used in the Trial

Information regarding the medications that were administered in the trial is displayed in Table 1.

Table 1-Information on the medications administered in the AI447009 trial

Unit	Formulation	Product ID Number	Product Batch Number	Label Batch Number
BMS-650032 Capsule	100 mg	252847	8J42946	9C56282
BMS-790052 Capsule	10 mg (as free base)	257456	8K42126	9C56264

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood samples that were obtained included asunaprevir blood samples beginning on days 7 and 21 at predose and up to ^{(b)(4)} hours postdose for both the morning and evening doses and daclatasvir blood samples beginning on days 7 and 21 at predose and up to 24 hours postdose.

Bioanalysis

The method and bioanalysis of asunaprevir and daclatasvir are acceptable. Asunaprevir and daclatasvir plasma samples were analyzed using a validated LC/MS/MS method in EDTA anticoagulated plasma by [(b)(4)] (TNJM09046). The blood samples for analysis of asunaprevir and daclatasvir appears to have been collected in tubes containing K_2EDTA as an anticoagulant.

For the AI447009 plasma samples that were analyzed for asunaprevir, [(b)(4)]

The lower limit of quantification for daclatasvir was 1 ng/mL and the upper limit of quantification was 1000 ng/mL. There were no precision or accuracy issues identified for daclatasvir based on the bioanalytical report. For the AI447009 trial, precision and accuracy were evaluated using plasma daclatasvir QC samples at 3 ng/mL, 40 ng/mL, 400 ng/mL, and 800 ng/mL. The corresponding daclatasvir inter-run accuracy values were 1.3% for 3 ng/mL, 0.3% for 40 ng/mL, -0.3% for 400 ng/mL, and -2.5% for 800 ng/mL. The daclatasvir inter-run precision values were 6.3% for 3 ng/mL, 5.2% for 40 ng/mL, 4.6% for 400 ng/mL, and 4.7% for 800 ng/mL. In addition, for the daclatasvir dilution QC samples at 5000 ng/mL, the inter-run accuracy and precision were -4% and 2.6%, respectively with a dilution factor of 20 and the inter-run accuracy and precision were -7.4% and 4.2%, respectively with a dilution factor of 10.

Of the samples selected for incurred sample reanalysis for asunaprevir

Of the samples selected for incurred sample reanalysis for daclatasvir (less than 100 in total), no samples were not within 20% using the percentage values of the repeat and original concentrations. However, it is not clear whether the total number of asunaprevir or daclatasvir samples that were reanalyzed represents 7% of the total number of samples that were initially analyzed.

For the AI447009 trial, in response to an information request, the applicant stated that the daclatasvir plasma samples were stored at the trial site at -20°C for up to 13 days and the bioanalytical laboratory at -20°C for up to 16 days and asunaprevir

For the TNJM09046 method, the generated long term stability data for asunaprevir or daclatasvir in EDTA anticoagulated plasma included stability data at-20°C for 153 days. For the AI447009 trial, the generated long term stability data appears to covers the duration of long term stability data necessary for asunaprevir or daclatasvir.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for asunaprevir or daclatasvir. For the noncompartmental analysis, asunaprevir or daclatasvir plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, and $AUC_{(0-tau)}$.

Statistical Analysis

Statistical analyses were conducted that included the following comparisons and

90% confidence intervals were derived for asunaprevir or daclatasvir when comparing asunaprevir 200 mg twice daily coadministered with daclatasvir 30 mg once daily (Treatment C-test arms) to asunaprevir 600 mg twice daily (Treatment A-reference arm), or daclatasvir 60 mg once daily (Treatment B-reference arms).

10. Results

10.1 Subject Demographics

Table 2-AI447009 subject demographics

```
                              BMS32/BMS32+BMS52    BMS52/BMS32+BMS52         Total
                                   N = 14               N = 14             N = 28
-----------------------------------------------------------------------------------------
AGE
  N                                   14                   14                 28
  MEAN                              35.3                 31.9               33.6
  MEDIAN                            36.5                 28.5               31.0
  MIN , MAX                 19 ,     49          21 ,     46          19 ,    49
  STANDARD DEVIATION              10.38                 7.90               9.22

AGE CATEGORIZATION (%)
  < 65                        14  (100.0)          14  (100.0)          28  (100.0)

GENDER (%)
  MALE                        12  ( 85.7)          13  ( 92.9)          25  ( 89.3)
  FEMALE                       2  ( 14.3)           1  (  7.1)           3  ( 10.7)

RACE (%)
  WHITE                        8  ( 57.1)           8  ( 57.1)          16  ( 57.1)
  BLACK/AFRICAN AMERICAN       5  ( 35.7)           6  ( 42.9)          11  ( 39.3)
  OTHER                        1  (  7.1)           0                    1  (  3.6)

ETHNICITY (%)
  HISPANIC/LATINO              3  ( 21.4)           2  ( 14.3)           5  ( 17.9)
  NOT HISPANIC/LATINO         11  ( 78.6)          12  ( 85.7)          23  ( 82.1)
```

10.2 Concomitant Medications

One subject received prune juice on multiple days during the trial which is not expected to significantly alter the conclusions of the trial. No other concomitant medications were administered in the trial.

10.3 Pharmacokinetic and Statistical Analysis

Asunaprevir

(b) (4)

Daclatasvir

Table 5-Daclastasvir multiple dosing pharmacokinetic parameters with daclatasvir 60 mg once daily and asunaprevir 200 mg twice daily combined with daclatasvir 30 mg once daily

Treatment (Study Day)	Cmax (ng/mL) Geo. Mean [N] (CV)	AUC(TAU) (ng•h/mL) Geo. Mean [N] (CV)	Cmin (ng/mL) Geo. Mean [N] (CV)	Tmax (h) Median [N] (Min - Max)
B	1567.20 [14] (24)	12964.68 [14] (25)	185.54 [14] (39)	1.50 [14] (1.0-3.0)
C				(b) (4)

Treatment B: BMS-790052 60 mg QD (N = 14).
Treatment C: BMS-650032 200 mg Q12h + BMS-790052 30 mg QD (N = 26).

> *Reviewer note: the C_{min} was defined as the plasma trough concentration 24 hours postdose.*

Table 6-Dose normalized statistical analyses for daclatasvir

Treatment	Cmax (ng/mL) Geo. Mean (CV)	AUC(TAU) (ng•h/mL) Geo. Mean (CV)	Cmin (ng/mL) Geo. Mean (CV)
B	1495.99 (24)	12704.04 (25)	163.22 (39)
C			(b) (4)
C vs. B	GMR (90% CI)	GMR (90% CI)	GMR(90% CI)
	1.069 (0.971,1.176)	1.202 (1.113,1.298)	1.330 (1.221,1.449)

Treatment B: BMS-790052 60 mg QD.
Treatment C: BMS-650032 200 mg Q12h + BMS-790052 30 mg QD normalized to 60 mg by multiplying 2.

10.4 Safety Analysis

No deaths occurred during the trial and one serious adverse event of elevated creatine phosphokinase was reported that resulted in discontinuation from the trial.

11. Discussion and Conclusions

Based on the results from the AI447009 trial, the following conclusions can be made.

- The trial results suggest that when comparing morning and evening doses at each dose level, the differences in asunaprevir exposure (b) (4)

- When daclatasvir exposure was dose normalized to 60 mg, the daclatasvir C_{min}, C_{max}, and $AUC_{(0-24h)}$ were increased by 33%, 7%, and 20%, respectively. Only the 90% confidence interval for daclatasvir C_{max} was within the standard "no effect" 90% confidence interval limits of 80%-125%.

However, it is important to note that based on the analyses that was conducted during the NDA review, dose proportionality was not observed for daclatasvir and dose proportionality could not be determined for asunaprevir. The trial results do not permit a definitive conclusion to be made regarding whether a dose adjustment for either asunaprevir or daclatasvir is necessary when coadministered together.

TMC435HPC1005 Trial

1. Title

A Phase 1, 2-panel, open-label, randomized, crossover trial in healthy subjects to investigate the pharmacokinetic interaction between simeprevir (i.e., TMC435) and the NS5A inhibitor daclatasvir (i.e., BMS-790052; DCV)

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted by Janssen Research & Development from May 12, 2011 to July 13, 2011.

3. Objectives

The primary objective was to evaluate the effect of:
- Steady-state concentrations of TMC435 on the steady-state pharmacokinetics of BMS-790052 in healthy subjects;
- Steady-state concentrations of BMS-790052 on the steady-state pharmacokinetics of TMC435 in healthy subjects.

The secondary objective was to explore short-term safety and tolerability following coadministration of TMC435 and BMS-790052 in healthy subjects.

4. Trial Design

The study was a Phase 1, 2-panel, open-label, randomized, 2-way crossover study in healthy subjects (**Figure 1**). Subjects were randomized within a panel. No randomization between panels took place.

Figure 1 – Schematic Overview of the Study

a) Panel 1 (n=18)   Session I   at least 7 days washout*   Session II

| Group 1 (n = 9) | Treatment A | → | Treatment B |
| Group 2 (n = 9) | Treatment B | → | Treatment A |

b) Panel 2 (n=24)

| Group 1 (n = 12) | Treatment C | → | Treatment D |
| Group 2 (n = 12) | Treatment D | → | Treatment C |
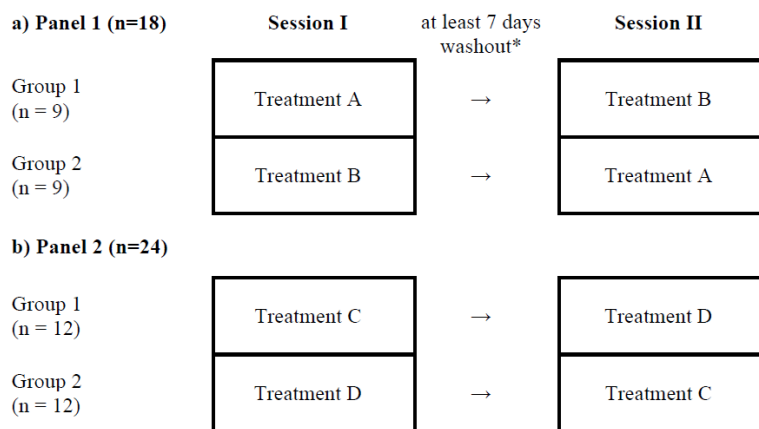
* Day 7 of a treatment session is the first day of the washout period

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Treatment A: BMS-790052 60 mg q.d. was administered for 7 days.
Treatment B, TMC435 150 mg q.d. and BMS-790052 60 mg q.d. were coadministered for 7 days.
Treatment C, TMC435 150 mg q.d. was administered for 7 days.
Treatment D, TMC435 150 mg q.d. and BMS-790052 60 mg q.d. were coadministered for 7 days.

Note: all oral administration were under fed condition.

5. Excluded Medications, Restrictions or Exceptions

All medication had to have been discontinued at least 14 days before the first intake of study drug (Day 1 of Session I), except for paracetamol (acetaminophen) or ibuprofen. Subjects could not use any other medication until the follow-up visit scheduled between 5-7 days after the last intake of study medication or after dropout except for paracetamol or ibuprofen. Subjects could also not use any systemic herbal medications or dietary supplements including products containing St. John's wort from 14 days before the first intake of study drug until the follow-up visit scheduled between 5-7 days after the last intake of study medication.

6. Rationale for Doses Used in the Trial

The dosage regimen of DCV (60 mg QD) and simeprevir (150 mg QD) are consistent with the recommended dosage regimen in the DCV and simeprevir U.S. prescribing information.

7. Drugs Used in the Trial

TMC435, 150 mg q.d. (G007), administered as 1 capsule of 150 mg (batch number: 11B03/G007).

BMS-790052, 60 mg q.d., administered as 2 tablets of 30 mg (batch number: 1B66991).

8. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

Table 1 - Sampling schedule

Treatments A, B, C, and D:

Day	Time (hours)	Blood Sample Drug[a]	Blood Sample Safety[b]	Urine Sample	Vital Signs[c]	ECG	Other[d]
-1							Admission to the unit; Physical examination; Urine drug screening (to include cotinine and alcohol); Serum pregnancy test (all women).
1		X[e,f]	X[e]	X[e]	X[e]	X[e]	Study medication intake[g].
2-3							Study medication intake[g].
4			X[e]				Study medication intake[g].
5		X[h]					Study medication intake[g].
6		X[h]					Study medication intake[g].
7	predose	X[h]	X[e]	X[e]	X[e]	X[e]	Standardized breakfast[i].
	0						Study medication intake[g,i].
	0.5	X					
	1	X					Resume water intake.
	1.5	X					
	2	X					
	3	X					
	4	X					Resume normal diet as provided by unit.
	5	X					
	6	X			X	X	
	9	X					
	12	X					
	16	X					
8	24	X	X	X	X	X	Physical examination; Discharge from unit.

[a] For determination of TMC435 and/or BMS-790052, as applicable.

[b] Hematology and biochemistry. Biochemistry sample had to be taken fasted for at least 10 hours. Coagulation was included in the predose safety sampling of Day 4 and Day 7.

[c] Blood pressure and pulse: supine after 5 minutes, standing after 1 minute.

[d] Adverse events and concomitant medication were monitored throughout the study from signing of the ICF onwards until last study-related visit.

[e] Within 2 hours before intake of study medication.

[f] In case Treatment A or C were given in Session 2, samples had to be taken for determination of both TMC435 and BMS-790052 to confirm complete washout.

[g] Treatment A: BMS-790052 60 mg q.d. for 7 days; Treatment B and D: coadministration of TMC435 150 mg q.d. and BMS-790052 60 mg q.d. for 7 days; Treatment C: TMC435 150 mg q.d. for 7 days. All intakes of study medication took place under fed conditions.

[h] Immediately before intake of study medication.

[i] Study medication had to be taken within 10 minutes of completing a standardized breakfast consisting of 4 slices of bread, 1 slice of ham, 1 slice of cheese, butter, jelly and 2 cups of decaffeinated coffee or tea with milk and/or sugar, if desired (containing approximately fat: 21 g, carbohydrates: 67 g, proteins: 19 g; Calories: 533). Standardized breakfast was to be ingested entirely within 30 minutes.

Bioanalytical method for DCV(BMS-790052)
The method and bioanalysis of DCV are acceptable.

Analyte	LLOQ (ng/mL)	ULOQ (ng/mL)	Between-run %CV[a]	Within-run %CV[a]	Mean %Deviation from Nominal Concentration[a]
BMS-790052	2.00	2000	≤ 3.5	≤ 2.8	± 3.7

a: Maximum value from analytical QCs.

Bioanalytical method for simeprevir (TMC435)

The method and bioanalysis of TMC435 are acceptable. TMC435 plasma samples were analyzed using a validated LC/MS/MS method in human EDTA plasma by $\qquad$ (b) (4)

The lower limit of quantification for TMC435 was 2.0 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for TMC435 based on the bioanalytical report. The precision and accuracy were evaluated using plasma TMC435 QC samples at four concentration levels: 2.0 ng/mL, 5.81 ng/mL, 76.1 ng/mL, and 1560 ng/mL.

Analyte interference evaluation showed that human plasma blanks had no interference on the quantification of TMC435.

All samples were analyzed within the time (1184 days) demonstrated long-term storage stability in human plasma at a freezer (-20 °C or colder).

Pharmacokinetic Assessments

Noncompartmental analysis was performed for DCV and simeprevir. The PK parameters assessed include t_{max}, C_{min}, C_{max}, $C_{ss,av}$, $AUC_{(24h)}$, AUC_{last}, and fluctuation index (*defined as percentage fluctuation (variation between maximum and minimum concentration at steady-state), calculated as: 100 x ([Cmax - Cmin] /Css,av).*

For drug-drug interaction assessment, Ratio C_{min},test/ref, Ratio C_{max},test/ref, and Ratio AUC_{24h},test/ref were calculated.

Statistical Analysis

. The primary PK parameters were Cmin, Cmax, and AUC24h,. All observations for test and reference, paired and unpaired, were included in the statistical analysis. The analysis was performed for each panel separately. For each panel, a linear mixed effects model was fitted on the log-transformed primary PK parameters of TMC435 (Panel 2) and BMS-790052 (Panel 1) with treatment, sequence, and period as fixed effects (factors) and subject as a random effect to estimate the least square (LS) means and intra-subject variance. Using these estimated LSmeans and intra-subject variance, the point estimate and 90% confidence intervals (CIs) for the difference in means on a log scale between Treatment B and

Treatment A (Panel 1) and between Treatment D and Treatment C (Panel 2) were constructed. The limits of the CIs were retransformed using antilogarithms to obtain 90% CIs for the ratios of the mean AUCs and Cmax of the test to reference formulation.

Period effects were considered significant at the level ≤ 5% and sequence effects were considered significant at the level ≤10%.

9. Results

9.1 Subject Demographics and Disposition

Table 2-Subject demographics

Demographic parameter	Panel 1			Panel 2		
	Treatment sequence A/B	Treatment sequence B/A	Total	Treatment sequence C/D	Treatment sequence D/C	Total
	N = 10	N = 9	N = 19	N = 12	N = 13	N = 25
Age at Screening, years						
Mean (SD)	34.3 (6.73)	32.8 (5.87)	33.6 (6.21)	30.8 (8.85)	39.8 (9.73)	35.5 (10.20)
Median (Range)	32.5 (26, 45)	32.0 (24, 45)	32.0 (24, 45)	28.0 (19, 47)	41.0 (23, 53)	36.0 (19, 53)
Weight, kg						
Mean (SD)	80.5 (7.88)	79.6 (7.37)	80.1 (7.44)	77.9 (9.16)	80.0 (13.08)	79.0 (11.19)
Median (Range)	81.5 (63, 92)	79.0 (65, 89)	81.0 (63, 92)	77.0 (63, 93)	79.0 (57, 99)	79.0 (57, 99)
Height, cm						
Mean (SD)	175.8 (4.26)	176.1 (8.02)	175.9 (6.14)	171.3 (8.53)	173.8 (10.07)	172.6 (9.26)
Median (Range)	176.0 (169, 182)	177.0 (166, 192)	177.0 (166, 192)	172.0 (159, 185)	175.0 (156, 192)	173.0 (156, 192)
BMI, kg/m²						
Mean (SD)	26.05 (2.395)	25.71 (2.512)	25.89 (2.388)	26.46 (1.365)	26.37 (2.790)	26.41 (2.179)
Median (Range)	26.70 (22.1, 29.4)	26.20 (20.3, 28.4)	26.30 (20.3, 29.4)	26.85 (23.1, 28.2)	26.30 (20.9, 29.6)	26.80 (20.9, 29.6)
Sex, n (%)						
Female	0	1 (11.1)	1 (5.3)	2 (16.7)	3 (23.1)	5 (20.0)
Male	10 (100)	8 (88.9)	18 (94.7)	10 (83.3)	10 (76.9)	20 (80.0)
Race, n (%)						
Asian	0	0	0	1 (8.3)	1 (7.7)	2 (8.0)
Black or African American	8 (80.0)	7 (77.8)	15 (78.9)	7 (58.3)	5 (38.5)	12 (48.0)
White	2 (20.0)	2 (22.2)	4 (21.1)	4 (33.3)	6 (46.2)	10 (40.0)
Multiple: Black or African American, White	0	0	0	0	1 (7.7)	1 (4.0)
Ethnicity, n (%)						
Hispanic or Latino	1 (10.0)	5 (55.6)	6 (31.6)	3 (25.0)	3 (23.1)	6 (24.0)
Not Hispanic or Latino	9 (90.0)	4 (44.4)	13 (68.4)	9 (75.0)	10 (76.9)	19 (76.0)
Country, n (%)						
USA	10 (100.0)	9 (100.0)	19 (100.0)	12 (100.0)	13 (100.0)	25 (100.0)
Type of Smoker, n (%)						
Nonsmoker	10 (100.0)	9 (100.0)	19 (100.0)	12 (100.0)	13 (100.0)	25 (100.0)

N = total numbers of subjects with data; n = number of events

9.2 Concomitant Medications

The concomitant medications that were administered in the trial are not expected to significantly alter the conclusions of the trial.

9.3 Pharmacokinetic and Statistical Analysis

Simeprevir (TMC435)

The linear mean plasma concentration-time profiles of TMC435 of Treatment B (Panel 1) and Treatments C and D (Panel 2) are presented in **Figure 2**.

Figure 2 - Mean Plasma Concentration-Time Curves of TMC435 (Including SD) After Administration of TMC435 Alone (Treatment C, Panel 2) and in Combination With BMS-790052 (Treatment B, Panel 1 and Treatment D, Panel 2)
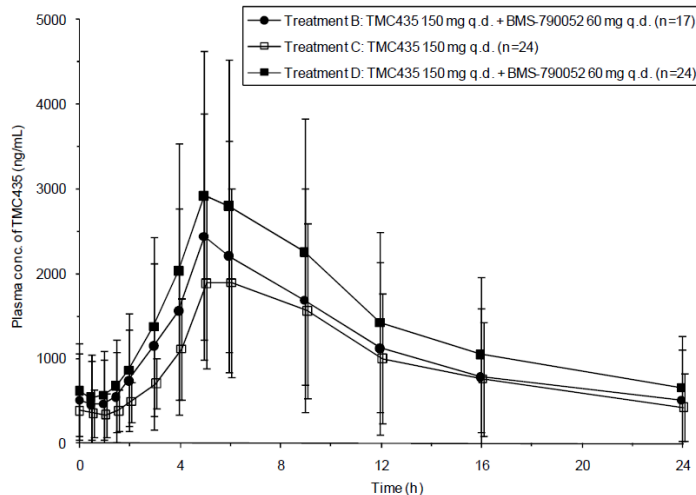
A summary list of key PK parameters of TMC435 for Treatments B, C and D is presented in **Table 3**.

Table 3 - PK Results of TMC435 After Administration of TMC435 Alone (Treatment C) and in Combination With BMS-790052 (Treatment B and D)

Pharmacokinetics of TMC435 (mean ± SD, t_{max}: median [range])	Treatment C: TMC435 150 mg q.d. (reference)			Treatment D: TMC435 150 mg q.d. + BMS-790052 60 mg q.d. (test)			Treatment B: TMC435 150 mg q.d. + BMS-790052 60 mg q.d.		
n		24			24			17[a]	
Day 5									
C_{0h}, ng/mL	356.5	±	253.4	570.3	±	424.0	461.1	±	374.3
Day 6									
C_{0h}, ng/mL	354.5	±	289.2	579.3	±	465.5	478.9	±	508.3
Day 7									
C_{0h}, ng/mL	384.1	±	300.7	615.7	±	565.1	507.2	±	548.8
C_{min}, ng/mL	317.1	±	250.8	533.5	±	497.3	439.4	±	508.1
C_{max}, ng/mL	2095	±	1109	3005	±	1741	2477	±	1422
t_{max}, h		5.0 (5.0 - 9.0)			5.0 (5.0 - 9.0)			5.0 (5.0 - 6.0)	
AUC_{24h}, ng.h/mL	22880	±	15410	34500	±	24890	26740	±	21920
$C_{ss,av}$, ng/mL	953.2	±	642.0	1437	±	1037	1114	±	913.1
Fluctuation index, %	213.3	±	55.48	205.0	±	61.96	211.6	±	57.77

[a] n=18 for Day 5

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The statistical results comparing the pharmacokinetics of TMC435 between test (TMC435 +BMS-790052, Treatment D) and reference treatment (TMC435 alone, Treatment C) in Panel 2 are presented in **Table 4**.

Table 4 – Summary of the Statistical Analysis of the Pharmacokinetic Parameters of TMC435 After Administration of TMC435 Alone at 150 mg q.d. (Treatment C) and in Combination With BMS-790052 at 60 mg q.d. (Treatment D) in Panel 2

| | LSmeans[a] | | | | p-value | |
Parameter	TMC435 150 mg q.d. (reference)	TMC435 150 mg q.d. + BMS-790052 60 mg q.d. (test)	LSmeans ratio	90% CI[b]	Period	Sequence
C_{min}, ng/mL	224.6	334.2	1.49	1.33 - 1.67	0.3015	0.7744
C_{max}, ng/mL	1844	2565	1.39	1.27 - 1.52	0.6805	0.8165
AUC_{24h}, ng.h/mL	18530	26610	1.44	1.32 - 1.56	0.3835	0.8551
	Median[a]				p-value	
Parameter	TMC435 150 mg q.d. (reference)	TMC435 150 mg q.d. + BMS-790052 60 mg q.d. (test)	Treatment difference median	90% CI, h[b]	Period	Sequence
t_{max}, h	5.0	5.0	0.00	(-0.50) - (0.50)	0.1959	0.1930

[a] n = 24 for reference and test
[b] 90% confidence intervals

After intake of TMC435 in the presence of BMS-790052, Cmin, Cmax, and AUC24h were 1.49, 1.39, and 1.44 fold higher, respectively, compared to after administration of TMC435 alone, based on the ratios of the LSmeans.

For tmax of TMC435, no treatment difference was observed.

No significant period or sequence effects were observed.

Daclatasvir (DCV, BMS-790052)

The linear mean plasma concentration-time profiles of BMS-790052 of Treatments A and B (Panel 1) and Treatment D (Panel 2) are presented in **Figure 3**.

