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APPLICATION NUMBER:

208624Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY (OCP) REVIEW

NDA	208624
Date of Submission	September 28, 2015
Brand Name	VIEKIRA XR™
Generic Names	Dasabuvir (ABT-333)/Ombitasvir (ABT-267)/Paritaprevir (ABT-450)/ Ritonavir
Clinical Pharmacology Review Team	Vikram Arya, Ph.D., FCP, Luning (Ada) Zhang, Ph.D, Jeffry Florian, Ph.D, Islam Younis, Ph.D.
OCP Division	Division of Clinical Pharmacology 4
OND Division	Division of Antiviral Products (DAVP)
Applicant	Abbvie Inc.
Formulation; strength(s) to-be-marketed	Extended Release Tablets; 200 mg/8.33 mg/50 mg/33.33 mg Dasabuvir/Ombitasvir/Paritaprevir/Ritonavir
Proposed Indication	Treatment of HCV Genotype 1 Infection
Submission Type	505 (b)(1) New Drug Application
Review Type	Standard Review

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1 Executive Summary

Abbvie Inc. is seeking approval of VIEKIRA XR ™ (dasabuvir, ombitasvir, paritaprevir, and ritonavir) extended release fixed dose tablets for the treatment of genotype 1 chronic hepatitis C infection. Dasabuvir is a NS5B polymerase inhibitor, ombitasvir is a non-structural protein 5A [NS5A] inhibitor, and paritaprevir is a NS3/4A protease inhibitor and the three drugs are direct acting antivirals (DAA). VIEKIRA PAK™, a combination of ombitasvir/paritaprevir/ritonavir co-formulated immediate release tablets and dasabuvir immediate release tablets is approved for the treatment of genotype 1 chronic hepatitis C infection. The remainder of this review will refer to VIEKIRA XR™ as "3-QD" and VIEKIRA PAK™ as "3-DAA".

3-QD was developed with the objective of providing a once-daily dosing alternative to the currently approved 3-DAA. Because dasabuvir is the only DAA which is dosed twice daily as part of 3-DAA, the dasabuvir component of the regimen was the main focus of the formulation development efforts with the objective of developing a once-daily regimen of the DAAs.

Table 1 provides a description of the pivotal trials conducted as part of the clinical development program.

Table 1: Pivotal Trials Conducted as Part of the Clinical Development Program

Trial #	Brief Description of the Trial
M14-566	Assessment of the relative bioavailability of VIEKIRA XR relative to VIEKIRA PAK after ***single dose*** (Part 1) and ***steady state*** (Part 2) administration under **non-fasting** conditions.
M14-240	Comparison of the pharmacokinetic parameters of the various components of VIEKIRA XR and VIEKIRA PAK under ***fasting conditions*** and the effect of food ***(high fat breakfast)*** on VIEKIRA XR.

The applicant provided the results of an exposure-response analysis as supportive evidence to show no significant differences in efficacy between 3-QD and 3-DAA. Exposures for all three compounds of the 3-QD were either similar or lower than that observed for the 3-DAA. As such, no additional safety analysis was done beyond those analyses already discussed in the clinical pharmacology review for the 3-DAA (NDA # 206619).

The applicant conducted several additional pharmacokinetic studies that supported the development of 3-QD (such as relative bioavailability studies comparing various formulations in order to select the pivotal 3-QD formulation and study to investigate the regional bioavailability of dasabuvir), however; these studies were considered supportive to development of the formulation used in trials M14-566 and M14-240.

Because 3-QD relies on the safety and efficacy findings from 3-DAA on the basis of demonstrating non-clinically relevant differences in exposures of the various components of 3-QD and 3-DAA, clinical and bioanalytical inspections were conducted for trial M14-566. The results of both inspections indicated that the data from trial M14-566 can be used for regulatory review and decision making purposes. Please refer to the review from the Office of Study Integrity and Surveillance (OSIS) for details.

1.1 Recommendation

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

2 Question based review (QBR)

2.1 What is the proposed to-be-marketed formulation and dosing regimen of 3-QD?

The 3-QD tablet is a fixed-dose combination tablet which consists of an extended release (ER) layer of dasabuvir and an immediate release layer of ombitasvir, paritaprevir, and ritonavir. The proposed dosing regimen of the 3-QD tablet will be 3 tablets taken once daily with food and the proposed indication is identical to the approved indication of 3-DAA.

The 3-QD tablets used in trials M14-566 and M14-240 (b)(4) (b)(4) (b)(4) **The final commercial product will be the pale yellow coated 3-QD tablet.**

Although the (b) (4) coated 3-QD tablets were not evaluated in clinical trials, the applicant conducted dissolution studies to compare the dissolution profiles of the (b) (4) film-coated and (b) (4) film-coated profiles and the results suggest that the differences in the color of the coating are not expected to result in differences in bioavailability between 3-QD and 3-DAA. Please refer to the Biopharmaceutics review for further details. Table 2 shows the comparison of the 3-QD and 3-DAA.

Table 2: Comparison of 3-QD and 3-DAA

	3-QD	3-DAA
Amount per tablet	200 mg dasabuvir, 8.33 mg ombitasvir, 50 mg paritaprevir, 33.3 mg ritonavir	250 mg dasabuvir, 12.5 mg ombitasvir, 75 mg paritaprevir, 50 mg ritonavir
Total daily dose	600 mg dasabuvir, 25 mg ombitasvir, 150 mg paritaprevir, 100 mg ritonavir	500 mg dasabuvir, 25 mg ombitasvir, 150 mg paritaprevir, 100 mg ritonavir
Dosing frequency	Once daily for all the components	Once daily for ombitasvir, paritaprevir and ritonavir; twice daily for dasabuvir.
# tablets/day*	3	4
Need for Ribavirin?	Similar for 3-QD and 3-DAA	

*excluding ribavirin; yellow highlighted areas reflect differences between 3-QD and 3-DAA
Source: Prepared by the reviewer

2.2 What is the relative bioavailability of the various components of the 3-QD regimen relative to the various components of 3-DAA regimen?

The applicant assessed the bioavailability of the 3-QD relative to 3-DAA in trial M14-566, a two-part trial in which the relative bioavailability of the 3-QDD was assessed after single dose (part 1) and multiple dose (Part 2) **under non fasting conditions** (approximately 40% of the daily calories from fat and up to 45% of daily calories from carbohydrates [approximately 2,200 total calories/day]).

Table 3 shows the comparison of C_{max}, AUC_t and AUC_{inf} after single dose administration of 3-QD and 3-DAA. Of note, although the applicant assessed the concentrations of M1 (the metabolite of dasabuvir) in trial M14-566 (and trial M14-240), the conclusions from both trials are made on the basis of dasabuvir (the parent moiety). Table 4 shows the comparison of C_{max}, AUC_t and AUC_{inf} after multiple dose administration of 3-QD and 3-DAA.

Based on comparison of the pharmacokinetic parameters after multiple dose administration under non-fasting conditions, the mean C_{24hrs} of dasabuvir was decreased by 29 % and the lower bound of the 90 % CI suggest that the mean C_{24hrs} of dasabuvir decreased by up to 38 %. The clinical relevance of this decrease in the mean C_{24hrs} of dasabuvir is discussed in response to question 2.3.

Based on comparison of the mean pharmacokinetic parameters after multiple dose administration under non-fasting conditions, the mean C_{max} of paritaprevir and ritonavir decreased by 28 % and 21%, respectively, however; these changes are not expected to alter the efficacy of 3-QD as compared to 3-DAA because antiviral efficacy is generally driven by the minimum steady state concentrations (C_{minss}) and/or total systemic exposures (AUC).

The applicant also assessed the bioavailability of 3-QD relative to 3-DAA under fasting conditions in trial M14-240. Compared with administration of 3-DAA under fasting conditions, administration of 3-QD under fasting conditions decreased the mean systemic exposure of dasabuvir and paritaprevir by approximately 68 % and 21 %, respectively and there were no changes in the exposures of ombitasvir (Table 6).

Of note, because 3-DAA is labeled to be administered under fed conditions and 3-QD will also be labeled to be given under fed conditions, the review primarily focuses on the effect of food on various DAAs after administration of 3-QD and the comparison of exposures of various DAAs under fed conditions (high fat and moderate fat conditions) after administration of 3-QD and 3-DAA.

