CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206843Orig1s001, s003

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 206843 (S-1 through S-3, SDN 68 and 69)	Original Submission Date: August 5, 2015
Brand Name	Daklinza
Generic Name	Daclatasvir
Reviewer	Stanley Au, Pharm.D., BCPS
Clinical Pharmacology Team Leader	Shirley Seo, Ph.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products (DAVP)
Applicant	BMS
Formulation; strength(s)	Daclatasvir 30 mg and 60 mg tablets
Indication	Treatment of chronic hepatitis C infection
Review Type	Efficacy supplement

Table of Contents

1 Executive Summary

This review documents and supports the clinical pharmacology reviewer comments for an efficacy supplement that includes revisions to the daclatasvir U.S. prescribing information.

Daclatasvir, a hepatitis C virus NS5A inhibitor, is currently approved for the treatment of genotype 3 chronic hepatitis C infection. The applicant, BMS, submitted an efficacy supplement containing revisions applicable to the drug-drug interaction information for multiple concomitant medications (see section 2). As part of the submission, results were submitted for drug-drug interaction trials that evaluated concomitant use of daclatasvir with buprenorphine/naloxone, dolutegravir, or certain antiretrovirals (darunavir/ritonavir, lopinavir/ritonavir).

Additionally, the applicant also submitted in vitro reports that included evaluating whether daclatasvir is a substrate of OCT1 or BCRP.

The applicant's proposed changes to the daclatasvir U.S. prescribing information and the revisions proposed by the Office of Clinical Pharmacology are outlined below in section 2.

1.1 Recommendation

With the exception of the changes proposed by the Office of Clinical Pharmacology that are outlined in section 2, the applicant's revisions to the daclatasvir U.S. prescribing information are acceptable.

1.2 Postmarketing Commitments or Requirements

There are no postmarketing commitments or requirements for this NDA supplement.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

A) <u>In vitro reports</u>

The submitted data from one of the in vitro reports does not support (b) (4) daclatasvir U.S. prescribing information (USPI) that daclatasvir is an OCT1 substrate. An additional in vitro BCRP substrate study for daclatasvir was also conducted. The report from the in vitro study states that the results support the conclusion that daclatasvir is not a BCRP substrate, consistent with previous results. However, the applicant's approach does not appear to be consistent with the current FDA recommended approach for determining whether a drug is a BCRP substrate.

B) Clinical drug-drug interaction trials

Buprenorphine/naloxone

Increases in buprenorphine or norbuprenorphine exposure were observed with concomitant use of daclatasvir. The applicant proposes to state in section 7 that with concomitant use of daclatasvir, no clinically relevant changes in buprenorphine exposure were observed. However, based on discussions with the analgesia clinical pharmacology review team, a clinical comment addressing concomitant use of daclatasvir with buprenorphine or buprenorphine/naloxone will be proposed instead (see section 2).

Buprenorphine statistical analyses (dose normalized to 8 mg) with and without concomitant use of daclatasvir-all completers

Treatment and Comparison	Cmax (ng/mL) Adjusted Geometric Mean [N]	C24 (ng/mL) Adjusted Geometric Mean [N]	AUC(TAU) (ng.h/mL) Adjusted Geometric Mean [N]
C	2.55 [11]	0.417 [9]	18.8 [9]
D	3.31 [11]	0.486 [9]	25.7 [9]
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
D vs C	1.299 (1.029,1.640)	1.165(1.028,1.321)	1.371(1.240,1.516)

GMR = geometric mean ratio

Treatment Code: C: Buprenorphine/naloxone 8/2 to 24/6 mg QD on Day 1, D: Buprenorphine/naloxone 8/2 to 24/6 mg QD and Daclatasvir 60mg QD on Day 2-9

Norbuprenorphine statistical analyses (dose normalized to 8 mg) with and without concomitant use of daclatasvir-all completers

Treatment and Comparison	Cmax (ng/mL) Adjusted Geometric Mean [N]	C24 (ng/mL) Adjusted Geometric Mean [N]	AUC(TAU) (ng.h/mL) Adjusted Geometric Mean [N]
C	1.85 [11]	0.901 [9]	25.4 [9]
D	3.06 [11]	1.31 [9]	41.1 [9]
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
D vs C	1.654(1.376,1.987)	1.458(1.124,1.890)	1.618(1.298,2.017)

GMR = geometric mean ratio

Treatment Code: C: Buprenorphine/naloxone 8/2 to 24/6 mg QD on Day 1, D: Buprenorphine/naloxone 8/2 to 24/6 mg QD and Daclatasvir 60 mg QD on Day 2-9

Darunavir/ritonavir and lopinavir/ritonavir

Two separate trials evaluated the potential drug-drug interaction between daclatasvir and darunavir/ritonavir or lopinavir/ritonavir. AI444093 evaluated the effect of darunavir/ritonavir or lopinavir/ritonavir on daclatasvir exposure. Overall, increases in daclatasvir exposure ($AUC_{[0\text{-}tau]}$) were observed with concomitant use of either

darunavir/ritonavir or lopinavir/ritonavir. No dose adjustment for daclatasvir with darunavir/ritonavir or lopinavir/ritonavir is proposed by the applicant, which is acceptable.

Non dose normalized daclatasvir statistical analyses with and without concomitant use of darunavir/ritonavir

PK Parameter	Treatment and Comparison	Adjusted Geometric Mean	90% CI
Cmax (ng/mL)	A	1335	(1121, 1589)
	B	512	(433, 606)
	B versus A	0.384	(0.348, 0.423)
AUC(TAU) (ng•h/mL)	A	12677	(10500, 15305)
	B	8910	(7404, 10721)
	B versus A	0.703	(0.658, 0.750)

Non dose normalized daclatasvir statistical analyses with and without concomitant use of lopinavir/ritonavir

PK Parameter	Treatment and Comparison	Adjusted Geometric Mean	90% CI
Cmax (ng/mL)	C	1412	(1249, 1596)
	D	475	(427, 529)
	D versus C	0.337	(0.306, 0.371)
AUC(TAU) (ng•h/mL)	C	13799	(12168, 15649)
	D	7961	(7132, 8886)
	D versus C	0.577	(0.535, 0.622)

AI444043 evaluated the effect of daclatasvir on darunavir or lopinavir exposure (when coadministered with ritonavir). Decreased darunavir exposure and increased lopinavir exposure were observed with concomitant use of daclatasvir. The applicant proposes to state in section 7 that with concomitant use of daclatasvir, no clinically relevant changes in darunavir or lopinavir exposure (when coadministered with ritonavir) were observed, which is acceptable. The clinical relevance of the changes in darunavir or lopinavir exposure is discussed in the AI44043 trial review (see section 3).

Darunavir statistical analyses (darunavir/ritonavir 600 mg/100 mg BID) with and without concomitant use of daclatasvir 30 mg QD

	Treatment and Comparison		
Parameter Statistic	**Darunavir/Ritonavir 600/100 mg BID on Day -1 (Treatment A)**	**Darunavir/Ritonavir 600/100 mg BID and Daclatasvir 30 mg QD on Day 14 (Treatment B)**	**Treatment B vs. Treatment A**
Cmax (ng/mL) Adjusted Geo. Mean (90% CI)	7581	7366	0.972 (0.80, 1.17)
AUC(0-12) (ng.h/mL) Adjusted Geo. Mean (90% CI)	59019	53112	0.900 (0.73, 1.11)
C12 (ng/mL) Adjusted Geo. Mean (90% CI)	3062	3011	0.983 (0.67, 1.44)

Abbreviations: Geo.Mean = geometric mean; CI = confidence interval, BID = twice daily dosing; QD = once daily dosing

Lopinavir statistical analyses (lopinavir/ritonavir 400 mg/100 mg BID) with and without concomitant use of daclatasvir 30 mg QD

	Treatment and Comparison		
Parameter Statistic	**Lopinavir/Ritonavir 400/100 mg BID on Day -1 (Treatment A)**	**Lopinavir/Ritonavir 400/100 mg BID and Daclatasvir 30 mg QD on Day 14 (Treatment B)**	**Treatment B vs. Treatment A**
Cmax (ng/mL) Adjusted Geo. Mean (90% CI)	10123	12332	1.22 (1.06, 1.41)
AUC(0-12) (ng.h/mL) Adjusted Geo. Mean (90% CI)	92599	106517	1.15 (0.77, 1.72)
C12 (ng/mL) Adjusted Geo. Mean (90% CI)	4430	6801	1.54 (0.46, 5.07)

Abbreviations: Geo.Mean = geometric mean; CI = confidence interval, BID = twice daily dosing; QD = once daily dosing

Dolutegravir

Overall, no clinically relevant changes in daclatasvir exposure are observed with concomitant use of dolutegravir and increases in dolutegravir exposure were observed with concomitant use of daclatasvir. The applicant proposes to state in section 7 that with concomitant use of daclatasvir and dolutegravir, no clinically relevant changes in either daclatasvir or dolutegravir exposure were observed, which is acceptable. The clinical relevance of the changes in dolutegravir exposure is discussed in the AI444273 (201102) trial review (see section 3).

Daclatasvir statistical analyses with and without concomitant use of dolutegravir

Plasma DCV PK Parameter	GLS Mean		GLS Mean Ratio (90% CI)
	DCV 60 mg q24h Alone (N=12)	DCV 60 mg q24h + DTG 50 mg q24h (N=12)	DCV + DTG vs. DCV Alone
AUC(0-τ) (µg*hr/mL)	11.4	11.2	0.978 (0.831, 1.15)
Cmax (µg/mL)	1.20	1.23	1.03 (0.843, 1.25)
Cτ (µg/mL)	0.166	0.176	1.06 (0.876, 1.29)
CL/F (L/hr)	5.25	5.36	1.02 (0.868, 1.203)
t1/2 (hr)	8.58	8.42	0.982 (0.814, 1.18)

Dolutegravir statistical analyses with and without concomitant use of daclatasvir

Plasma DTG PK Parameter	GLS Mean		GLS Mean Ratio (90% CI)
	DTG 50 mg q24h Alone (N=12)	DTG 50 mg q24h + DCV 60 mg q24h (N=12)	DTG + DCV vs. DTG Alone
AUC(0-τ) (µg*hr/mL)	35.7	47.3	1.33 (1.11, 1.59)
Cmax (µg/mL)	2.65	3.43	1.29 (1.07, 1.57)
Cτ (µg/mL)	0.771	1.12	1.45 (1.25, 1.68)
CL/F (L/hr)	1.40	1.06	0.753 (0.627, 0.905)
t1/2 (hr)	13.9	16.2	1.17 (1.01, 1.35)

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2 Labeling Recommendations

(Clinical Pharmacology reviewer note: the revisions to the daclatasvir USPI were ongoing at the time the review was finalized.)

Applicant revisions	Review team edits
Section 7 Table 7-Established and Other Potentially Significant Drug Interactions **Concomitant Drug Class: Drug Name** / **Effect on Concentration[a]** / **Clinical Comment** *HIV antiviral agents* Protease inhibitors: Atazanavir with ritonavir (b) (4) Indinavir Nelfinavir ↑ Daclatasvir Decrease DAKLINZA dose to 30 mg once daily (b) (4) (b) (4) Non-nucleoside reverse	Section 7 *Clinical pharmacology notes:* *1) There is inconsistency in the proposed information regarding the mangement of the daclatasvir plus darunavir/ritonavir drug-drug interaction.* (b) (4) Table 7 provides clinical recommendations for established or potentially significant drug interactions between DAKLINZA and other drugs [*see Contraindications (4)*]. Clinically relevant increase in concentration is indicated as "↑" and clinically relevant decrease as "↓" [for drug interaction data, *see Clinical Pharmacology (12.3)*].

transcriptase inhibitors (NNRTI): Efavirenz[b] Etravirine Nevirapine	↓ Daclatasvir	Increase DAKLINZA dose to 90 mg once daily (b) (4) [redacted]

[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, Tables 9 and 10)*].