Figure 3 - Mean Plasma Concentration-Time Curves of BMS-790052 (Including SD) After Administration of BMS-790052 Alone (Treatment A, Panel 1) and in Combination with TMC435 (Treatment B, Panel 1 and Treatment D, Panel 2)
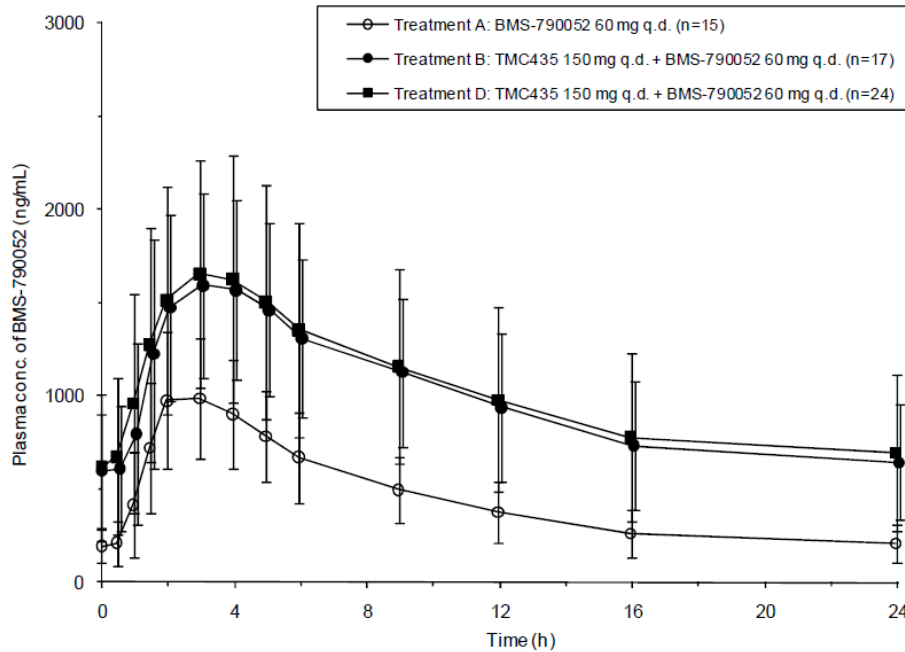
A summary list of key PK parameters of TMC435 for Treatments A, B, and D is presented in **Table 5**.

Table 5- PK Results of BMS-790052 After Administration of BMS-790052 Alone at (Treatment A, Panel 1) and in Combination With TMC435 (Treatment B & D)

Pharmacokinetics of BMS-790052 (mean ± SD, t_{max}: median [range])	Treatment A: BMS-790052 60 mg q.d. (reference)			Treatment B: TMC435 150 mg q.d. + BMS-790052 60 mg q.d. (test)			Treatment D: TMC435 150 mg q.d. + BMS-790052 60 mg q.d.		
n	15[a]			17[b]			24		
Day 5									
C_{0h}, ng/mL	232.7	±	111.7	584.4	±	275.0	656.7	±	375.5
Day 6									
C_{0h}, ng/mL	200.0	±	98.08	584.6	±	280.7	616.3	±	350.9
Day 7									
C_{0h}, ng/mL	192.4	±	90.06	598.1	±	303.3	616.8	±	391.5
C_{min}, ng/mL	181.3	±	87.87	577.9	±	297.9	592.3	±	370.9
C_{max}, ng/mL	1052	±	343.5	1685	±	508.4	1755	±	668.2
t_{max}, h	2.0 (1.5 - 4.0)			3.0 (1.5 - 4.0)			3.0 (1.0 - 4.0)		
AUC_{24h}, ng.h/mL	10680	±	4021	23450	±	9063	24590	±	11760
$C_{ss,av}$, ng/mL	444.9	±	167.5	976.9	±	377.6	1025	±	490.2
Fluctuation index, %	202.7	±	38.75	122.8	±	36.83	125.6	±	31.15

[a] n=16 for Day 5

[b] n=18 for Day 5

The statistical results comparing the pharmacokinetics of BMS-790052 between test (BMS-790052 + TMC435, Treatment B) and reference treatment (BMS-790052 alone, Treatment A) in Panel 1 are presented in **Table 6**.

Table 8- Summary of the Statistical Analysis of the PK Parameters of BMS 790052 After Administration of BMS-790052 Alone at 60 mg q.d. (Treatment A) and in Combination With TMC435 at 150 mg q.d. (Treatment B) in Panel 1

| Parameter | LSmeans[a] | | LSmeans ratio | 90% CI[c] | p-value | |
	BMS-790052 60 mg q.d. (reference)	BMS-790052 60 mg q.d. + TMC435 150 mg q.d. (test)			Period	Sequence
C_{min}, ng/mL	181.6	487.2	2.68	2.42 - 2.98	0.0347[*]	0.9003
C_{max}, ng/mL	1045	1568	1.50	1.39 - 1.62	0.6513	0.6479
AUC_{24h}, ng.h/mL	10770	21150	1.96	1.84 - 2.10	0.1145	0.6304

| Parameter | Median[b] | | Treatment difference median | 90% CI, h[c] | p-value | |
	BMS-790052 60 mg q.d. (reference)	BMS-790052 60 mg q.d. + TMC435 150 mg q.d. (test)			Period	Sequence
t_{max}, h	3.0	2.0	0.00	(0.00) - (0.75)	0.1751	0.9447

[a] n=17 for test and n=15 for reference

[b] n=14 for test and reference

[c] 90% confidence intervals

[*] Statistically significant difference

After intake of BMS-790052 in the presence of TMC435, Cmin, Cmax, and AUC24h were, respectively, 2.68, 1.50, and 1.96 fold higher compared to after administration of BMS-790052 alone, based on the ratios of the LSmeans.

For tmax of BMS-790052, no treatment difference was observed.

A significant period effect was observed for Cmin, however, this was not considered to impact the overall outcome of the study, as a randomized cross-over design was applied. No significant sequence effects were observed.

9.4 Safety Analysis

No deaths or other SAEs were reported in this study. Except for 1 subject (5.3%) in Panel 1 with a grade 1 AE (lipase increased) and a grade 3 AE (blood amylase increased) leading to discontinuation during coadministration of TMC435 and BMS-790052, no AEs leading to permanent discontinuation or grade 3 or 4 AEs were reported during this study.

10. Sponsor's Conclusions

After the combined intake of simeprevir (TMC435) and daclatasvir (BMS-790052), Cmin, Cmax, and AUC24h were 1.49, 1.39, and 1.44 fold higher, respectively, for TMC435 and 2.68, 1.50 and 1.96 fold higher, respectively, for BMS-790052, compared to after intake of the compounds alone, based on the ratios of the LSmeans.

For tmax of TMC435 and BMS-790052, no treatment difference was observed.

The combination of TMC435 150 mg q.d. and BMS-790052 60 mg q.d. was generally safe and well tolerated in healthy subjects.

11. Reviewer's Assessment

The TMC435HPC1005 trial adequately evaluated the drug-drug interaction potential when simeprevir and daclatasvir are coadministered. The sponsor's conclusions are valid.

Given the magnitude of increase in DCV Cmin, Cmax and AUC24h (ranging from 1.5 fold to 1.96 fold) when coadministered with simeprevir 150 mg in healthy subjects, a dose reduction (e.g. from 60 mg to 30 mg) for DCV may be considered when DCV is coadministered with simeprevir in patients.

Food effect trial-asunaprevir

Trial Number	Title	Page Number
		(b) (4)

Food effect trial-daclatasvir

Trial Number	Title	Page Number
AI444039	Bioavailability of BMS-790052 Phase 3 (b) (4) Tablet Relative to Phase 2 (b) (4) Tablet and the Effect of a High Fat Meal and Light Meal on the Pharmacokinetics of BMS-790052 when Administered as the Phase 3 (b) (4) Tablet in Healthy Subjects	122

(b) (4)

1. Title

Study to Assess the Effects of a High-Fat Meal on the Bioavailability of the 100 mg (b) (4) Formulation of Asunaprevir in Healthy Subjects

(b) (4)

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Hepatic impairment trial-daclatasvir

Trial Number	Title	Page Number
AI444013	Single-Dose Pharmacokinetics of BMS-790052 in Subjects with Hepatic Impairment Compared to Healthy Subjects	347

1. Title

Multiple-Dose Pharmacokinetics of BMS-650032 in Subjects with Hepatic Impairment Compared to Healthy Subjects

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<u>AI444013</u>

1. Title

Single-Dose Pharmacokinetics of BMS-790052 in Subjects with Hepatic Impairment Compared to Healthy Subjects

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at multiple sites from March 31, 2009 (trial initiation) to September 22, 2009 (trial completion).

3. Objectives

The objectives of the trial included evaluating the single dose pharmacokinetics of daclatasvir in subjects with hepatic impairment.

4. Trial Design

AI444013 was an open label clinical trial that enrolled hepatically impaired subjects (Child Pugh class A, B, or C) or healthy subjects 18 to 70 years old. Information on the trial design is displayed in Figure 1.

Figure 1-AI444013 trial design
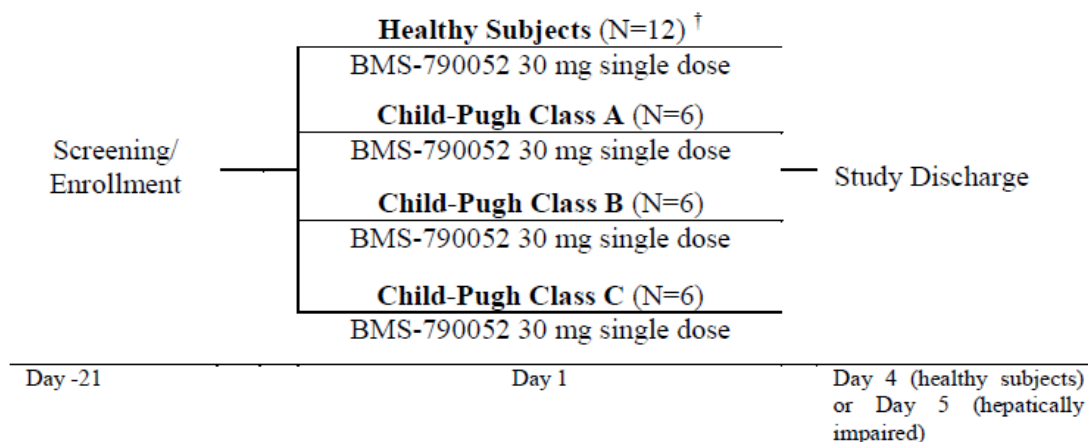
BMS-790052 will be administered under fasted conditions.

[†] Four (4) healthy subjects will be matched (1:1) to the first 4 hepatically impaired subjects in each Child-Pugh class.

5. Excluded Medications, Restrictions or Exceptions

For hepatically impaired subjects, the protocol excluded the use of specific medications. In healthy subjects, unless otherwise approved, prescription medications were not permitted within 4 weeks prior to medication administration. Nonprescription

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medications, including herbal products, were not permitted within 2 weeks prior to medication administration; however the trial allowed for exceptions in hepatically impaired subjects. In general, for healthy subjects, prescription and nonprescription medications, including herbal products, were not permitted during the trial. Hepatically impaired subjects were allowed to receive medications for the treatment of cirrhosis.

6. Dosage and Administration

The trial arms, including the doses that were administered, are specified in Figure 1. Daclatasvir was administered under fasted conditions after fasting for 10 hours.

7. Rationale for Doses Used in the Trial

The daclatasvir single dose of 30 mg was selected to account for potential safety issues in hepatically impaired subjects with increased daclatasvir exposure.

8. Drugs Used in the Trial

Information regarding the daclatasvir formulation that was administered in the trial is displayed in Table 1.

Table 1-Information on the daclatasvir formulation administered in the AI444013 trial

Drug Product	Formulation	Product Identification Number	Product Batch Number
BMS-790052-05, 10 mg	Capsule	790052-R010-005	8K42126

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood samples that were obtained included daclatasvir blood samples at predose and up to 96 hours postdose in heptically impaired subjects and up to 72 hours postdose in healthy subjects.

Bioanalysis

The method and bioanalysis of daclatasvir are acceptable. Daclatasvir plasma samples were analyzed using a validated LC/MS/MS method in EDTA anticoagulated plasma by (b) (4) (TNJM08199.00). The blood samples for analysis of daclatasvir appear to have been collected in tubes containing K_2EDTA.

For the AI444013 plasma samples that were analyzed for daclatasvir, the lower limit of quantification for daclatasvir was 0.5 ng/mL and the upper limit of quantification was

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500 ng/mL. There were no precision or accuracy issues identified for daclatasvir based on the bioanalytical report. For the AI444013 trial, precision and accuracy were evaluated using plasma daclatasvir quality control (QC) samples at 1.5 ng/mL, 20 ng/mL, 200 ng/mL and 400 ng/mL. The corresponding daclatasvir inter-run accuracy values were 4% for 1.5 ng/mL, 4% for 20 ng/mL, 7% for 200 ng/mL and 2.3% for 400 ng/mL. The daclatasvir inter-run precision values were 8% for 1.5 ng/mL, 4.9% for 20 ng/mL, 3.8% for 200 ng/mL and 4.4% for 400 ng/mL. In addition, for the daclatasvir dilution QC samples at 5000 ng/mL (with dilution factors ranging from 10 to 20), the inter-run accuracy ranged from -2% to -6.4% and inter-run precision ranged from 0.9% to 6.2%.

For the plasma protein binding method, daclatasvir plasma samples were analyzed using a validated LC/MS/MS method in EDTA anticoagulated plasma by ⬚ (b) (4) (TNJM08147.00). For the AI444013 plasma protein binding samples that were analyzed for daclatasvir, the lower limit of quantification for daclatasvir was 0.05 ng/mL and the upper limit of quantification was 50 ng/mL. There were no precision or accuracy issues identified for daclatasvir based on the bioanalytical report. For the AI444013 trial, precision and accuracy were evaluated using plasma daclatasvir quality control (QC) samples at 0.150 ng/mL, 2 ng/mL, 20 ng/mL and 40 ng/mL. The corresponding daclatasvir inter-run accuracy values were 6% for 0.150 ng/mL, 6% for 2 ng/mL, 5.5% for 20 ng/mL and 5.8% for 40 ng/mL. The daclatasvir inter-run precision values were 5.8% for 0.150 ng/mL, 5.6% for 2 ng/mL, 4.6% for 20 ng/mL and 5.3% for 40 ng/mL. In addition, for the daclatasvir dilution QC samples at 200 ng/mL, the inter-run accuracy was 0% and inter-run precision was 6.1%.

Of the samples selected for incurred sample reanalysis for daclatasvir (total number less than 50) using method TNJM08199.00, two samples were not within 20% using the percentage values of the repeat and original concentrations. However, it is not clear whether the total number of daclatasvir samples that were reanalyzed represents 7% of the total number of samples that were initially analyzed.

For the AI444013 trial, in response to an information request, the applicant stated that the daclatasvir plasma samples were stored at the trial site at -20°C for up to 50 days, at -20°C for up to 109 days at the central laboratory and the bioanalytical laboratory at -20°C for up to 15 days. For the TNJM08199.00 method, the generated long term daclatasvir stability data included stability data in EDTA anticoagulated plasma at -20°C for 385 days. For the AI444013 trial, the generated long term stability data appears to covers the duration of long term stability data necessary for daclatasvir.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for daclatasvir. For the noncompartmental analysis, daclatasvir plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, and $AUC_{(0-inf)}$.

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Statistical Analysis

The statistical analyses included comparing each hepatic impairment group to the corresponding matched controls group and 90% confidence intervals were derived.

10. Results

10.1 Subject Demographics

Table 2A-AI444013 subject demographics (hepatic impairment groups)

	BMS Chld Pgh A N = 6		BMS Chld Pgh B N = 6		BMS Chld Pgh C N = 6		Group ABC Hepatic N = 18	
AGE								
N		6		6		6		18
MEAN		47.7		57.3		53.0		52.7
MEDIAN		46.5		58.5		53.5		52.5
MIN , MAX	41 ,	58	47 ,	65	42 ,	68	41 ,	68
STANDARD DEVIATION		6.41		6.83		8.94		8.12
AGE CATEGORIZATION (%)								
< 65	6	(100.0)	5	(83.3)	5	(83.3)	16	(88.9)
>= 65	0		1	(16.7)	1	(16.7)	2	(11.1)
GENDER (%)								
MALE	4	(66.7)	3	(50.0)	4	(66.7)	11	(61.1)
FEMALE	2	(33.3)	3	(50.0)	2	(33.3)	7	(38.9)
RACE (%)								
WHITE	5	(83.3)	6	(100.0)	6	(100.0)	17	(94.4)
BLACK/AFRICAN AMERICAN	0		0		0		0	
AMERICAN INDIAN/ALASKA NATIVE	0		0		0		0	
OTHER	1	(16.7)	0		0		1	(5.6)
ETHNICITY (%)								
HISPANIC/LATINO	2	(33.3)	1	(16.7)	2	(33.3)	5	(27.8)
NOT HISPANIC/LATINO	4	(66.7)	5	(83.3)	4	(66.7)	13	(72.2)

Table 2B-AI444013 subject demographics (matched comtrol groups)

	BMS Control A N = 4		BMS Control B N = 4		BMS Control C N = 4		Control ABC Healthy N = 12	
AGE								
N		4		4		4		12
MEAN		50.8		51.5		52.5		51.6
MEDIAN		49.5		53.0		56.5		51.0
MIN , MAX	46 ,	58	38 ,	62	34 ,	63	34 ,	63
STANDARD DEVIATION		5.12		12.37		13.23		9.86
AGE CATEGORIZATION (%)								
< 65	4	(100.0)	4	(100.0)	4	(100.0)	12	(100.0)
GENDER (%)								
MALE	3	(75.0)	1	(25.0)	3	(75.0)	7	(58.3)
FEMALE	1	(25.0)	3	(75.0)	1	(25.0)	5	(41.7)
RACE (%)								
WHITE	4	(100.0)	3	(75.0)	3	(75.0)	10	(83.3)
BLACK/AFRICAN AMERICAN	0		0		1	(25.0)	1	(8.3)
AMERICAN INDIAN/ALASKA NATIVE	0		1	(25.0)	0		1	(8.3)
ETHNICITY (%)								
HISPANIC/LATINO	1	(25.0)	2	(50.0)	3	(75.0)	6	(50.0)
NOT HISPANIC/LATINO	3	(75.0)	2	(50.0)	1	(25.0)	6	(50.0)

Reference ID: 3615478

10.2 Concomitant Medications

The concomitant medications that were administered in the trial included medications that subjects were receiving prior to the trial in the hepatically impaired groups and ibuprofen in the control groups. The conclusions of the trial are not expected to be significantly altered by the concomitant medications that were administered in the trial.

10.3 Pharmacokinetic and Statistical Analysis

Table 3-Daclatasvir pharmacokinetic parameters in hepatically impaired subjects and control groups

Child-Pugh Class	Cmax (ng/mL) Geo.Mean (%CV)	AUC(0-T) (ng•h/mL) Geo.Mean (%CV)	AUC(INF) (ng•h/mL) Geo.Mean (%CV)	Tmax (h) Median (Min - Max)	T-HALF (h) Mean (SD)	CLT/F (mL/min) Geo.Mean (CV)	CLu/F (mL/min) Geo.Mean (CV)	Vss/F (mL) Geo. Mean (CV)
A (N = 6)	380 (44)	4151 (43)	4174 (43)	1.5 (1 - 2)	12.3 (2.49)	120 (85)	19529 (66)	98557 (67)
B (N = 6)	382 (23)	4490 (38)	4550 (39)	1.0 (1 - 4)	15.0 (4.59)	110 (47)	12028 (52)	111612 (24)
C (N = 6)	317 (65)	4534 (74)	4649 (78)	1.5 (1 - 4)	17.2 (10.55)	108 (78)	12468 (61)	123034 (56)
A+B+C (N = 18)	358 (44)	4388 (56)	4453 (59)	1.3 (1 - 4)	14.8 (6.71)	112 (71)	14307 (66)	110614 (51)
CA (N = 4)	808 (35)	7057 (30)	7145 (31)	1.0 (1-2)	11.7 (1.53)	70 (34)	14696 (18)	58983 (26)
CB (N = 4)	670 (23)	6841 (31)	6952 (32)	1.3 (1-2)	12.2 (3.50)	72 (35)	11619 (44)	61727 (24)
CC (N = 4)	627 (24)	7621 (17)	7786 (18)	1.5 (1-2)	13.1 (1.52)	64 (17)	9612 (25)	63113 (11)
CA+CB+CC (N = 12)	698 (30)	7165 (24)	7286 (25)	1.3 (1-2)	12.4 (2.23)	69 (29)	11796 (33)	61250 (19)

Note: A = Child-Pugh Class A Hepatic Impairment; CA = Matching Healthy Control for A; B = Child-Pugh Class B Hepatic Impairment; CB = Matching Healthy Control for B; C = Child-Pugh Class C Hepatic Impairment; CC = Matching Healthy Control for C

Reference ID: 3615478

Table 4-Daclatasvir pharmacokinetic parameters using unbound concentrations in hepatically impaired subjects and control groups

Child-Pugh Class	Cmax$_u$ (ng/mL) Geo. Mean (CV)	AUC(INF)$_u$ (ng•h/mL) Geo. Mean (CV)
A (N=6)	2.33 (55)	25.60 (67)
B (N=6)	3.49 (42)	41.57 (42)
C (N=6)	2.73 (74)	40.10 (78)
A+B+C (N=18)	2.81 (56)	34.95 (66)
CA (N=4)	3.85 (21)	34.02 (20)
CB (N=4)	4.15 (34)	43.03 (43)
CC (N=4)	4.19 (36)	52.02 (26)
CA+CB+CC (N=12)	4.06 (29)	42.39 (35)

Note: A = Child-Pugh Class A Hepatic Impairment; CA = Matching Healthy Control for A; B = Child-Pugh Class B Hepatic Impairment; CB = Matching Healthy Control for B; C = Child-Pugh Class C Hepatic Impairment; CC = Matching Healthy Control for C

Reference ID: 3615478

Table 5-Daclatasvir statistical analyses for hepatically impaired subjects and control groups

Treatment and Comparison	Cmax (ng/mL) Adjusted Geo.Mean	AUC(INF) (ng•h/mL) Adjusted Geo.Mean	AUC(0-T) (ng•h/mL) Adjusted Geo.Mean
A	379.97	4174.39	4150.84
Control	697.65	7285.52	7165.37
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
A vs. Control	0.545(0.380,0.781)	0.573(0.400,0.820)	0.579(0.405,0.829)
B	382.01	4549.69	4490.05
Control	697.65	7285.52	7165.37
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
B vs. Control	0.548(0.430,0.698)	0.624(0.470,0.830)	0.627(0.474,0.828)
C	317.01	4649.18	4533.83
Control	697.65	7285.52	7165.37
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
C vs. Control	0.454(0.301,0.685)	0.638(0.397,1.025)	0.633(0.399,1.004)
(A+B+C)	358.34	4452.98	4388.18
Control	697.65	7285.52	7165.37
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
(A+B+C) vs. Control	0.514(0.385,0.685)	0.611(0.440,0.850)	0.612(0.443,0.847)

Table 6-Daclatasvir protein binding and free fraction

Hepatic Function Group	Mean (SD) fu at 1 hr	Mean (SD) % PB at 1 hr	Mean (SD) fu at 4 hr	Mean (SD) % PB at 4 hr	Mean (SD) fu for all time points	Mean (SD) %PB for all time points
A (N = 6)	0.0068 (0.00192)	99.32 (0.192)	0.0061 (0.00226)	99.39 (0.226)	0.0064 (0.00204)	99.36 (0.204)
B (N = 6)	0.0094 (0.00207)	99.06 (0.207)	0.0096 (0.00378)	99.04 (0.378)	0.0095 (0.00268)	99.05 (0.268)
C (N = 6)	0.0101 (0.00448)	98.99 (0.448)	0.0103 (0.00500)	98.97 (0.500)	0.0102 (0.00465)	98.98 (0.465)
A+B+C (N = 18)	0.0088 (0.00323)	99.12 (0.323)	0.0086 (0.00409)	99.14 (0.409)	0.0087 (0.00354)	99.13 (0.354)
CA (N = 4)	0.0053 (0.00122)	99.47 (0.122)	0.0044 (0.00105)	99.56 (0.105)	0.0048 (0.00105)	99.52 (0.105)
CB (N = 4)	0.0063 (0.00146)	99.37 (0.146)	0.0064 (0.00191)	99.36 (0.191)	0.0064 (0.00167)	99.36 (0.167)
CC (N = 4)	0.0064 (0.00075)	99.36 (0.075)	0.0071 (0.00140)	99.29 (0.140)	0.0067 (0.00107)	99.33 (0.107)
CA+CB+CC (N = 12)	0.0060 (0.00119)	99.40 (0.119)	0.0060 (0.00181)	99.40 (0.181)	0.0060 (0.00145)	99.40 (0.145)