Table 3: Comparison of Point Estimates, and 90 % CI of C_{max}, AUC_t and AUC_{inf} after single dose administration of 3-QD (test) and 3-DAA (reference)

Pharmacokinetic Parameter (units)	Central Value[a] Test (Regimen A)	Central Value[a] Reference (Regimen B)	Relative Bioavailability Point Estimate[b]	Relative Bioavailability 90% Confidence Interval[c]
		Dasabuvir		
C_{max} (ng/mL)[d]	1076	1142	0.942	0.871 – 1.018
AUC_t (ng•h/mL)	12830	14945	0.858	0.787 – 0.936
AUC_∞ (ng•h/mL)	13013	15080	0.863	0.793 – 0.939
		Dasabuvir M1		
C_{max} (ng/mL)[d]	512	577	0.887	0.813 – 0.967
AUC_t (ng•h/mL)	5604	6942	0.807	0.734 – 0.888
AUC_∞ (ng•h/mL)	5737	7119	0.806	0.736 – 0.883
		Paritaprevir		
C_{max} (ng/mL)[e]	623	910	0.685 0.690[f] (0.091)[g]	0.625 – 0.750
AUC_t (ng•h/mL)	4475	5274	0.849	0.790 – 0.911
AUC_∞ (ng•h/mL)	4505	5302	0.850	0.792 – 0.912
		Ombitasvir		
C_{max} (ng/mL)	125	130	0.960	0.926 – 0.995
AUC_t (ng•h/mL)	1664	1605	1.037	1.011 – 1.064
AUC_∞ (ng•h/mL)	1795	1734	1.035	1.009 – 1.062

Pharmacokinetic Parameter (units)	Central Value[a] Test (Regimen A)	Central Value[a] Reference (Regimen B)	Relative Bioavailability Point Estimate[b]	Relative Bioavailability 90% Confidence Interval[c]
		Ritonavir		
C_{max} (ng/mL)	1146	1395	0.821	0.777 – 0.867
AUC_t (ng•h/mL)	7591	8308	0.914	0.880 – 0.949
AUC_∞ (ng•h/mL)	8223	8911	0.923	0.893 – 0.953

Regimen A = Three Film-Coated ER-12 bilayer tablets (total dose of dasabuvir/ombitasvir/paritaprevir/r is 600/25/150/100 mg) administered in the morning under non-fasting conditions on Day 1 of each corresponding period (test regimen).

Regimen B = Two ombitasvir/paritaprevir/r co-formulated tablets (total dose of 25/150/100 mg) with one dasabuvir IR tablet (250 mg) administered under non-fasting conditions in the morning and one dasabuvir IR tablet (250 mg) administered under non-fasting conditions in the evening on Day 1 of each corresponding period (reference regimen).

a. Exponentiation of the least squares means for logarithms.

b. Exponentiation of the difference (test minus reference) of the least squares means for logarithms.

c. Exponentiation of the endpoints of confidence intervals for the difference of the least squares means for logarithms.

d. For dasabuvir and dasabuvir M1 from Regimen B, C_{max} comparisons shown are for C_{max} over 0 to 120 hours.

e. For paritaprevir C_{max}, intra subject variability was > 30% (53%).

f. Central value ratio: Per the definition in FDA and EMA guidances of highly variable drug bioequivalence study, the central value ratio (per protocol for paritaprevir C_{max}, based on the bioequivalence criteria for highly variable drugs) should be within 0.8 – 1.25 to meet BE criterion.

g. 95% upper confidence bound: Per the definition in FDA and EMA guidances of highly variable drug bioequivalence study, the 95% upper confidence bound (per protocol reference-scaled analysis of paritaprevir C_{max}, based on the bioequivalence criteria for highly variable drugs) was > 0, which indicates failure of BE criterion.

Source: Section 2.7.1 Biopharmaceutics Studies and Analytical Methods. Page 58-59.

Table 4: Comparison of the Central Value, Point Estimates, and 90 % CI of C_{max}, AUC_t and AUC_{inf} after multiple dose administration of 3-QD (test) and 3-DAA (reference)

	Central Value[a]		Relative Bioavailability	
Pharmacokinetic Parameter (units)	Test (Regimen A)	Reference (Regimen B)	Point Estimate[b]	90% Confidence Interval[c]
		Dasabuvir		
C_{max} (ng/mL)[d]	797	880	0.905	0.823 - 0.995
AUC_{24} (ng•h/mL)	8767	9823	0.892	0.809 – 0.985
C_{24} (ng/mL)	116	163	0.710	0.622 – 0.812
		Dasabuvir M1		
C_{max} (ng/mL)[d]	448	565	0.793	0.714 - 0.880
AUC_{24} (ng•h/mL)	4595	5294	0.868	0.782 - 0.963
C_{24} (ng/mL)	48.1	72.1	0.666	0.577 - 0.769
		Ombitasvir		
C_{max} (ng/mL)	127	122	1.040	1.005 – 1.077
AUC_{24} (ng•h/mL)	1367	1254	1.090	1.063 – 1.117
C_{24} (ng/mL)	29.5	26.9	1.098	1.064 – 1.132
		Paritaprevir		
C_{max} (ng/mL)	1452	2011	0.722	0.638 – 0.818
AUC_{24} (ng•h/mL)	8645	9608	0.900	0.814 – 0.994
C_{24} (ng/mL)	33.7	31.9	1.055	0.970 – 1.147
		Ritonavir		
C_{max} (ng/mL)	1328	1676	0.793	0.746 – 0.842
AUC_{24} (ng•h/mL)	8604	9630	0.893	0.846 – 0.943
C_{24} (ng/mL)	36.1	35.8	1.009	0.946 – 1.075

Regimen A = Three Film-Coated ER-12 bilayer tablets (total dose of dasabuvir/ombitasvir/paritaprevir/r is 600/25/150/100 mg) administered in the morning under non-fasting conditions on Days 1 through 14 of each corresponding period (test regimen).

Regimen B = Two ombitasvir/paritaprevir/r co-formulated tablets (total dose of 25/150/100 mg) with one dasabuvir IR tablet (250 mg) administered under non-fasting conditions in the morning and one dasabuvir IR tablet (250 mg) administered under non-fasting conditions in the evening on Days 1 through 14 of each corresponding period (reference regimen).

a. Exponentiation of the least squares means for logarithms.
b. Exponentiation of the difference (test minus reference) of the least squares means for logarithms.
c. Exponentiation of the endpoints of confidence intervals for the difference in the least squares means between the test and reference regimens for logarithms.
d. For dasabuvir and dasabuvir M1 from Regimen B, C_{max} comparisons shown are for C_{max} over 0 to 72 hours.

Source: Section 2.7.1 Biopharmaceutics Studies and Analytical Methods. Page 63

2.3 Will differences in the pharmacokinetic parameters between the 3-QD and the 3-DAA result in differences in efficacy between 3-QD and 3-DAA regimen?

Lower dasabuvir C_{trough} under fed conditions in patients infected with HCV genotype 1a

The impact of a 38% decrease in dasabuvir C_{trough} under fed conditions with the 3QD regimen on SVR_{12} in HCV genotype 1a patients is not predicted to be clinically relevant. In all genotype 1a patients and genotype 1a patients with multiple patient factors indicative of poorer response as predicted by the exposure-SVR_{12} model (male, cirrhosis, IL28B non-CC genotype), a decrease in SVR_{12} of 0.6% and 1.0%, respectively, is predicted for the 3QD regimen compared to the 3-DAA regimen (Table 5).

Table 5: Predicted Effects of 38% Lower Dasabuvir C_{trough} on SVR_{12}

Population	No. of patients	Observed SVR_{12}%	Predicted SVR_{12}% for 3-DAA (95%CI)	Predicted SVR_{12}% for 3QD (95%CI)	SVR_{12}% Decrease
All patients	1253	95.0	96.8 (96.6-97.1)	96.2 (95.9-96.5)	0.6
Cirrhotic, male, IL28B non-CC patients	118	92.4	94.5 (93.6-95.4)	93.5 (92.4-94.5)	1.0

Source: Reviewer's independent analysis utilizing the applicant's model.

The SVR_{12} rate for genotype 1b patients was greater than 99% across all studies and much higher than the response rate for genotype 1a patients. Therefore, genotype 1b patients were not included in the exposure-SVR12 analysis. Due to the high observed response rate in these populations, lower dasabuvir and paritaprevir exposures from the 3-QD compared to 3-DAA are expected to have minimal impact on SVR12 under fasting or fed conditions. Given the impact of food on exposures, as noted above, the 3-QD should be administered under fed conditions, similar to labeling for the 3-DAA.