Table 7-Established and Other Potentially Significant Drug Interactions

Concomitant Drug Class: Drug Name	**Effect on Concentration[a]**	**Clinical Comment**
HIV antiviral agents		
Protease inhibitors: Atazanavir with ritonavir Indinavir Nelfinavir	↑ Daclatasvir	Decrease DAKLINZA dose to 30 mg once daily
Other antiretrovirals: Cobicistat containing antiretroviral regimens	↑ Daclatasvir	Decrease DAKLINZA dose to 30 mg once daily except with darunavir combined with cobicistat.
[redacted]		(b) (4)
Non-nucleoside reverse transcriptase inhibitors (NNRTI): Efavirenz[b] Etravirine Nevirapine	↓ Daclatasvir	Increase DAKLINZA dose to 90 mg once daily.

[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, Tables 9 and10)*].

<table>
<tr><th>Applicant revisions</th><th>Clinical Pharmacology reviewer revisions</th></tr>
<tr><td>Section 7

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, darunavir (with ritonavir), (b) (4) methadone, midazolam, tacrolimus, or tenofovir with concomitant use of daclatasvir.</td><td>Section 7

Clinical pharmacology reviewer comment: Please see the AI444064 trial review for a rationale for the proposed changes.

Based on the results of drug interaction trials [see Clinical Pharmacology (12.3)], no clinically relevant changes in exposure were observed for cyclosporine, darunavir (with ritonavir) (b) (4) methadone, midazolam, tacrolimus, or tenofovir with concomitant use of daclatasvir.

Table 7-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>Narcotic Analgesic/Treatment of Opioid Dependence: buprenorphine, buprenorphine/ naloxone</td><td>↑ buprenorphine
↑ norbuprenorphine</td><td>For buprenorphine or buprenorphine/naloxone, no adjustment is needed but clinical monitoring is recommended.</td></tr>
</table>
</td></tr>
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<table>
<tr><td>Applicant revisions</td><td>Clinical Pharmacology reviewer revisions (changes highlighted)</td></tr>
<tr><td>Section 7

None</td><td>Section 7

Clinical pharmacology reviewer comment: Based on discussions with the cardiovascular clinical pharmacology team, the dose adjustment recommendations in the digoxin USPI should be based on changes in digoxin AUC or trough concentrations.

Table 7-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>Antiarrhythmic:
Digoxin[b]</td><td>↑ Digoxin</td><td><u>Patients already receiving daclatasvir initiating digoxin</u>: Initiate treatment using the lowest appropriate digoxin dosage. 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 digoxin dosage by approximately 15% to 30% or by modifying the dosing frequency and continue monitoring.</td></tr>
</table>
</td></tr>
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Applicant revisions	Clinical Pharmacology reviewer revisions
Section 12 Distribution (b) (4)	Section 12 (b) (4)

Applicant revisions

Section 12

Table 9. Effect of DAKLINZA on the Pharmacokinetics of Concomitant Drugs

Concomitant Drug	Co administered Drug Dose	DAKLINZA Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination /No Combination (90% CI)		
			C_{max}	AUC	C_{min}[a]
Darunavir	600 mg BID with ritonavir 100 mg BID	30 mg QD	0.97 (0.80, 1.17)	0.90 (0.73, 1.11)	0.98 (0.67, 1.44)

Concomitant Drug	Co administered Drug Dose	DAKLINZA Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination /No Combination (90% CI)		
			C_{max}	AUC	C_{min}[a]
Lopinavir	400 mg BID with ritonavir 100 mg BID	30 mg QD	1.22 (1.06, 1.41)	1.15 (0.77, 1.72)	1.54 (0.46, 5.07)

Clinical Pharmacology reviewer revisions (changes highlighted)

Section 12

Table 9. Effect of DAKLINZA on the Pharmacokinetics of Concomitant Drugs

Concomitant Drug	Co administered Drug Dose	DAKLINZA Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination /No Combination (90% CI)		
			C_{max}	AUC	C_{min}[a]
Darunavir[d]	600 mg BID with ritonavir 100 mg BID	30 mg QD	0.97 (0.80, 1.17)	0.90 (0.73, 1.11)	0.98 (0.67, 1.44)

Concomitant Drug	Co administered Drug Dose	DAKLINZA Dose	Ratio of Pharmacokinetic Parameters of Coadministered Drug Combination /No Combination (90% CI)		
			C_{max}	AUC	C_{min}[a]
Lopinavir[d]	400 mg BID with ritonavir 100 mg BID	30 mg QD	1.22 (1.06, 1.41)	1.15 (0.77, 1.72)	1.54 (0.46, 5.07)

[d] Samples up to 6 hours collected; C_{0h} substituted for C_{12h} concentration value

Applicant revisions

Section 12

Table 10. Effect of Coadministered Drugs on DAKLINZA Pharmacokinetics

Concomitant Drug	Co administered Drug Dose	DAKLINZA Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}[a]
Darunavir/ ritonavir	800 mg/100 mg QD	30 mg QD, (b) (4)	(b) (4)		

Clinical Pharmacology reviewer revisions

Clinical pharmacology reviewer note: Consistent with the displaying of non dose normalized daclatasvir data in the drug-drug interaction tables for atazanavir/ritonavir and efavirenz, non dose normalized daclatasvir data will be recommended in the drug-drug interaction tables for darunavir/ritonavir and lopinavir/ritonavir.

Section 12

Table 10. Effect of Coadministered Drugs on DAKLINZA Pharmacokinetics

Concomitant Drug	Co administered Drug Dose	DAKLINZA Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}[a]
Darunavir/ ritonavir	800 mg/100 mg QD	(b) (4) 30 mg QD (test arm)	0.38 (0.35, 0.42)[b]	0.70 (0.66 0.75)[b]	NA

[b] Observed, non-dose normalized data.

Applicant revisions

Section 12

Table 10. Effect of Coadministered Drugs on DAKLINZA Pharmacokinetics

Concomitant Drug	Co administered Drug Dose	DAKLINZA Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}[a]
Lopinavir/ ritonavir	400 mg/100 mg BID	30 mg QD, (b) (4)	(b) (4)		

Clinical Pharmacology reviewer revisions

Section 12

Table 10. Effect of Coadministered Drugs on DAKLINZA Pharmacokinetics

Concomitant Drug	Co administered Drug Dose	DAKLINZA Dose	Ratio of Pharmacokinetic Parameters of Daclatasvir Combination/No Combination (90% CI)		
			C_{max}	AUC	C_{min}[a]
Lopinavir/ ritonavir	400 mg/100 mg BID	(b) (4) 30 mg QD (test arm)	0.34 (0.31, 0.37)[b]	0.58 (0.54 0.62)[b]	NA

[b] Observed, non-dose normalized data.

3 Individual Trial Reviews

AI444043

1. Title

A Phase 3, open label study of safety and efficacy with BMS-790052 (daclatasvir) plus PEG-interferon alfa-2a and ribavirin in previously untreated HCV patients coinfected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV)

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

The trial was conducted from December 13, 2011 (trial initiation) to September 10, 2014 (trial completion).

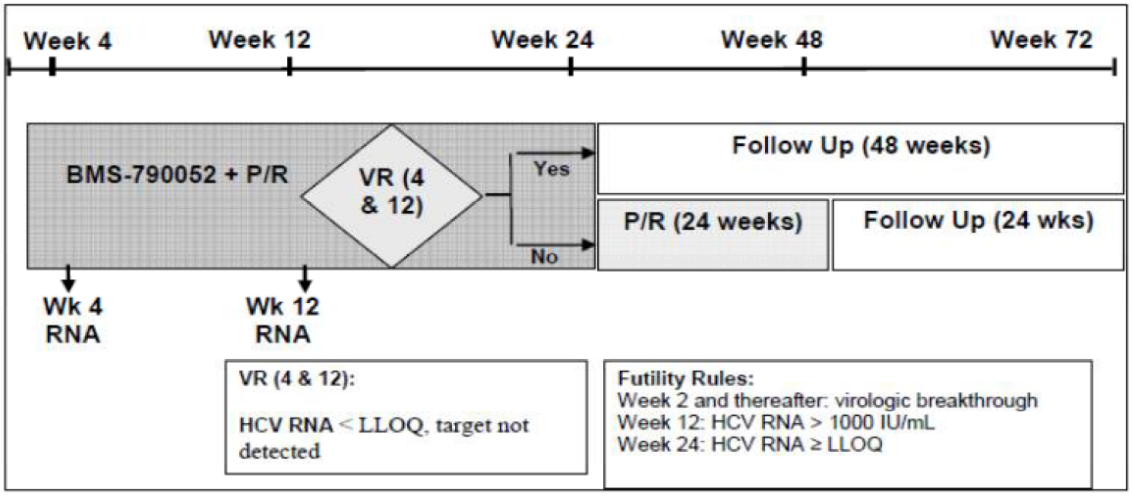
3. Objectives

The overall trial evaluated the efficacy of daclatasvir. The objectives of the pharmacokinetic subtrial included evaluating the effect of daclatasvir on the pharmacokinetics of antiretrovirals (e.g. darunavir/ritonavir or lopinavir/ritonavir) administered twice daily.

4. Trial Design

AI444043 enrolled chronic hepatitis C infected, genotype 1a or genotype 1b male and female subjects 18 to 70 years old. Information on the trial design is displayed in Figure 1. As part of the trial, intensive pharmacokinetic sampling was conducted in the first eighteen subjects receiving darunavir/ritonavir (600 mg/100 mg twice daily [BID]) and the first eighteen subjects receiving lopinavir/ritonavir (400 mg/100 mg BID) at certain sites.

Figure 1-AI444043 trial design



5. Excluded Medications, Restrictions or Exceptions

The permitted antiretroviral medications for the trial included atazanavir/ritonavir, darunavir/ritonavir, efavirenz, lopinavir/ritonavir, nevirapine, raltegravir, and rilpivirine. With the exception of the antiretrovirals that were allowed in the trial, the medications that were not permitted in the trial included moderate to strong cytochrome P450 (CYP) 3A inhibitors and CYP3A inducers.

6. Dosage and Administration

Daclatasvir was administered with or without a meal. This is consistent with the recommendations in the U.S. prescribing information (USPI) for daclatasvir. No specific information was included in the protocol regarding administration of antiretovirals and food or meal requirements. With use of antiretrovirals, the daclatasvir dosage regimen was 60 mg once daily (QD) with the following exceptions: a) with concomitant use of atazanavir/ritonavir, darunavir/ritonavir or lopinavir/ritonavir, the daclatasvir dosage regimen was 30 mg once daily (QD), and b) with concomitant use of efavirenz or nevirapine, the daclatasvir dosage regimen was 90 mg once daily (QD). According to the trial protocol, antiretrovirals were dosed according to country specific prescribing information.

7. Rationale for Doses Used in the Trial

The daclatasvir dosage regimens (with or without dosage adjustments) were based on the applicant's expectations regarding CYP inhibition or induction effects on daclatasvir exposure for concomitantly administered antiretrovirals.

8. Drugs Used in the Trial

Information on the daclatasvir formulations administered in the trial is displayed in Table 1. The report does not provide information regarding whether the administered daclatasvir formulations are the U.S. commercially marketed formulations. In response to an information request, the applicant stated that the 30 mg and 60 mg Phase 3 daclatasvir formulations were administered.

According to the trial protocol, antiretrovirals were not considered trial medications.

Table 1-Daclatasvir formulations administered in the AI444043 trial

Drug Product	Formulation	Product Batch Numbers
BMS-790052 -05 60 mg (as the free base)	Film-coated tablet	1M49091, 2D72563, 1G66277, 2G72986
BMS-790052 -05 30 mg (as the free base)	Film-coated tablet	1K68499

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

Sample Collection

The blood samples that were obtained included darunavir or lopinavir predose and postdose blood samples on day -1 and at week 2 up to 6 hours (in the absence of a C_{12h} sample, the C_{0h} [defined in the trial report as the predose trough concentration] was substituted) and trough and postdose blood samples up to 4 hours at week 2 for daclatasvir.

Bioanalysis

Bioanalytical information for daclatasvir is not provided in this review because the applicant is not proposing to include exposure information for daclatasvir from the AI444043 trial in the daclatasvir USPI.

Based on the information included in the AI444043 darunavir and lopinavir bioanalytical report, it appears that at least some samples were analyzed for both the darunavir and lopinavir analytes. It is not clear why this was performed for an open label trial.