Figure 2-Daclatasvir AUC(0-inf) versus albumin concentrations
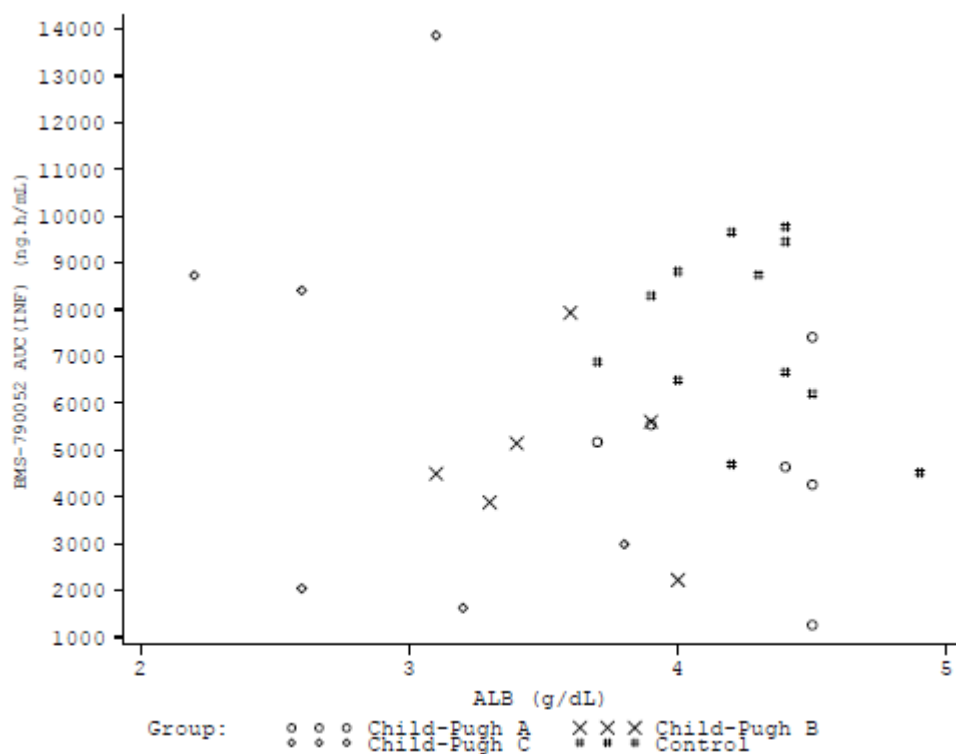
Figure 3-Daclatasvir free fraction versus albumin concentrations
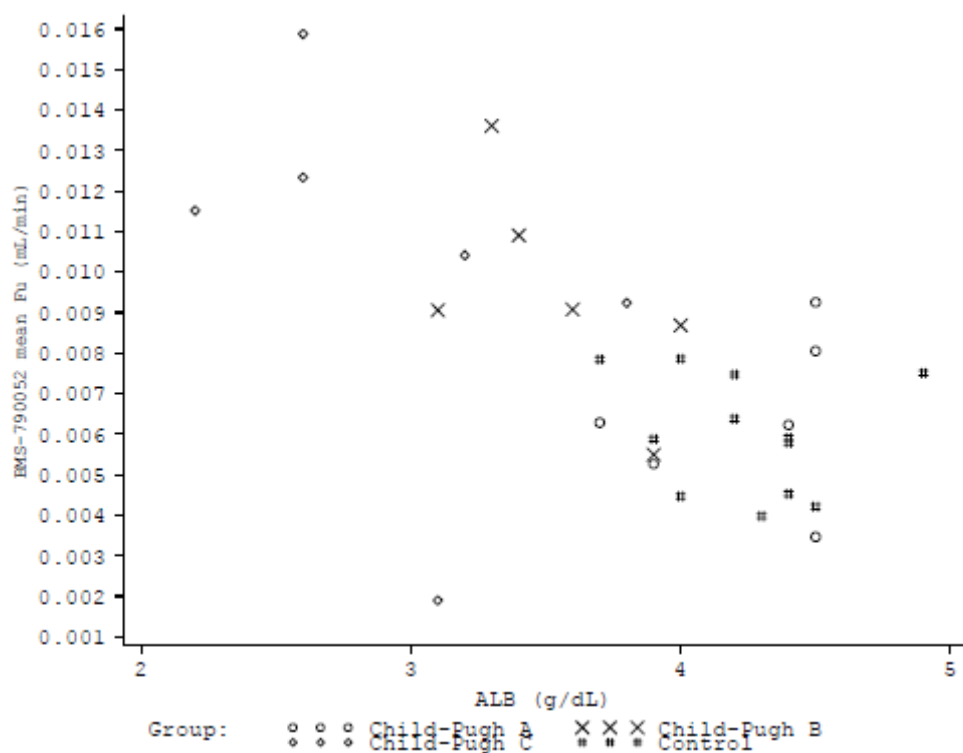
Reference ID: 3615478

10.4 Safety Analysis

No deaths, serious adverse events or adverse events resulting in discontinuation were reported for the trial.

11. Discussion and Conclusions

Based on the results from the AI444013 trial, the following conclusions can be made.

- When a single dose of daclatasvir 30 mg was administered, the following changes in daclatasvir exposure were observed when compared to the corresponding matched control group:
  – Child Pugh A: C_{max} and $AUC_{(0-inf)}$ decreased by 45.5% and 42.7%, respectively.
  – Child Pugh B: C_{max} and $AUC_{(0-inf)}$ decreased by 45.2% and 37.6%, respectively.
  – Child Pugh C: C_{max} and $AUC_{(0-inf)}$ decreased by 54.6% and 36.2%, respectively.

  For all parameters in all categories of hepatic impairment, none of the 90% confidence intervals were within 80% to 125%.
- An increased free fraction was observed for hepatically impaired subjects in Child Pugh categories A, B and C compared to the corresponding matched control group at each measured time point.
- No discernable relationship was observed when comparing either daclatasvir $AUC_{(0-inf)}$ versus albumin concentrations or daclatasvir free fraction versus albumin concentrations.

Overall, decreases in total daclatasvir exposure were observed in all categories of hepatic impairment that were evaluated (Child Pugh A, B and C). Based on the available information from this trial and the daclatasvir exposure-response analysis, dosage adjustments are not necessary to compensate for the changes in total daclatasvir exposure.

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Mass balance trial-asunaprevir

(b) (4)

Mass balance trial-daclatasvir

Trial Number	Title	Page Number
AI444006	Pharmacokinetics and Metabolism of [14C]-labeled BMS-790052 in Healthy Male Subjects	367

356

1. Title

Pharmacokinetics and Metabolism of [14C] BMS-650032 in Healthy Male Subjects

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<u>AI4444006</u>

1. Title

Pharmacokinetics and Metabolism of [14C]-labeled BMS-790052 in Healthy Male Subjects

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at one site from September 19, 2008 (trial initiation) to October 17, 2008 (trial completion).

3. Objectives

The objectives of the trial included evaluating the metabolism of daclatasvir.

4. Trial Design

AI444006 was an open label clinical trial that enrolled healthy male subjects 18 to 45 years old. Information on the trial design is displayed in Figure 1.

Figure 1-AI444006 trial design
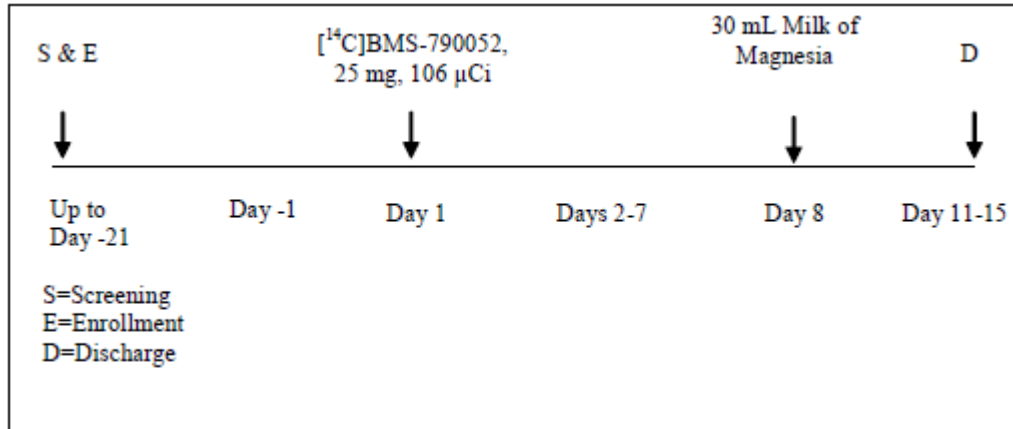
5. Excluded Medications, Restrictions or Exceptions

Unless otherwise approved, prescription medications were not permitted within 4 weeks and prescription and nonprescription acid modifying medications and nonprescription medications, including herbal products, were not permitted within 2 weeks prior to medication administration. In general, prescription and nonprescription medications, including herbal products, were not permitted during the trial.

6. Dosage and Administration

The trial design, including the daclatasvir dose that was administered, is specified in Figure 1. The single 25 mg daclatasvir oral dose was administered under fasted conditions after fasting for 10 hours. For daclatasvir, the applicant is proposing to administer the medication with or without food.

7. Rationale for Doses Used in the Trial

The daclatasvir single dose of 25 mg was selected based on the anticipated range of therapeutic daclatasvir dosage regimens.

8. Drugs Used in the Trial

Information regarding the daclatasvir formulation that was administered in the trial is displayed in Table 1.

Table 1-Information on the daclatasvir formulation administered in the AI444006 trial

Drug Product	Product Identification Number	Label Batch Number	Product Batch Number
[^{14}C] BMS-790052 for oral solution 25 mg/vial (as the free base)	790052-H025-002	8H32779	8H34387

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood samples that were obtained included daclatasvir samples at predose and up to 144 hours postdose. Both blood and plasma daclatasvir concentrations were measured for total radioactivity at predose and up to 144 hours postdose. Samples were also collected at predose and up to 240 hours postdose to evaluate daclatasvir metabolites. Urine and fecal samples were also collected up to 240 hours.

Bioanalysis

The total radioactivity was measuring using liquid scintillation counting. The measurement of the radioactivity will not be discussed in detail as part of this review.

The method and bioanalysis of daclatasvir are acceptable. Daclatasvir plasma samples were analyzed using a validated LC/MS/MS method in K_2EDTA anticoagulated plasma by BMS (method validated under study number TSLS08-229). The blood samples for analysis of daclatasvir appear to have been collected in tubes containing K_2EDTA.

For the AI444006 plasma samples that were analyzed for daclatasvir, the lower limit of quantification for daclatasvir was 0.5 ng/mL and the upper limit of quantification was 500 ng/mL. There were no precision or accuracy issues identified for daclatasvir based on the bioanalytical report. For the AI444006 trial, precision and accuracy were evaluated using plasma daclatasvir quality control (QC) samples at 1.5 ng/mL, 20 ng/mL, 200 ng/mL and 400 ng/mL. The corresponding daclatasvir inter-run accuracy values were 5.3% for 1.5 ng/mL, 2% for 20 ng/mL, 1% for 200 ng/mL and 0% for 400 ng/mL. The daclatasvir inter-run precision values were 2.8% for 1.5 ng/mL, 5.2% for 20 ng/mL,.2.6% for 200 ng/mL and 4.9% for 400 ng/mL. In addition, for the daclatasvir dilution QC samples at 5000 ng/mL, the inter-run accuracy and precision were 6.8% and 4.4%, respectively.

For the AI444006 trial, in response to an information request, the applicant stated that the daclatasvir plasma samples were stored at the trial site at -20°C for up to 22 days, and the bioanalytical laboratory at -70°C for up to 35 days. For the daclatasvir method validated under study number TSLS08-229, there were no separate long term stability experiments that were conducted. Instead, the method validation report references the method validated under study number TNJS07-177a. The method validated under study number TNJS07-177a conducted long term stability experiments in EDTA anticoagulated plasma at -20°C for 387 days and -70°C for 7 days (of note, long term stability for the 0.15 ng/mL QC failed at -70°C for 14 days). There is insufficient long term stability data generated at -70°C for the method validated under study number TSLS07-177a. However, for daclatasvir in general, assuming that any method differences do not impact stability, there appears to be sufficient long term stability data generated by other methods at -70°C (e.g. 44 days of -80°C daclatasvir long term stability data validated in K_2EDTA anticoagulated plasma under study number TNJS11-132) to support the daclatasvir concentration data.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for daclatasvir. For the noncompartmental analysis, plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, and AUC.

10. Results

10.1 Subject Demographics

Table 2-AI444006 subject demographics

```
-------------------------------------------------
                                 BMS-790052 25 MG
                                     N = 6
-------------------------------------------------
AGE
  N                                      6
  MEAN                                  29.8
  MEDIAN                                27.0
  MIN , MAX                      23 ,    42
  STANDARD DEVIATION                     7.25

AGE CATEGORIZATION (%)
  < 65                             6  (100.0)

GENDER (%)
  MALE                             6  (100.0)

RACE (%)
  WHITE                            1  ( 16.7)
  BLACK/AFRICAN AMERICAN           4  ( 66.7)
  ASIAN                            1  ( 16.7)

ETHNICITY (%)
  HISPANIC/LATINO                  1  ( 16.7)
  NOT HISPANIC/LATINO              5  ( 83.3)
```

10.2 Concomitant Medications

No concomitant medications were administered in the trial.

10.3 Pharmacokinetic and Statistical Analysis

Table 3-Single dosing plasma daclatasvir pharmacokinetic parameters with 25 mg oral dosing of radiolabeled daclatasvir

Cmax (ng/mL) geo. mean (CV)	AUC(0-T) (ng/mL) geo. mean (CV)	AUC(INF) (ng.h/mL) geo. mean (CV)	Tmax (h) median (min-max)	T-HALF (h) mean (SD)	CLT/F (mL/min) geo. mean (CV)
532	4677	4692	1.25	10.38	88.8
(37)	(29)	(29)	(0.5-3.0)	(1.99)	(25)

Note: N = 6 for all pharmacokinetic parameters
Abbreviations: AUC = area under the concentration time curve; CLT/F = apparent total body clearance; Cmax = maximum observed concentration; CV = coefficient of variation of geo = geometric; h = hour; INF = infinite time; T-HALF = terminal phase half life; Tmax = time to maximum observed concentration

Table 4-Total radioactivity plasma single dosing daclatasvir pharmacokinetic parameters with 25 mg oral dosing of radiolabeled daclatasvir

Cmax (ng-equiv/mL) Geo. Mean (CV)	AUC(0-T) (ng-equiv.h/mL) Geo. Mean (CV)	AUC(INF) (ng-equiv.h/mL) Geo. Mean (CV)	Tmax (h) Median (Min-Max)	T-HALF (h) Mean (SD)	CLT/F (mL/Min) Geo. Mean (CV)	AUC(BMS-790052)/ AUC(TRA) (%) Geo. Mean (CV)	%UR Mean (SD)	%FE Mean (SD)	%TOTAL Mean (SD)
574	4906	4932	1.00	12.2	84.5	95.1	6.61	87.7	94.3
(30)	(30)	(29)	(1.0-3.0)	(2.61)	(25)	(1)	(2.39)	(2.82)	(1.64)

Note: N = 6 for all pharmacokinetic parameters

Abbreviations: AUC = area under the concentration time curve; CLT/F = apparent total body clearance; Cmax = maximum observed concentration; CV = coefficient of variation; h = hour; INF = infinite time; Min = minimum; Max = maximum; SD = standard deviation; T-HALF = terminal phase half life; Tmax = time to maximum observed concentration; TRA = total radioactivity; %FE = percent of TRA excreted in feces; %UR = percent of TRA excreted in urine; %TOTAL = percent of TRA recovered.

Table 5-Total radioactivity blood single dosing daclatasvir pharmacokinetic parameters with 25 mg oral dosing of radiolabeled daclatasvir

Cmax (ng-equiv/ mL) Geo. Mean (CV)	AUC(0-T) (ng-equiv.h/ mL) Geo.Mean (CV)	AUC(INF) (ng-equiv.h/ mL) Geo.Mean (CV)	Tmax (h) Median (Min-Max)	T-HALF (h) Mean (SD)	CLT/F (mL/min) Geo.Mean (CV)	Plasma AUC(TRA)/ Blood AUC(TRA) (%) Geo.Mean (CV)
357	2199	2781	1.25	5.38	150	177
(26)	(27)	(25)	(0.5-3.0)	(0.85)	(22)	(4)

Note: N = 6 for all pharmacokinetic parameters
Abbreviations: AUC = area under the concentration time curve; CLT/F = apparent total body clearance; Cmax = maximum observed concentration; CV = coefficient of variation; h = hour; INF = infinite time; Min = minimum; Max = maximum; SD = standard deviation; T-HALF = terminal phase half life; Tmax = time to maximum observed concentration; TRA = total radioactivity

Table 6-Total radioactivity recovered in feces and urine with 25 mg oral single dosing of radiolabeled daclatasvir

Collection Interval	Urine				Feces			
	Amount Recovered (% of Dose)		Cumulative Amount Recovered (% of Dose)		Amount Recovered (% of Dose)		Cumulative Amount Recovered (% of Dose)	
	n[a]	Mean (SD)	n[b]	Mean (SD)	n[a]	Mean (SD)	n[b]	Mean (SD)
Pre-Dose	N/A	N/A	6	0.0 (0.00)	N/A	N/A	6	0.0 (0.00)
0 - 24 hours[c]	6	5.66 (1.93)	6	5.66 (1.93)	4	12.77 (18.13)	6	8.51 (15.51)
24 - 48 hours	6	0.81 (0.37)	6	6.47 (2.28)	6	46.06 (26.14)	6	54.58 (29.42)
48 - 72 hours	4	0.21 (0.10)	6	6.61 (2.39)	5	19.18 (13.93)	6	70.56 (16.29)
72 - 96 hours	N/A	N/A	6	6.61 (2.39)	6	13.66 (14.74)	6	84.23 (2.81)
96 - 120 hours	N/A	N/A	6	6.61 (2.39)	5	2.5 (2.60)	6	86.31 (2.33)
120 - 144 hours	N/A	N/A	6	6.61 (2.39)	6	0.78 (0.89)	6	87.09 (2.74)
144 - 168 hours	N/A	N/A	6	6.61 (2.39)	6	0.21 (0.06)	6	87.3 (2.75)
168 - 192 hours	N/A	N/A	6	6.61 (2.39)	5	0.28 (0.14)	6	87.53 (2.70)
192 - 216 hours	N/A	N/A	6	6.61 (2.39)	5	0.13 (0.08)	6	87.64 (2.78)
216 - 240 hours	N/A	N/A	6	6.61 (2.39)	4	0.15 (0.04)	6	87.74 (2.82)
Total	N/A	N/A	6	6.61 (2.39)	N/A	N/A	6	87.74 (2.82)

In a separate report evaluating daclatasvir parent drug and daclatasvir metabolites, 52.5% of the dose in feces and 6.4% of the dose in urine was identified as daclatasvir parent drug.

Table 7-Percentage distribution of radioactivity and percentage of dose in parentheses in urine and feces with 25 mg oral single dosing of radiolabeled daclatasvir

	Percentage distribution of radioactivity and percentage of dose[b]	
	Urine (0-72 h for human)[C]	Feces (0-144 h for human)[C]
Parent	96.4 (6.4)	60.3 (52.5)
M1	ND	ND
M2	2.8 (0.2)	17.5 (15.2)
M4	0.8 (0.1)	4.6 (4.0)
M7	ND	ND
M9	ND	ND
M11	ND	ND
M20	ND	3.9 (3.4)
M27	ND	ND
M6	ND	1.2 (1.0)
M12	ND	ND
M13	ND	2.2 (1.9)
M15	ND	1.0 (0.9)
M16	ND	1.2 (1.0)
M17	ND	ND
M21	ND	2.7 (2.4)
M24	ND	ND
Total[d]	100	94.6

Abbreviations: ND= not detected by radioactivity

b. Radioactive peaks are reported as a percentage of total radioactivity eluted from the column after background subtraction

c. Percent dose recovery values for parent and metabolites in human urine and feces were calculated based on the mean cumulative dose recovery values in 0-72 h urine (6.61%) and 0-144 h feces (87.1%), respectively, which were reported in reference 6 (DCN 930036334, page 51, Table 9.2.2C).

d. The total sample radioactivity (sum of radioactive peaks) was less that 100% due to the presence of small unidentified radioactive peaks

10.4 Safety Analysis

No deaths, serious adverse events or adverse events resulting in discontinuation were reported for the trial.

11. Discussion and Conclusions

Based on the results from the AI444006 trial, the following conclusions can be made:

- In plasma, daclatasvir parent drug was the major contributor to total radioactivity.
- For the 25 mg single dose of radiolabeled daclatasvir, the majority of the dose was eliminated through the fecal route (88%) with 7% eliminated renally.
- Approximately half of the dose in feces was identified as daclatasvir parent drug (53%) and virtually the entire total dose in urine was identified as daclatasvir parent drug (6%).

Multiple dosing trial-asunaprevir

Multiple dosing trial-daclatasvir

Trial Number	Title	Page Number
AI444004	Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study to Evaluate the Antiviral Activity and Safety, Tolerability, and Pharmacokinetics of BMS-790052 in Subjects Infected with Hepatitis C Virus Genotype 1	382

1. Title

Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study to Evaluate the Antiviral Activity and Safety, Tolerability, Pharmacokinetics of BMS-650032 in Subjects Infected with Hepatitis C Virus Genotype 1

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<u>AI444004</u>

1. Title

Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study to Evaluate the Antiviral Activity and Safety, Tolerability, and Pharmacokinetics of BMS-790052 in Subjects Infected with Hepatitis C Virus Genotype 1

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at multiple sites from May 19, 2008 (trial initiation) to June 25, 2009 (trial completion).

3. Objectives

The objectives of the trial included evaluating the multiple dose pharmacokinetics of daclatasvir.

4. Trial Design

AI444004 was a clinical trial that enrolled hepatitis C infected, genotype 1 subjects 18 to 60 years old. Information on the trial design is displayed in Figure 1. Subjects received daclatasvir or placebo for 14 days.

Figure 1-AI444004 trial design

	Dose Panel 1 (n=5)	Dose Panel 2 (n=5)	Dose Panel 3 (n=5)	Dose Panel 4 (n=5)	Dose Panel 5 (n=5)	Dose Panel 6 (n=5)
Dose and Regimen	1 mg BMS-790052 or placebo QD	10 mg BMS-790052 or placebo QD	30 mg BMS-790052 or placebo QD	60 mg BMS-790052 or placebo QD	30 mg BMS-790052 or placebo BID	100 mg BMS-790052 or placebo QD

5. Excluded Medications, Restrictions or Exceptions

Unless otherwise approved, prescription medications were not permitted within 4 weeks and nonprescription medications, including herbal products, were not permitted within 2 weeks prior to medication administration. In general, prescription and nonprescription medications, including herbal products, were not permitted during the trial.

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6. Dosage and Administration

The trial arms, including the dosage regimens that were administered, are specified in Figure 1. Daclatasvir or placebo was administered under fasted conditions.

7. Rationale for Doses Used in the Trial

The daclatasvir multiple dosing regimens of 1 mg to 100 mg were selected based on the anticipated range of therapeutic daclatasvir dosage regimens.

8. Drugs Used in the Trial

Information regarding the daclatasvir or placebo formulations that were administered in the trial is displayed in Table 1.

Table 1-Information on the daclatasvir or placebo formulations administered in the AI444004 trial

Drug Product	Formulation	Product ID Number	Product Batch Number	Label Batch Number
BMS-790052, 1 mg	Capsule	790052-R001-004	8A45235	8A42234
BMS-790052, 10 mg	Capsule	790052-R010-005	8A42899, 8A43359, 8F41843	8A42930, 8G38784
BMS-790052, 100 mg	Capsule	790052-R100-006	8A43351	8B33515
Placebo for 1 mg, 10 mg and 100 mg	Capsule	NA	4J87417	NA

Reference ID: 3615478

9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood samples were obtained that included the samples listed below.

Table 2-AI444004 blood sampling schedule for pharmacokinetic analysis

Study Day	Time (Event) Hour	Time (Relative To AM Dosing) Hour:Min	Sample for PK	Sample for Protein Binding
1 and 14	0 (predose)	00:00[a]	X	X[a]
1 and 14	0.5 (post-dose)	00:30	X	
1 and 14	1 (post-dose)	01:00	X	
1 and 14	1.5 (post-dose)	01:30	X	
1 and 14	2 (post-dose)	02:00[a]	X	X[a]
1 and 14	3 (post-dose)	03:00	X	
1 and 14	4 (post-dose)	04:00	X	
1 and 14	6 (post-dose)	06:00	X	
1 and 14	8 (post-dose)	08:00	X	
1 and 14	12 (post-dose)	12:00	X	
15	0	24:00	X	
16	0	48:00	X	
17	0	72:00	X	
2, 3, 4, 5, 7, 9, 11, 13	0 (predose)	00:00	X	

[a] An additional 10 mL of blood sample will be collected for protein binding determination at indicated timepoints on Day 14 only.

Bioanalysis

The method and bioanalysis of daclatasvir are acceptable. Daclatasvir plasma samples were analyzed using a validated LC/MS/MS method in EDTA anticoagulated plasma by ░░░░░░░░ [(b) (4)] (TNJM07177.00). The blood samples for analysis of daclatasvir appear to have been collected in tubes containing K_2EDTA.