2.4 What is the effect of food on the exposures of the various components of the 3-QD regimen?

The effect of food on the various components of 3-QD was evaluated in trial M14-240. Table 6 shows the comparison of C_{max}, AUC_t and AUC_{inf} after single dose administration of 3-QD and 3-DAA under fasting conditions and the effect of food (high fat) on the pharmacokinetics of 3-QD.

Compared with administration of 3-QD under fasting conditions, administration of the 3-QD formulation under fed conditions resulted in an approximately 6-fold higher mean exposure of dasabuvir, 5-fold higher mean exposure of paritaprevir, and 2-fold higher mean exposure of ombitasvir. Based on the available exposure-response (safety) analysis, the increase in ombitasvir exposures is not expected to be clinically relevant; hence the remainder of the review focuses on comparison of dasabuvir and paritaprevir exposures.

Table 6: Comparison of the Central Value, Point Estimates, and 90 % CI of C_{max}, AUC_t and AUC_{inf} after single dose administration of 3-QD and 3-DAA under fasting conditions and the effect of food (high fat) on the pharmacokinetics of 3-QD

Regimens Test vs. Reference	Pharmacokinetic Parameter (units)	Central Value[a]		Relative Bioavailability	
		Test	Reference	Point Estimate[b]	90% Confidence Interval[c]
		Dasabuvir			
A vs. B Food Effect	C_{max} (ng/mL)	1377	208	6.625	5.547 – 7.911
	AUC_t (ng•h/mL)	19624	3083	6.366	5.419 – 7.478
	AUC_∞ (ng•h/mL)	19798	3347	5.915	5.059 – 6.916
B vs. C Relative Bioavailability in Fasted Condition	C_{max} (ng/mL)[d]	208	800	0.260	0.218 – 0.309
	AUC_t (ng•h/mL)	3083	10394	0.297	0.253 – 0.348
	AUC_∞ (ng•h/mL)	3347	10551	0.317	0.272 – 0.370
		Dasabuvir M1 Metabolite			
A vs. B Food Effect	C_{max} (ng/mL)	621	95.1	6.529	5.398 – 7.896
	AUC_t (ng•h/mL)	8272	1111	7.445	6.201 – 8.938
	AUC_∞ (ng•h/mL)	8407	1277	6.585	5.552 – 7.809
B vs. C Relative Bioavailability in Fasted Condition	C_{max} (ng/mL)[d]	95.1	315	0.302	0.250 – 0.363
	AUC_t (ng•h/mL)	1111	4206	0.264	0.220 – 0.317
	AUC_∞ (ng•h/mL)	1277	4303	0.297	0.250 – 0.352
		Ombitasvir			
A vs. B Food Effect	C_{max} (ng/mL)	104	50.9	2.055	1.828 – 2.310
	AUC_t (ng•h/mL)	1430	716	1.997	1.841 – 2.167
	AUC_∞ (ng•h/mL)	1558	785	1.985	1.829 – 2.154
B vs. C Relative Bioavailability in Fasted Condition	C_{max} (ng/mL)	50.9	53.6	0.948	0.844 – 1.066
	AUC_t (ng•h/mL)	716	720	0.994	0.901 – 1.096
	AUC_∞ (ng•h/mL)	785	790	0.994	0.903 – 1.094
		Paritaprevir			
A vs. B Food Effect	C_{max} (ng/mL)	481	80.5	5.967	4.623 – 7.702
	AUC_t (ng•h/mL)	3918	835	4.693	3.862 – 5.704
	AUC_∞ (ng•h/mL)	3944	857	4.600	3.800 – 5.569
B vs. C Relative Bioavailability in Fasted Condition	C_{max} (ng/mL)	80.5	115	0.701	0.543 – 0.904
	AUC_t (ng•h/mL)	835	1060	0.787	0.648 – 0.957
	AUC_∞ (ng•h/mL)	857	1083	0.792	0.654 – 0.958
		Ritonavir			
A vs. B Food Effect	C_{max} (ng/mL)	837	401	2.088	1.754 – 2.486
	AUC_t (ng•h/mL)	6545	3022	2.166	1.885 – 2.488
	AUC_∞ (ng•h/mL)	6702	3150	2.128	1.862 – 2.432
B vs. C Relative Bioavailability in Fasted Condition	C_{max} (ng/mL)	401	445	0.901	0.735 – 1.103
	AUC_t (ng•h/mL)	3022	3312	0.913	0.781 – 1.066
	AUC_∞ (ng•h/mL)	3150	3433	0.917	0.790 – 1.066

Regimen A = 3QD Regimen: three ER-12 bi-layer tablets (total dose of dasabuvir/ombitasvir/paritaprevir/r was 600/25/150/100 mg) administered in the morning under non-fasted conditions (high-fat breakfast).

Regimen B = 3QD Regimen: three ER-12 bi-layer tablets (total dose of dasabuvir/ombitasvir/paritaprevir/r was 600/25/150/100 mg) administered in the morning under fasted conditions.

Regimen C: 3-DAA Regimen: two ombitasvir/paritaprevir/r co-formulated tablets (total dose of 25/150/100 mg) QD with one dasabuvir IR tablet (250 mg) administered under fasted conditions in the morning and one dasabuvir IR tablet (250 mg) administered under fasted conditions in the evening.

a. Exponentiation of the least squares means for logarithms.

b. Exponentiation of the difference (test minus reference) in the least squares means between the test and reference regimens for logarithms.

c. Exponentiation of the endpoints of confidence intervals for the difference in the least squares means between the test and reference regimens for logarithms.

d. C_{max} was calculated from 0 to 72 hours post-morning dose for Regimen C.

Source: Section 2.7.1 Biopharmaceutics Studies and Analytical Methods. Page 71-72

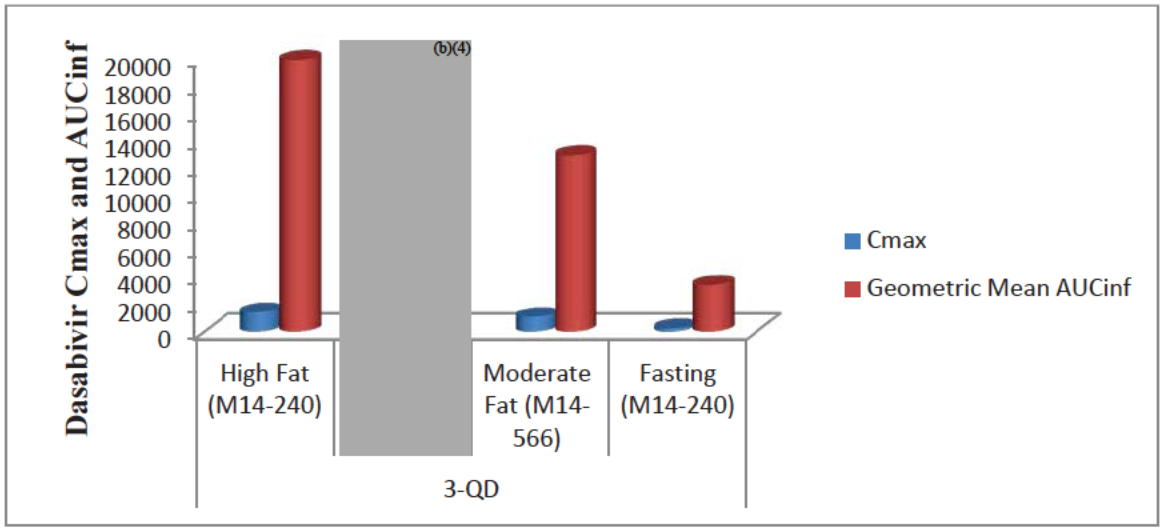
2.5 Are there differences between fasting and fed (moderate fat and high fat) conditions on the pharmacokinetics of dasabuvir and paritaprevir after administration of 3-QD?

Yes, there are differences between fasting and fed (moderate fat and high fat) conditions on the pharmacokinetics of dasabuvir and paritaprevir after administration of 3-QD.

Dasabuvir:

Figure 1 shows the cross trial comparison of mean C_{max} and AUC of dasabuvir across trials in which 3-QD was administered under fed (moderate fat and high fat) and fasting conditions.