The method and bioanalysis of darunavir is acceptable. Darunavir plasma samples were analyzed using a validated LC/MS/MS method in K_3EDTA anticoagulated plasma by (b) (4) (P1002.01) that was also used to measure the lopinavir analyte. The blood samples for analysis of darunavir appear to have been collected in tubes containing K_2EDTA as an anticoagulant. For the AI444043 bioanalysis, initially for the first seven runs, calibration curve standards and quality control samples were prepared in K_3EDTA anticoagulated plasma (only the lopinavir runs were accepted). For subsequent runs, calibration curve standards and quality control samples were prepared in K_2EDTA anticoagulated plasma.

For the AI444043 plasma samples that were analyzed for darunavir, the lower limit of quantification for darunavir was 10 ng/mL and the upper limit of quantification was 10000 ng/mL. There were no precision or accuracy issues identified for darunavir based on the bioanalytical report. For the AI444043 trial, precision and accuracy were evaluated using plasma darunavir quality control (QC) samples at 30 ng/mL, 75 ng/mL, 300 ng/mL, 1200 ng/mL and 7500 ng/mL. The corresponding darunavir inter-run accuracy values were 1.03% for 30 ng/mL, 0.306% for 75 ng/mL, 1.44% for 300 ng/mL, 0.998% for 1200 ng/mL and -1.77% for 7500 ng/mL. The darunavir inter-run precision values were 3.91% for 30 ng/mL, 2.91% for 75 ng/mL, 2.14% for 300 ng/mL, 1.73% for 1200 ng/mL and 2.32% for 7500 ng/mL. In addition, for the darunavir dilution QC samples (2x dilution) at 7500 ng/mL, the accuracy and precision were -0.331% and 2.95%, respectively.

Of the samples selected for incurred sample reanalysis for darunavir that were quantifiable [71 out of 78 samples], all but one sample was within 20% using the percentage values of the repeat and original concentrations. The bioanalytical report

states that approximately 10% of the subject samples were reanalyzed (the current FDA recommendation is 7%).

For the AI444043 trial, the applicant provided information indicating that darunavir samples were stored at the trial site for no more than 2 days at -20°C, at the central laboratory for approximately 180 days at -20°C or (b) (4) for no more than 103 days at -20°C. Specific information regarding whether current reference standards were used as part of the stability evaluations was not included and the anticoagulant used for the stability samples was not consistently provided by (b) (4). The darunavir method generated long term stability data for darunavir including stability data at -20°C for 449 days (a table of contents for the method validation indicates the anticoagulant used was K_2EDTA). For the AI444043 trial, the generated long term stability data appears to covers the duration of long term stability data necessary for darunavir.

The method and bioanalysis of lopinavir is acceptable. Lopinavir plasma samples were analyzed using a validated LC/MS/MS method in K_3EDTA anticoagulated plasma by (b) (4) (P1002.01) that was also used to measure the darunavir analyte. The blood samples for analysis of lopinavir appear to have been collected in tubes containing K_2EDTA as an anticoagulant. For the AI444043 bioanalysis, initially for the first seven runs, calibration curve standards and quality control samples were prepared in K_3EDTA anticoagulated plasma. For subsequent runs, calibration curve standards and quality control samples were prepared in K_2EDTA anticoagulated plasma.

For the AI444043 plasma samples that were analyzed for lopinavir, the lower limit of quantification for lopinavir was 10 ng/mL and the upper limit of quantification was 10000 ng/mL. There were no precision or accuracy issues identified for lopinavir based on the bioanalytical report. For the AI444043 trial, precision and accuracy were evaluated using plasma lopinavir quality control (QC) samples at 30 ng/mL, 75 ng/mL, 300 ng/mL, 1200 ng/mL and 7500 ng/mL. The corresponding lopinavir inter-run accuracy values were 0.982% for 30 ng/mL, 1.67% for 75 ng/mL, 2.22% for 300 ng/mL, 1.85% for 1200 ng/mL and -3.23% for 7500 ng/mL. The lopinavir inter-run precision values were 3.79% for 30 ng/mL, 3.2% for 75 ng/mL, 3.57% for 300 ng/mL, 4.63% for 1200 ng/mL and 10.6% for 7500 ng/mL. In addition, for the lopinavir dilution QC samples (2x dilution) at 7500 ng/mL, the inter-run accuracy and precision were 0.509% and 3.34%, respectively and for the lopinavir dilution QC samples (20x dilution) at 7500 ng/mL, the inter-run accuracy and precision were 5.33% and 1.76%, respectively.

Of the samples selected for incurred sample reanalysis for lopinavir that were quantifiable, all but three samples were within 20% using the percentage values of the repeat and original concentrations. The bioanalytical report states that approximately 10% of the subject samples were reanalyzed (the current FDA recommendation is 7%). However, there were a large number of reassayed lopinavir samples that were reported as BLQ (the specific reason was not provided in the bioanalytical report), so the actual number of reassayed lopinavir samples with available comparative data was significantly less (approximately 35% [29 out of 82 samples] of the reassayed samples excluding one sample that was reassayed again).

For the AI444043 trial, the applicant provided information indicating that lopinavir samples were stored at the trial site for no more than 2 days at -20°C, at the central laboratory for approximately 180 days at-20°C or [(b) (4)] for no more than 97 days at -20°C. Specific information regarding whether current reference standards were used as part of the stability evaluations was not included and the anticoagulant used for the stability samples was not consistently provided by [(b) (4)]. The lopinavir method generated long term stability data for lopinavir including stability data at -20°C for 449 days (a table of contents for the method validation indicates the anticoagulant used was K_2EDTA). For the AI444043 trial, the generated long term stability data appears to covers the duration of long term stability data necessary for lopinavir.

Pharmacokinetic Assessments

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

Statistical Analysis

The statistical analyses included deriving 90% confidence intervals for darunavir and lopinavir pharmacokinetic parameters comparing the test arm (darunavir/ritonavir or lopinavir/ritonavir in combination with daclatasvir) to the reference arm (darunavir/ritonavir or lopinavir/ritonavir alone).

10. Results

10.1 Subject Demographics

Table 2-AI444043 subject demographics

	HAART					
	DCV 30 MG N=132	DCV 60 MG N=39	DCV 90 MG N=106	HAART Total N=277	Non-HAART N=24	Total N=301
AGE (YEARS)						
N	132	39	106	277	24	301
MEAN	47.0	47.9	46.5	47.0	36.0	46.1
MEDIAN	47.0	50.0	47.0	47.0	34.5	47.0
MIN, MAX	22, 69	28, 61	27, 65	22, 69	24, 55	22, 69
Q1, Q3	42.0, 52.0	39.0, 54.0	40.0, 52.0	41.0, 52.0	28.5, 45.5	39.0, 52.0
STANDARD DEVIATION	9.72	9.03	9.42	9.49	9.02	9.90
AGE CATEGORIZATION (%)						
<65	125 (94.7)	39(100.0)	104 (98.1)	268 (96.8)	24(100.0)	292 (97.0)
>=65	7 (5.3)	0	2 (1.9)	9 (3.2)	0	9 (3.0)
GENDER (%)						
MALE	105 (79.5)	32 (82.1)	79 (74.5)	216 (78.0)	13 (54.2)	229 (76.1)
FEMALE	27 (20.5)	7 (17.9)	27 (25.5)	61 (22.0)	11 (45.8)	72 (23.9)
RACE (%)						
WHITE	110 (83.3)	34 (87.2)	83 (78.3)	227 (81.9)	22 (91.7)	249 (82.7)
BLACK/AFRICAN AMERICAN	19 (14.4)	5 (12.8)	20 (18.9)	44 (15.9)	1 (4.2)	45 (15.0)
NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER	1 (0.8)	0	0	1 (0.4)	0	1 (0.3)
ASIAN OTHER	1 (0.8)	0	3 (2.8)	4 (1.4)	1 (4.2)	5 (1.7)
OTHER	1 (0.8)	0	0	1 (0.4)	0	1 (0.3)
REGION (%)						
EUROPE	79 (59.8)	20 (51.3)	44 (41.5)	143 (51.6)	19 (79.2)	162 (53.8)
NORTH AMERICA	44 (33.3)	14 (35.9)	45 (42.5)	103 (37.2)	4 (16.7)	107 (35.5)
SOUTH AMERICA	4 (3.0)	3 (7.7)	14 (13.2)	21 (7.6)	0	21 (7.0)
AUSTRALIA	5 (3.8)	2 (5.1)	3 (2.8)	10 (3.6)	1 (4.2)	11 (3.7)

10.2 Concomitant Medications

The concomitant medications that were administered in the trial included medications for cardiovascular and gastrointestinal conditions. 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 notes: a) The daclatasvir data in Table 3A and Table 3B are provided for information purposes only. The relevant daclatasvir bioanalytical information for the AI444043 trial was not reviewed, b) The C_{12h} or C_{24h} values were defined in the trial report as the trough 12 hour or 24 hour post dose concentrations. For darunavir and lopinavir, C_{12h} concentration samples were not drawn and the C_{0h} concentration samples were substituted. For daclatasvir, C_{24h} concentration samples were not drawn and the C_{0h} concentration samples were substituted.

Table 3A-Daclatasvir pharmacokinetic parameters with concomitant use of darunavir/ritonavir 600 mg/100 mg BID and historical data

	Treatment		
Parameter Statistic	**Daclatasvir 30 mg**	**Daclatasvir 60[a] mg**	**Study AI444032 Daclatasvir 60 mg**
Cmax (ng/mL) Geo.Mean [N] (%CV)	375 [11] (41.0)	749 [11] (41.0)	973 [14] (36)
AUC(0-24) (ng.h/mL) Geo.Mean [N] (%CV)	4816 [11] (42.6)	9633 [11] (42.6)	9495 [14][b] (36)
C24 (ng/mL) Geo.Mean [N] (%CV)	95.3 [11] (57.2)	191 [11] (57.2)	147 [14] (48)

[a] Dose-normalized to 60 mg DCV
[b] AUC(TAU)
Abbreviations: CV = coefficient of variation; Geo.Mean = geometric mean;
Note: AUC(0-24) and AUC(TAU) are used interchangeably

Table 3B-Daclatasvir pharmacokinetic parameters with concomitant use of lopinavir/ritonavir 400 mg/100 mg BID and historical data

	Treatment		
Parameter Statistic	**Daclatasvir 30 mg**	**Daclatasvir 60 mg[a]**	**Study AI444032 Daclatasvir 60 mg**
Cmax (ng/mL) Geo.Mean [N] (%CV)	354 [5] (31.0)	709 [5] (31.0)	973 [14] (36)
AUC(0-24) (ng.h/mL) Geo.Mean [N] (%CV)	5746 [5] (29.4)	11493 [5] (29.4)	9495 [14][b] (36)
C24 (ng/mL) Geo.Mean [N] (%CV)	165 [5] (27.0)	330 [5] (27.0)	147 [14] (48)

[a] Dose-normalized to 60 mg DCV
[b] AUC(TAU)
Abbreviations: Geo.Mean = geometric mean; CV = coefficient of variation
Note: AUC(0-24) and AUC(TAU) are used interchangeably

Table 4-Darunavir pharmacokinetic parameters (darunavir/ritonavir 600 mg/100 mg BID) with and without concomitant use of daclatasvir 30 mg QD

Parameter Statistic	Treatment	
	Darunavir/Ritonavir 600/100 mg BID on Day -1 (Treatment A)	Darunavir/Ritonavir 600/100 mg BID and Daclatasvir 30 mg QD on Day 14 (Treatment B)
Cmax (ng/mL) Geo.Mean [N] (%CV)	7699 [8] (34.52)	7374 [9] (33.93)
Tmax (h) Median [N] (Min - Max)	3.03 [8] (1.00-6.00)	2.50 [9] (1.00-5.33)
AUC(0-12) (ng.h/mL) Geo.Mean [N] (%CV)	61232 [8] (41.1)	53188 [9] (38.1)
C12 (ng/mL) Geo.Mean [N] (%CV)	3062 [8] (63.0)	3011 [8] (42.7)

Abbreviations: Geo.Mean = geometric mean; CV = coefficient of variation, BID = twice daily dosing; QD = once daily dosing

Table 5-Darunavir statistical analyses (darunavir/ritonavir 600 mg/100 mg BID) with and without concomitant use of daclatasvir 30 mg QD