For the AI444004 plasma samples that were analyzed for daclatasvir, the lower limit of quantification for daclatasvir was 0.05 ng/mL and the upper limit of quantification was 50 ng/mL. There were no precision or accuracy issues identified for daclatasvir based on the bioanalytical report. For the AI444004 trial, precision and accuracy were evaluated

using plasma daclatasvir quality control (QC) samples at 0.150 ng/mL, 2 ng/mL, 20 ng/mL and 40 ng/mL. The corresponding daclatasvir inter-run accuracy values were 2.7% for 0.150 ng/mL, 2.5% for 2 ng/mL, 2% for 20 ng/mL and 2.3% for 40 ng/mL. The daclatasvir inter-run precision values were 8.5% for 0.150 ng/mL, 5.3% for 2 ng/mL, 5.5% for 20 ng/mL and 5.7% for 40 ng/mL. In addition, for the daclatasvir dilution QC samples at 200 ng/mL (with dilution factors ranging from 10 to 100), the inter-run accuracy ranged from -1.5% to -14% and inter-run precision ranged from 3.6% to 7.6%.

For the plasma protein binding method, daclatasvir plasma samples were analyzed using a validated LC/MS/MS method in EDTA anticoagulated plasma by ⬛⬛⬛⬛ (b) (4) (TNJM08147.00). For the AI444004 plasma protein binding samples that were analyzed for daclatasvir, the lower limit of quantification for daclatasvir was 0.05 ng/mL and the upper limit of quantification was 50 ng/mL. There were no precision or accuracy issues identified for daclatasvir based on the bioanalytical report. For the AI444004 trial, precision and accuracy were evaluated using plasma daclatasvir quality control (QC) samples at 0.150 ng/mL, 2 ng/mL, 20 ng/mL and 40 ng/mL. The corresponding daclatasvir inter-run accuracy values were 12% for 0.150 ng/mL, 4% for 2 ng/mL, -2% for 20 ng/mL and -1.8% for 40 ng/mL. The daclatasvir inter-run precision values were 8.9% for 0.150 ng/mL, 6.8% for 2 ng/mL, 11.9% for 20 ng/mL and 8.1% for 40 ng/mL. In addition, for the daclatasvir dilution QC samples at 200 ng/mL (with dilution factors ranging from 20 to 50), the inter-run accuracy ranged from 1% to 2% and inter-run precision ranged from 4% to 9.9%.

For the AI444004 trial, in response to an information request, the applicant stated that the daclatasvir plasma samples were stored at the trial site at -20°C for up to 61 days, at -20°C for up to 52 days at the central laboratory and the bioanalytical laboratory at -20°C for up to 103 days. The bioanalytical report also states that some samples were stored at -70°C (the specific duration was not specified but it appears to be 7 days or less). For the TNJM07177.00 method, the generated long term daclatasvir stability data included stability data in EDTA anticoagulated plasma at -20°C for 387 days and -70°C for 7 days (of note, long term stability for the 0.15 ng/mL QC failed at 70°C for 14 days). For the AI444004 trial, the generated long term stability data appears to covers the duration of long term stability data necessary for daclatasvir.

Pharmacokinetic Assessments

Noncompartmental analysis was performed for daclatasvir. For the noncompartmental analysis, daclatasvir plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, and $AUC_{(0-tau)}$.

Statistical Analysis

The statistical analyses included deriving descriptive statistics for daclatasvir pharmacokinetic parameters.

10. Results

10.1 Subject Demographics

Table 3-AI444004 subject demographics

Characteristics	Placebo (n=6)	BMS-790052 Dose (N=4 per dose)					
		1 mg QD	10 mg QD	30 mg QD	60 mg QD	30 mg BID	100 mg QD
Age, years							
Mean (SD)	48 (4)	39 (10)	46 (13)	47 (4)	39 (7)	45 (6)	44 (7)
Range	43-54	29-48	29-59	43-52	29-47	38-53	34-49
Gender, n (%)							
Male	5 (83.3)	3 (75)	3 (75)	4 (100)	3 (75)	4 (100)	3 (75)
Female	1 (16.7)	1 (25)	1 (25)	0 (0)	1 (25)	0 (0)	1 (25)
Race, n (%)							
White	6 (100)	4 (100)	2 (50)	4 (100)	2 (50)	4 (100)	3 (75)
Black/African American	0 (0)	0 (0)	2 (50)	0 (0)	1 (25)	0 (0)	1 (25)
Native Hawaiian/ Other Pacific islander	0 (0)	0 (0)	0 (0)	0 (0)	1 (25)	0 (0)	0 (0)
BMI, kg/m^2							
Mean (SD)	28.4 (5.4)	29.4 (5.5)	29.9 (2.6)	30.9 (3.9)	29.2 (3.4)	28.1 (2.5)	26.7 (3.0)
Range	19.3-34.9	23.5-34.9	27.6-32.5	26.3-35.0	25.0-33.3	25.4-31.4	22.8-30.1

10.2 Concomitant Medications

The concomitant medications that were administered in the trial included various pain relief medications. The conclusions of the trial are not expected to be significantly altered by the concomitant medications that were administered in the trial.

Table 4-Daclatasvir pharmacokinetic parameters with various daclatasvir dosage regimens

Treatment	Study Day	Cmax (ng/mL) Geo. Mean [N] (CV)	Cmin (ng/mL) Geo. Mean [N] (CV)	Tmax (h) Median [N] (Min-Max)	AUC(TAU) (ng•h/mL) Geo. Mean [N] (CV)	T-HALF (h) Mean [N] (SD)
TRT A	1	15.731[4] (48)	1.212[4] (105)	2.000[4] (1.00-3.00)	111.8[4] (54)	NA NA
	14	10.430[4] (76)	1.234[4] (95)	1.250[4] (1.00-2.00)	92.0[4] (80)	11.68[4] (2.214)
TRT B	1	159.665[4] (41)	15.141[4] (49)	1.000[4] (1.00-2.00)	1113.6[4] (38)	NA NA
	14	154.196[4] (49)	23.674[4] (53)	1.250[4] (1.00-1.50)	1332.1[4] (46)	14.31[4] (3.848)
TRT C	1	483.365[4] (25)	41.114[4] (34)	1.000[4] (0.50-1.00)	3528.6[4] (19)	NA NA
	14	555.878[4] (38)	61.635[4] (42)	1.000[4] (1.00-1.50)	4391.3[4] (27)	12.99[4] (2.039)
TRT D	1	1409.202[4] (13)	129.822[4] (25)	1.500[4] (1.50-3.00)	10691.5[4] (20)	NA NA
	14	1726.383[4] (21)	254.602[4] (42)	1.000[4] (1.00-2.00)	15120.9[4] (35)	12.81[4] (1.233)
TRT E	1	563.569[4] (26)	171.330[4] (53)	2.500[4] (1.50-3.00)	3307.2[4][a] (36)	NA NA
	14	831.792[4] (37)	206.941[4] (74)	1.750[4] (1.00-2.00)	5431.6[4] (35)	13.04[4] (3.654)
TRT F	1	1960.732[4] (21)	174.642[4] (21)	1.500[4] (1.00-1.50)	15136.1[4] (19)	NA NA
	14	1853.925[4] (26)	287.852[4] (37)	1.750[4] (1.00-2.00)	17592.8[4] (15)	15.19[4] (3.411)

Treatments: A=1mg QD, B=10mg QD, C=30mg QD, D=60mg QD, E=30mg BID, F=100mg QD

[a] AUC(TAU) = AUC over 12 hour dosing interval for Treatment E

Table 5-Evaluation of relationship between dose and daclatasvir pharmacokinetic parameters on day 14 using a power model

PK Parameter	Point Estimate of Intercept	Point Estimate of Slope	90% CI for Slope
Cmax	10.593	1.172	(1.063,1.281)
AUC(TAU)	90.826	1.177	(1.076,1.279)
Cmin	1.276	1.213	(1.087, 1.340)

Clinical Pharmacology reviewer note: The trial was not powered to evaluate dose proportionality.

Table 6-Daclatasvir protein binding (%) and free fraction (%) for various daclatasvir dosage regimens on Day 14

Treatment	Time (h)	Plasma Protein Binding (%) Mean [N] (SD)	Free Fraction (%) Mean [N] (SD)
TRT A	0	NA	NA
		NA	NA
	2	99.299[2]	0.701[2]
		(0.1066)	(0.1066)
TRT B	0	98.881[3]	1.119[3]
		(0.1608)	(0.1608)
	2	99.039[4]	0.961[4]
		(0.1202)	(0.1202)
TRT C	0	99.063[3]	0.937[3]
		(0.0989)	(0.0989)
	2	99.121[3]	0.879[3]
		(0.0872)	(0.0872)
TRT D	0	99.031[4]	0.969[4]
		(0.2393)	(0.2393)
	2	99.018[4]	0.982[4]
		(0.2438)	(0.2438)
TRT E	0	99.293[4]	0.707[4]
		(0.1365)	(0.1365)
	2	99.267[4]	0.733[4]
		(0.1677)	(0.1677)
TRT F	0	99.196[4]	0.804[4]
		(0.2190)	(0.2190)
	2	99.291[4]	0.709[4]
		(0.1324)	(0.1324)

Treatments: A=1mg QD, B=10mg QD, C=30mg QD, D=60mg QD, E=30mg BID, F=100mg QD
NA = Not applicable

10.4 Safety Analysis

No deaths, serious adverse events or adverse events resulting in discontinuation were reported for the trial.

10.5 Other information

Table 7-Mean change in $\log_{10}$ HCV RNA from baseline to day 14

Treatment Group	Treatment Mean Change in $\log_{10}$ HCV RNA	Lower 90% Confidence Bound	Upper 90% Confidence Bound	Change from Placebo	P-value vs. Placebo
1 mg QD	-1.89	-3.38	-0.39	-1.29	0.7632
10 mg QD	-2.32	-3.81	-0.82	-1.73	0.5050
30 mg QD	-1.68	-3.17	-0.18	-1.09	0.8690
60 mg QD	-1.34	-3.07	0.39	-0.75	0.9823
30 mg BID	-3.55	-5.27	-1.82	-2.95	0.1215
100 mg QD	-1.35	-3.07	0.38	-0.75	0.9817
Placebo	-0.59	-1.81	0.63		

Note: P-values and CIs were adjusted using Dunnett's procedure
Subjects AI444004-4-138, AI444004-6-117 and AI444004-10-146 were excluded due to baseline genotypic drug resistance

11. Discussion and Conclusions

Based on the results from the AI444004 trial, the following conclusions can be made.

- When daclatasvir was administered from 1 mg to 100 mg (as a $^{(b)\,(4)}$ formulation), overall, greater than dose proportional increases were observed for C_{max}, $AUC_{(0\text{-}tau)}$, and C_{min} when evaluated using a power model. However, the trial was not powered to evaluate dose proportionality.
- Over the range of daclatasvir multiple dosing regimens from 1 mg to 100 mg, the plasma protein binding was approximately 99% or greater across all the daclatasvir dosage regimens at predose and 2 hours postdose.

Renal impairment trial-asunaprevir

Renal impairment trial-daclatasvir

Trial Number	Title	Page Number
AI444063	Single Dose Pharmacokinetics And Safety Of Daclatasvir In Subjects With Renal Function Impairment	400

1. Title

Open-Label, Parallel Group, Multiple Dose Study to Evaluate the Pharmacokinetics and Safety of Asunaprevir in Subjects with Renal Function Impairment

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AI444063

1. Title

Single Dose Pharmacokinetics And Safety Of Daclatasvir In Subjects With Renal Function Impairment

2. Information Regarding the Clinical Trial Site and Duration of the Trial

The trial was conducted at multiple sites from September 11, 2012 (trial initiation) to June 8, 2013 (trial completion).

3. Objectives

The objectives of the trial included evaluating the single dose pharmacokinetics of daclatasvir in subjects with renal impairment.

4. Trial Design

AI444063 was an open label clinical trial that enrolled renally impaired subjects or healthy subjects 18 years old or older. Information on the trial design is displayed in Figure 1.

Figure 1-AI444063 trial design

Screening	Admit to clinic	Daclatasvir 60 mg orally (single dose)[a]	Subjects remain in clinic	Study Discharge
Within 21 days of Day 1	Day -1	Day 1	Days 2-5	Day 5

[a] Subjects on hemodialysis will have hemodialysis completed prior to dosing on Day 1 and may have next hemodialysis after the 48 hour PK sample has been drawn.

5. Excluded Medications, Restrictions or Exceptions

For healthy subjects, unless otherwise approved, the protocol excluded the use of medications, including nonprescription medications, herbal products, within one week prior to medication administration. In general, for healthy subjects, prescription and nonprescription medications, including herbal products, were not permitted during the trial. Renally impaired subjects and end stage renal disease subjects were allowed to receive medically necessary medications.

Table 1-AI444063 treatment groups

Group	Description	eGRF $(mL/min/1.73m^2)$	CLcr (mL/min)
A	Control (normal) GFR	≥ 90	≥ 90
B	Mild decrease in GFR	60-89	60-89
C	Moderate decrease in GFR	30-59	30-59
D	Severe decrease in GFR	15-29	15-29
5	End Stage Renal Disease (ESRD)	< 15 not on dialysis	< 15 not on dialysis
		Requiring dialysis	Requiring dialysis

Clinical pharmacology reviewer notes: the Group B presented in Table 1 is different than the Group B that is included in section 10 (ESRD subjects requiring hemodialysis). All ESRD subjects in the trial were receiving hemodialysis.

6. Dosage and Administration

The trial arms, including the doses that were administered, are specified in Figure 1. Daclatasvir was administered under fasted conditions after fasting for 10 hours.

7. Rationale for Doses Used in the Trial

The daclatasvir single dose of 60 mg is the proposed recommended dose.

8. Drugs Used in the Trial

Information regarding the daclatasvir formulation that was administered in the trial is displayed in Table 2.

Table 2-Information on the daclatasvir formulation administered in the AI444063 trial

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
Daclatasvir (BMS-790052-05) Film Coated Tablet	60 mg (as the free base)	(b)(4) ablets per bottle / open label	N/A	A plain, green, biconvex, pentagonal film coated tablet	15°C to (b)(4) C (59°F to F) (b)(4)

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9. Sample Collection, Bioanalysis, Pharmacokinetic Assessments, and Statistical Analysis

Sample Collection

The blood and urine samples were obtained that included the samples listed below.

Table 3-AI444063 blood and urine sampling schedule for pharmacokinetic analysis

Study Day[a]	Time (Event) Hour	Time (Relative To Dosing) Hour: Min	PK Blood Sample	Blood Sample for Protein Binding[b]	PK Urine Sample[c]
1	0 (predose)	00:00	X		X[a]
1	0.5	00:30	X		X (0-12 hrs)
1	1	01:00	X	x	
1	1.5	01:30	X		
1	2	02:00	X		
1	3	03:00	X		
1	4	04:00	X	x	
1	6	06:00	X		
1	8	08:00	X		
1	12	12:00	X		X (12-24 hrs)
2	0	24:00	X		
2	12	36:00	X		X (24-48 hrs)
3	0	48:00	X		
4	0	72:00	X		X (48-72 hrs)
5	0	96:00	X		X (72-96 hrs)

[a] Samples to be obtained prior to study drug administration

[b] An additional sample of blood will be collected for protein binding determination at the indicated time points.

[c] Not applicable for subjects who are anuric.

Bioanalysis

Clinical pharmacology reviewer note: *The bioanalysis of daclatasvir urine samples will not be discussed because urine pharmacokinetic data is not proposed for inclusion in the daclatasvir U.S. prescribing information.*

The method and bioanalysis of daclatasvir are acceptable. Daclatasvir plasma samples were analyzed using a validated LC/MS/MS method in EDTA anticoagulated plasma by

(TNJM11132.01). The blood samples for analysis of daclatasvir appear to have been collected in tubes containing K_2EDTA.

For the AI444063 plasma samples that were analyzed for daclatasvir, the lower limit of quantification for daclatasvir was 2 ng/mL and the upper limit of quantification was 2000 ng/mL. There were no precision or accuracy issues identified for daclatasvir based on the bioanalytical report. For the AI444063 trial, precision and accuracy were evaluated using plasma daclatasvir quality control (QC) samples at 6 ng/mL, 80 ng/mL, 800 ng/mL and 1600 ng/mL. The corresponding daclatasvir inter-run accuracy values were 2.5% for 6 ng/mL, 2.5% for 80 ng/mL, -2.5% for 800 ng/mL and -1.9% for 1600 ng/mL. The daclatasvir inter-run precision values were 4.7% for 6 ng/mL, 3.4% for 80 ng/mL, 3.1% for 800 ng/mL and 3.6% for 1600 ng/mL. In addition, for the daclatasvir dilution QC samples at 10000 ng/mL, the inter-run accuracy was -8.4% and inter-run precision was 3.9%.

For the plasma protein binding method, daclatasvir plasma samples were analyzed using a validated LC/MS/MS method in EDTA anticoagulated plasma by (TNJM08147.00). For the AI444063 plasma protein binding samples that were analyzed for daclatasvir, the lower limit of quantification for daclatasvir was 0.05 ng/mL and the upper limit of quantification was 50 ng/mL. There were no precision or accuracy issues identified for daclatasvir based on the bioanalytical report. For the AI444063 trial, precision and accuracy were evaluated using plasma daclatasvir quality control (QC) samples at 0.150 ng/mL, 2 ng/mL, 20 ng/mL and 40 ng/mL. The corresponding daclatasvir inter-run accuracy values were 3.3% for 0.150 ng/mL, -2.5% for 2 ng/mL, -8% for 20 ng/mL and -4% for 40 ng/mL. The daclatasvir inter-run precision values were 5.6% for 0.150 ng/mL, 3.9% for 2 ng/mL, 3.2% for 20 ng/mL and 3.3% for 40 ng/mL. In addition, for the daclatasvir dilution QC samples at 200 ng/mL, the inter-run accuracy (with dilution factors ranging from 10 to 40), the inter-run accuracy ranged from -3.5% to 1.5% and inter-run precision ranged from 4.1% to 4.6%.

Of the samples selected for incurred sample reanalysis for daclatasvir (total number less than 50) using method TNJM11132.01, all samples were within 20% using the percentage values of the repeat and original concentrations. However, it is not clear whether the total number of daclatasvir samples that were reanalyzed represents 7% of the total number of samples that were initially analyzed.

For the AI444063 trial, in response to an information request, the applicant stated that the daclatasvir plasma samples were stored at the trial site at -20°C for up to 78 days, at -20°C for up to 70 days at the central laboratory and the bioanalytical laboratory at -20°C for up to 43 days. For the TNJM11132.01 method, the generated long term daclatasvir stability data included stability data in K_2EDTA anticoagulated plasma at -20°C for 686 days and at -80°C for 658 days. For the AI444063 trial, the generated long term stability data appears to covers the duration of long term stability data necessary for daclatasvir.

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Pharmacokinetic Assessments

Noncompartmental analysis was performed for daclatasvir. For the noncompartmental analysis, daclatasvir plasma pharmacokinetic parameters were calculated, including t_{max}, C_{max}, and $AUC_{(0\text{-inf})}$.

Statistical Analysis

The statistical analyses included comparing each renal impairment group to subjects with normal renal function and 90% confidence intervals were derived. Additionally, a regression analysis was performed that excluded end stage renal disease subjects.

10. Results

10.1 Subject Demographics

Table 4-AI444063 subject demographics

Characteristic	Group A (N=12)	Group B (N=12)	Group C (N=6)	Group D (N=6)	All Subjects (N = 36)
Age, years					
Mean (SD)	48.6 (8.5)	49.0 (11.7)	62.0 (12.6)	66.3 (9.9)	53.9 (12.6)
Range	34-61	27-66	48-76	50-75	27-76
Gender, N (%)					
Male	11 (91.7)	11 (91.7)	4 (66.7)	4 (66.7)	30 (83.3)
Female	1 (8.3)	1 (8.3)	2 (33.3)	2 (33.3)	6 (16.7)
Race, N (%)					
White	8 (66.7)	3 (25.0)	3 (50.0)	4 (66.7)	18 (50.0)
Black/African American	4 (33.3)	9 (75.0)	3 (50)	2 (33.3)	18 (50.0)
Weight, kg					
Mean (SD)	90.4 (9.7)	94.1 (17.8)	99.8 (18.2)	82.7 (17.8)	91.9 (15.8)
Range	73.6-107.1	66.8-126.7	74.5-117.0	62.9-113.0	62.9-126.7
Body Mass Index, screening kg/m^2					
Mean (SD)	28.4 (2.4)	28.5 (4.9)	33.5 (3.1)	27.9 (5.4)	29.2 (4.3)
Range	23.2-31.8	20.4-36.2	29.6-37.8	22.0-37.3	20.4-37.8

10.2 Concomitant Medications

The concomitant medications that were administered in the trial included medically necessary medications that subjects were receiving in the renally impaired or end stage renal disease groups. The conclusions of the trial are not expected to be significantly altered by the concomitant medications that were administered in the trial.

10.3 Pharmacokinetic and Statistical Analysis

Clinical pharmacology reviewer note: In Group B (end state renal disease), the trial report states that hemodialysis occurred prior to day 1 dosing and the next hemodialysis session did not occur until after the 48 hour sample was collected.

Table 5-Regression analysis for daclatasvir for renally impaired subjects (excluding end stage renal disease subjects)

RENAL FUNCTION MEASURE	PARAMETER	CLCR/eGFR AND COMPARISON	ESTIMATED GEOMETRIC MEAN	ESTIMATED 90% CI
Cockcroft-Gault Creatinine Clearance (mL/min)	Cmax (ng/mL)	15	1477.963	(1153.781, 1893.230)
		30	1437.176	(1167.250, 1769.522)
		60	1358.949	(1172.483, 1575.069)
		90	1284.979	(1116.572, 1478.787)
		15 vs. 90	1.150	(0.899, 1.472)
		30 vs. 90	1.118	(0.918, 1.362)
		60 vs. 90	1.058	(0.958, 1.167)
	AUC(INF) (ng.h/mL)	15	27052.861	(20955.989, 34923.539)
		30	24062.540	(19416.385, 29820.474)
		60	19036.977	(16349.171, 22166.659)
		90	15061.024	(13029.752, 17408.961)
		15 vs. 90	1.796	(1.393, 2.316)
		30 vs. 90	1.598	(1.304, 1.958)
		60 vs. 90	1.264	(1.142, 1.399)
MDRD Based eGFR mL/min/1.73m^2)	Cmax (ng/mL)	15	1445.062	1148.148, 1818.759)
		30	1397.177	(1165.745, 1674.556)
		60	1306.116	(1140.076, 1496.338)
		90	1220.989	(1002.906, 1486.495)
		15 vs. 90	1.184	(0.852, 1.644)
		30 vs. 90	1.144	(0.880, 1.488)
		60 vs. 90	1.070	(0.938, 1.220)
	AUC(INF) (ng.h/mL)	15	25422.842	(20006.201, 32306.027)
		30	21829.257	(18076.194, 26361.549)
		60	16094.174	(13968.673, 18543.096)
		90	11865.838	(9666.714, 14565.251)
		15 vs. 90	2.143	(1.522, 3.017)
		30 vs. 90	1.840	(1.399, 2.419)
		60 vs. 90	1.356	(1.183, 1.555)

Table 6-Regression analysis for daclatasvir for renally impaired subjects using unbound concentrations (excluding end stage renal disease subjects)

RENAL FUNCTION MEASURE	PARAMETER	CLCR/eGFR AND COMPARISON	ESTIMATED GEOMETRIC MEAN	ESTIMATED 90% CI
Cockcroft-Gault Creatinine Clearance (mL/min)	Cmaxu (ng/mL)	15	8.638	(6.993, 10.671)
		30	8.694	(7.280, 10.383)
		60	8.807	(7.764, 9.988)
		90	8.921	(7.913, 10.057)
		15 vs. 90	0.968	(0.785, 1.195)
		30 vs. 90	0.975	(0.824, 1.153)
		60 vs. 90	0.987	(0.908, 1.074)
	AUC(INF)u (ng.h/mL)	15	158.117	(123.271, 202.813)
		30	145.563	(118.092, 179.425)
		60	123.367	(106.355, 143.100)
		90	104.556	(90.784, 120.416)
		15 vs. 90	1.512	(1.180, 1.938)
		30 vs. 90	1.392	(1.142, 1.698)
		60 vs. 90	1.180	(1.069, 1.303)
MDRD Based eGFR mL/min/1.73m^2)	Cmaxu (ng/mL)	15	8.607	(7.080, 10.464)
		30	8.701	(7.461, 10.148)
		60	8.892	(7.922, 9.980)
		90	9.087	(7.688, 10.739)
		15 vs. 90	0.947	(0.717, 1.252)
		30 vs. 90	0.958	(0.766, 1.197)
		60 vs. 90	0.979	(0.875, 1.094)
	AUC(INF)u (ng.h/mL)	15	151.431	(120.091, 190.948)
		30	135.947	(113.261, 163.176)
		60	109.567	(95.532, 125.663)
		90	88.306	(72.417, 107.680)
		15 vs. 90	1.715	(1.231, 2.388)
		30 vs. 90	1.540	(1.181, 2.007)
		60 vs. 90	1.241	(1.087, 1.417)

Table 7-Daclatasvir pharmacokinetic parameters for renally impaired subjects and normal renal function subjects

	C-G CLcr Method				Protocol-Specified Method			
PARAMETER STATISTIC	GROUP				GROUP			
	A	B	C	D	A	B	C	D
Cmax (ng/mL)								
Geo. Mean [N]	1111 [11]	1085 [10]	1746 [5]	1207 [6]	1111 [11]	1112 [12]	1710 [7]	1312 [6]
(%CV)	(39)	(15)	(31)	(33)	(39)	(21)	(26)	(32)
Tmax (h)								
Median [N]	1.00 [11]	1.25 [10]	1.00 [5]	1.5 [6]	1.00 [11]	1.51 [12]	1.00 [7]	1.50 [6]
(Min - Max)	·(1.00-2.00)	(1.00-4.00)	(1.00-2.00)	(1.00-3.00)	(1.00-2.00)	(1.00-4.00)	(1.00-1.50)	(1.00-2.00)
AUC(0-T) (ng•h/mL)								
Geo. Mean [N]	11093 [11]	13935 [10]	24344 [5]	21239 [6]	11093 [11]	14868 [12]	22356 [7]	22384 [6]
(%CV)	(40)	(25)	(36)	(37)	(40)	(28)	(50)	(34)
AUC(INF) (ng•h/mL)								
Geo. Mean [N]	11215 [11]	14257 [10]·	24790 [5]	21947 [6]	11215 [11]	15211 [12]	22772 [7]	23108 [6]
(%CV)	(40)	·(25)·	(35)	(39)	(40)	(28)	(51)	(36)
T-HALF (h)								
Mean [N]	14.0 [11]	16.4 [10]	17.2 [5]	20.8 [6]	14.0 [11]	16.4 [12]	16.8 [7]	20.9 [6]
(SD)	(3.49)	(6.02)	(3.21)	(5.04)	(3.49)	(5.71)	(3.75)	(5.08)
CLT/F (mL/min)								
Geo. Mean [N]	89.2 [11]	70.1 [10]	40.3 [5]	45.6 [6]	89.2 [11]	65.7 [12]	43.9 [7]	43.3 [6]
(%CV)	(26)	(33)·	(27)	(31)	(26)	(35)	(40)	(32)

A: Normal renal function control subjects, B: Subjects with ESRD requiring hemodialysis,
C: Subjects with moderate renal impairment, D: Subjects with severe renal impairment.
Protocol specified grouping method is based on creatinine clearance for normal healthy subjects, and based on eGFR for moderate and severe renal impairment and end-stage renal disease patients.