Figure 1: Cross trial comparison of mean C_{max} and AUC of dasabuvir across trials in which 3-QD was administered under fed (moderate fat and high fat) and fasting conditions



Notes:
1) High Fat: 753 Kcal, 55.3 % Kcal from fat.
2) In trial M14-566, applicant used "standardized breakfast" (676 Kcal and 43 % Kcal from fat) and defined it as "moderate fat" in the tables from which the data was used.
3) Source: Prepared by the reviewer using data from tables 32 and 33 in Section 2.7.1 Biopharmaceutics Studies and Analytical Methods, Pages 85-86.

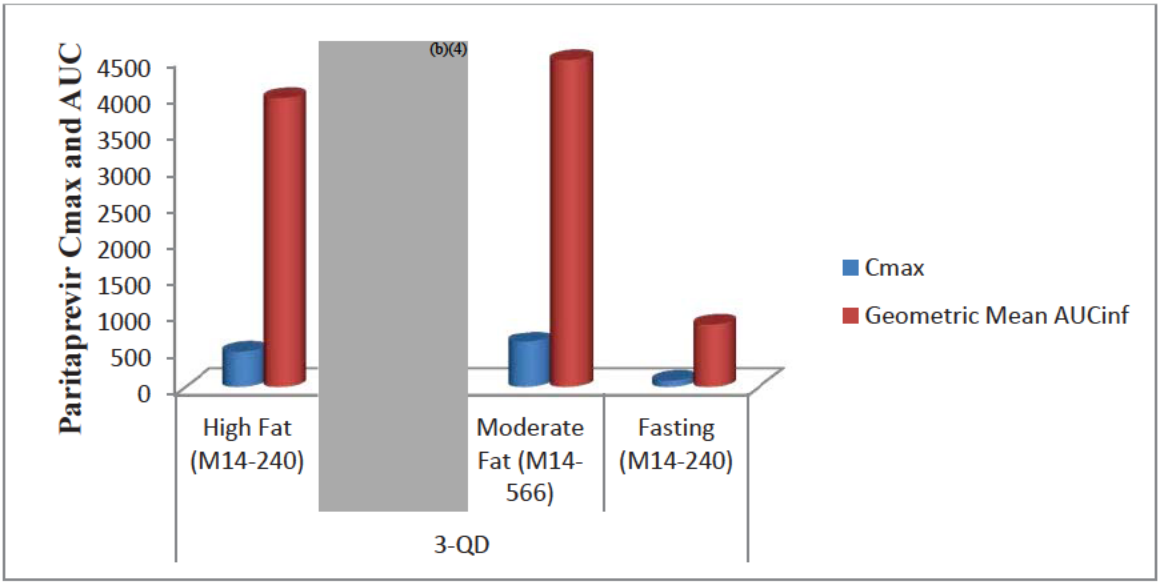
The mean exposures of dasabuvir from 3-QD administered with a high fat meal (trial M14-240) were either similar (based on results from trial (b)(4), an exploratory PK trial which compared the pharmacokinetics of various 3-QD formulations to the 3-DAA) or approximately 50 % higher (based on results from trial M14-566) as compared with dasabuvir exposures after a moderate fat meal. It should be noted that there were differences in dasabuvir exposures with a moderate fat meal between trial M14-566 and M14-240 irrespective of whether 3-QD or 3-DAA was administered (data not shown for the 3-DAA) which indicates study-to-study variability rather than differences in the effect of high fat vs moderate fat on

the exposures of dasabuvir. **Overall, after taking into account the cross-study variability, the mean dasabuvir exposures under moderate fat and high fat conditions were similar. Further, the mean dasabuvir exposures under moderate fat and high fat conditions were higher than the mean dasabuvir exposures under fasting conditions.**

Paritaprevir:

Figure 2 shows the cross trial comparison of mean C_{max} and AUC of paritaprevir across trials in which 3-QD was administered under fed (moderate fat and high fat) and fasting conditions.

Figure 2: Cross trial comparison of mean C_{max} and AUC of paritaprevir across trials in which 3-QD was administered under fed (moderate fat and high fat) and fasting conditions



Source: Prepared by the reviewer using data from tables 36 and 37 in Section 2.7.1 Biopharmaceutics Studies and Analytical Methods, Page 89 and 90.

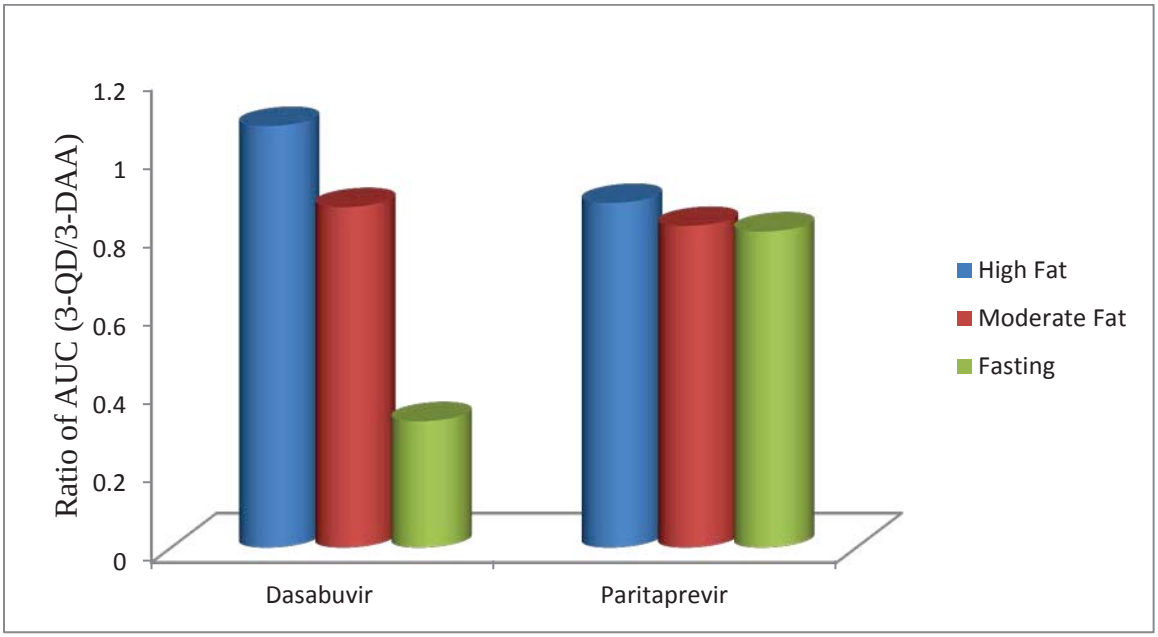
Based on cross trial comparison and considering the inter-study variability, **mean paritaprevir exposures after administration of the 3-QD formulation under moderate fat and high fat conditions were similar. Further, the mean paritaprevir exposures under moderate fat and high fat conditions were higher than the mean paritaprevir exposures under fasting conditions.**

Cross trial comparison of dasabuvir and paritaprevir exposures under different meal conditions

Because all safety and efficacy data were generated using 3-DAA, the ratio of the mean systemic exposures of dasabuvir and paritaprevir under fasting conditions and under various meal conditions after administration of 3-DAA and 3-QD were compared (Figure 3). **Of note, this analysis is useful to assess if there are**

clinically relevant changes in the dasabuvir and paritaprevir exposures if a patient switches treatment from 3-DAA to 3-QD.

Figure 3: Comparison of the ratio of the mean systemic exposures of dasabuvir and paritaprevir under fasting conditions and under various meal conditions after administration of 3-QD and 3-DAA



Source: Prepared by the reviewer using either mean AUC from trials M14-566 and and M1-240 (when data was available for a given meal condition), or data from food effect trials conducted using 3-DAA

Under fed conditions (moderate fat or high fat), the mean exposures of dasabuvir and paritaprevir are expected to be similar after administration of 3-QD and 3-DAA. On the other hand, under fasting conditions, the mean systemic exposures of dasabuvir and paritaprevir are anticipated to be lower (~68 % and ~20 %, respectively) after administration of 3-QD as compared to 3-DAA under fasting conditions. Of note, the lower dasabuvir and paritaprevir exposures from the 3-QD under fasting conditions may also help to explain, in part, the significant food effect on dasabuvir and paritaprevir in trial M14-240 as compared to the previous food-effect evaluations conducted with 3-DAA.

Overall, based on the available information and the analysis described above, 3-QD is recommended to be taken with food.

3 Labeling Recommendations

Labeling recommendations were under discussion at the time of finalizing this review.