Parameter Statistic	Treatment and Comparison		
	Darunavir/Ritonavir 600/100 mg BID on Day -1 (Treatment A)	Darunavir/Ritonavir 600/100 mg BID and Daclatasvir 30 mg QD on Day 14 (Treatment B)	Treatment B vs. Treatment A
Cmax (ng/mL) Adjusted Geo. Mean (90% CI)	7581	7366	0.972 (0.80, 1.17)
AUC(0-12) (ng.h/mL) Adjusted Geo. Mean (90% CI)	59019	53112	0.900 (0.73, 1.11)
C12 (ng/mL) Adjusted Geo. Mean (90% CI)	3062	3011	0.983 (0.67, 1.44)

Abbreviations: Geo.Mean = geometric mean; CI = confidence interval, BID = twice daily dosing; QD = once daily dosing

Table 6-Lopinavir pharmacokinetic parameters (lopinavir/ritonavir 400 mg/100 mg BID) with and without concomitant use of daclatasvir 30 mg QD

	Treatment	
Parameter Statistic	**Lopinavir/Ritonavir 400/100 mg BID on Day -1 (Treatment A)**	**Lopinavir/Ritonavir 400/100 mg BID and Daclatasvir 30 mg QD on Day 14 (Treatment B)**
Cmax (ng/mL) Geo.Mean [N] (%CV)	10323 [4] (21.4)	11910 [5] (12.1)
Tmax (h) Median [N] (Min - Max)	3.99 [4] (2.92-5.42)	4.00 [5] (1.83-5.98)
AUC(0-12) (ng.h/mL) Geo.Mean [N] (%CV)	92420 [4] (31.0)	104847 [5] (16.2)
C12 (ng/mL) Geo.Mean [N] (%CV)	4430 [4] (58.0)	6801 [5] (23.0)

Abbreviations: Geo.Mean = geometric mean; CV = coefficient of variation, BID = twice daily dosing; QD = once daily dosing

Table 7-Lopinavir statistical analyses (lopinavir/ritonavir 400 mg/100 mg BID) with and without concomitant use of daclatasvir 30 mg QD

	Treatment and Comparison		
Parameter Statistic	**Lopinavir/Ritonavir 400/100 mg BID on Day -1 (Treatment A)**	**Lopinavir/Ritonavir 400/100 mg BID and Daclatasvir 30 mg QD on Day 14 (Treatment B)**	**Treatment B vs. Treatment A**
Cmax (ng/mL) Adjusted Geo. Mean (90% CI)	10123	12332	1.22 (1.06, 1.41)
AUC(0-12) (ng.h/mL) Adjusted Geo. Mean (90% CI)	92599	106517	1.15 (0.77, 1.72)
C12 (ng/mL) Adjusted Geo. Mean (90% CI)	4430	6801	1.54 (0.46, 5.07)

Abbreviations: Geo.Mean = geometric mean; CI = confidence interval, BID = twice daily dosing; QD = once daily dosing

10.4 Safety Analysis

Safety information for the AI444043 trial is provided below.

Table 8-AI444043 safety information

	HAART					
	DCV 30 mg (N=132)	DCV 60 mg (N=39)	DCV 90 mg (N=106)	HAART Total (N=277)	Non-HAART Total (N=24)	Total (N=301)
Adverse Events						
Deaths	0	1 (2.6)	1 (0.9)	2 (0.7)	0	2 (0.7)
SAEs	12 (9.1)	6 (15.4)	6 (5.7)	24 (8.7)	0	24 (8.0)
AEs Leading to Discontinuation of Study Therapy	7 (5.3)	4 (10.3)	6 (5.7)	17 (6.1)	1 (4.2)	18 (6.0)
Grade 3 to 4 AEs	46 (34.8)	12 (30.8)	35 (33.0)	93 (33.6)	4 (16.7)	97 (32.2)
Most frequent AEs (>20% overall)						
Fatigue	45 (34.1)	16 (41.0)	47 (44.3)	108 (39.0)	6 (25.0)	114 (37.9)
Neutropenia	42 (13.8)	7 (17.9)	35 (33.0)	84 (30.3)	4 (16.7)	88 (29.2)
Anemia	33 (25.0)	10 (25.6)	34 (32.1)	77 (27.8)	4 (16.7)	81 (26.9)
Asthenia	40 (30.3)	7 (17.9)	19 (17.9)	66 (23.8)	12 (50.0)	78 (25.9)
Headache	29 (22.0)	13 (33.3)	28 (26.4)	70 (25.3)	7 (29.2)	77 (25.6)
Decreased appetite	32 (24.2)	9 (23.1)	27 (25.5)	68 (24.5)	5 (20.8)	73 (24.3)
Insomnia	36 (27.3)	10 (25.6)	17 (16.0)	63 (22.7)	3 (12.5)	66 (21.9)
Pyrexia	28 (21.2)	6 (15.4)	19 (17.9)	53 (19.1)	12 (50.0)	65 (21.6)

11. Discussion and Conclusions

Based on the results from the AI444043 trial, the following conclusions can be made:

- When daclatasvir 30 mg once daily was coadministered with darunavir/ritonavir 600 mg/100 mg twice daily, darunavir C_{max}, $AUC_{(0\text{-}tau)}$, and C_{12h} were decreased by 2.8%, 10%, and 1.7% respectively, when compared with darunavir/ritonavir 600 mg/100 mg twice daily. The 90% confidence intervals for darunavir $AUC_{(0\text{-}tau)}$ and C12 were not within the standard "no effect" 90% confidence interval limits of 80%-125%.
- When daclatasvir 30 mg once daily was coadministered with lopinavir/ritonavir 400 mg/100 mg twice daily, the lopinavir C_{max}, $AUC_{(0\text{-}tau)}$, and C_{12h} were increased by 22%, 15%, and 54% respectively, when compared with lopinavir/ritonavir 400 mg/100 mg twice daily. The 90% confidence intervals for lopinavir C_{max}, $AUC_{(0\text{-}tau)}$, and C12 were not within the standard "no effect" 90% confidence interval limits of 80%-125%.

The magnitude of change in darunavir exposure with concomitant use of daclatasvir is within the observed magnitude of change in darunavir exposure with other concomitant medications where no dose adjustment or other clinical recommendation is applicable to darunavir based on the information in the darunavir USPI. The magnitude of change in lopinavir exposure does not warrant a dose adjustment for lopinavir based on the available safety information for lopinavir/ritonavir.

AI444064

Clinical pharmacology reviewer note: the methadone-daclatasvir drug-drug interaction data was previously reviewed during the initial NDA submission for daclatasvir.

1. Title

A Phase 1, open-label, drug-drug interaction study between methadone and daclatasvir, and between buprenorphine/naloxone and daclatasvir

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

The trial was conducted from January 11, 2013 (trial initiation) to December 31, 2013 (trial completion).

3. Objectives

The objectives of the trial included evaluating the effect of daclatasvir on the pharmacokinetics of buprenorphine.

4. Trial Design

AI444064 enrolled male and female subjects 18 to 65 years old receiving buprenorphine/naloxone maintenance therapy. Information on the trial design is displayed in Figure 1.

Figure 1-AI444064 trial design

	Treatment C	Treatment D		
Part 2	Buprenorphine/naloxone 8/2 to 24/6 mg QD	Buprenorphine/naloxone 8/2 to 24/6 mg QD + DCV 60 mg QD	Buprenorphine/naloxone 8/2 to 24/6 mg QD + DCV 60 mg QD	Study Discharge
	Day 1 Buprenorphine / naloxone PK (24h)	Days 2-8	Day 9 Buprenorphine/naloxone + DCV PK (24h)	Day 10

5. Excluded Medications, Restrictions or Exceptions

According to the trial protocol, unless otherwise approved, use of prescription or nonprescription acid modifying medications within 4 weeks prior to administering trial medication and nonprescription and natural (herbal) medications 2 weeks prior to administering trial medication and during the trial was not permitted.

6. Dosage and Administration

The trial arms, including the dosage regimens that were administered, are specified in Figure 1. Buprenorphine/naloxone and daclatasvir were administered under fasted conditions. The daclatasvir USPI permits dosing with or without food. The buprenorphine/naloxone USPI do not include specific dosing recommendations with regards to food or meals.

7. Rationale for Doses Used in the Trial

The daclatasvir, dosing regimens of 60 mg once daily, is consistent with the recommendations in the U.S. prescribing information. The buprenorphine/naloxone doses are consistent with the recommendations in the buprenorphine/naloxone USPI.

8. Drugs Used in the Trial

Information on the daclatasvir formulation administered in the trial is displayed in Table 1. Buprenorphine/naloxone was provided by the clinical trial site. The report does not provide information regarding whether the administered buprenorphine/naloxone or daclatasvir formulations are the U.S. commercially marketed formulations.

Table 1-Formulations administered in the AI444064 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

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

Sample Collection

The blood samples that were obtained included daclatasvir predose and postdose blood samples starting on day 9 up to 24 hours and buprenorphine and norbuprenorphine predose and postdose blood samples starting on days 1 and 9 up to 24 hours.

Bioanalysis

Bioanalytical information for daclatasvir is not provided in this review because the applicant is not proposing to include exposure information for daclatasvir from the AI444064 trial in the daclatasvir USPI.

The method and bioanalysis of buprenorphine are acceptable.

Buprenorphine plasma samples were analyzed using a validated LC/MS/MS method in K_3EDTA anticoagulated plasma by (b) (4) (a combined method used to analyze buprenorphine, norbuprenorphine and naloxone). The blood samples for analysis of buprenorphine appear to have been collected in tubes containing K_2EDTA (not K_3EDTA) as an anticoagulant, however it appears that the buprenorphine calibration curve standards and quality control samples were prepared in K_2EDTA anticoagulated plasma.

For the plasma samples from the AI444064 trial that were analyzed for buprenorphine, the lower limit of quantification for buprenorphine was 20 pg/mL and the upper limit of quantification was 10000 pg/mL. There were no precision or accuracy issues identified for buprenorphine based on the bioanalytical report. For the AI444064 trial, precision and accuracy were evaluated using plasma buprenorphine quality control (QC) samples at 50 pg/mL, 120 pg/mL, 450 pg/mL, 1600 pg/mL and 7500 pg/mL. The corresponding buprenorphine inter-run accuracy values were 7.89% for 50 pg/mL, 2.88% for 120 pg/mL, 6.71% for 450 pg/mL, 1.88% for 1600 pg/mL and 1.59% for 7500 pg/mL. The buprenorphine inter-run precision values were 1.90% for 50 pg/mL, 0.801% for 120 pg/mL, 1.10% for 450 pg/mL, 1.69% for 1600 pg/mL and 2.37% for 7500 pg/mL. In addition, for the buprenorphine dilution QC samples (5x dilution) at 7500 ng/mL, the accuracy and precision were 0.778% and 0.916%, respectively.

Of the samples selected for incurred sample reanalysis for buprenorphine, all samples were within 20% using the percentage values of the repeat and original concentrations. The bioanalytical report states that approximately 10% of the subject samples were reanalyzed (the current FDA recommendation is 7%).

For the AI444064 trial, the applicant provided information indicating that buprenorphine samples were stored at the trial site for no more than 50 days at -20°C, at the central laboratory for no more than 55 days at-20°C or (b) (4) for no more than 196 days at -20°C. Specific information regarding whether current reference standards were used as part of the stability evaluations was not provided by (b) (4). For the AI444064 trial, the applicant does not have sufficient long term stability data in K_2EDTA anticoagulated plasma with only the buprenorphine analyte. However the long term buprenorphine stability data of 309 days at-20°C combined with 50 ng/mL naltrexone in K_2EDTA anticoagulated plasma generated by (b) (4) appears sufficient. Additionally, long term buprenorphine stability data of 404 days at-20°C in K_3EDTA anticoagulated plasma generated by (b) (4) is also available.