Reference ID: 3615478

Table 8-Daclatasvir statistical analyses for renally impaired subjects and normal renal function subjects

PK PARAMETER	TREATMENT AND COMPARISON	C-G CLcr Method		Protocol-Specified Method	
		ADJUSTED GEOMETRIC MEAN	90% CI	ADJUSTED GEOMETRIC MEAN	90% CI
Cmax	GRP A	1009	(804,1268)	1089	(885, 1338)
(ng/mL)	GRP B	984	(779., 1242)	1098	(901, 1338)
	GRP C	1951	(1442, 2640)	1744	(1398, 2175)
	GRP D	1172	(913, 1504)	1309	(1009, 1699)
	GRP B vs GRP A	0.975·	(0.765, 1.242)	1.008	(0.801, 1.269)
	GRP C vs GRP A	1.933	(1.260, 2.964)	1.602	(1.194, 2.148)
	GRP D vs GRP A	1.161	(0.858, 1.571)	1.203	(0.873, 1.658)
AUC(0-T))	GRP A	11469	(9111, 14436)	11978	(9530, 15056)
(ng•h/mL)	GRP B	14386	(11372, 18197)	15882	(12759, 19771)
	GRP C	24194	(17832, 32826)	22471	(17596, 28696)
	GRP D	21832	(16969, 28090)	23367	(17518, 31168)
	GRP B vs GRP A	1.254	(0.982, 1.602)	1.326	(1.028, 1.710)
	GRP C vs GRP A	2.110	(1.370, 3.248)	1.876	(1.355, 2.597)
	GRP D vs GRP A	1.904	(1.403,2.584)	1.951	(1.368, 2.782)
AUC(INF)	GRP A	11638	(9236, 14663)	12114	(9618, 15258)
(ng•h/mL)	GRP B	14771	(11665, 18703)	16248	(13027, 20266)
	GRP C	24430	(17982, 33190)	22814	(17826, 29198)
	GRP D	22521	(17485, 29008)	24041	(17977, 32150)
	GRP B vs GRP A	1.269	(0.992, 1.623)	1.341	(1.037, 1.734)
	GRP C vs GRP A	2.099	(1.361, 3.238)	1.984	(1.357, 2.614)
	GRP D vs GRP A	1.935	(1.424, 2.630)	1.984	(1.387, 2.839)

Group Codes: A: Normal renal function control subjects, B: Subjects with ESRD requiring hemodialysis, C: Subjects with moderate renal impairment, D: Subjects with severe renal impairment. Protocol specified grouping method is based on creatinine clearance for normal healthy subjects, and based on eGFR for moderate and severe renal impairment and end-stage renal disease patients.

Table 9-Daclatasvir protein binding and free fraction (grouped using Cockcroft-Gault equation)

Renal Function Group	Mean (SD) fu at 1 hr	Mean (SD) % PB at 1 hr	Mean (SD) fu at 4 hr	Mean (SD) % PB at 4 hr	Mean (SD) fu for all time points	Mean (SD) %PB for all time points
GRP A (N = 11)	0.008 (0.0019)	99.2 (0.195)	0.007 (0.0015)	99.3 (0.153)	0.008 (0.0016)	99.3 (0.161)
GRP B (N = 10)	0.007 (0.0020)	99.3 (0.202)	0.006 (0.0011)	99.4 (0.110)	0.007 (0.0014)	99.3 (0.142)
GRP C (N=5)	0.006 (0.0017)	99.4 (0.170)	0.005 (0.0007)	99.5 (0.073)	0.005 (0.0012)	99.5 (0.120)
GRP D (N=6)	0.006 (0.0013)	99.4 (0.1270)	0.006 (0.0018)	99.4 (0.175)	0.006 (0.0014)	99.4 (0.140)

Group Code: A: Normal renal function control subjects, B: Subjects with ESRD requiring hemodialysis, C: Subjects with moderate renal impairment, D: Subjects with severe renal impairment

Table 10-Daclatasvir pharmacokinetic parameters for renally impaired subjects and normal renal function subjects using unbound concentrations (grouped using Cockcroft-Gault equation)

Renal Function Group	$Cmax_u$ (ng/mL) Geo. Mean (CV)	$AUC(INF)_u$ (ng•h/mL) Geo. Mean (CV)
GRP A (N = 11)	8.31 (34)	83.8 (37)
GRP B (N = 10)	7.67 (36)	101 (31)
GRP C (N=5)	10.21 (20)	145 (13)
GRP D (N=6)	7.68 (33)	140 (43)

A: Normal renal function control subjects, B: Subjects with ESRD requiring hemodialysis, C: Subjects with moderate renal impairment, D: Subjects with severe renal impairment.

Table 11-Daclatasvir statistical analyses for renally impaired subjects and normal renal function subjects using unbound concentrations (grouped using Cockcroft-Gault equation)

PK PARAMETER	TREATMENT AND COMPARISON	ADJUSTED GEOMETRIC MEAN	90% CI
Cmaxu (ng/mL)	GRP A	7.43	(5.89, 9.36)
	GRP B	6.85·	(5.41, 8.67)
	GRP C	11.82	(8.70, 16.07)
	GRP D	7.50	(5.82, 9.67)
	GRP B vs GRP A	0.922·	(0.721, 1.179)
	GRP C vs GRP A	1.591	(1.031, 2.456)
	GRP D vs GRP A	1.010	(0.743, 1.374)
·AUC(INF)u (ng•h/mL)	·GRP A·	85.6	(65.5, 112)
	·GRP B·	103	(78.2, 135)
	GRP C	148	(104, 211)
	GRP D	144	(108, 193)
	GRP B vs GRP A·	1.201·	(0.903, 1.596)
	GRP C vs GRP A	1.728	(1.047, 2.854)
	GRP D vs GRP A	1.684	(1.181, 2.402)

A: Normal renal function control subjects, B: Subjects with ESRD requiring hemodialysis, C: Subjects with moderate renal impairment, D: Subjects with severe renal impairment

10.4 Safety Analysis

No deaths, serious adverse events or adverse events resulting in discontinuation were reported for the trial.

11. Discussion and Conclusions

Based on the results from the AI444063 trial, the following conclusions can be made.

- When a single dose of daclatasvir 60 mg was administered, using a regression analysis, the following changes in daclatasvir exposure were observed when compared to subjects with normal renal function using Cockcroft-Gault as the measurement of renal function:
    - 15 mL/min: C_{max} and $AUC_{(0-inf)}$ increased by 15% and 79.6%, respectively and the corresponding unbound C_{max} decreased by 3.2% and $AUC_{(0-inf)}$ increased by 51.2%.

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- 30 mL/min: C_{max} and $AUC_{(0-inf)}$ increased by 11.8% and 59.8%, respectively and the corresponding unbound C_{max} decreased by 2.5% and $AUC_{(0-inf)}$ increased by 39.2%.
- 60 mL/min: C_{max} and $AUC_{(0-inf)}$ increased by 5.8% and 26.4%, respectively and the corresponding unbound C_{max} decreased by 1.3% and $AUC_{(0-inf)}$ increased by 18%.
- When a single dose of daclatasvir 60 mg was administered, the following changes in daclatasvir exposure were observed when compared to subjects with normal renal function using Cockcroft-Gault as the measurement of renal function (an analysis was not provided for mild renal impairment subjects):
    - Group B (end stage renal disease subjects): C_{max} decreased by 2.5% and $AUC_{(0-inf)}$ increased by 26.9% and the corresponding unbound C_{max} decreased by 7.8% and $AUC_{(0-inf)}$ increased by 20.1%.
    - Group C (moderate renal impairment subjects): C_{max} and $AUC_{(0-inf)}$ increased by 93.3% and 109.9%, respectively and the corresponding unbound C_{max} and $AUC_{(0-inf)}$ increased by 59.1% and 72.8%, respectively.
    - Group D (severe renal impairment subjects): C_{max} and $AUC_{(0-inf)}$ increased by 16.1% and 93.5%, respectively and the and the corresponding unbound C_{max} and $AUC_{(0-inf)}$ increased by 1% and 68.4%, respectively.

  For all parameters in all categories of renal impairment, none of the 90% confidence intervals were within 80% to 125%.
- No discernable changes in daclatasvir free fraction was observed for any of the renally impaired groups compared to the subjects with normal renal function at each measured time point.

Based on the daclatasvir exposure-response or exposure-safety information, dosage adjustments are not necessary to compensate for the changes in daclatasvir total or unbound exposure based on the information from either of the analyses that were conducted.

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In vitro studies

NDA	Page Number
Reviews for asunaprevir	412
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NDA 206843-summary of in vitro studies

1) 930022297

A) PAMPA permeability model

Type of Study: Non-GLP

Method: Incubation of BMS-790052 in 96-well PAMPA model followed by sample analysis using a UV plate reader. The study was conducted at 100 µM concentration at pH 5.5 and 7.4 with 4-hour incubation at room temperature.

Tabulated Results:

pH	A-to-B, Pc (nm/sec)
5.5	442 ± 168
7.4	486 ± 183

Additional Information: Data source: Lead Profiling ECN Report BMS-790052 [1]

B) Caco-2 model evaluating daclatasvir as a P-gp substrate

Type of Study: Non-GLP

Method: Incubation of 0.3 µM BMS-790052 (either alone or with the P-gp inhibitor ketoconazole (50 µM) or cyclosporin (50 µM)) in Caco-2 cells and measurement of permeability across the Caco-2 cell monolayers. Samples analyzed by HPLC/UV.

Tabulated Results:

BMS-790052, Pc values in the absence of P-gp inhibitors			
Apical pH	A-to-B, Pc (nm/sec)	B-to-A. Pc (nm/sec)	B-to-A / A-to-B ratio
5.5	<15	658 ± 228	>44
6.5	<15	375 ± 97	>25
7.4	<15	364 ± 101	>24

BMS-790052, Pc values in the presence of P-gp inhibitors						
	Ketoconazole			Cyclosporine		
Apical pH	A-to-B Pc (nm/sec)	B-to-A Pc (nm/sec)	B-to-A / A-to-B ratio	A-to-B Pc (nm/sec)	B-to-A Pc (nm/sec)	B-to-A / A-to-B ratio
7.4	129 ± 35	200 ± 44	1.6	178 ± 25	136 ± 35	0.8

Clinical pharmacology reviewer note: the net flux ratio for daclatasvir in the absence of P-pp inhibitors was 2 or greater and ratio was decreased by greater than 50% or to unity, the recommended criteria in the February 2012 guidance: Drug Interaction Studies -Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations, indicating that daclatasvir is a P-gp substrate.

C) Caco-2 model evaluating daclatasvir as a P-gp inhibitor

Type of Study: Non-GLP

Method: Bi-directional permeability of digoxin assessed in absence and presence of BMS-790052. Samples analyzed by liquid scintillation counter.

Tabulated Results:

Compound	% inhibition of P-gp at 10 µM	IC$_{50}$ (µM) of P-gp inhibition
BMS-790052	89.1	4.4
Verapamil	69.7	Not determined

Additional Information: BMS-790052 is likely to be a potent P-gp inhibitor. A steep dose response curve, with negligible inhibition at 1 µM followed by ~ 60% inhibition at 5 µM was noticed.
Data source: BMS Notebook 63644 Page 213-216

D) Daclatasvir protein binding

Study system:	In vitro			
Target entity, Test system and method:	BMS-790052, equilibrium dialysis followed by LC/MS/MS			
Study Type:	Non-GLP			

Species	Concentration Tested (μM)	% Bound	Study No./ Document Control No.	Location in Dossier
Mouse	10	98.2 ± 0.8		
Rat	10	98.3 ± 0.1		
Dog	10	96.5 ± 0.7		
Monkey	10	95.1 ± 0.1		
Rabbit	10	99.5 ± 0.1		
Human	10	95.6 ± 0.3		

Additional Information: Serum samples (N = 3 for serum) were dialyzed against Krebs-Ringer buffer (pH 7.4) at 37°C for 4 hours using a 12,000 - 14,000 dalton molecular weight-cutoff membrane. Experiments were performed in triplicate and the compound was stable in sera of all species at least up to 4 hours.

E) HEK-293 model evaluating daclatasvir as a human OATP1B1 inhibitor
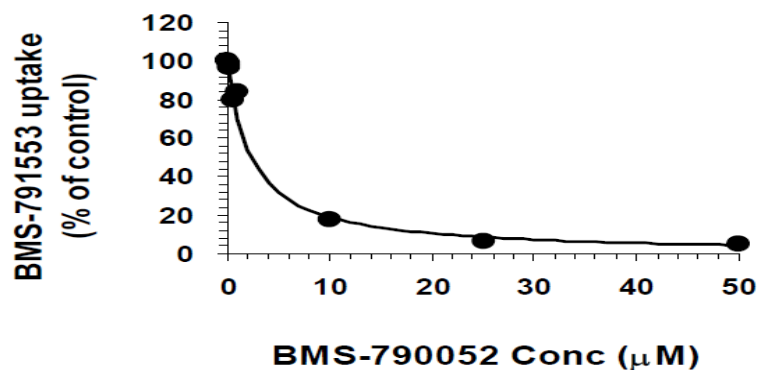
Clinical pharmacology reviewer note: the IC_{50} was estimated as 2.3 μM and based on the daclatasvir C_{max}, daclatasvir potentially inhibits human OATP1B1.

2) 930053227

HEK-293 model evaluating daclatasvir as a human OATP1B3 inhibitor

	CCK-8 Uptake (% of control)
Control	100.0 ± 11.8
+ 0.01 µM BMS-790052	79.7 ± 11.0
+ 0.1 µM BMS-790052	101.5 ± 8.8
+ 0.5 µM BMS-790052	105.3 ± 8.3
+ 1 µM BMS-790052	69.7 ± 2.6
+ 5 µM BMS-790052	53.5 ± 6.8
+ 10 µM BMS-790052	36.3 ± 7.9
+ 25 µM BMS-790052	15.6 ± 1.2

unit: % of control, mean ± SD, n = 3

Clinical pharmacology reviewer note: The reported IC_{50} for daclatasvir inhibition of human OATP1B3 was 5.7±1.3 µM. Based on the daclatasvir C_{max} value, daclatasvir potentially inhibits human OATP1B3.

3) 930051248

MDCK-BCRP model evaluating daclatasvir as a human BCRP inhibitor

Inhibitors	Inhibitor concentration (μM)	Pc (nm/sec)		Efflux ratio	% Inhibition	IC$_{50}$ (μM)
		A to B	B to A			
no inhibitor (control)	0	193 ± 2	477 ± 34	2.5		
BMS-790052	0.1	180 ± 5	431 ± 37	2.4	11.8	10.9 ± 8.6
	1	179 ± 7	441 ± 49	2.5	7.7	
	5	183 ± 4	454 ± 55	2.5	4.5	
	20	255 ± 17	304 ± 36	1.2	82.8	
	50	218 ± 6	235 ± 19	1.1	94.2	
FTC	10	207 ± 8	218 ± 28	1.1	96.0	
Cyclosporin A	10	145 ± 9	221 ± 13	1.5	73.3	

Note: Recovery >75%

Clinical pharmacology reviewer notes: The substrate used was 1 μM of [^{3}H]genistein. The reported IC$_{50}$ for daclatasvir inhibition of human BCRP was 10.9 μM. Based on the available information and the daclatasvir C$_{max}$ value, daclatasvir potentially inhibits human BCRP.

4) 930066927

MDCK-P-gp model evaluating daclatasvir as a human P-gp inhibitor

Inhibitors	Inhibitor concentration (μM)	Pc (nm/sec)		Efflux ratio	% Inhibition	IC50 (μM)
		A to B	B to A			
no inhibitor (control)	0	16 ± 0.4	169 ± 6.7	10.3		
BMS-790052	0.1	11 ± 0.9	163 ± 6.7	14.5	0.5	>7.0
	0.5	17 ± 2.8	174 ± 9.9	10.4	-3.1	
	1	16 ± 4.3	182 ± 8.7	11.2	-8.6	
	5	18 ± 0.6	173 ± 5.7	9.7	-2.0	
	7	17 ± 3.3	140 ± 2.4	8.5	18.7	
	10	14 ± 3.8	140 ± 1.9	9.8	17.5	
Quinidine	10	36 ± 0.6	57 ± 3	1.6	86.0	
Ketoconazole	10	30 ± 0.9	88 ± 4.6	2.9	62.3	

Clinical pharmacology reviewer note: The substrate used was 1 μM [^{3}H]digoxin. Based on the available information, daclatasvir potentially inhibits P-gp.

5) 930047552

IC$_{50}$ values for daclatasvir inhibition of cytochrome P450 enzymes in human liver microsomes

Enzyme	CYP assay	BMS-790052[a]	
		Without preincubation	With 30 min preincubation
CYP1A2	Tacrine 1'-hydroxylation	>40	>40
CYP2B6	Bupropion hydroxylation	>40	>40
CYP2C8	Amodiaquine *N*-deethylation	>40	>40
CYP2C9	Diclofenac 4'-hydroxylation	>40	>40
CYP2C19	S-mephenytoin 4'-hydroxylation	>40	>40
CYP2D6	Dextromethorphan *O*-demethylation	>40	>40
CYP3A4[b]	Midazolam 1'-hydroxylation	31.8	13.5
CYP3A4	Testosterone 6β-hydroxylation	11.0	8.9

a. IC50 values for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 are an average from two tests.
b. The IC50 values for inhibition of midazolam 1'-hydroxylation activity of CYP3A4 are from a separated study and were reported previously.[1]

6) 930066932

A) Study information

Transporters	Probe Substrate	Incubation time (min)	Test compounds	Positive Control Inhibitor
OAT1	p-aminohippuric acid (PAH) (1μM)	1.5	BMS-790052 (0.02, 0.07, 0.22, 0.67, 2.0, 8.0 μM)	Probenecid (0.14-100.0 μM)
OAT3	estrone-3-sulfate (E3S) (1μM)	1.5	BMS-790052 (0.07, 0.22, 0.67, 2.0, 4.0, 8.0 μM)	Probenecid (0.41-100.0 μM)
OCT1	Metformin (1μM)	1.5	BMS-790052 (0.07, 0.22, 0.67, 2.0, 4.0, 8.0 μM)	PYR (0.41-100.0 μM)
OCT2	Metformin (1μM)	1.5	BMS-790052 (0.07, 0.22, 0.67, 2.0, 4.0, 8.0μM)	PYR (0.41-100.0 μM)

B) Evaluation of daclatasvir as a human OCT2 inhibitor

BMS-790052 (μM)	uptake (pmol/mg/1.5 min)	SD (pmol/mg/1.5 min)	% of control
0.00	46.31	2.87	100.00
0.07	60.31	4.54	130.24
0.22	49.65	4.88	107.23
0.67	81.96	15.03	176.99
2.00	37.80	11.59	81.63
4.00	47.51	8.36	102.60
8.00	21.37	2.62	46.14

C) IC$_{50}$ value for daclatasvir inhibition of human OCT2

Transporter	BMS-790052 (μM)	PYR (μM)
OCT2	7.3	2.8

D) Evaluation of daclatasvir as a human OAT1 inhibitor

BMS-790052 (μM)	PAH uptake (pmol/mg/1.5 min)	SD (pmol/mg/1.5 min)	% control
0.00	12.35	3.23	100.00
0.02	19.56	6.26	158.37
0.07	15.10	3.08	122.27
0.22	13.47	1.50	109.07
0.67	11.90	3.09	96.40
2.00	9.46	0.29	76.60
8.00	8.91	2.09	72.14

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E) Evaluation of daclatasvir as a human OAT3 inhibitor

BMS-790052 (μM)	E3S uptake (pmol/mg/1.5 min)	SD (pmol/mg/1.5 min)	% control
0.00	65.82	2.03	100.00
0.07	59.95	6.32	91.08
0.22	59.68	8.69	90.68
0.67	60.87	4.43	92.48
2.00	60.98	8.20	92.64
4.00	49.41	0.01	75.07
8.00	48.82	17.81	74.17

F) IC$_{50}$ value for daclatasvir inhibition of OAT1 and OAT3

Transporter	BMS-790052 (μM)	Probenecid (μM)
OAT1	> 8	16.7
OAT3	> 8	6.1

Clinical pharmacology reviewer note: Based on the predicted unbound C_{max}/IC$_{50}$ calculations, daclatasvir is not predicted to inhibit OAT1, OAT3 or OCT2.

7) 930051246

Evaluation of daclatasvir ([³H]daclatasvir) as a human BCRP substrate in MDCK-WT and MDCK-BCRP cells

Cell type	Pc (nm/sec)		Efflux ratio	Efflux ratio$_{BCRP}$/ Efflux ratio$_{wild\ type}$
	A to B	B to A		
Wild type	17.4 ± 3	215.8 ± 10	12.4	
BCRP	12 ± 1	130 ± 5	10.8	0.9

Note: Recovery >78%

Clinical pharmacology reviewer note: the applicant states that based on a ratio of 0. 9 (as indicated above), daclatasvir is not a BCRP substrate. However this is not the recommended approach in the February 2012 guidance: Drug Interaction Studies-Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendation.

8) 930066617

Evaluation of daclatasvir ([³H]daclatasvir) as a human OATP1B1 or OATP1B3 substrate in HEK-293 cells

Cell Type	BMS-790052 (10 nM) (pmol/mg/2 min, mean ± SD, n = 3)	BMS-790052 (10 nM) + BSP (50 µM) (pmol/mg/2 min, mean ± SD, n = 3)
mock/HEK cells	1.06 ± 0.04	0.98 ± 0.01
OATP2B1/HEK cells	1.03 ± 0.10	0.95 ± 0.04
OATP1B1/HEK cells	1.02 ± 0.02	0.88 ± 0.01
OATP1B3/HEK cells	0.93 ± 0.02	0.79 ± 0.06

Clinical pharmacology reviewer note: BSP (bromosulfophthalein) was used as an OATP inhibitor. Based on the available information, daclatasvir is not predicted to be an OATP1B1 or OATP1B3 substrate.