4 Appendices

4.1 Individual Trial Reviews (pages 15 through 34)

4.2 Pharmacometrics Review (pages 35 through 48)

Relative Bioavailability Trial

M14-566

Title

A Comparison of the Bioavailability of Dasabuvir, Ombitasvir, ABT-450 and Ritonavir Combination Regimen Bilayer Tablets (Film Coated Quad ER-12: Dasabuvir/Ombitasvir/ABT-450/r 600 mg/25 mg/150 mg/100 mg QD) and the Phase 3 Clinical Reference Regimen (Ombitasvir/ABT-450/r 25 mg/150 mg/100 mg QD +Dasabuvir 250 mg BID) in Healthy Adults

Trial Period

August 1, 2014 to November 13, 2014
Final report date: August 6, 2015

Trial Objectives

The objectives of this study were:

- **Part 1:** To evaluate the bioavailability of dasabuvir, ombitasvir, ABT-450 and ritonavir from the 3QD regimen (Film-Coated Quad ER-12; dasabuvir/ombitasvir/ABT-450/r 600 mg/25 mg/150 mg/100 mg QD) compared to the 3-DAA regimen (ombitasvir/ABT-450/r 25/150/100 mg QD + dasabuvir 250 mg BID) **after 1 day dosing.**
- **Part 2:** To evaluate the bioavailability of dasabuvir, ombitasvir, ABT-450 and ritonavir from the 3QD regimen (Film-Coated Quad ER-12; dasabuvir/ombitasvir/ABT-450/r 600 mg/25 mg/150 mg/100 mg QD) compared to the 3-DAA regimen (ombitasvir/ABT-450/r 25/150/100 mg QD + dasabuvir 250 mg BID) **after 14-day multiple dosing (steady state).**

Trial Design

Phase 1, non-fasting, open label, two part study. Adult male and female subjects (N = 154) in general good health were selected to participate in Part 1 and Part 2 of the study and were randomly assigned in equal numbers to two sequences of regimens A and B as shown in table 1.

Table 1: Sequence Groups in Trial M14-566

Part 1					
Subject Numbers	N	Period 1	Period 2	Period 3	Period 4
101 – 188[a]	44	A	B	A	B
	44	B	A	B	A
Part 2					
Subject Numbers	**N**	**Period 1 Regimens**		**Period 2 Regimens**	
201 – 266[b]	33	A		B	
	33	B		A	

a. Four subjects were withdrawn from Part 1 of the study: two due to positive urine cotinine, one due to withdrawal of consent and one for failure to check-in in Period 2.

b. Five subjects were withdrawn from Part 2 of the study: one due to positive urine cotinine, two due to withdrawal of consent and two subjects discontinued study drug due to an adverse event.

Source: Final Study Report of Trial M14-566, page 36.

The various regimens evaluated in the trial were as follows:

Regimen A (3QD regimen): Three Film-Coated Quad ER-12 bilayer tablets (total dose of dasabuvir/ombitasvir/ABT-450/r/ is 600/25/150/100 mg) administered in the morning under non-fasting conditions on Day 1 of each corresponding period in Part 1; and Study Days 1 through 14 of each corresponding period in Part 2 **(Test Regimen).**

Regimen B (3-DAA regimen): Two ombitasvir/ABT-450/r co-formulated tablets (total dose of 25/150/100 mg) with one dasabuvir IR tablet (250 mg) administered under non-fasting conditions in the morning and one dasabuvir IR tablet (250 mg) administered under non-fasting conditions in the evening on Day 1 of each corresponding period in Part 1 and Study Days 1 through 14 of each corresponding period in Part 2 **(Reference Regimen).**

Each dose of study drug was administered orally with approximately 240 mL of water approximately 30 minutes after the start of standardized breakfast. The evening dose of dasabuvir as part of Regimen B was taken orally with approximately 240 mL of water approximately 30 minutes after the start of the evening snack.

Subjects enrolled in Part 1 received single day doses of each regimen on two occasions upon completion. Subjects enrolled in Part 2 received two regimens for 14 days each upon completion. A washout interval of at least 10 days separated the doses of the study periods.

Subjects received a standardized diet, providing approximately 40% of the daily calories from fat and up to 45% of daily calories from carbohydrates (approximately 2,200 total calories/day) for all meals during confinement.

Discussion of Trial Design

In Part 1, bioavailability of dasabuvir, ombitasvir, ABT -450 and ritonavir from the 3QD and the 3-DAA regimens were compared after subjects received 1-day dosing of the test- and reference-regimens on two occasions. With the known high within-subject variability (approximately 60%CV) of ABT-450 pharmacokinetics, a large sample size would have been required for the standard two-way crossover design to meet the "within ± 20% criterion", hence, the applicant used a 2-regimen, 4-period, 2-sequence fully replicated crossover study design. This replicated crossover design enabled the calculation of the within - subject variability for the reference regimen's pharmacokinetic parameters, to demonstrate that ABT-450 was highly variable, thereby utilizing a scaled ap proach to compare the bioavailability of the test regimen to that of the reference regimen.

In Part 2, bioavailability of dasabuvir, ombitasvir, ABT-450 and ritonavir from the 3QD and the 3-DAA regimens was compared at steady state (14-day multiple dosing) in a two-period, randomized, crossover design.

Identity of Investigational Products

Table 2 shows the identity of investigational products used in the trial

Table 2: Identity of investigational products used in the trial

	3-DAA Regimen		3QD Regimen
	Dasabuvir	Ombitasvir/ABT-450/ Ritonavir	Dasabuvir/Ombitasvir/ ABT-450/Ritonavir
Mode of Administration	Oral	Oral	Oral
Dosage Form	Film-Coated Tablet	Film-Coated Tablet	Film-Coated Quad ER-12 Bilayer Tablet
Strength	250 mg	12.5/75/50 mg	200/8.33/50/33.33 mg
Manufacturing Site	AbbVie Inc. Ireland NL B.V.	AbbVie Inc. Cork, Ireland	AbbVie Inc. Cork, Ireland
Manufacturing Date	(b)(4)		
Bulk Product Lot Number	14-001469	14-002317	14-003856
Finishing Lot Number	14-003976	14-003974	14-003973
Formulation (Material Master Identification Code)	(b)(4)		
Potency (% of Label Claim)			
Batch Size			
Proposed Full-Scale Production Batch Size			
Retest Date			

Source: Final Study Report of Trial M14-566, page 48

Sample Collection

Blood samples for ABT-450, ritonavir, ombitasvir, dasabuvir, and dasabuvir M1 were collected as follows:

- prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 36, 48, 72, 96 and 120 hours after dosing on Day 1 of each period in Part 1.
- prior to dosing (0 hour) and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 36, 48, and 72 after dosing on Day 14 of each period in Part 2.
- or upon subject discontinuation due to an adverse event

In addition, in part 2, C_{trough} samples were drawn immediately prior to the morning dose on study days 7, 9, 11 and 13 in each period.

Pharmacokinetic Analysis

The pharmacokinetic parameters of ABT-450, ritonavir, ombitasvir, dasabuvir, and dasabuvir M1 were calculated using non-compartmental methods.

Results

Bioanalytical methods

Table 3: Bioanalytical assay parameters

Analyte	Calibration Curve Range (ng/mL)	LLOQ (ng/mL)	QC Concentrations (ng/mL)	% CV	% Bias
ABT-267	0.465-313	0.465	1.21, 151, 265	3.4 % to 5.5 %	0.8 to 6.6 %
ABT-450	0.610-411	0.610	1.6, 200, 351	3.8 % to 7.4 %	1.4 % to 8.8 %
Ritonavir	4.98-3350	4.98	13.2, 1650, 2890	3.1 % to 5.5 %	-0.3 % to 5.3 %
ABT-333	4.61-3110	4.61	12, 1500, and 2630	4.2 % to 6.2 %	0.8 % to 4.7 %
ABT-333 M1	4.82-3250	4.82	13.2, 1650, 2890	3.2 % to 3.7 %	-1 % to 3.8 %

The bioanalytical methods were acceptable.

Subject Disposition and Demographics

A total of 88 healthy volunteers were dosed during Part 1 of the study. Four subjects were

withdrawn from Part 1 of the study: two (Subjects 157 and 185) due to positive urine cotinine, one (Subject 176) due to withdrawal of consent and one (Subject 135) for failure to check-in in Period 2.

A total of 66 healthy volunteers were dosed during Part 2 of the study. Five subjects were withdrawn from Part 2 of the study: one (Subject 218) due to positive urine cotinine, two (Subjects 214 and 249) due to withdrawal of consent and two (Subjects 226 and 258) due to adverse events.