For the plasma samples from the AI444064 trial that were analyzed for norbuprenorphine, the lower limit of quantification for norbuprenorphine was 20 pg/mL and the upper limit of quantification was 10000 pg/mL. There were no precision or accuracy issues identified for norbuprenorphine based on the bioanalytical report. For the AI444064 trial, precision and accuracy were evaluated using plasma norbuprenorphine quality control (QC) samples at 50 pg/mL, 120 pg/mL, 450 pg/mL, 1600 pg/mL and 7500 pg/mL. The corresponding norbuprenorphine inter-run accuracy

values were 9.11% for 50 pg/mL, 5.34% for 120 pg/mL, 9.86% for 450 pg/mL, 7.05% for 1600 pg/mL and 6.46% for 7500 pg/mL. The norbuprenorphine inter-run precision values were 3.25% for 50 pg/mL, 1.43% for 120 pg/mL, 1.73% for 450 pg/mL, 3.14% for 1600 pg/mL and 2.72% for 7500 pg/mL. In addition, for the norbuprenorphine dilution QC samples (5x dilution) at 7500 ng/mL, the accuracy and precision were 8.27% and 0.77%, respectively.

Of the samples selected for incurred sample reanalysis for norbuprenorphine, all samples were within 20% using the percentage values of the repeat and original concentrations. The bioanalytical report states that approximately 10% of the subject samples were reanalyzed (the current FDA recommendation is 7%).

For the AI444064 trial, the applicant provided information indicating that norbuprenorphine samples were stored at the trial site for no more than 50 days at -20°C, at the central laboratory for no more than 55 days at-20°C or (b) (4) for no more than 196 days at -20°C. Specific information regarding whether current reference standards were used as part of the stability evaluations was not provided by (b) (4). For the AI444064 trial, the applicant does not have sufficient long term stability data in K_2EDTA anticoagulated plasma with only the norbuprenorphine analyte. However the long term norbuprenorphine stability data of 309 days at-20°C combined with 50 ng/mL naltrexone in K_2EDTA anticoagulated plasma generated by (b) (4) appears sufficient. Additionally, long term norbuprenorphine stability data of 404 days at-20°C in K_3EDTA anticoagulated plasma generated by (b) (4) is also available.

Pharmacokinetic Assessments

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

Statistical Analysis

The statistical analyses included deriving 90% confidence intervals for buprenorphine or norbuprenorphine pharmacokinetic parameters comparing the test arm (buprenorphine/naloxone in combination with daclatasvir) to the reference arm (buprenorphine/naloxone alone).

10. Results

10.1 Subject Demographics

Table 2-AI444064 subject demographics

	Total N = 11	
AGE		
N		11
MEAN		31.8
MEDIAN		31.0
MIN , MAX	22 ,	42
STANDARD DEVIATION		5.55
AGE CATEGORIZATION (%)		
18 - 65	11	(100.0)
GENDER (%)		
MALE	10	(90.9)
FEMALE	1	(9.1)
RACE (%)		
WHITE	11	(100.0)
ETHNICITY (%)		
HISPANIC/LATINO	3	(27.3)
NOT HISPANIC/LATINO	8	(72.7)

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.

10.3 Pharmacokinetic and Statistical Analysis

Table 3-Buprenorphine pharmacokinetic parameters (dose normalized to 8 mg) with and without concomitant use of daclatasvir-evaluable subjects

Parameter Statistic	Treatment C	Treatment D
Cmax (ng/mL)		
Geo.Mean [N]	2.55 [11]	3.31 [11]
(%CV)	(51)	(51)
Tmax (h)		
Median [N]	1.00 [11]	1.47 [11]
(Min - Max)	(0.520 - 2.03)	(0.470 - 2.38)
AUC(TAU) (ng.h/mL)		
Geo.Mean [N]	19.2 [11]	25.7 [9]
(%CV)	(54)	(50)
C24 (ng/mL)		
Geo.Mean [N]	0.403 [11]	0.486 [9]
(%CV)	(51)	(51)

Treatment Code: C: Buprenorphine/naloxone 8/2 to 24/6 mg QD on Day 1, D: Buprenorphine/naloxone 8/2 to 24/6 mg QD and Daclatasvir 60mg QD on Day 2-9

Clinical pharmacology reviewer note: a) Based on the information included in the AI444064 trial report, it appears that two subjects (AI444064-2-8 and AI444064-2-13) did not have a 24 hour sample drawn prior to buprenorphine/naloxone administration on day 10 and were excluded from the "completer"analysis, however the PK data with buprenorphine/naloxone administered by itself for these subjects was included in the "evaluable" analysis, b) The C24 values were defined in the trial report as the 24 hour post dose concentrations.

Table 4-Buprenorphine statistical analyses (dose normalized to 8 mg) with and without concomitant use of daclatasvir-all completers

Treatment and Comparison	Cmax (ng/mL) Adjusted Geometric Mean [N]	C24 (ng/mL) Adjusted Geometric Mean [N]	AUC(TAU) (ng.h/mL) Adjusted Geometric Mean [N]
C	2.55 [11]	0.417 [9]	18.8 [9]
D	3.31 [11]	0.486 [9]	25.7 [9]
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
D vs C	1.299 (1.029,1.640)	1.165(1.028,1.321)	1.371(1.240,1.516)

GMR = geometric mean ratio

Treatment Code: C: Buprenorphine/naloxone 8/2 to 24/6 mg QD on Day 1, D: Buprenorphine/naloxone 8/2 to 24/6 mg QD and Daclatasvir 60mg QD on Day 2-9

Table 5-Buprenorphine statistical analyses (dose normalized to 8 mg) with and without concomitant use of daclatasvir-evaluable subjects

Treatment and Comparison	C24 (ng/mL) Adjusted Geometric Mean [N]	AUC(TAU) (ng.h/mL) Adjusted Geometric Mean [N]
C	0.403[11]	19.2 [11]
D	0.470 [9]	26.3 [9]
	GMR(90% CI)	GMR(90% CI)
D vs C	1.167(1.026,1.326)	1.369(1.237,1.515)

GMR = geometric mean ratio

Treatment Code: C: Buprenorphine/naloxone 8/2 to 24/6 mg QD on Day 1, D: Buprenorphine/naloxone 8/2 to 24/6 mg QD and Daclatasvir 60 mg QD on Day 2-9

Table 6-Norbuprenorphine pharmacokinetic parameters (dose normalized to 8 mg) with and without concomitant use of daclatasvir-evaluable subjects

Parameter Statistic	Treatment C	Treatment D
Cmax (ng/mL)		
Geo.Mean [N]	1.85 [11]	3.06 [11]
(%CV)	(45)	(46)
Tmax (h)		
Median [N]	1.05 [11]	1.00 [11]
(Min - Max)	(0.980 - 6.00)	(0.470 - 2.38)
AUC(TAU) (ng.h/mL)		
Geo.Mean [N]	26.4 [11]	41.1 [9]
(%CV)	(46)	(48)
C24 (ng/mL)		
Geo.Mean [N]	0.935 [11]	1.31 [9]
(%CV)	(47)	(51)

Treatment Code: C: Buprenorphine/naloxone 8/2 to 24/6 mg QD on Day 1, D: Buprenorphine/naloxone 8/2 to 24/6 mg QD and Daclatasvir 60mg QD on Day 2-9

Table 7-Norbuprenorphine statistical analyses (dose normalized to 8 mg) with and without concomitant use of daclatasvir-all completers

Treatment and Comparison	Cmax (ng/mL) Adjusted Geometric Mean [N]	C24 (ng/mL) Adjusted Geometric Mean [N]	AUC(TAU) (ng.h/mL) Adjusted Geometric Mean [N]
C	1.85 [11]	0.901 [9]	25.4 [9]
D	3.06 [11]	1.31 [9]	41.1 [9]
	GMR(90% CI)	GMR(90% CI)	GMR(90% CI)
D vs C	1.654(1.376,1.987)	1.458(1.124,1.890)	1.618(1.298,2.017)

GMR = geometric mean ratio

Treatment Code: C: Buprenorphine/naloxone 8/2 to 24/6 mg QD on Day 1, D: Buprenorphine/naloxone 8/2 to 24/6 mg QD and Daclatasvir 60 mg QD on Day 2-9

Table 8-Norbuprenorphine statistical analyses (dose normalized to 8 mg) with and without concomitant use of daclatasvir-evaluable subjects

Treatment and Comparison	C24 (ng/mL) Adjusted Geometric Mean [N]	AUCTAU (ng.h/mL) Adjusted Geometric Mean [N]
C	0.935 [11]	26.4 [11]
D	1.34 [9]	42.2 [9]
	GMR(90% CI)	GMR(90% CI)
D vs C	1.440(1.118,1.853)	1.603(1.288,1.995)

GMR = geometric mean ratio

Treatment Code: C: Buprenorphine/naloxone 8/2 to 24/6 mg QD on Day 1, D: Buprenorphine/naloxone 8/2 to 24/6 mg QD and Daclatasvir 60 mg QD on Day 2-9

Table 9-Daclatasvir pharmacokinetic parameters with concomitant use of buprenorphine naloxone

Parameter	Unit	Statistic	Treatment D
Cmax	ng/mL	N	11
		GEO.MEAN	1338.471
		%CV	16
Tmax	h	N	11
		MEDIAN	1.000
		MIN	0.98
		MAX	1.60
AUC(TAU)	ng.h/mL	N	11
		GEO.MEAN	11822.353
		%CV	26
C24	ng/mL	N	11
		GEO.MEAN	175.999
		%CV	39

Treatment Code D: Buprenorphine/naloxone 8/2 to 24/6 mg QD and Daclatasvir 60 mg QD on Day 2-9

10.4 Safety Analysis

According to the trial report, no deaths or serious adverse events were reported for the trial.

11. Discussion and Conclusions

Based on the results from the AI444064 trial, the following conclusions can be made:

- For the completer population, when daclatasvir 60 mg once daily was coadministered with buprenorphine/naloxone (dose normalized to 8 mg), the dose normalized buprenorphine. C_{max}, $AUC_{(0\text{-}tau)}$ and C_{24h} were increased by 29.9%, 37.1%, and 16.5%, respectively. The 90% confidence intervals for dose normalized buprenorphine C_{max}, $AUC_{(0\text{-}tau)}$ and C_{24h} were not within the standard "no effect" 90% confidence interval limits of 80%-125%.

- For the completer population, when daclatasvir 60 mg once daily was coadministered with buprenorphine/naloxone (dose normalized to 8 mg), the dose normalized norbuprenorphine C_{max}, $AUC_{(0\text{-}tau)}$ and C_{24h} were increased by 65.4%, 61.8%, and 45.8%, respectively. The 90% confidence intervals for dose normalized norbuprenorphine C_{max}, $AUC_{(0\text{-}tau)}$ and C_{24h} were not within the standard "no effect" 90% confidence interval limits of 80%-125%.

For buprenorphine, the applicant is currently proposing to state in section 7 of the daclatasvir USPI that no clinically relevant changes in buprenorphine exposure were observed. However, based on discussions with the analgesia clinical pharmacology review team, the FDA will propose to instead include a clinical comment stating that no adjustment is needed for buprenorphine or buprenorphine/naloxone but clinical monitoring is recommended with concomitant use of buprenorphine or buprenorphine/naloxone plus daclatasvir.

For norbuprenorphine, based on the currently available information, the changes in norbuprenorphine exposure are not anticipated to have a clinically relevant impact.

AI444093

1. Title

A Phase 1 clinical study to assess the effect of darunavir/ritonavir or lopinavir/ritonavir on the pharmacokinetics of daclatasvir in healthy subjects

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

The trial was conducted from June 4, 2014 (trial initiation) to July 29, 2014 (trial completion).

3. Objectives

The objectives of the trial included evaluating the effect of darunavir/ritonavir or lopinavir/ritonavir on the multiple dose pharmacokinetics of daclatasvir administered once daily.

4. Trial Design

AI444093 enrolled healthy male and female subjects 18 to 49 years old. Information on the trial design is displayed in Figure 1.