9) 930066867

A) Evaluation of daclatasvir metabolism to the M2 metabolite (805215) in human liver microsomes

Inhibitors	Enzyme inhibited	Relative formation of BMS-805215 (%)	
		2 µM BMS-790052	20 µM BMS-790052
Reversible inhibitors			
Solvent control	No inhibitor control	**100**	**100**
Furafylline	CYP1A2	94.0±6.4	101±3.7
Troleandomycin	CYP3A4/5	4.44±0.19	12.9±1.2
Thio-TEPA	CYP2B6	96.8±10	87.0±4.5
Diethyldithiocarbamate	CYP2E1	63.8±1.0	73.8±2.9
ABT	All CYP	2.93±0.46	5.12±0.24
Time dependent inhibitors			
Solvent control	No inhibitor control	**100**	**100**
Tranylcypromine	CYP2A6	98.7±11	97.2±0.8
Ketoconazole	CYP3A4/5	6.92±0.66	11.9±0.33
Montelucast	CYP2C8	92.2±5.3	91.8±7.2
Benzylnirvanol	CYP2C19	103±8.5	98.0±3.8
Sulfaphenazole	CYP2C9	106±9.8	94.1±6.0
Quinidine	CYP2D6	105±12	92.0±3.8

B) Evaluation of daclatasvir metabolism to the M1 metabolite (821647) in human liver microsomes

Inhibitors	Enzyme inhibited	Relative formation of BMS-821647 (%)	
		2 µM BMS-790052	20 µM BMS-790052
Reversible inhibitors			
Solvent control	No inhibitor control	**100**	**100**
Furafylline	CYP1A2	92.4±9.6	97.5±2.6
Troleandomycin	CYP3A4/5	93.3±9.5	88.8±5.4
Thio-TEPA	CYP2B6	121.0±9.0	105.0±5.6
Diethyldithio-carbamate	CYP2E1	47.9±3.7	55.8±0.9
ABT	All CYP	3.34±0.26	5.14±0.25
Time dependent inhibitors			
Solvent control	No inhibitor control	**100**	**100.0**
Tranylcypromine	CYP2A6	104±14	96.5±2.0
Ketoconazole	CYP3A4/5	85.3±12	77.3±5.0
Montelucast	CYP2C8	14.5±0.6	14.7±1.4
Benzylnirvanol	CYP2C19	110±12	94.5±3.0
Sulfaphenazole	CYP2C9	104±11	91.0±6.3
Quinidine	CYP2D6	102±12	90.2±6.0

C) Evaluation of daclatasvir metabolism to the M2 metabolite (805215) with human enzymes

Enzymes	% Formation at 2µM BMS-790052	% Formation at 10µM BMS-790052
Insect control	<0.1	<0.1
CYP1A2	<0.1	<0.1
CYP2A6	<0.1	<0.1
CYP2B6	<0.1	<0.1
CYP2C8	0.422±0.008	0.829±0.105
CYP2C9	<0.1	<0.1
CYP2C19	0.104±0.012	0.214±0.010
CYP2D6	<0.1	<0.1
CYP2E 1	<0.1	<0.1
CYP2J2	<0.1	<0.1
CYP3A4	**100±2.16**	**100±4.48**
CYP3A5	7.60±6.19	10.9±1.8
FMO3	<0.1	<0.1
FMO5	<0.1	<0.1
HLM	18.2±1.6	28.8±2.3

D) Evaluation of daclatasvir metabolism to the M1 metabolite (821647) with human enzymes

Enzymes	% Formation at 2µM BMS-790052	% Formation at 10µM BMS-790052
Insect control	0	0
CYP1A2	0	0
CYP2A6	0	0
CYP2B6	0	0
CYP2C8	93.1±1.8	61.7±6.2
CYP2C9	0	0
CYP2C19	0	0
CYO2D6	0	0
CYP2E1	0	0
CYP2J2	0	0
CYP3A4	6.23±0.54	3.49±0.07
CYP3A5	3.01±0.40	1.50±0.27
FMO3	0	0
FMO5	0	0
HLM	**100±11**	**100±2.4**

Clinical pharmacology reviewer note: Based on the data, daclatasvir CYP2C8 contributed to the formation of the M1 metabolite (821647) and CYP3A4 contributed to the formation of the M2 metabolite (805215).

10) 930069481

Daclatasvir in vitro protein binding in human plasma

Test concentration	% Bound	Standard deviation for %Bound
0.1 μM BMS-790052	97.9	0.248
1 μM BMS-790052	98.0	0.120
10 μM BMS-790052	97.7	0.244

Clinical pharmacology reviewer note: Based on the in vitro data, daclatasvir protein binding is concentration independent.

11) 930066871

Change in mRNA for CYP1A2, CYP 2B6 and CYP 3A

CYP1A2: mRNA levels				
Treatment	Concentration	CYP1A2 mRNA levels (fold change) [a]		
		HC3-15	HC1-18	HC5-10
Dimethyl sulfoxide	0.1% (v/v)	1.00	1.00	1.00
BMS-790052	0.16 μg/mL	0.872	0.876	0.828
BMS-790052	0.32 μg/mL	0.724	0.747	0.638
BMS-790052	0.75 μg/mL	0.649	0.640	0.660
BMS-790052	1.6 μg/mL	0.708	0.708	0.994
BMS-790052	2.5 μg/mL	0.521	0.718	0.578
BMS-790052	4 μg/mL	0.558	0.632	0.646
BMS-790052	6 μg/mL	0.539	0.526	0.498
BMS-790052	9.6 μg/mL	0.650	0.458	1.36
Omeprazole	50 μM	104	41.7	64.5
Flumazenil	50 μM	0.973	0.519	0.917

a   Values are relative to vehicle control, normalized to GAPDH and are the average of triplicate determinations, rounded to three significant figures unless indicated otherwise (e.g., n = 2).

CYP2B6: mRNA levels				
Treatment	Concentration	CYP2B6 mRNA levels (fold change) [a]		
		HC3-15	HC1-18	HC5-10
Dimethyl sulfoxide	0.1% (v/v)	1.00	1.00	1.00
BMS-790052	0.16 μg/mL	0.914	0.890	1.04
BMS-790052	0.32 μg/mL	0.932	0.895	0.900
BMS-790052	0.75 μg/mL	1.04	0.820	1.04
BMS-790052	1.6 μg/mL	1.25	1.02	2.35
BMS-790052	2.5 μg/mL	1.30	1.25	1.47
BMS-790052	4 μg/mL	1.54	1.28	2.42
BMS-790052	6 μg/mL	2.01	1.54	3.28
BMS-790052	9.6 μg/mL	2.65	1.66	3.95
Phenobarbital	750 μM	9.20	7.54	12.8
Flumazenil	50 μM	0.938	0.589	0.787

a   Values are relative to vehicle control, normalized to GAPDH and are the average of triplicate determinations, rounded to three significant figures unless indicated otherwise (e.g., n = 2).

CYP3A4: mRNA levels				
Treatment	Concentration	CYP3A4 mRNA levels (fold change) [a]		
		HC3-15	HC1-18	HC5-10
Dimethyl sulfoxide	0.1% (v/v)	1.00	1.00	1.00
BMS-790052	0.16 μg/mL	1.38	1.45	1.21
BMS-790052	0.32 μg/mL	1.44	1.66	1.34
BMS-790052	0.75 μg/mL	2.50	2.27	1.47
BMS-790052	1.6 μg/mL	5.59	5.70	4.91
BMS-790052	2.5 μg/mL	7.48	9.22	3.70
BMS-790052	4 μg/mL	12.8	12.1	6.35
BMS-790052	6 μg/mL	20.3	13.2	6.68
BMS-790052	9.6 μg/mL	27.3	13.0	8.76
Rifampin	10 μM	26.0	18.1	8.15
Flumazenil	50 μM	0.859	1.26	0.764

a   Values are relative to vehicle control, normalized to GAPDH and are the average of triplicate determinations, rounded to three significant figures unless indicated otherwise (e.g., n = 2).

11) 930068344

A) Daclatasvir R$_3$ values for CYP induction

Enzyme	CYP1A2			CYP2B6			CYP3A4		
Donor	HC3-15	HC1-18	HC5-10	HC3-15	HC1-18	HC5-10	HC3-15	HC1-18	HC5-10
R3	NI	NI	NI	0.66	NI	0.59	0.11	0.15	0.27

Abbreviation: NI, no induction

Clinical pharmacology reviewer note; Based on the R$_3$ values, daclatasvir is predicted to induce CYP2B6 and CYP3A.

B) CYP 2B6 mechanistic static model

1) Equations

$$AUCR = \left(\frac{1}{[A_g \times B_g \times C_g] \times (1-F_g) + F_g} \right) \times \left(\frac{1}{[A_h \times B_h \times C_h] \times f_m + (1-f_m)} \right)$$

	Gut	Liver
Reversible inhibition	$A_g = \dfrac{1}{1 + \dfrac{[I]_g}{K_i}}$	$A_h = \dfrac{1}{1 + \dfrac{[I]_h}{K_i}}$
Time-dependent inhibition	$B_g = \dfrac{k_{deg.g}}{k_{deg.g} + \dfrac{[I]_g \times k_{inact}}{[I]_g + K_I}}$	$B_h = \dfrac{k_{deg.h}}{k_{deg.h} + \dfrac{[I]_h \times k_{inact}}{[I]_h + K_I}}$
Induction	$C_g = 1 + \dfrac{d \bullet E_{max} \bullet [I]_g}{[I]_g + EC_{50}}$	$C_h = 1 + \dfrac{d \bullet E_{max} \bullet [I]_h}{[I]_h + EC_{50}}$

$[I]_h = f_{u,b} \times ([I]_{max,b} + F_a \times K_a \times Dose/Q_h)$,

$[I]_g = F_a \times K_a \times Dose/Q_{en}$

$f_{u,b} = f_u \div (Cb/Cp)$

$[I]_{max,b} = Cmax \times (C_b/C_p)$

2) Parameters

Parameters	BMS-790052	Bupropion (for CYP2B6)
Dose (mg)	60	NA
Cmax (μg/mL)	1.73[a]	NA
MW (g/mol)	738.89	NA
f_u	0.02[b]	NA
C_b/C_p	0.76[c]	NA
[I]max,b (μM)	1.78	NA
$f_{u, b}$	0.026	NA
$K_a(min^{-1})$	0.1[d]	NA
Fa	1[d]	NA
Q_h (L/hr/70 kg)	97[d]	NA
Qen (L/hr/70 kg)	18[d]	NA
d	1	NA
F_g	NA	1.0
F_m	NA	0.50

[a] BMS-790052 Cmax at steady state following once daily oral dosing of 60 mg BMS-790052 to HCV subjects for 14 days.
[b] Based on protein binding of BMS-790052 in human plasma at 1 μM (98.0%).[8]
[c] Mean blood-to-plasma concentration ratio of BMS-790052 (10 μM).[9]
[d] Suggested value in the FDA guidance
Abbreviation: NA, not applicable

3) Results

Enzyme	CYP2B6		
Probe substrate	Bupropion		
Donor	HC3-15	HC1-18	HC5-10
Ag	1	1	1
Ah	1	1	1
Cg	4.12	1	6.72
Ch	1.06	1	1.07
AUCR	0.97	1	0.96

Abbreviation: NA, not applicable

Clinical pharmacology reviewer note; Based on the AUCR values, daclatasvir is not predicted to inhibit or induce CYP2B6.

4.2 **Consult Reviews**

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

NDA:	206843(Daclatasvir) and 206844 (Asunaprevir)
Drug	Daclatasvir / Asunaprevir (Abbreviated as DCV/ASV)
Trade Name	To be determined
Pharmacometrics Reviewer	Fang Li, Ph.D.
Pharmacometrics Team Leader (Acting)	Jeffry A. Florian, Ph.D.
Clinical Pharmacology Review	Stanley Au, Pharm.D.
Clinical Pharmacology Team Leader	Shirley Seo, Ph.D.
Sponsor	Bristol Myers Squibb
Submission Type; Code	Original New Drug Application (New Molecular Entity), Priority
Indication	Treatment of Chronic Hepatitis C Infection

1   SUMMARY OF FINDINGS

1.1   Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1   Is there any evidence of significant exposure-response analysis for efficacy with asunaprevir/daclatasvir (ASV/DCV) treatment in patients infected with genotype 1b hepatitis C virus (HCV)?

No, for both daclatasvir and asunaprevir, PK/PD analyses of Phase 3 data from AI447026 and AI447028 (ASV/DCV dual therapy) showed a flat exposure-response relationship for efficacy endpoint (SVR12) over the exposure range observed in the Phase 3 studies. This flat relationship suggests that exposures for 100 mg BID ASV and 60 mg QD DCV may be on the plateau of the exposure-response curve.

Individual daclatasvir and asunaprevir exposures for subjects receiving ASV/DCV treatment in the Phase 3 trials were estimated based on the final population PK models of daclatasvir and asunaprevir, respectively. Estimated steady-state average concentration (   ) (b) (4) for ASV and 24 hours for DCV), from two Phase 3 studies (AI447026 and AI447028) for 100 mg BID ASV and 60 mg QD DCV were used for exposure-response analysis. The primary efficacy endpoint

SVR12 was evaluated as the dependent response measures using logistic regression analyses and individual Css,avg of daclatasvir and asunaprevir were treated as independent measures. A non-significant flat and a marginally significant shallow exposure-response relationship between ASV(⬛⬛⬛ (b) (4)) and DCV (p=0.0204) exposures and SVR12 was identified over the range of ASV and DCV exposures observed in AI447026 and AI447028, as shown in Figure 1 and Table 1. The shallow exposure-response relationship does not necessitate any dose adjustments as a means of increasing SVR12 rate in those subjects with the lowest exposures in the Phase 3 trials.

In addition to ASV and DCV exposure, the effect of baseline factors (i.e., including gender and NS5A viral polymorphisms) on the probability of achieving SVR12 was explored by the reviewer. The NS5A polymorphisms Y93H and L31F/I/M/V were found to be significant predictors of SVR12. Subjects with Y93H and L31F/I/M/V were observed and predicted to have significantly lower SVR12 rate than subjects without the mutations (Figure 2).

Figure 1: Relationship between the Proportion of Subjects Achieving SVR12 and either DCV or ASV Css the AI447026 and AI447028 Trials

(b) (4)
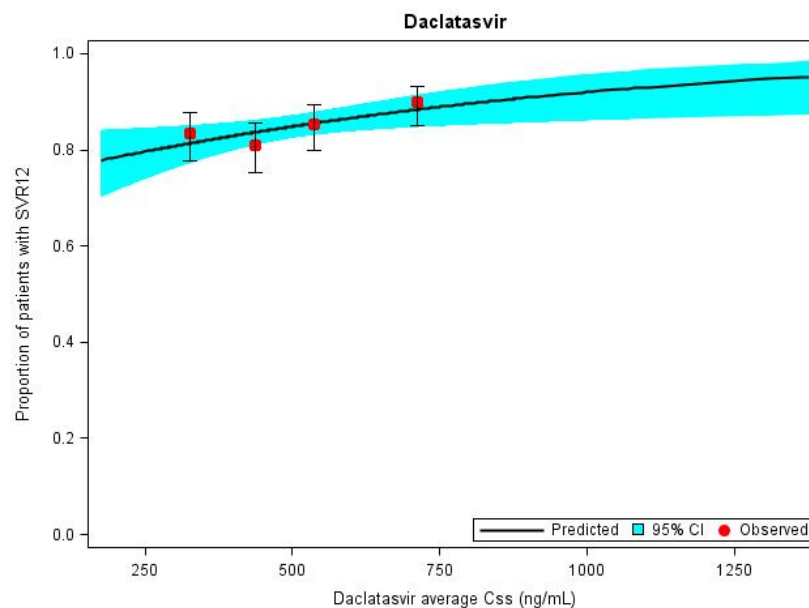
Table 1: **Primary Efficacy of ASV/DCV Dual Therapy in HCV 1b Subjects by Exposure Groups (Pooled Data from AI447026 and AI447028)**

	SVR12				
	Q1	**Q2**	**Q3**	**Q4**	**Total**
DCV	180/216(83%)	175/216(81%)	184/216(85%)	194/216(90%)	733/864(85%)
ASV					(b) (4)

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Figure 2: Relationship between the Proportion of Subjects Achieving SVR12 and DCV Exposure (C$_{ss,avg}$) in Subjects with Y93H and L31F/I/M/V Polymorphisms.
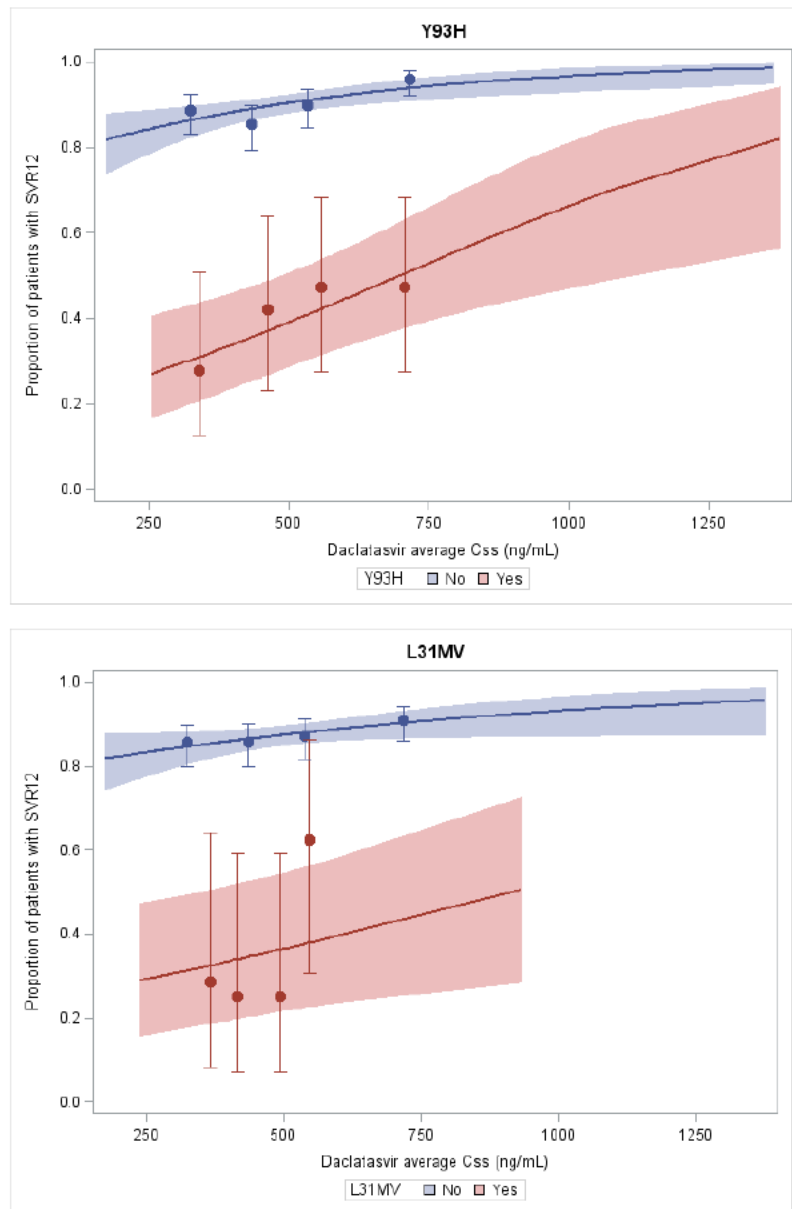
Note: Plotted data points are observed quartile mean (95% CI). The shaded areas are model-estimated 95% CI based on a logistic regression analysis.

1.1.2 Is There any Exposure-Response Relationship between Safety Events of Interest (Laboratory ALT, AST, Total Bilirubin Elevations) and ASV and DCV Exposures?

There was no significant relationship between DCV exposure and event rate for grade 2 or higher on-treatment ALT and AST elevation. However, ___ (b) (4) ___ ASV exposure (b) (4)

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[REDACTED] (b) (4). This was consistent with observations from Phase 2 studies of DCV/ASV [REDACTED] (b) (4).

[REDACTED] (b) (4)

The exposure-response analysis for safety was conducted using the combined safety data from the two Phase 3 trials AI447028 and AI447026. Relationship between the probability of AEs related to abnormal liver enzymes and DCV or ASV exposure were explored by the reviewer. The submitted data only allowed the FDA reviewer to conduct exposure-response analysis for the ASV/DCV combination treatment. The analysis dataset consisted of AE records from 863 ASV/DCV-treated subjects.

The reviewer analyzed the relationship between elevated liver enzymes (ALT, AST, and TB) which may be indicative of drug-related liver injury, and DCV and ASV exposures. Events were considered on-treatment if they occurred after week 2 of treatment but before week 4 of treatment follow-up. Baseline and early laboratory assessments were excluded from the on-treatment event analysis as it is common for patients infected with HCV to have elevated baseline ALT/AST levels due to the ongoing HCV infection.

Higher ASV exposure was observed to be associated with a greater probability of grade 1 or higher ALT or AST elevation By contrast, higher DCV exposure was not found to be associated with greater probability of liver enzyme abnormalities (Figure not shown). More clinically relevant liver enzyme elevations are those on-treatment grade 2 or higher ALT, AST, or TB elevation excluding pretreatment and post-treatment abnormalities. Their relationships with ASV and DCV were explored. A marginally significant relationship between clinically relevant liver enzyme increase and ASV concentrations were observed with the p-value for ALT, AST and TB of 0.0204, 0.0002, and <0.0001, respectively (Figure 3).Because only a few subjects were observed with grade 3 or higher liver enzyme AEs in ASV/DCV-treated subjects, neither DCV nor ASV was identified to have significant relationship with the probability of grade 3 or 4 liver enzyme elevation.

Figure 3: Exposure-Reponses Relationships between ASV Exposures (AUC) and the Proportion of Subjects with On-treatment Grade 2 and Above Liver Enzyme (ALT, AST, TB) Abnormalities
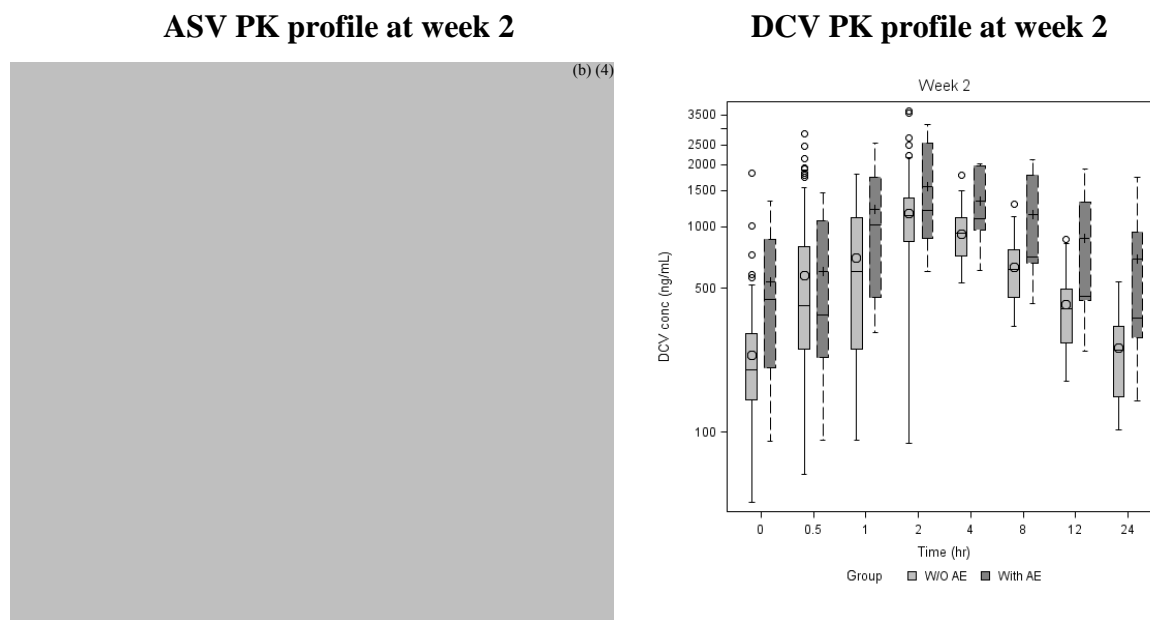
Asunaprevir

(b) (4)

Daclatasvir

Note: The points are observed quartile mean. The shaded areas are model-estimated 95% CI based on a logistic analysis.