Table 4 shows the demographic summary of subjects enrolled in the trial.

Table 4: Demographic Summary of All Subjects

	Mean ± SD	Min – Max
	Part 1 (N = 88)	
Age (years)	37.7 ± 8.97	19 – 55
Weight (kg)	73.2 ± 11.8	48 – 105
Height (cm)	166 ± 10.6	148 – 202
Sex	41 Males (46.6%) and 47 Females (53.4%)	
Race	77 White (87.5%), 8 Black or African American (9.1%), 2 American Indian/Alaska Native (2.3%), 1 Multi-Race (1.1%)	
	Part 2 (N = 66)	
Age (years)	36.5 ± 9.47	20 – 55
Weight (kg)	73.9 ± 12.8	49 – 104
Height (cm)	168 ± 10.4	143 – 191
Sex	45 Males (68.2%) and 21 Females (31.8%)	
Race	62 White (93.9%), 4 Black or African American (6.1%)	

SD = standard deviation; Min = minimum; Max = maximum

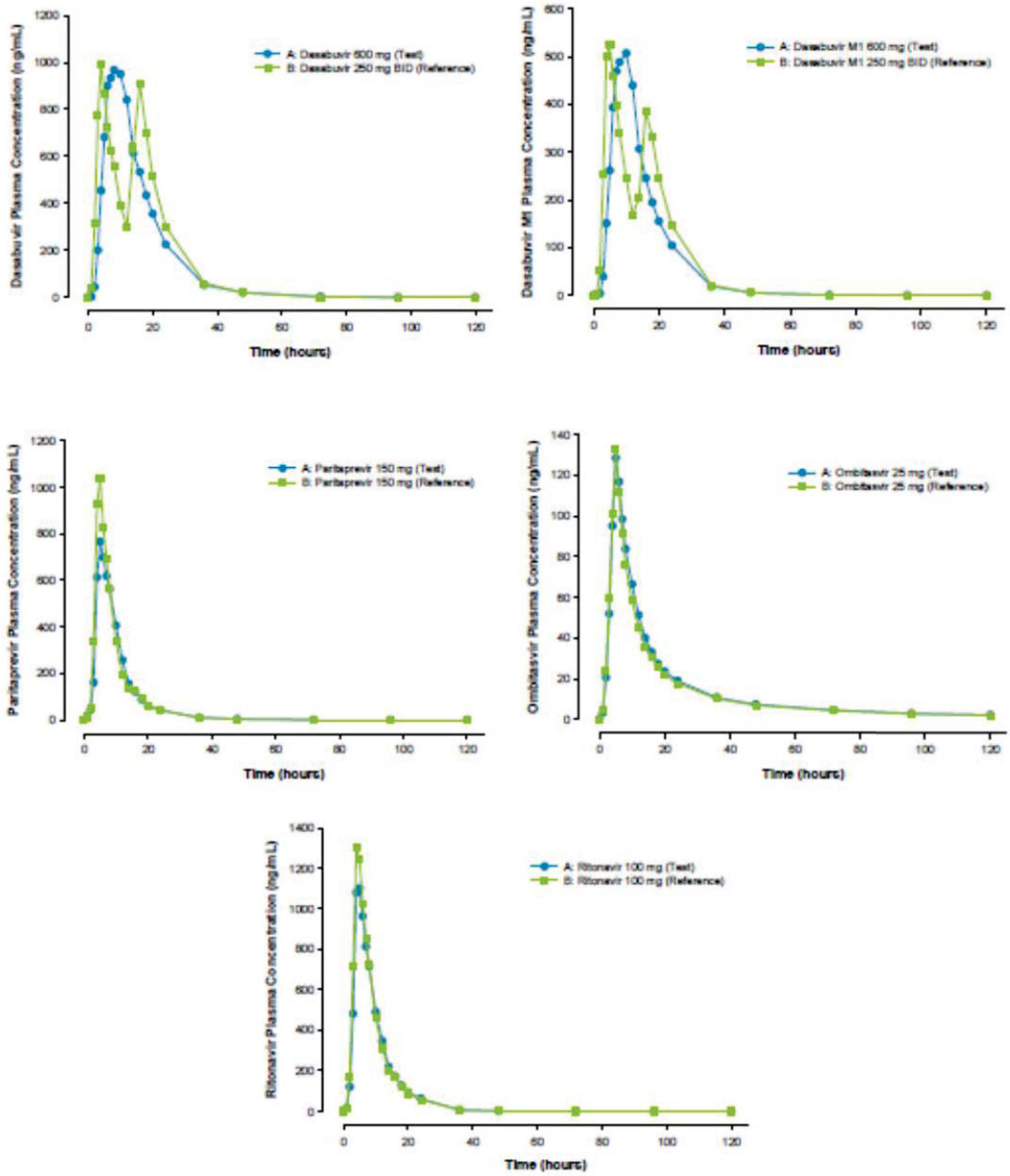
Source: Final Study Report of Trial M14-566, page 86

Pharmacokinetics

Part 1 (Comparison after administration of single dose of 3-QD and 3-DAA regimen)

Fig 1 shows the mean plasma concentration of dasabuvir, dasabuvir M1, ombitasvir, paritaprevir, and ritonavir

Fig 1: Mean plasma concentration of dasabuvir, dasabuvir M1, ombitasvir, paritaprevir, and ritonavir



Source: Section 2.7.1. Summary of Biopharmaceutic Studies and Associated Analytical Methods; Page 55

Table 5 shows the geometric mean (arithmetic mean ± SD) pharmacokinetic parameters of dasabuvir, dasabuvir M1, ombitasvir, paritaprevir, and ritonavir.

Table 5: Geometric mean (arithmetic mean ± SD) pharmacokinetic parameters of dasabuvir, dasabuvir M1, ombitasvir, paritaprevir, and ritonavir

Pharmacokinetic Parameter (units)	Regimen A (Test) 3QD Regimen	Regimen B (Reference) 3-DAA Regimen
	Dasabuvir	
N[a]	172	171
C_{max} (ng/mL)[b]	1060 (1210 ± 556)	1130 (1210 ± 412)
T_{max} (h)[c]	8.0 (4.0 – 18.0)	4.0 (2.0 – 8.0)
AUCt (ng•h/mL)	12700 (15200 ± 8220)	14800 (15900 ± 6020)
AUC_{∞} (ng•h/mL)	12900 (15300 ± 8230)	14900 (16100 ± 6040)
$t_{1/2}$ (h)[d]	6.91 ± 1.99	5.83 ± 1.18
	Dasabuvir M1	
N[a]	172	171
C_{max} (ng/mL)[b]	505 (605 ± 343)	572 (625 ± 248)
T_{max} (h)[c]	8.0 (4.0 – 18.0)	4.0 (3.0 – 10.0)
AUCt (ng•h/mL)	5550 (6970 ± 4240)	6890 (7540 ± 3090)
AUC_{∞} (ng•h/mL)	5680 (7060 ± 4230)	7130 (7770 ± 3080)
$t_{1/2}$ (h)[d]	5.77 ± 1.41	4.81 ± 0.77
	Ombitasvir	
N[a]	172	169
C_{max} (ng/mL)	124 (133 ± 43.7)	131 (138 ± 42.3)
T_{max} (h)[c]	5.0 (3.0 – 10.0)	5.0 (4.0 – 10.0)
AUC_t (ng•h/mL)	1660 (1770 ± 562)	1630 (1700 ± 486)
AUC_{∞} (ng•h/mL)	1800 (1910 ± 630)	1760 (1840 ± 549)
$t_{1/2}$ (h)[d]	37.9 ± 15.3	39.2 ± 14.2
	Paritaprevir	
N[a]	172	169
C_{max} (ng/mL)	618 (996 ± 967)	935 (1380 ± 1110)
T_{max} (h)[c]	5.0 (2.0 – 12.0)	5.0 (3.0 – 10.0)
AUC_t (ng•h/mL)	4460 (6450 ± 5520)	5470 (7250 ± 5360)
AUC_{∞} (ng•h/mL)	4490 (6480 ± 5520)	5490 (7270 ± 5370)
$t_{1/2}$ (h)[d]	6.15 ± 1.46	6.02 ± 1.36
	Ritonavir	
N[a]	172	169
C_{max} (ng/mL)	1130 (1320 ± 634)	1430 (1560 ± 624)
T_{max} (h)[c]	4.0 (3.0 – 12.0)	4.0 (2.0 – 8.0)
AUC_t (ng•h/mL)	7450 (9140 ± 5610)	8610 (9800 ± 5550)
AUC_{∞} (ng•h/mL)	8090 (9360 ± 5550)[e]	8750 (9920 ± 5550)
$t_{1/2}$ (h)[d]	4.52 ± 0.99[e]	4.47 ± 0.86

Regimen A = Three ER-12 bi-layer tablets (total dose of dasabuvir/ombitasvir/paritaprevir/r was 600/25/150/100 mg) administered in the morning under non-fasted conditions.