Figure 1-AI444093 trial design

Screening and Check-in	**Period 1**	**Period 2**	**Study Discharge (Last Visit/End of Study)**
Group 1:	Treatment A	Treatment B	
Group 2:	Treatment C	Treatment D	
Days -21 through -1	**Days 1 - 4**	**Days 5 through 14**	**Day 15**
	Daily PK sampling prior to morning dose on Days 2 and 3, serial 24-hour PK sampling on Day 4	**Daily PK sampling prior to morning dose on Days 12 and 13; serial 24-hour PK sampling on Day 14**	

Group 1:

Treatment A: 60 mg DCV tablet QD on Days 1 through 4

Treatment B: 30 mg DCV tablet QD plus 800 mg/100 mg DRV tablet/RTV capsule QD on Days 5 through 14

Group 2:

Treatment C: 60 mg DCV tablet QD on Days 1 through 4

Treatment D: 30 mg DCV tablet QD plus 400 mg/100 mg LPV/RTV (2 x 200 mg/50 mg) tablets BID on Days 5 through 14

5. Excluded Medications, Restrictions or Exceptions

According to the trial protocol, unless otherwise approved, use of prescription or nonprescription acid modifying medications within 4 weeks prior to administering trial medication and nonprescription and natural (herbal) medications 2 weeks prior to administering trial medication and during the trial was not permitted.

6. Dosage and Administration

The trial arms, including the dosage regimens that were administered, are specified in Figure 1. Daclatasvir, darunavir/ritonavir or lopinavir/ritonavir were administered with food. This is consistent with the recommendations in the U.S. prescribing information (USPI) for these medications. The daclatasvir USPI and the lopinavir/ritonavir USPI permits dosing with or without food and the darunavir USPI recommends dose administration with food.

7. Rationale for Doses Used in the Trial

The daclatasvir, darunavir/ritonavir or lopinavir/ritonavir dosing regimens of 60 mg once daily, 800 mg/100 mg once daily and 400 mg/100 mg twice daily, respectively are consistent with the recommendations in the corresponding U.S. prescribing information. The daclatasvir dosage regimen of 30 mg once daily is the recommended dosage regimen with concomitant use of strong CYP3A inhibitors.

8. Drugs Used in the Trial

Information on the formulations administered in the trial is displayed in Table 1. The report does not provide information regarding whether the administered formulations are the U.S. commercially marketed formulations.

Table 1-Formulations administered in the AI444093 trial

Investigational Medicinal Product	Tablet/Capsule Strength	Batch Number	Expiration
Daclatasvir	60 mg	3L71909	31-May-2015
Daclatasvir	30 mg	3K77707	31-May-2015
Darunavir	800 mg	14CG929	Feb-2016
Ritonavir	100 mg	1013416	06-Dec-2015
Lopinavir/ritonavir	200 mg/50 mg	1011493	05-Sep-2016

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

Sample Collection

The blood samples that were obtained included daclatasvir predose and postdose blood samples starting on days 4 and 14 up to 24 hours.

Bioanalysis

The method and bioanalysis of daclatasvir is acceptable. Daclatasvir plasma samples were analyzed using a validated LC/MS/MS method in EDTA anticoagulated plasma by (b) (4) ((b) (4) 11132.04). The blood samples for analysis of daclatasvir appear to have been collected in tubes containing K_2EDTA as an anticoagulant.

For the AI444093 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 AI444093 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 -0.8% for 6 ng/mL, 0.5% for 80 ng/mL, 1.5% for 800 ng/mL, and 0% for 1600 ng/mL. The daclatasvir inter-run precision values were 3.5% for 6 ng/mL, 1.9% for 80 ng/mL, 1.5% for 800 ng/mL, and 3.1% for 1600 ng/mL. In addition, for the daclatasvir dilution QC samples (20x dilution) at 10000 ng/mL, the accuracy and precision were -1.4% and 1.3%, respectively.

Of the samples selected for incurred sample reanalysis for daclatasvir, all quantifiable 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% (the current FDA recommendation) of the total number of samples that were initially analyzed.

For the AI444093 trial, the applicant provided information indicating that daclatasvir samples were stored at the trial site for no more than 20 days at -70°C or at (b) (4) for no more than 40 days at -20°C. The bioanalytical report states that the maximum duration of sample storage was 40 days. (b) (4) 11132 generated long term stability data for daclatasvir including stability data in K_2EDTA anticoagulated plasma at -20°C for 686 days and at -80°C for 658 days. For the AI444093 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 C_{max}

and $AUC_{(0\text{-}tau)}$.

Statistical Analysis

The statistical analyses included deriving 90% confidence intervals for daclatasvir pharmacokinetic parameters comparing the test arm (darunavir/ritonavir or lopinavir/ritonavir in combination with daclatasvir) to the reference arm (daclatasvir alone).

10. Results

10.1 Subject Demographics

Table 2-AI444093 subject demographics

	Group 1 Treatment AB N = 14	Group 2 Treatment CD N = 14
Age (years)		
Mean (SD)	33.2 (9.46)	32.9 (8.56)
Median (min, max)	30.0 (19, 48)	31.0 (22, 49)
Age categorization (%)		
< 65 (years)	14 (100.0)	14 (100.0)
≥ 65 (years)	---	---
Gender (%)		
Male	9 (64.3)	10 (71.4)
Female	5 (35.7)	4 (28.6)
Race (%)		
White	7 (50.0)	10 (71.4)
Black/African American	7 (50.0)	2 (14.3)
Asian	---	1 (7.1)
Other	---	1 (7.1)
Ethnicity (%)		
Hispanic/Latino	6 (42.9)	8 (57.1)
Not Hispanic/Latino	8 (57.1)	6 (42.9)

Treatment A (Group 1): 60 mg DCV tablet QD on Days 1 through 4
Treatment B (Group 1): 30 mg DCV tablet QD plus 800 mg/100 mg DRV tablet/RTV capsule QD on Days 5 through 14
Treatment C (Group 2): 60 mg DCV tablet QD on Days 1 through 4
Treatment D (Group 2): 30 mg DCV tablet QD plus 400 mg/100 mg LPV/RTV (2 x 200 mg/50 mg) tablets BID on Days 5 through 14
Abbreviations: max = maximum; min = minimum; SD = standard deviation

10.2 Concomitant Medications

The concomitant medications that were administered in the trial included acetaminophen, diphenhydramine, and loperamide. 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 3A-Daclatasvir pharmacokinetic parameters with and without concomitant use of darunavir/ritonavir

Parameter Statistic	Treatment A	Treatment B
Cmax (ng/mL)		
Geo. Mean (N)	1335 (14)	493 (11)
(%CV)	(38)	(36)
Cmax/D (ng/mL/mg)		
Geo. Mean (N)	22.2 (14)	16.4 (11)
(%CV)	(38)	(36)
Tmax (h)		
Median (N)	2.00 (14)	3.00 (11)
(Min - Max)	(1.00 - 6.00)	(1.00 - 6.00)
AUC (TAU) (ng•h/mL)		
Geo. Mean (N)	12677 (14)	8295 (11)
(%CV)	(41)	(39)
AUC (TAU)/D ([ng•h/mL]/mg)		
Geo. Mean (N)	211 (14)	276 (11)
(%CV)	(41)	(39)
C24 (ng/mL)		
Geo. Mean (N)	225 (14)	250 (11)
(%CV)	(54)	(45)
C24/D (ng/mL/mg)		
Geo. Mean (N)	3.75 (14)	8.34 (11)
(%CV)	(54)	(45)

Treatment A (Group 1): 60 mg DCV tablet QD on Days 1 through 4

Treatment B (Group 1): 30 mg DCV tablet QD plus 800 mg/100 mg DRV tablet/RTV capsule QD on Days 5 through 14

Table 3B-Daclatasvir pharmacokinetic parameters with and without concomitant use of lopinavir/ritonavir

Parameter Statistic	Treatment C	Treatment D
Cmax (ng/mL)		
Geo. Mean (N)	1412 (14)	476 (13)
(%CV)	(28)	(21)
Cmax/D (ng/mL/mg)		
Geo. Mean (N)	23.5 (14)	15.9 (13)
(%CV)	(28)	(21)
Tmax (h)		
Median (N)	2.00 (14)	2.00 (13)
(Min - Max)	(1.00 - 6.00)	(1.00 - 11.9)
AUC (TAU) (ng•h/mL)		
Geo. Mean (N)	13799 (14)	7855 (12)
(%CV)	(26)	(23)
AUC (TAU)/D ([ng•h/mL]/mg)		
Geo. Mean (N)	230 (14)	262 (12)
(%CV)	(26)	(23)
C24 (ng/mL)		
Geo. Mean (N)	225 (14)	280 (12)
(%CV)	(36)	(29)
C24/D (ng/mL/mg)		
Geo. Mean (N)	3.76 (14)	9.33 (12)
(%CV)	(36)	(29)

Treatment C (Group 2): 60 mg DCV tablet QD on Days 1 through 4

Treatment D (Group 2): 30 mg DCV tablet QD plus 400 mg/100 mg LPV/RTV (2 x 200 mg/50 mg) tablets BID on Days 5 through 14

Table 4A-Daclatasvir statistical analyses with and without concomitant use of darunavir/ritonavir (non dose normalized and dose normalized)

PK Parameter	Treatment and Comparison	Adjusted Geometric Mean	90% CI
Cmax (ng/mL)	A	1335	(1121, 1589)
	B	512	(433, 606)
	B versus A	0.384	(0.348, 0.423)
AUC(TAU) (ng•h/mL)	A	12677	(10500, 15305)
	B	8910	(7404, 10721)
	B versus A	0.703	(0.658, 0.750)
Cmax/D (ng/mL/mg)	A	22.2	(18.7, 26.5)
	B	17.1	(14.4, 20.2)
	B versus A	0.768	(0.697, 0.846)
AUC(TAU)/D ([ng•h/mL]/mg)	A	211	(175, 255)
	B	297	(247, 357)
	B versus A	1.406	(1.317, 1.501)

Treatment A (Group 1): 60 mg DCV tablet QD on Days 1 through 4

Treatment B (Group 1): 30 mg DCV tablet QD plus 800 mg/100 mg DRV tablet/RTV capsule QD on Days 5 through 14

Table 4B-Daclatasvir statistical analyses with and without concomitant use of lopinavir/ritonavir (non dose normalized and dose normalized)

PK Parameter	Treatment and Comparison	Adjusted Geometric Mean	90% CI
Cmax (ng/mL)	C	1412	(1249, 1596)
	D	475	(427, 529)
	D versus C	0.337	(0.306, 0.371)
AUC(TAU) (ng•h/mL)	C	13799	(12168, 15649)
	D	7961	(7132, 8886)
	D versus C	0.577	(0.535, 0.622)
Cmax/D (ng/mL/mg)	C	23.5	(20.8, 26.6)
	D	15.8	(14.2, 17.6)
	D versus C	0.673	(0.611, 0.742)
AUC(TAU)/D ([ng•h/mL]/mg)	C	230	(203, 261)
	D	265	(238, 296)
	D versus C	1.154	(1.070, 1.244)

Treatment C (Group 2): 60 mg DCV tablet QD on Days 1 through 4

Treatment D (Group 2): 30 mg DCV tablet QD plus 400 mg/100 mg LPV/RTV (2 x 200 mg/50 mg) tablets BID on Days 5 through 14

10.4 Safety Analysis

According to the trial report, no deaths or serious adverse events were reported for the trial.

11. Discussion and Conclusions

Based on the results from the AI444093 trial, the following conclusions can be made:

- When daclatasvir was coadministered with darunavir/ritonavir 800 mg/100 mg once daily, the dose normalized daclatasvir C_{max} was decreased by 23.2%, and the dose normalized daclatasvir $AUC_{(0\text{-}tau)}$ was increased by 40.6%, respectively, when compared with daclatasvir 60 mg once daily. The 90% confidence intervals for dose normalized daclatasvir C_{max} and $AUC_{(0\text{-}tau)}$ were both not within the standard "no effect" 90% confidence interval limits of 80%-125%.
- When daclatasvir was coadministered with lopinavir/ritonavir 400 mg/100 mg twice daily, the dose normalized daclatasvir C_{max} was decreased by 32.7%, and the dose normalized daclatasvir $AUC_{(0\text{-}tau)}$ was increased by 15.4%, respectively, when compared with daclatasvir 60 mg once daily. The 90% confidence intervals for dose normalized daclatasvir C_{max} was not within the standard "no effect" 90% confidence interval limits of 80%-125%.