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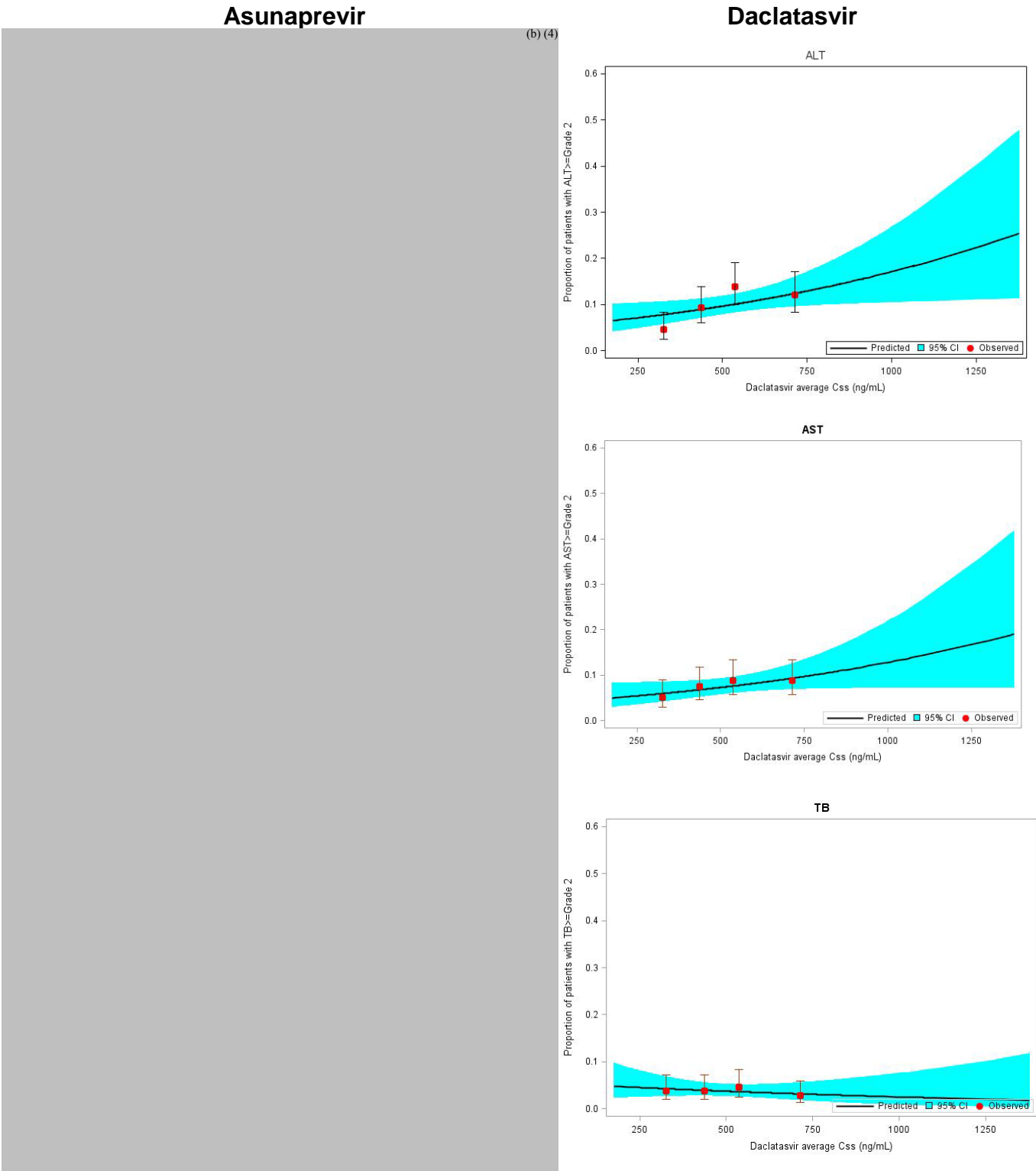
Besides liver toxicity, the FDA review team explored indications of hypersensitivity such as pyrexia and increased eosinophilia. The AEs of concern included pyrexia and increased eosinophilia within two weeks of reported pyrexia cases with or without liver enzyme elevation. The pharmacometrics reviewer explored the role of DCV or ASV exposure in subjects identified as having these AEs of concern. A total of 16 Japanese subjects in study AI447026 and 3 Caucasians in study AI447028 were identified with pyrexia and increased eosinophilia (Table 2). As indicated in Figure 4, the exposure of DCV and ASV in the 16 subjects was higher than those without AEs at week 2, but the difference disappeared after week 2 when treatment continues.

While ASV and DCV exposures in the 16 subjects with AEs of interest (pyrexia and eosinophilia with or with liver function abnormalities) appear to be elevated compared to subjects who did not experience the AEs of interest, the small number of subjects precludes determination of an exposure-driven relationship for the adverse events. In addition, the ASV and DCV exposures for the 16 subjects were within the range of predicted concentrations for the 7026 and 7028 trials. Overall, we concluded that the differences in ASV or DCV exposure do not appear to play a major role in contributing to the reported AEs of interest.

Table 2: Comparison of Model-Estimated ASV and DCV exposure in Japanese Subjects

Group	N	ASV AUC$_{(0-tau)}$ (ng*hr/mL) Mean (SD)	DCV AUC$_{(0-tau)}$ (ng*hr/mL) Mean (SD)
Trial 7026 (Japan) Pyrexia & Eosinophilia Within 2 Weeks	16	(b) (4)	14100 (5544)
Trial 7026 (Japan) No Pyrexia But increased eosinophils	206		12216 (3378)
Trial 7028 (Global)	641		12289 (4411)

Figure 4: PK profile at Week 2 Categorized by Occurrence of AEs of Interest in Japanese Subjects

ASV PK profile at week 2


(b) (4)

DCV PK profile at week 2

1.1.3 Are there any covariates that significantly influence PK parameters of daclatasvir or asunaprevir and are dose adjustments needed based on these covariates?

Daclatasvir: Clinical studies demonstrated that no dose adjustment was necessary in the following specific populations: elderly patients, males or females, patients with severe renal impairment, patients with liver cirrhosis, and patients with moderate to severe hepatic impairment.

Effects of the following intrinsic factors on the pharmacokinetics of daclatasvir were evaluated in the population PK analysis: age, sex, body weight, race, ALT, AST, creatinine clearance (CrCL), and cirrhosis status. Significant covariates identified in the final model included sex, race, genotype, baseline CrCL and ALT change on CL/F (Figure 5), and sex, race, and body weight on Vc/F. Only the impact of female gender on clearance was outside of the 80-125% boundary while the impact of all other significant covariates was within the 80-125% range. Female subjects showed a 33% higher steady AUC after 60 mg dose than male subjects. Dose adjustments for daclatasvir based on these covariates are not necessary, due to a lack of significant exposure-response relationships for either efficacy or safety. Other intrinsic factors were not identified as having a significant effect on daclatasvir clearance.

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Figure 5: Relationship between Population PK Clearance Estimates for Daclatasvir and Covariates of Body Weight, Age, Baseline ALT, Baseline CrCL, Race, and Sex
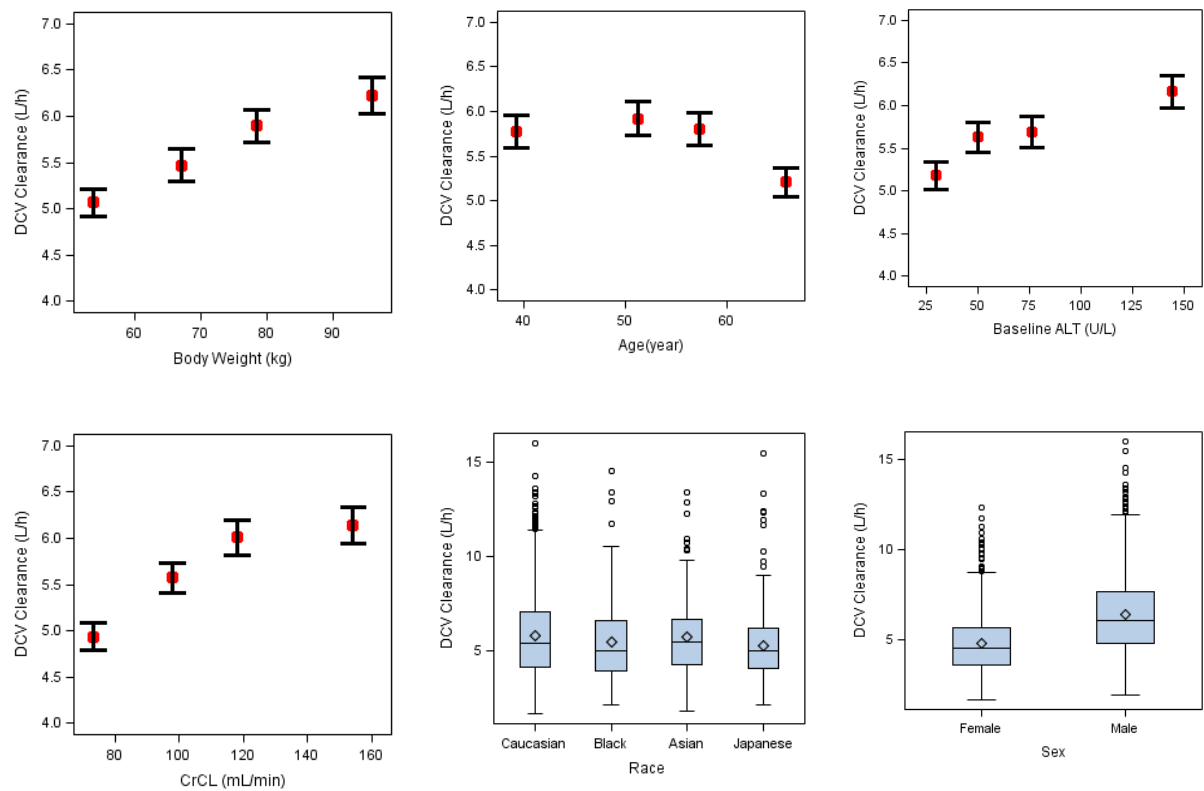

Note: The box and quartile plots are based on empirical Bayesian individual estimates.

(b) (4)

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1.1.4 Based on the PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The dose-exposure relationship after multiple doses of DCV were explored using population PK datasets derived from Phase 2 and Phase 3 studies. Model-estimated exposure for DCV versus planned doses were summarized (Table 3, Figure 7) and assessed via a power model (logAUC=intercept +slope*logDose) (Table 4). The results indicated that the increase in DCV exposure after multiple doses was slightly more than dose proportional in subjects with HCV genotype 1b infection.

Figure 7: Plots of Model-Estimated AUC$_{0\_24}$ vs. Dose for DCV
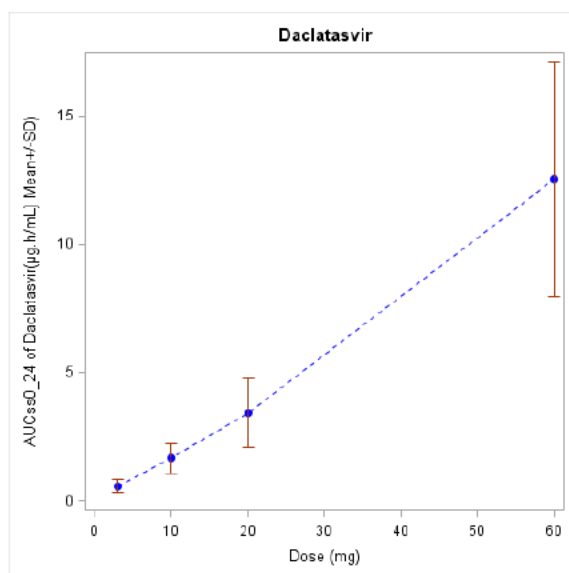
Table 3: Dose and Model-Estimated PK Parameters for DCV

DCV DOSE (mg)	N	CL/F (L/h) Mean (SD)	AUC$_{0\_24}$ (µg.h/mL) Mean (SD)
3	12	6.15 (2.38)	0.57 (0.26)
10	47	6.94 (2.77)	1.65 (0.59)
20	355	6.69 (2.41)	3.42 (1.33)
60	1735	5.42(1.96)	12.55 (4.57)

Table 4: Regression Analyses of LogAUC$_{tau}$ vs. LogDose for DCV

	Point Estimate of Intercept	Point Estimate of Slope	95% CI for Slope
DCV	-2.24	1.149	(1.12,1.18)

1.2 Recommendations

The Division of Pharmacometrics (Office of Clinical Pharmacology) has reviewed this application from a clinical pharmacology perspective and recommends [redacted] (b) (4)

No exposure-response analyses for pegylated-interferon/ribavirin/ASV/DCV (QUAD) therapy were submitted to the Agency for review. The overall high SVR rates from this trial (93.2-100%) suggest that an exposure-response relationship for the range of ASV and DCV exposures with that regimen are not likely to be identified. In addition, the

inclusion of pegylated-interferon and ribavirin in the regimen would hinder identification of safety signals associated with DCV and ASV treatment. As such, the review of exposure-response data from the QUAD study was deemed not necessary.

The reviewer agrees with the sponsor's conclusions from the population PK analyses and exposure-response analysis that no dose adjustment are necessary for DCV or ASV based on the evaluated covariates (body weight, age, race, ALT, AST, and race).

1.3   Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in <u>underline blue font</u>.

Please refer to the accompanying sections of the QBR.

2   PERTINENT REGULATORY BACKGROUND

BMS submitted two NDAs to the Division of Antiviral Drug Products, Center for Drug Evaluation and Research of FDA on March 31, 2014 to seek marketing approval of daclatasvir (DCV, NDA206843) and asunaprevir (ASV, NDA206844) for the treatment of adults with chronic hepatitis C infection   (b) (4)
                    Both molecules were proposed for use in combination with other agents.

Daclatasvir is a hepatitis C virus (HCV) NS5A replication complex inhibitor. It is available in strengths of 30 mg and 60 mg tablets. The proposed dosing regimen for daclatasvir is 60 mg once daily with or without food in combination with other agents.

Asunaprevir is a hepatitis C virus (HCV) NS3/4A protease inhibitor indicated for the treatment of chronic HCV infection   (b) (4)

The initially proposed combined therapy by BMS included DCV/ASV, DCV/SOF, and DCV/ASV/pegIFN/RBV. On March 9, FDA informed BMS that FDA was unable to use information from study AI444040 (DCV/SOF) to support regulatory action on labeling, therefore, relevant information should be removed from the draft labels.

Three open-label phase 3 studies (AI447026, AI447028, AI447029) and two supporting Phase 2 studies (AI447011, AI447017) were submitted to support the efficacy and safety of the dual combination therapy of ASV/DCV   (b) (4)
                    . The primary analyses by the sponsor have shown that the SVR12 rates achieved with the DCV/ASV therapy in HCV GT-1b-infected prior non-responders were 82.4% in AI447028, 80.5% in AI447026, and 83.3 in AI447011. Similar SVR12 rates were achieved with DCV/ASV therapy in INF/RBV-based therapy intolerant/ineligible GT-1b subjects (82.6% in AI447028, 88.1% in AI447026, and 63.6 in AI447017, indicating the dual therapy with DCV/ASV was effective for those patients.

The SVR12 rates achieved with DCV Quad therapy (DCV 60 mg QD/ASV 100 mg BID/pegIFNα/RBV) in GT-1 prior non-responders was 93.2% in AI447029 and 95.0% in AI447011. In GT-4 prior non-responders, the SVR12 rates achieved by DCV Quad therapy were 100% in study AI449029.

In addition to efficacy and safety data, the sponsor submitted two population PK analyses, one for DCV and one for ASV, as well as exposure-response analysis for DCV/ASV. As of this review cycle, the sponsor did not submit exposure-response analysis for the QUAD therapy. As a result, the focus of this pharmacometrics review focused solely on DCV/ASV DUAL therapy treatment.

3   RESULTS OF SPONSOR'S ANALYSIS

3.1   Population PK analysis-Daclatasvir

Objectives: The objectives of the population PK analysis of daclatasvir were to:

- Estimate typical values and inter-patient variability (IIV) of PK parameters in the HCV patient population.
- Determine the effects of demographic, pathophysiologic, and hepatitis C virus (HCV) disease-related covariates on the PK of daclatasvir to better understand clinical factors that might affect the PK in individual patients.
- Provide individual patient PK parameter estimates for subsequent exposure-response (ER) analysis.

Data: The population PK dataset was pooled from 11 clinical studies (AI444010, AI444011, AI444014, AI444021, AI444022, AI444031, AI444040, AI447011, _(b) (4)_, AI447026 and AI447028) . A total of 2149 subjects with 19,542 quantifiable plasma DCV concentrations were included in the final dataset. Among which, 1167 subjects (54.3%) were male and 982 subjects (45.7%) were female. The datasets consisted of 1440 (67.0%) white, 156 (7.3%) black, and 339 (15.8%) Japanese patients. The summary of subject characteristics and laboratory values is demonstrated in Table 5 and Table 6.

Table 5: **Summary of Baseline Demographic and Characteristics Data**

Covariate	Statistic	Value
Age (years)	Mean (SD)	54 (11)
(N=2149)	Median (min,max)	55 (18 to 79)
Weight (kg)	Mean (SD)	74 (17)
(N=2149)	Median (min,max)	73 (36 to 126)
Gender (N=2149)		
Female	N (%)	982 (45.7%)
Male	N (%)	1167 (54.3%)
Race (N=2149)		
White	N (%)	1440 (67.0%)
Black/African American	N (%)	156 (7.3%)
American Indian or Alaska Native	N (%)	4 (0.2%)
Asian (non-Japanese)	N (%)	178 (8.3%)
Native Hawaiian or other Pacific Islander	N (%)	2 (0.1%)
Other	N (%)	30 (1.4%)
Japanese	N (%)	339 (15.8%)

Table 6: **Summary of Baseline Clinical Laboratory Data**

ALT (U/L)	Mean (SD)	62 (39)
(N=2149)	Median (min,max)	51 (12 to 595)
AST (U/L)	Mean (SD)	75 (50)
(N=2149)	Median (min,max)	62 (5 to 475)
Creatinine Clearance (mL/min)	Mean (SD)	111 (32)
(N=2149)	Median (min,max)	108 (40 to 250)

Population PK Model

Base Model:

The selected base model to describe the PK of DCV was a 2-compartment model as described in Figure 8. Absorption of DCV was modeled as zero-order release of the drug followed by a first-order absorption into the central compartment. Inter-individual variability was estimated in CL/F, Vc/F, and Ka, with interaction between CL/F and Vc/F. The residual error model was additive in log-transformed DCV plasma concentration.

Figure 8: **Two-compartment PK model with Zero-order Release and First order Absorption**
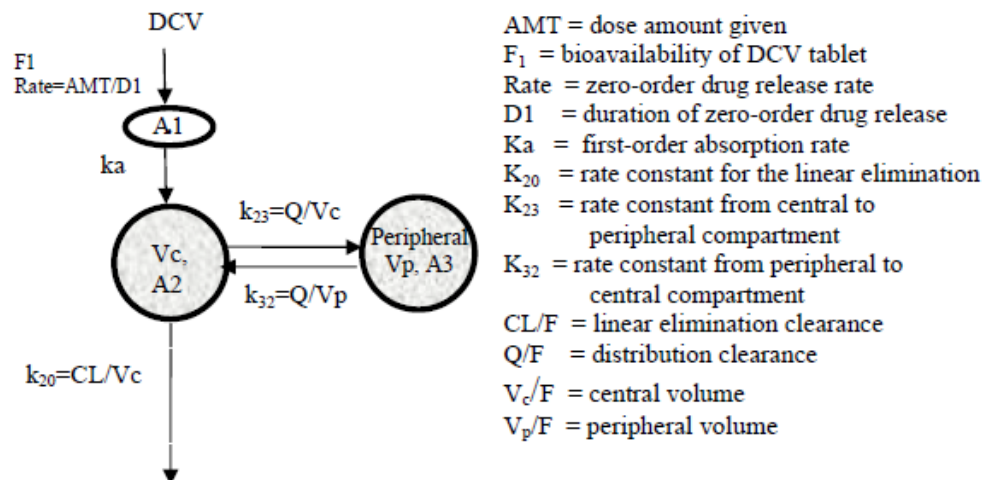
Source: Figure 5.1.1-1 of sponsor's population PK report

The parameter estimates for the base PK model are summarized in Table 7. The corresponding goodness-of-fit plots are shown in Figure 9**.**

Table 7: Parameter Estimates and Standard Errors from the Base Structural Pharmacokinetic Model for Daclatasvir

Parameters	Symbol	Estimate (RSE %)	95% CI
Fixed Effect			
CL/F (L/hr)	$\exp(\theta_1)$	5.42 (1.09 %)	5.30 – 5.54
Vc/F (L)	$\exp(\theta_2)$	55.7 (1.44 %)	54.2 – 57.3
Q (L/hr)	$\exp(\theta_3)$	3.1 (7.65 %)	2.66 – 3.60
Vp (L)	$\exp(\theta_4)$	29.4 (7.69 %)	25.3 – 34.1
Ka (1/hr)	$\exp(\theta_5)$	3.16 (6.24 %)	2.79 – 3.57
D1 (hr)	$\exp(\theta_6)$	0.884 (4.12 %)	0.816 – 0.959
Random Effect			
Omega CL/F (%)	ω_{CL}	38.6 (3.52 %)	37.2 – 39.9
Omega Vc/F (%)	ω_{Vc}	33.9 (5.64 %)	32.0 – 35.7
Omega CL/F*Vc/F (%)	$\mathrm{sqrt}(\omega_{CL.Vc})$	33.9 (8.63 %)	30.9 – 36.7
Omega ka (%)	ω_{ka}	147 (6.02 %)	138 – 155
Residual			
Sigma (%)	σ	41.1 (2.4 %)	40.1 – 42.1

RSE of the fixed effect was presented as NONMEM estimated SE x 100% RSE of the random effect (ω) and residual variability (σ) were relative to the estimated variance (ω^2 or σ^2).

Source: Table 5.1.1-1 of sponsor's population PK report

Figure 9: Goodness-of-fit Plots for the Base Structural PK Model of Daclatasvir
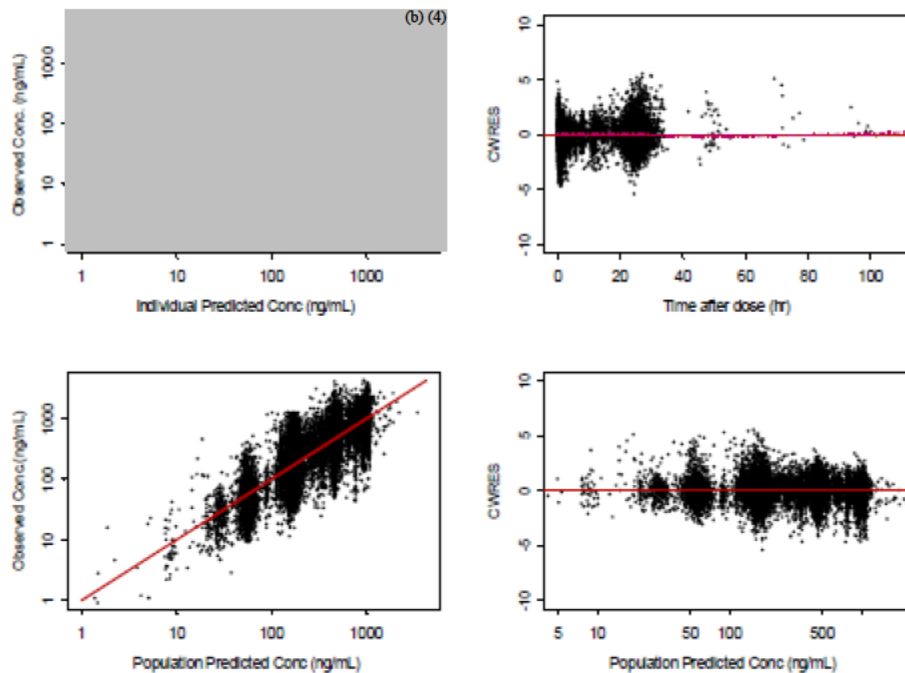
Source: Figure 5.1.1-2 of sponsor's population PK report

Final Model

Full population PK model was constructed via forward inclusion of covariates of interest and then reduction step by removing covariates to check MVOF. The resulted model was then refined to the final model. The parameter estimates of the final model were summarized as shown in the Table 8. The magnitude of the intersubject variability was large for ka (194% CV), but was modest for CL (35.1% CV) and V_c (29.5% CV). The calculated η-shrinkage values were 29.2% for ka, 5.94% for CL, and 16.4% for Vc. The model was evaluated by goodness-of-fit plots and visual predictive checks (VPC) (Figure 10 **and** Figure 11).

The effect of covariates on daclatasvir PK and exposure are presented in Figure 12 and Figure 13.