Regimen B = Two ombitasvir/paritaprevir/r co-formulated tablets (total dose of 25/150/100 mg) QD with one dasabuvir IR tablet (250 mg) administered under non-fasted conditions in the morning and one dasabuvir IR tablet (250 mg) administered under non-fasted conditions in the evening.

a. N represents the total number of pharmacokinetic profiles available (2 per subject from the replicate design).

b. C_{max} was calculated based on data from 0 to 120 hours post-morning dose for Regimen B.

c. Median (range). For Regimen B, dasabuvir and dasabuvir M1 T_{max} values were determined after first dose (morning dose).

d. Harmonic mean ± pseudo-standard deviation.

e. N = 170 because AUC_{∞} and beta could not be calculated for two subjects.

Source: Section 2.7.1. Summary of Biopharmaceutic Studies and Associated Analytical Methods; Page 56-57

Table 6 shows the C_{max} and AUC ratios of central values and 90 % confidence intervals for dasabuvir, dasabuvir M1, ombitasvir, paritaprevir, and ritonavir in part 1 of study M14-566

Table 6: C_{max} and AUC ratios of central values and 90 % confidence intervals for dasabuvir, dasabuvir M1, ombitasvir, paritaprevir, and ritonavir in part 1 of study M14-566

	Central Value[a]		Relative Bioavailability	
Pharmacokinetic Parameter (units)	Test (Regimen A)	Reference (Regimen B)	Point Estimate[b]	90% Confidence Interval[c]
	Dasabuvir			
C_{max} (ng/mL)[d]	1076	1142	0.942	0.871 – 1.018
AUC_t (ng•h/mL)	12830	14945	0.858	0.787 – 0.936
AUC_∞ (ng•h/mL)	13013	15080	0.863	0.793 – 0.939
	Dasabuvir M1			
C_{max} (ng/mL)[d]	512	577	0.887	0.813 – 0.967
AUC_t (ng•h/mL)	5604	6942	0.807	0.734 – 0.888
AUC_∞ (ng•h/mL)	5737	7119	0.806	0.736 – 0.883
	Paritaprevir			
C_{max} (ng/mL)[e]	623	910	0.685 0.690[f] (0.091)[g]	0.625 – 0.750
AUC_t (ng•h/mL)	4475	5274	0.849	0.790 – 0.911
AUC_∞ (ng•h/mL)	4505	5302	0.850	0.792 – 0.912
	Ombitasvir			
C_{max} (ng/mL)	125	130	0.960	0.926 – 0.995
AUC_t (ng•h/mL)	1664	1605	1.037	1.011 – 1.064
AUC_∞ (ng•h/mL)	1795	1734	1.035	1.009 – 1.062
	Ritonavir			
C_{max} (ng/mL)	1146	1395	0.821	0.777 – 0.867
AUC_t (ng•h/mL)	7591	8308	0.914	0.880 – 0.949
AUC_∞ (ng•h/mL)	8223	8911	0.923	0.893 – 0.953

Regimen A = Three Film-Coated ER-12 bilayer tablets (total dose of dasabuvir/ombitasvir/paritaprevir/r is 600/25/150/100 mg) administered in the morning under non-fasting conditions on Day 1 of each corresponding period (test regimen).

Regimen B = Two ombitasvir/paritaprevir/r co-formulated tablets (total dose of 25/150/100 mg) with one dasabuvir IR tablet (250 mg) administered under non-fasting conditions in the morning and one dasabuvir IR tablet (250 mg) administered under non-fasting conditions in the evening on Day 1 of each corresponding period (reference regimen).

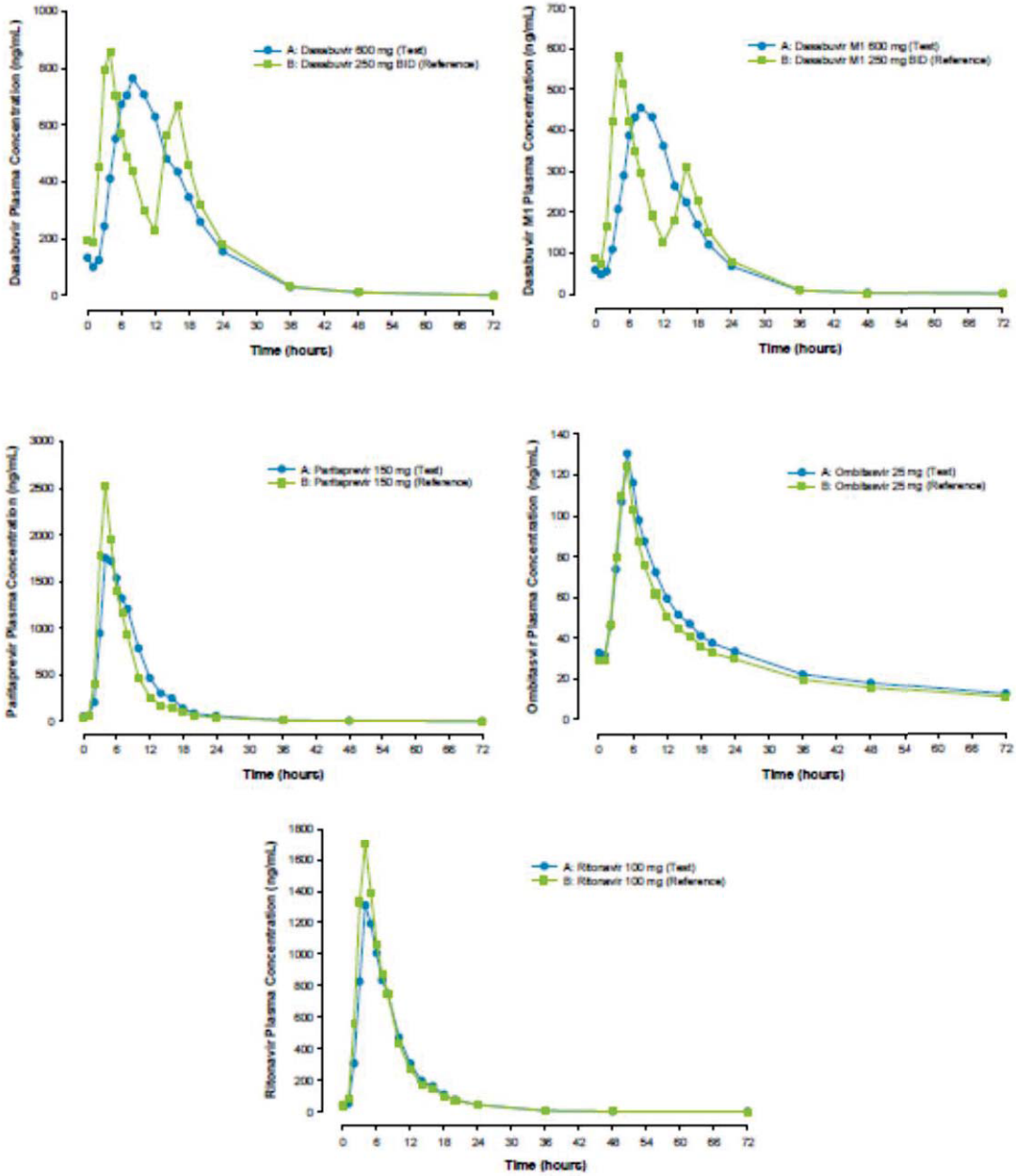
a. Exponentiation of the least squares means for logarithms.
b. Exponentiation of the difference (test minus reference) of the least squares means for logarithms.
c. Exponentiation of the endpoints of confidence intervals for the difference of the least squares means for logarithms.
d. For dasabuvir and dasabuvir M1 from Regimen B, C_{max} comparisons shown are for C_{max} over 0 to 120 hours.
e. For paritaprevir C_{max}, intra subject variability was > 30% (53%).
f. Central value ratio: Per the definition in FDA and EMA guidances of highly variable drug bioequivalence study, the central value ratio (per protocol for paritaprevir C_{max}, based on the bioequivalence criteria for highly variable drugs) should be within 0.8 – 1.25 to meet BE criterion.
g. 95% upper confidence bound: Per the definition in FDA and EMA guidances of highly variable drug bioequivalence study, the 95% upper confidence bound (per protocol reference-scaled analysis of paritaprevir C_{max}, based on the bioequivalence criteria for highly variable drugs) was > 0, which indicates failure of BE criterion.