Currently, no dose adjustment for daclatasvir is proposed in the revisions to the daclatasvir USPI with concomitant use of darunavir/ritonavir or lopinavir/ritonavir. The applicant proposes to include a clinical comment for daclatasvir with concomitant use of darunavir/ritonavir and other HIV protease inhibitors with moderate CYP3A inhibition effects similar to the existing one for moderate CYP3A inhibitors. The applicant also proposes to include darunavir/ritonavir and lopinavir/ritonavir in the list of medications with no clinically significant changes in exposure with concomitant use of daclatasvir in the daclatasvir USPI (please see the AI444043 clinical pharmacology review).

The applicant's proposed recommendations require further revisions. The magnitude of change in AUC for daclatasvir with darunavir/ritonavir coadministration is similar to the magnitude of change in daclatasvir AUC with cyclosporine coadministration. The current daclatasvir USPI states that changes in daclatasvir exposure were not clinically relevant with concomitant use of cyclosporine and daclatasvir. Therefore the clinical comment for daclatasvir with darunavir/ritonavir coadministration does not appear to be necessary.

AI444273 (201102)

1. Title

A Phase 1, open-label, crossover study to evaluate the drug interaction between dolutegravir and daclatasvir in healthy adult subjects

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

The trial was conducted from March 18, 2014 (trial initiation) to May 15, 2014 (trial completion).

3. Objectives

The objectives of the trial included evaluating the effect of dolutegravir on the pharmacokinetics of daclatasvir and vice versa.

4. Trial Design

AI444273 enrolled healthy male and female subjects 18 to 65 years old. Information on the trial design is displayed in Figure 1.

Figure 1-AI444273 (201102) trial design

Sequence	Subjects	Period 1 Days 1-5	Washout ≥7 Days	Period 2 Days 1-5	Period 3 Days 1-5
1	6	Treatment A[1]		Treatment B[2]	Treatment C[3]
2	6	Treatment B[2]		Treatment A[1]	Treatment C[3]

1. Treatment A = DTG 50mg q24h x 5 days
2. Treatment B = DCV 60mg q24h x 5 days
3. Treatment C = DCV 60mg q24h + DTG 50mg q24h x 5 days

5. Excluded Medications, Restrictions or Exceptions

Unless otherwise approved, use of prescription or nonprescription medications was not permitted within 7 days (or 14 days for enzyme inducers) or five half-lives (whichever was longer) before the first dose until after follow up.

Antacids, vitamins and calcium or iron supplements were also not permitted from 24 hours before the first dose and during the trial, including follow up.

6. Dosage and Administration

The trial arms, including the dosage regimens that were administered, are specified in Figure 1. Daclatasvir and dolutegravir were administered under fasting conditions. This is consistent with the recommendations in the U.S. prescribing information (USPI) for these medications. The daclatasvir USPI permits dosing with or without food and the dolutegravir USPI recommends dose administration with or without a meal or food.

7. Rationale for Doses Used in the Trial

The daclatasvir and dolutegravir dosing regimens of 60 mg once daily and 50 mg once daily, respectively are consistent with the recommendations in the corresponding U.S. prescribing information.

8. Drugs Used in the Trial

Information on the formulations administered in the trial is displayed in Table 1. The report does not provide information regarding whether the administered formulations are the U.S. commercially marketed formulations. In response to an information request, the applicant stated that the Phase 3 daclatasvir formulations were administered.

Table 1-Formulations administered in the AI444273 (201102) trial

Product name:	Dolutegravir	Daclatasvir
Dosage form:	Tablet	Tablet
Unit dose strength(s)/Dosage level(s):	50mg = 1 tablet Dose = 50mg	60mg = 1 tablet Dose = 60mg
Physical description:	9 mm white, film-coated, round tablets debossed with SV 572 on one side and 50 on the other side	A plain, green, biconvex, pentagonal film-coated tablet
Manufacturer/ source of procurement:	(b) (4)	Bristol Myers Squibb
Batch Number	132371884	1L66791

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

Sample Collection

The blood samples that were obtained included daclatasvir predose and postdose blood samples starting on day 5 in periods 1 to 3 up to 24 hours and dolutegravir predose and postdose blood samples starting on day 5 in periods 1 to 3 up to 24 hours.

Bioanalysis

The method and bioanalysis of daclatasvir is acceptable. Daclatasvir plasma samples were analyzed using a validated LC/MS/MS method in EDTA anticoagulated plasma by [redacted] ([redacted]11132.04). The blood samples for analysis of daclatasvir appear to have been collected in tubes containing K_2EDTA as an anticoagulant.

For the AI444273 (201102) 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 AI444273 (201102) 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 1.3% for 6 ng/mL, 0.1% for 80 ng/mL, -3.6% for 800 ng/mL, and -3.1% for 1600 ng/mL. The daclatasvir inter-run precision values were 2.5% for 6 ng/mL, 0.6% for 80 ng/mL, 1.5% for 800 ng/mL, and 1.9% for 1600 ng/mL.

Of the samples selected for incurred sample reanalysis for daclatasvir, all samples were within 20% using the percentage values of the repeat and original concentrations with the exception of one sample that was excluded because it appeared that the wrong sample was reanalyzed. The bioanalytical report states that least 10% of the subject samples were reanalyzed (the current FDA recommendation is 7%).

For the AI444273 (201102) trial, the applicant provided information indicating that daclatasvir samples were stored at -20°C and the bioanalytical report states that the maximum duration of sample storage was 50 days. [redacted]11132 generated long term stability data for daclatasvir including stability data in K_2EDTA anticoagulated plasma at -20°C for 686 days and at -80°C for 658 days. For the AI444273 (201102) trial, the generated long term stability data appears to covers the duration of long term stability data necessary for daclatasvir.

The method and bioanalysis of dolutegravir is acceptable. Dolutegravir plasma samples were analyzed using a validated LC/MS/MS method in K_2EDTA anticoagulated plasma by [redacted] (P1170.02). The blood samples for analysis of dolutegravir appear to have been collected in tubes containing K_2EDTA as an anticoagulant.

For the AI444273 (201102) plasma samples that were analyzed for dolutegravir, the lower limit of quantification for dolutegravir was 20 ng/mL and the upper limit of quantification was 20000 ng/mL. There were no precision or accuracy issues identified for dolutegravir based on the bioanalytical report. For the AI4440273 (201102) trial, precision and accuracy were evaluated using plasma dolutegravir quality control (QC) samples at 60 ng/mL, 160 ng/mL, 640 ng/mL, 2400 ng/mL and 15200 ng/mL. The corresponding dolutegravir inter-run accuracy values were 1.84% for 60 ng/mL, 2.11% for 160 ng/mL, 3.13% for 640 ng/mL, 0.974% for 2400 ng/mL and -7.66% for 15200 ng/mL. The dolutegravir inter-run precision values were 4.63% for 60 ng/mL, 4.06% for 160 ng/mL, 5.76% for 640 ng/mL, 3.2% for 2400 ng/mL and 5.58% for 15200 ng/mL

Of the samples selected for incurred sample reanalysis for dolutegravir, only one sample was not within 20% using the percentage values of the repeat and original concentrations. The bioanalytical report states that approximately 10% of the subject samples were reanalyzed (the current FDA recommendation is 7%).

For the AI444273 (201102) trial, the applicant provided information indicating that dolutegravir samples were stored at -20°C and based on the information in the bioanalytical report, it appears that that samples were stored for no more than 47 days at -20°C. Specific information regarding whether current reference standards were used as part of the stability evaluations or the anticoagulant used for the stability samples was not provided by (b) (4). For the AI444273 (201102) trial, the long term stability dolutegravir data of 558 days at-20°C and-70°C generated by (b) (4) using fresh calibration standards appears to cover the duration of long term stability data necessary for dolutegravir.

Pharmacokinetic Assessments

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

Statistical Analysis

The statistical analyses included deriving 90% confidence intervals for the following comparisons: a) daclatasvir pharmacokinetic parameters comparing the test arm (daclatasvir in combination with dolutegravir) to the reference arm (daclatasvir alone) and b) dolutegravir pharmacokinetic parameters comparing the test arm (daclatasvir in combination with dolutegravir) to the reference arm (dolutegravir alone).

10. Results

10.1 Subject Demographics

Table 2-AI444273 (201102) subject demographics

Demographics	Overall
Age in Years [Mean (SD)]	32.3 (10.1)
Sex [n (%)]	
Female	3 (25)
Male	9 (75)
BMI (kg/m^2) [Mean (SD)]	24.0 (3.0)
Height (cm) [Mean (SD)]	169.3 (7.2)
Weight (kg) [Mean (SD)]	69.0 (11.8)
Ethnicity [n (%)]	
Not Hispanic or Latino	12 (100)
Race [n (%)]	
African American/African Heritage	6 (50)
White – White/Caucasian/European Heritage	6 (50)

10.2 Concomitant Medications

The trial report states that no concomitant medications were administered in the trial.

10.3 Pharmacokinetic and Statistical Analysis

Clinical pharmacology reviewer note: C_{tau} was defined as the concentration at the end of the dosing interval

Table 3-Daclatasvir pharmacokinetic parameters with and without concomitant use of dolutegravir

DCV PK Parameter[a]	DCV 60 mg q24h Alone (N=12)	DCV 60 mg q24h + DTG 50 mg q24h (N=12)
AUC(0-τ) (µg*hr/mL)	11.4 (47.9)	11.2 (41.6)
Cmax (µg/mL)	1.19 (42.6)	1.22 (42.2)
Tmax (hr)	1.01 (1.00, 6.00)	1.00 (0.50, 4.00)
CL/F (L/hr)	5.25 (47.9)	5.36 (41.6)
Cτ (µg/mL)	0.166 (69.3)	0.176 (53.8)
t1/2 (hr)	8.58 (23.2)	8.42 (29.4)

a. Data are presented as geometric mean (CV%) except tmax is reported as median (min, max)

Table 4-Daclatasvir statistical analyses with and without concomitant use of dolutegravir

Plasma DCV PK Parameter	GLS Mean		GLS Mean Ratio (90% CI)
	DCV 60 mg q24h Alone (N=12)	DCV 60 mg q24h + DTG 50 mg q24h (N=12)	DCV + DTG vs. DCV Alone
AUC(0-τ) (µg*hr/mL)	11.4	11.2	0.978 (0.831, 1.15)
Cmax (µg/mL)	1.20	1.23	1.03 (0.843, 1.25)
Cτ (µg/mL)	0.166	0.176	1.06 (0.876, 1.29)
CL/F (L/hr)	5.25	5.36	1.02 (0.868, 1.203)
t1/2 (hr)	8.58	8.42	0.982 (0.814, 1.18)

Table 5-Dolutegravir pharmacokinetic parameters with and without concomitant use of daclatasvir

DTG PK Parameter[a]	DTG 50 mg q24h Alone (N=12)	DTG 50 mg q24h + DCV 60 mg q24h (N=12)
AUC(0-τ) (µg*hr/mL)	35.7 (34.7)	47.3 (26.3)
Cmax (µg/mL)	2.65 (32.0)	3.43 (24.5)
Tmax (hr)	2.00 (1.00, 4.00)	2.00 (1.00,3.00)
CL/F (L/hr)	1.40 (34.7)	1.06 (26.3)
Cτ (µg/mL)	0.771 (41.3)	1.11 (36.6)
t1/2 (hr)	13.9 (32.8)	16.2 (32.6)

Table 6-Dolutegravir statistical analyses with and without concomitant use of daclatasvir

Plasma DTG PK Parameter	GLS Mean		GLS Mean Ratio (90% CI)
	DTG 50 mg q24h Alone (N=12)	DTG 50 mg q24h + DCV 60 mg q24h (N=12)	DTG + DCV vs. DTG Alone
AUC(0-τ) (µg*hr/mL)	35.7	47.3	1.33 (1.11, 1.59)
Cmax (µg/mL)	2.65	3.43	1.29 (1.07, 1.57)
Cτ (µg/mL)	0.771	1.12	1.45 (1.25, 1.68)
CL/F (L/hr)	1.40	1.06	0.753 (0.627, 0.905)
t1/2 (hr)	13.9	16.2	1.17 (1.01, 1.35)

10.4 Safety Analysis

According to the trial report, no serious adverse events were reported for the trial.