Table 8: Parameter Estimates of the Final PK Model for Daclatasvir

Parameters	Symbol	Estimate (RSE %)	95% CI
Fixed Effect			
CL/F (L/hr)	$\exp(\theta_1)$	5.7 (1.58 %)	5.52 – 5.88
Vc/F (L)	$\exp(\theta_2)$	58.6 (2.0 %)	56.3 – 60.9
Q (L/hr)	$\exp(\theta_3)$	2.92 (7.41 %)	2.52 – 3.37
Vp (L)	$\exp(\theta_4)$	31.2 (7.46 %)	26.9 – 36.1
Ka (1/hr)	$\exp(\theta_5)$	3.16 (5.25 %)	2.85 – 3.5
D1 (hr)	$\exp(\theta_6)$	0.873 (3.52 %)	0.815 – 0.935
WT~Vc/F	θ_7	0.585 (8.32 %)	0.490 – 0.680
Female~CL/F	θ_8	-0.265 (6.64 %)	-0.299 – -0.231
Female~Vc/F	θ_9	-0.230 (10.8 %)	-0.279 – -0.181
Race Black~CL/F	θ_{10}	-0.0874 (36.8 %)	-0.151 – -0.0243
Race Asian~CL/F	θ_{11}	0.0682 (29.3 %)	0.029 – 0.107
Race Others ~CL/F	θ_{12}	-0.145 (43.7 %)	-0.269 – -0.0209
Race Black~Vc/F	θ_{13}	0.0123 (335 %)	-0.0685 – 0.0931
Race Asian~Vc/F	θ_{14}	0.193 (14.8 %)	0.137 – 0.249
Race Others~Vc/F	θ_{15}	-0.173 (41.1 %)	-0.312 – -0.0336
ALT~CL/F	θ_{16}	-0.0354 (19.1 %)	-0.0486 – -0.0222
BCrCL~CL/F	θ_{17}	0.133 (18.9 %)	0.0836 – 0.182
Genotype 1a~CL/F	θ_{18}	0.0929 (15 %)	0.0657 – 0.120
Random Effect			
Omega CL (%)	ω_{CL}	35.1 (3.64 %)	33.8 – 36.3
Omega Vc (%)	ω_{Vc}	29.5 (5.99 %)	27.8 – 31.2
Omega CL*Vc (%)	$\mathrm{sqrt}(\omega_{CL,Vc})$	27.3 (10.1 %)	24.5 – 29.9
Omega ka (%)	ω_{ka}	148 (5.8 %)	139 – 156
Residual			
Sigma (%)	σ	41 (2.39 %)	40 – 41.9

Note: Typical PK model was estimated for a white, 70 kg, male, genotype 1b HCV patient with baseline CrCL of 100 mL/min and no change in ALT. RSE % of the fixed effect was presented as NONMEM estimated SE x 100 %. RSE of the random effect (ω) and residual variability (σ) were relative to the estimated variance (ω^2 or σ^2). Source: 2014 01 02 DCV final model-review.ssc

*Source: Table 5.1.3-1 of the Sponsor's population PK report*

Figure 10: Goodness-of-Fit Plots for the Final PK Model of Daclatasvir
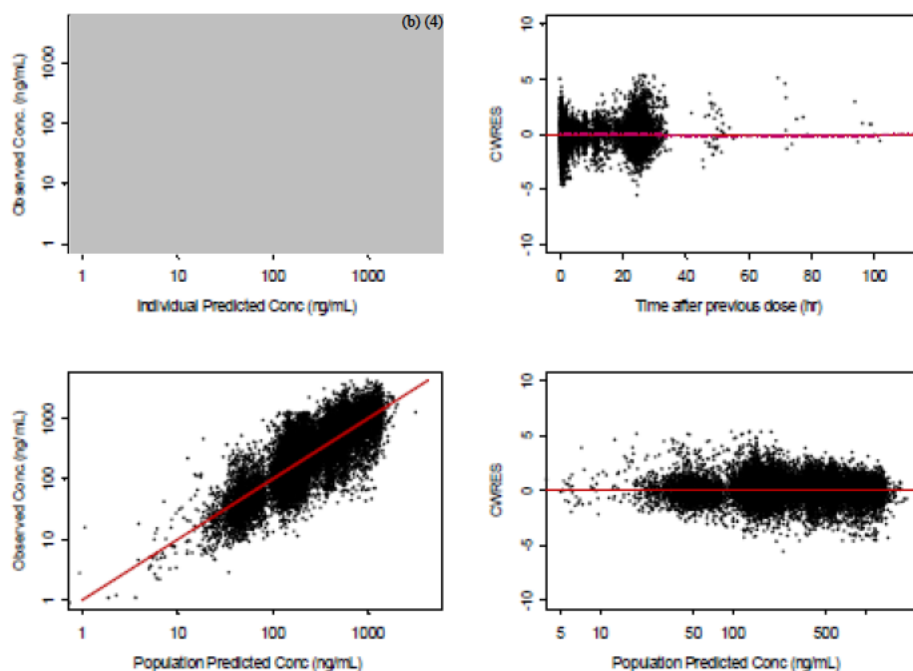
Source: Figure 5.2.1-1 of the sponsor's population PK report

Figure 11: Prediction-Corrected Visual Predictive Check (Normalized to 60 mg Regimen) of the Final Population PK Model Overlaid on the Median (5th and 95th Percentiles) of Observed Daclatasvir Data
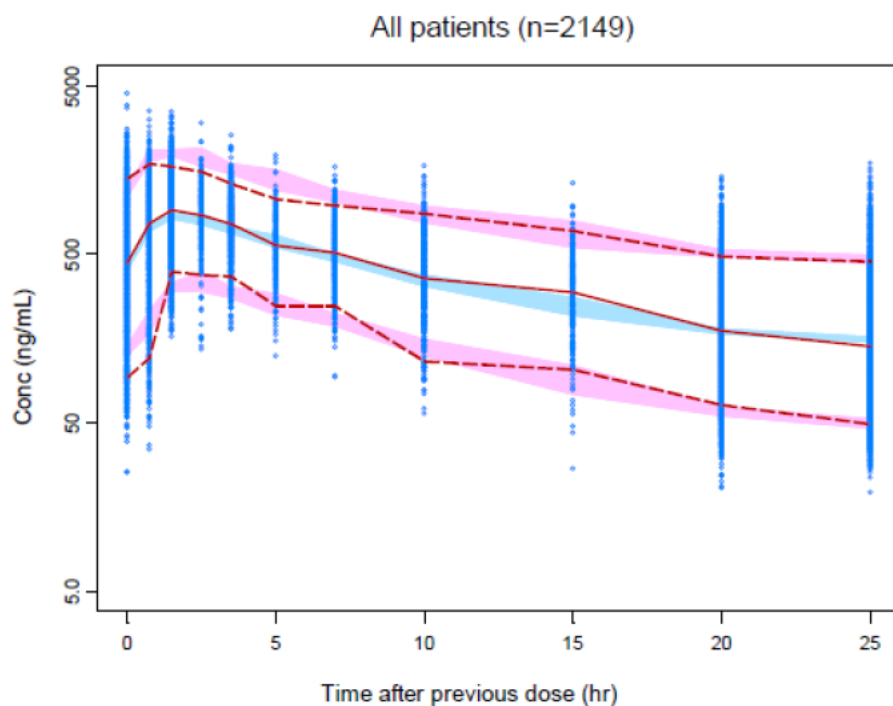
Shrinkage

The shrinkage of the final model parameters was minimal as presented in Table 9

Table 9: Shrinkage Estimates of Inter-Individual and Intra-Individual Variability of the Final Population PK Model

Parameter	Parameter Description	Shrinkage (%)
$\omega_{CL/F}$	IIV of CL/F	5.94
ω_{Vc}	IIV of Vc/F	16.4
ω_{ka}	IIV of Ka	29.2
σ	Residual error (%)	8.65

Effect of Covariate on PK Parameters of Daclatasvir

Figure 12: Impact of Covariate on PK Parameters of the Final Model
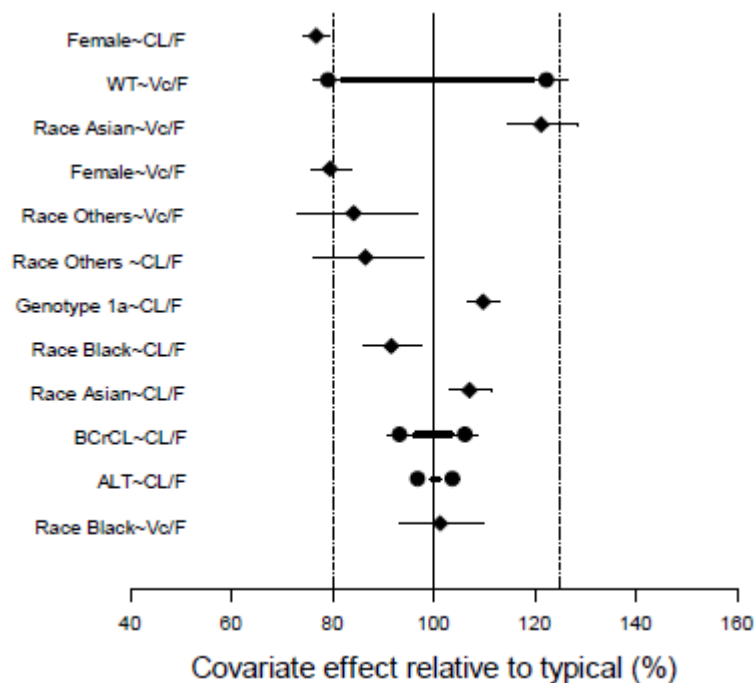
Note: Typical PK parameters were estimated for a white, 70 kg, male, genotype 1b HCV patient with baseline ALT of 60 IU/L and baseline CrCL of 100 mL/min. PK parameters at 5th percentile and 95th percentile of the population values of WT and BCrCL, or at different levels of the categorical covariates was compared with typical PK estimates. Dashed vertical lines indicate 80% and 125% difference from typical. Horizontal error bars indicate 95% CI of the values.

Effect of Covariates on Daclatasvir Exposure

Figure 13: Impact of Covariate on Steady State AUC

Steady State AUCss (ng.hr/mL)

AUC Range 6146.9 (-41.4%)	20627.1 (96.8%)
SEXF (0%)	(30.3%)
Race Others (0%)	(15.6%)
CrCL 170 mL/min (-6.8%)	64 mL/min (6.1%)
Race Black (0%)	(9.1%)
Genotype 1a (-8.9%)	(0%)
ALT/BALT 17 % (-6.1%)	117 % (0.6%)
Race Asian (-6.6%)	(0%)
WT 49 kg (0%)	103 kg (0%)

Base = 10482.8 ng.hr/mL

White, Male, Geno 1b, WT=70 kg, CrCL=100 mL/min
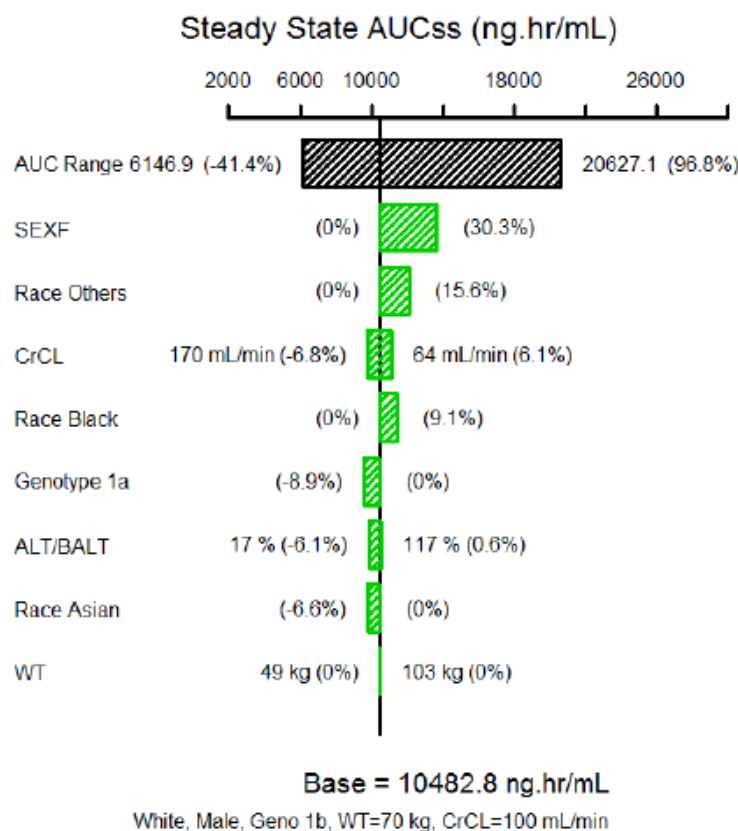
Note: Black bar represents 5th to 95th percentile of the exposure calculated using EBEs of the population after 10 doses of DCV 60 mg QD. The impact of a covariate on the exposure were calculated using the parameter(s) incorporating the isolated effect of that covariate, with other unaffected parameters fixed to the typical values (estimated for a white, male, genotype 1b HCV patient with baseline body weight of 70 kg, CrCL of 100 mL/min and no change of ALT). Continuous covariates were evaluated at 5th to 95th percentile of the population. SEXF is covariate effect of female gender.

Source: Figure 5.3.2-1 of the sponsor's report

Reviewer's Comment:

- *The population PK analysis is adequate in characterizing the PK profile of DCV in Phase II and III trials. The final model reasonably described the observed data. The estimated PK parameters, such as CL/F and Vc/F, are reasonable. The sponsor's analyses were verified by the reviewer, with no discordance identified. DCV steady state concentrations from the final population PK model were used by the sponsor and reviewer in subsequent exposure-response analyses.*

3.2 Population PK analysis-Asunaprevir

(b) (4)

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3.3   Exposure-response analysis for efficacy

Objectives: The primary objectives of exposure-response analysis of daclatasvir were to:

- To characterize the relationship between the exposures of asunaprevir (ASV) and daclatasvir (DCV) and SVR12 in subjects who were HCV genotype 1b treatment naive, non-responders to peginterferon α(pegIFNα)/ribavirn (RBV) or interferon β (IFNβ)/RBV, and IFN based therapy ineligible naive/intolerant receiving DUAL treatment.

Data: This exposure-response (E-R) efficacy analysis was performed using combined data in HCV-infected genotype 1b subjects who received the DUAL combination therapy DCV and ASV from four clinical studies (AI447011,   (b) (4), AI447026 and AI447028). The antiviral efficacy response was SVR12 (sustained virologic response at 12 weeks post treatment). The Css,avg (average plasma concentration at steady state) for ASV and DCV, calculated from individual *post-hoc* parameter estimates based on their respective population pharmacokinetic (PPK) model, were used as the summary measure of exposures.

Methods: The relationship between the probability of achieving SVR12 and the Css,avg for ASV and DCV was described using a logistic regression model, including assessments of the potential modulatory effects of selected covariates (race, baseline age, body weight, gender, NS5A polymorphisms of Y93H and L31MV, etc.) on the E-R relationship. A basic model was first developed to establish the relationship between ASV and DCV exposure and SVR12 without consideration of any potential effects of covariates. Subsequently, a full model was developed by identifying all significant covariates (p<0.05) with forward addition process. Lastly the final model was reached by retaining all statistically significant covariates (p<0.001) following a backward

elimination method. The model development was with NONMEM (Version 7.2, level 2.0, ICON Development Solutions).

Models: The final model was depicted using a logit expression as below:

$$\mu = \beta_0 + \beta_1 \times (C_{ssavg,ASV} - REF_{ASV}) + \beta_2 \times (C_{ssavg,DCV} - REF_{DCV})$$
$$+ \beta_3 \times (C_{ssavg,ASV} - REF_{ASV}) \times (C_{ssavg,DCV} - REF_{DCV})$$
$$+ \beta_4 \times Y93H + \beta_5 \times L31MV$$

The parameter estimates in the final model are summarized in Table 11.

Table 11: Summary of Final Model Parameter Estimates

Name[a]	Symbol	Estimate	Standard Error (RSE%)[b]	95% Confidence Interval[c]
Intercept	β_0	2.26	0.121 (5.35)	2.02 - 2.52
ASV	β_1			(b) (4)
DCV	β_2	0.00211	6.71E-04 (31.8)	7.36E-04 - 0.00332
Interactions between ASV and DCV	β_3	-5.60E-06	4.48E-06 (80.0)	-1.18E-05 - 3.17E-05
Presence of Y93H	β_4	-2.61	0.253 (9.69)	-3.22 - -2.17
Presence of L31M/V	β_5	-2.57	0.380 (14.8)	-3.42 - -1.81

a   Reference values for continuous covariates: ASV= (b) (4) , DCV=490 ng/mL; for categorical covariates: Y93H: Not present, L31MV: Not present

b   RSE% is the relative standard error (Standard Error as a percentage of Estimates)

c   Confidence Interval values are taken from bootstrap calculations (2000 successful out of a total of 2000)

Source: Table S-3 of the sponsor's report

As demonstrated in Table 8 and Figure 19 there was a shallow E-R relationship between DCV and SVR12, and there was a flat E-R relationship between ASV and SVR12; The presence of the NS5A baseline resistance polymorphisms Y93H and L31M/V were significant predictors of lower SVR12 in the final E-R model (p<0.001); Race, cirrhosis status and patient type were not significant covariates on SVR12.

Figure 19: Observed Proportion and Model Predicted Probability of SVR12 versus Css,avg for DCV
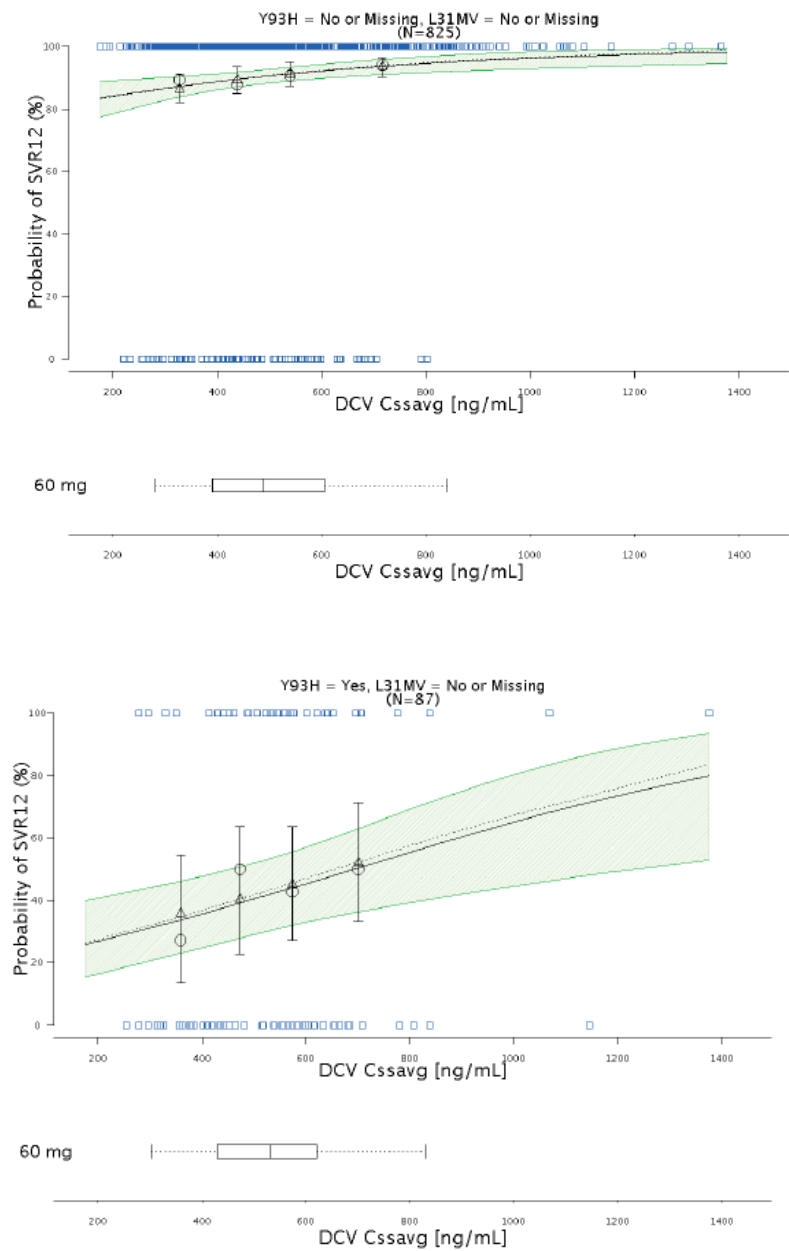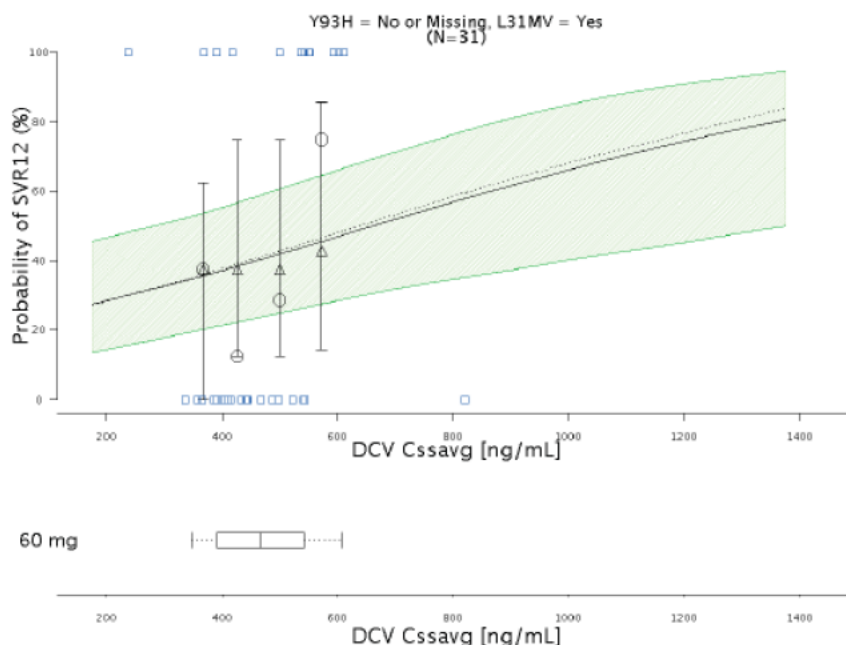
Source: Adapted from Figure 5.1.2-1 from sponsor's report

Table 12: Effect of Covariates on the Probability of Achieving SVR12 Based on the Final Model

Name	Comparator[a]	Predicted SVR12[b]	95% Confidence Interaval[b]
Reference	ASV= (b) (4) (median) DCV=490 ng/mL (median) No Y93H or L31MV mutation	0.906	0.883 - 0.926
Effects of ASV			(b) (4)
Effects of DCV	DCV=283 ng/mL (5th percentile)	0.863	0.823 - 0.899
	DCV=838 ng/mL (95th percentile)	0.950	0.921 - 0.972
Presence of Y93H	Presence of Y93H mutation	0.400	0.285 - 0.513
Presence of L31MV	Presence of L31MV mutation	0.413	0.246 - 0.601

Source: Table S-4 of sponsor's report

Reviewer's comments: The sponsor's analysis is acceptable. There was no significant E-R relationship for efficacy for DCV or ASV at exposure range achieved by the dual therapy of the ASV/DCV regimen. The sponsor's analysis is in line with the independent analysis by the pharmacometrics reviewer.

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3.4 Exposure-response analysis for safety

Objectives: The objectives of exposure-response analysis of daclatasvir were to:

- To characterize the relationship between the exposures of ASV (b) (4)

Data: The safety E-R analysis for ALT, AST, and Tbili elevations and safety assessment for pyrexia, eosinophilia, and rash were performed with data from 5 clinical studies (AI447011, AI447016, (b) (4), AI447026 and AI447028). Subjects for whom summary measures of ASV exposure and safety response were available were included in the model development analysis dataset. Records from AI447028 placebo group were also included in the analysis. The E-R analysis and the safety assessment were conducted with data from 1413 and 1419 subjects with HCV, respectively.

Methods: The safety E-R model was developed to describe relationship between PK-exposure (Cavgss) of ASV and severity grades for ALT, AST, Tbili, by characterizing the cumulative probability of achieving maximum grades 1 or 2 (GR1/2) and 3 or 4 (GR3/4) ALT, AST, or Tbili elevation severity, during treatment termed P(GR1/2) and P(GR3/4), respectively, as a function of ASV exposure and selected covariates that may modulate the E-R relationship, established by ordinal logistic regression. Covariates such as baseline age, weight, ALT, AST, and Total bilirubin levels, gender and race were also assessed as effect on the ASV slope term.

Models: The models for ALT, AST, and Tbili were depicted using logistic regression. The covariates tested for exposure-response included baseline age, body weight, gender, race, baseline ALT, AST, Tbili levels etc. The final models were achieved by removing insignificant covariates by backwards elimination. The parameter estimates in the final model for ALT are summarized in Table below:

Table 13: Summary of Final Model Parameter Estimates for ALT

Name (symbol)	Estimate	Standard Error (RSE%)[a]	95% Confidence Interval[b]
Intercept for GR1/2 (θ_1)	-2.12	0.980 (46.2)	-3.85 - -0.285
Intercept for GR3/4 (θ_2)	-2.98	0.145 (4.87)	-3.32 - -2.70
Slope of ASV			(b) (4)
Ribavirin effect on intercept (θ_5)	-0.349	0.166 (47.6)	-0.661 - -0.0261
DCV Cavgss effect on intercept (θ_{11})	-0.168	0.0263 (15.7)	-0.226 - -0.123
Age effect on intercept (θ_{12})	-0.438	0.239 (54.6)	-0.903 - -0.00545
Baseline ALT effect on intercept (θ_{13})	0.960	0.0975 (10.2)	0.797 - 1.15
PegIFN/Ribavirin Ineligible/Intolerant Patient Type effect on slope (θ_{17})	0.00165	7.67E-04 (46.5)	3.21E-04 - 0.00319
Treatment-naive Patient Type effect on slope (θ_{18})	0.00149	9.84E-04 (66.0)	-6.08E-04 - 0.00344
DCV Cavgss effect on slope (θ_{19})	3.61E-04	6.48E-04 (180)	-8.86E-04 - 0.00179

[a] RSE% is the relative standard error (Standard Error as a percentage of Estimate)

[b] Confidence interval values are taken from bootstrap calculations (498 successful out of a total of 500 runs)

Source: Table 5.1.1.3-1 of the sponsor's report

Observed and model predicted probability of Grade 1 and 2 and Grade 3 and 4 ALT increase versus Cavgss was explored. As demonstrated in Table 11 and Figure 20, there was a (b) (4) ASV (b) (4) and no significant E-R relationship between DCV and ALT increase. (b) (4)

Source: Figure 5.1.2 of the sponsor's report

Reviewer's comments: Independent E-R analysis for safety was conducted by FDA reviewer. The results are shown in section 1.1.2 above. The reviewer's analysis was in line with the sponsor's analysis and we concluded that ASV and DCV exposure achieved by dosing DCV 60 mg QD and ASV 100 mg BID did not result in severe elevation(grade 3 and above) of liver enzymes (ALT, AST, and total bilirubin)

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS AND TARGETED THERAPY GROUP REVIEW

NDA/BLA Number	206844
Submission Date	03/31/2014
Applicant Name	Bristol Myers Squibb
Generic Name	Asunaprevir
Proposed Indication	Chronic HCV Infection, Genotypes 1 and 4
Primary Reviewer	Jeff Kraft, PhD
Secondary Reviewer	Mike Pacanowski, PharmD, MPH

1   Background

(b) (4)

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Reference ID: 3615478