11. Discussion and Conclusions

Based on the results from the AI444273 (201102) trial, the following conclusions can be made:

- When daclatasvir 60 mg once daily was coadministered with dolutegravir 50 mg once daily, the daclatasvir C_{max} and C_{tau} were increased by 3% and 6%, respectively, and daclatasvir $AUC_{(0\text{-}tau)}$ was decreased by 2.2%, when compared with daclatasvir 60 mg once daily. The 90% confidence intervals for daclatasvir C_{tau} was not within the standard "no effect" 90% confidence interval limits of 80%-125%.
- When daclatasvir 60 mg once daily was coadministered with dolutegravir 50 mg once daily, the dolutegravir C_{max}, $AUC_{(0\text{-}tau)}$ and C_{tau} were increased by 29%, 33%, and 45%, respectively, when compared with dolutegravir 50 mg once daily. The 90% confidence intervals for dolutegravir C_{max}, $AUC_{(0\text{-}tau)}$ and C_{tau} were not within the standard "no effect" 90% confidence interval limits of 80%-125%.

Based on the results from the AI444273 (201102) trial, in general, no clinically relevant changes in daclatasvir exposure are observed with concomitant use of dolutegravir. Based on the available exposure-safety information for dolutegravir, no clinically relevant safety issues are anticipated based on the observed changes in dolutegravir exposure with concomitant use of daclatasvir.

Nonclinical reports

NCPK 139

1. Title

In vitro assessment of BMS-790052 as a substrate of human breast cancer resistance protein (BCRP)

2. Objectives

The objective of the study was to characterize whether daclatasvir is a BCRP substrate. A previous in vitro study (930051246) had also evaluated whether daclatasvir is a BCRP substrate.

3. Methods

The study evaluated MDCK wild type cells and MDCK cells that were transfected with BCRP. Daclatasvir concentrations of 0.1 µM and 1 µM were evaluated.

4. Results

Table 1-BCRP substrate experiments for daclatasvir

Cell type	Pc (nm/sec)		Efflux Ratio	Efflux ratio $_{BCRP}$/ Efflux ratio $_{wild\ type}$ (Ratio of ratios)
	A to B	B to A		
MDCK-WT (0.1µM BMS-790052)	53 ± 10	239 ± 17	4.5	0.9
MDCK-BCRP (0.1µM BMS-790052)	53 ± 6.2	213 ± 12	4.0	

Cell type	Pc (nm/sec)		Efflux Ratio	Efflux ratio $_{BCRP}$/ Efflux ratio $_{wild\ type}$ (Ratio of ratios)
	A to B	B to A		
MDCK-WT (1µM BMS-790052)	42 ± 3	307 ± 55	7.3	1.1
MDCK-BCRP (1 µM BMS-790052)	30 ± 2.2	251 ± 12	8.2	

5. Conclusions

The recommended criteria that describe a BCRP substrate are as follows: net flux ratio of ≥ 2 and inhibition of efflux by decreasing the efflux ratio more than 50% or to unity. The report states that the results support the conclusion that daclatasvir is not a BCRP substrate, consistent with previous results.

However, assuming the net flux ratio refers to the efflux ratio only, the applicant's approach is not consistent with the recommended approach for determining whether a drug is a BCRP substrate and a rationale for further adjusting using the wild type data was not provided.

NCPK 160

1. Title

Assessment of the hepatic uptake of BMS-790052 into human hepatocytes in suspension

2. Objectives

The objective of the study was to characterize uptake of daclatasvir in human hepatocytes.

3. Methods

Table 1-Incubation information

Test Compound	Incubation Concentration (µM)	Incubation Time (min)	Positive Inhibitor	Inhibitor Concentration (µM)
BMS-790052	0.2 or 1	0.25, 1.0, 1.5, 5	Probenecid,	1000
			Pyrimethamine	20
			Tenofovir	10
			TDF	10
			Rifamycin SV	100
			At low Temperature (4°C)	
Rosuvastatin	1.0	0.25, 1.0, 1.5, 5	Rifamycin SV	100

4. Results

Table 2-Uptake inhibition results for probenecid and pyrimethamine

Uptake rate (pmol/min/1 × 10^6 cells)	**37°C, without inhibitor**	37.1
	37°C, with Probenecid (1 mM)	14.3
	37°C, with Pyrimethamine(20 µM)	8.24
CLu (µL/min/1 × 10^6 cells)	**37°C, without inhibitor**	186
	37°C, with Probenecid (1 mM)	71.4
	37°C, with Pyrimethamine (20 µM)	41.2
Active uptake inhibited (%)	**Probenecid**	61.5
	Pyrimethamine	77.8

Clinical pharmacology reviewer note: the report states that probenecid is an OAT2 inhibitor and pyrimethamine is an OCT1 inhibitor.

Table 3-Uptake inhibition results for rifamycin, tenofovir and tenofovir diphosphate

Uptake rate (pmol/min/1 × 10^6 cells)	**37°C, without inhibitor**	168
	37°C, with Rifamycin SV (100 µM)	138
	37°C, with Tenofovir(10 µM)	169
	37°C, with TDF (10 µM)	159
	4°C, without inhibitor	13.7
CLu (µL/min/1 × 10^6 cells)	**37°C, without inhibitor**	168
	37°C, with Rifamycin SV (10 µM)	138
	37°C, with Tenofovir (10 µM)	169
	37°C, with TDF (10 µM)	159
	4°C, without inhibitor	13.7
Active uptake inhibited (%)	**Rifamycin SV**	17.7
	Tenofovir	No inhibition
	TDF	5.54
	Low temperature (4°C)	91.8

Clinical pharmacology reviewer note: the report states that rifamycin is an OATP and NTCP inhibitor and tenofovir or tenofovir diphosphate was intended to be an OCT1 inhibitor.

5. Conclusions

Based on the study results, it appears that OAT2 and OCT1 may be involved in the hepatic uptake of daclatasvir. Additionally, the report states that at lower temperatures (4°C), hepatic uptake would occur through passive diffusion only, and the magnitude of inhibition at 4°C supports the role of active transport in the hepatic uptake of daclatasvir.

NCPK 212

1. Title

In vitro assessment of the transport of bms-790052 by human organic cation transporter (OCT) 1, multidrug and toxin extrusion protein (MATE)1, and organic anion transporter (OAT) 2

2. Objectives

The objective of the study was to further characterize whether daclatasvir is an OAT2 and OCT1 substrate and to characterize whether daclatasvir is a MATE 1 substrate.

3. Methods

The study utilized human embryonic kidney-293 (HEK) cells and evaluated daclatasvir at 0.5 µM for the substrate experiments and 0.1 µM for the inhibitor experiments.

Table 1-Incubation information

Trans porter	BMS-790052 (Concentration)	Probe Substrate	Incubation Time (min)	Positive Control Inhibitor
OCT1	0.5 µM	NA	0.25, 0.5, 1.0, 2.0, 5.0, 10, 15, 30	NA
	0.1 µM	[^{3}H]MPP$^+$ (1.0 µM)	5.0	Tenofovir (1 µM) TDF (1 and 10 µM) PYR (50 or 100 µM)
MATE1	0.5 µM	NA	0.25, 0.5, 1.0, 2.0, 5.0, 10, 15, 30	NA
	0.1 µM	[^{3}H]MPP$^+$ (1.0 µM)	5.0	PYR (100 µM) IPM (200 µM)
OAT2	0.5 µM	NA	0.25, 0.5, 1.0, 2.0, 5.0, 10, 15, 30	NA
	0.1 µM	[^{3}H]PCV (1.0 µM)	5.0	BSP (50 µM) IMC (100 µM)

Abbreviations: NA: not applicable, [^{3}H]MPP$^+$: [^{3}H]1-methyl-4-phenylpyridinium, TDF: tenofovir disoproxil fumarate, PYR: pyrimethamine, [^{3}H]PCV: [^{3}H]penciclovir, BSP: bromosulfophthalein, IMC: indomethacin, IPM: indomethacin.

4. Results

Table 2-OCT1 substrate experiments for daclatasvir

	BMS-790052 Uptake (pmol/mg) (mean ± SD, N = 3)			
	OCT1/HEK		Mock/HEK	
Time (min)	37 °C	4 °C	37 °C	4 °C
0.25	9.42 ± 1.55	1.77 ± 0.477	7.44 ± 1.55	1.67 ± 0.287
0.5	14.9 ± 0.863	3.63 ± 0.628	12.7 ± 0.755	1.93 ± 0.0814
1	22.6 ± 0.791	6.29 ± 0.951	21.2 ± 1.03	4.80 ± 0.293
2	30.2 ± 1.60	7.86 ± 0.630	31.6 ± 0.649	4.92 ± 0.579
5	59.3 ± 0.815	15.1 ± 2.26	55.5 ± 2.56	8.85 ± 1.88
10	86.3 ± 0.253	21.6 ± 3.83	77.1 ± 1.75	14.4 ± 2.68
15	98.4 ± 0.146	23.9 ± 1.83	87.9 ±2.63	15.6 ± 5.32
30	103 ± 1.15	29.7 ± 0.844	99.6 ± 9.25	19.5 ± 4.11

Table 3- OCT1 substrate experiments for daclatasvir with inhibitors

	BMS-790052 Uptake (pmol/mg/5 min) (mean ± SD, N = 3)			
	Mock/HEK		OCT1/HEK	
Treatment	Mean	SD	Mean	SD
BMS-790052 alone	1.50	0.103	2.49[a]	0.186
with 1 µM TDF	1.28	0.214	2.13	0.155
with 10 µM TDF	1.29	0.126	2.13	0.141
with 100 µM PYR	1.62	0.051	1.60[b]	0.178

[a] $p < 0.05$ compared with mock/HEK cells

[b] $p < 0.05$ compared with OCT1/HEK cells in the absence of inhibitor

Table 4-MATE1 substrate experiments for daclatasvir

	BMS-790052 Uptake (pmol/mg) (mean ± SD, N = 3)			
	MATE1/HEK		Mock/HEK	
Time (min)	Mean	SD	Mean	SD
0.25	4.91	NA[a]	5.21	0.849
0.5	7.59	1.06	10.1	0.792
1	15.6	1.59	16.4	0.527
2	21.6	0.530	23.9	1.00
5	47.2	1.66	43.0	0.380
10	51.9	4.30	59.6	1.25
15	72.0	2.82	70.4	2.21
30	80.0	2.69	73.5	2.56

[a] Not applicable as N =1 for this data point.

Table 5-MATE1 substrate experiments for daclatasvir with inhibitors

	BMS-790052 Uptake (pmol/mg/5 min) (mean ± SD, N = 3-6)			
	Mock/HEK		MATE1/HEK	
Treatment	Mean	SD	Mean	SD
BMS-790052 alone	1.38	0.0788	0.806	0.488
with 100 µM PYR	1.62	0.124	1.46	0.108
with 200 µM IPM	6.47	0.555	5.81	0.564

Table 6-OAT2 substrate experiments for daclatasvir

	BMS-790052 Uptake (pmol/mg) (mean ± SD, N = 3)			
	OAT2/HEK		Mock/HEK	
Time (min)	Mean	SD	Mean	SD
0.25	4.61	1.17	7.44	1.55
0.5	7.48	0.870	12.7	0.755
1	13.1	0.982	21.2	1.03
2	20.1	2.45	31.6	0.649
5	41.8	1.14	55.5	2.56
10	59.2	2.13	77.1	1.75
15	64.1	2.22	87.9	2.63
30	71.0	2.43	99.6	9.25

Table 7-OAT2 substrate experiments for daclatasvir with inhibitors

	BMS-790052 Uptake (pmol/mg/5 min) (mean ± SD, N = 3-6)			
	Mock/HEK		OAT2/HEK	
Treatment	Mean	SD	Mean	SD
BMS-790052 alone	0.552	0.203	0.0951	0.0735
with 50 µM BSP	0.717	0.0301	0.469	0.0244
with 100 µM IMC	1.33	0.130	0.948	0.0482

5. Conclusions

The recommended criteria that describe a hepatic transporter substrate are as follows: Uptake is greater than two times the uptake in empty vector cells with inhibition (e.g. >50% reduction to unity) by an inhibitor at a concentration that is at a minimum 10 times its K_i.

The report states that the results support the conclusion that daclatasvir is an OCT1 substrate. However, for OCT1, the reported data did not meet the recommended criteria with regards to uptake.

The results of the study support the conclusion that daclatasvir is not an MATE1 or OAT2 substrate.

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