Source: Section 2.7.1. Summary of Biopharmaceutic Studies and Associated Analytical Methods; Page 58-59

Part 2 (Comparison after administration of multiple dose of 3-QD and 3-DAA regimen)

Fig 2 shows the mean plasma concentration of dasabuvir, dasabuvir M1, ombitasvir, paritaprevir, and ritonavir

Fig 2: Mean plasma concentration of dasabuvir, dasabuvir M1, ombitasvir, paritaprevir, and ritonavir



Source: Section 2.7.1. Summary of Biopharmaceutic Studies and Associated Analytical Methods; Page 60

Table 7 shows the geometric mean (arithmetic mean ± SD) pharmacokinetic parameters of dasabuvir, dasabuvir M1, ombitasvir, paritaprevir, and ritonavir.

Table 7: Geometric mean (arithmetic mean ± SD) pharmacokinetic parameters of dasabuvir, dasabuvir M1, ombitasvir, paritaprevir, and ritonavir

Pharmacokinetic Parameter (units)	Regimen A (Test) 3QD Regimen	Regimen B (Reference) 3-DAA Regimen
	Dasabuvir	
N	63	63
C_{max}[a] (ng/mL)	799 (896 ± 415)	879 (947 ± 357)
T_{max} (h)[b]	8.0 (4.0 – 18.0)	4.0 (2.0 – 6.0)
AUC_{24} (ng•h/mL)	8800 (10300 ± 5630)	9770 (10600 ± 4410)
C_{24} (ng/mL)	116 (155 ± 135)[d]	162 (183 ± 101)
$t_{1/2}$ (h)[c]	6.23 ± 1.89	5.48 ± 1.31
	Dasabuvir M1	
N	63	63
C_{max}[a] (ng/mL)	451 (527 ± 281)	562 (610 ± 241)
T_{max} (h)[b]	8.0 (4.0 – 18.0)	4.0 (3.0 – 6.0)
AUC_{24} (ng•h/mL)	4640 (5630 ± 3360)	5240 (5700 ± 2430)
C_{24} (ng/mL)	48.4 (67.9 ± 61.4)[d]	70.9 (79.8 ± 40.9)
$t_{1/2}$ (h)[c]	4.66 ± 1.11	4.08 ± 0.72[e]
	Ombitasvir	
N	63	63
C_{max} (ng/mL)	128 (135 ± 41.9)	121 (128 ± 42.7)
T_{max} (h)[b]	5.0 (3.0 – 7.0)	5.0 (4.0 – 6.0)
AUC_{24} (ng•h/mL)	1380 (1470 ± 504)	1240 (1330 ± 498)
C_{24} (ng/mL)	30.4 (33.5 ± 15.3)[d]	26.6 (29.6 ± 14.5)
$t_{1/2}$ (h)[c]	35.1 ± 12.0	35.0 ± 12.0

Pharmacokinetic Parameter (units)	Regimen A (Test) 3QD Regimen	Regimen B (Reference) 3-DAA Regimen
	Paritaprevir	
N	63	63
C_{max} (ng/mL)	1500 (2300 ± 1980)	1970 (2900 ± 2420)
T_{max} (h)[b]	5.0 (3.0 – 10.0)	4.0 (3.0 – 7.0)
AUC_{24} (ng•h/mL)	8930 (13600 ± 13100)	9300 (13300 ± 11000)
C_{24} (ng/mL)	34.6 (54.2 ± 76.5)[d]	30.4 (39.0 ± 28.5)
$t_{1/2}$ (h)[c]	5.25 ± 1.06	5.34 ± 0.89
	Ritonavir	
N	63	63
C_{max} (ng/mL)	1340 (1440 ± 561)	1680 (1830 ± 783)
T_{max} (h)[b]	4.0 (3.0 – 8.0)	4.0 (3.0 – 6.0)
AUC_{24} (ng•h/mL)	8660 (9470 ± 4040)	9580 (10700 ± 5300)
C_{24} (ng/mL)	36.2 (44.3 ± 33.8)[d]	35.1 (43.2 ± 31.5)
$t_{1/2}$ (h)[c]	4.56 ± 1.16	4.77 ± 1.11

Regimen A = Three ER-12 bi-layer tablets (total dose of dasabuvir/ombitasvir/paritaprevir/r was 600/25/150/100 mg) administered in the morning under non-fasted conditions for 14 days (test regimen).
Regimen B = Two ombitasvir/paritaprevir/r co-formulated tablets (total dose of 25/150/100 mg) QD with one dasabuvir IR tablet (250 mg) administered under non-fasted conditions in the morning and one dasabuvir IR tablet (250 mg) administered under non-fasted conditions in the evening for 14 days (reference regimen).

a. For dasabuvir and dasabuvir M1, C_{max} was calculated based on data from 0 to 72 hours post-morning dose for Regimen B.
b. Median (range). For Regimen B, dasabuvir and dasabuvir M1 T_{max} values were determined after first dose (morning dose).
c. Harmonic mean ± pseudo-standard deviation.
d. N = 62.
e. N = 60.

Source: Section 2.7.1. Summary of Biopharmaceutic Studies and Associated Analytical Methods; Page 61-62

Table 8 shows the C_{max} and AUC ratios of central values and 90 % confidence intervals for dasabuvir, dasabuvir M1, ombitasvir, paritaprevir, and ritonavir in part 2 of study M14-566

Table 8: C_{max} and AUC ratios of central values and 90 % confidence intervals for dasabuvir, dasabuvir M1, ombitasvir, paritaprevir, and ritonavir in part 2 of study M14-566

	Central Value[a]		Relative Bioavailability	
Pharmacokinetic Parameter (units)	Test (Regimen A)	Reference (Regimen B)	Point Estimate[b]	90% Confidence Interval[c]
		Dasabuvir		
C_{max} (ng/mL)[d]	797	880	0.905	0.823 - 0.995
AUC_{24} (ng•h/mL)	8767	9823	0.892	0.809 – 0.985
C_{24} (ng/mL)	116	163	0.710	0.622 – 0.812
		Dasabuvir M1		
C_{max} (ng/mL)[d]	448	565	0.793	0.714 - 0.880
AUC_{24} (ng•h/mL)	4595	5294	0.868	0.782 - 0.963
C_{24} (ng/mL)	48.1	72.1	0.666	0.577 - 0.769
		Ombitasvir		
C_{max} (ng/mL)	127	122	1.040	1.005 – 1.077
AUC_{24} (ng•h/mL)	1367	1254	1.090	1.063 – 1.117
C_{24} (ng/mL)	29.5	26.9	1.098	1.064 – 1.132
		Paritaprevir		
C_{max} (ng/mL)	1452	2011	0.722	0.638 – 0.818
AUC_{24} (ng•h/mL)	8645	9608	0.900	0.814 – 0.994
C_{24} (ng/mL)	33.7	31.9	1.055	0.970 – 1.147
		Ritonavir		
C_{max} (ng/mL)	1328	1676	0.793	0.746 – 0.842
AUC_{24} (ng•h/mL)	8604	9630	0.893	0.846 – 0.943
C_{24} (ng/mL)	36.1	35.8	1.009	0.946 – 1.075

Regimen A = Three Film-Coated ER-12 bilayer tablets (total dose of dasabuvir/ombitasvir/paritaprevir/r is 600/25/150/100 mg) administered in the morning under non-fasting conditions on Days 1 through 14 of each corresponding period (test regimen).

Regimen B = Two ombitasvir/paritaprevir/r co-formulated tablets (total dose of 25/150/100 mg) with one dasabuvir IR tablet (250 mg) administered under non-fasting conditions in the morning and one dasabuvir IR tablet (250 mg) administered under non-fasting conditions in the evening on Days 1 through 14 of each corresponding period (reference regimen).

a. Exponentiation of the least squares means for logarithms.
b. Exponentiation of the difference (test minus reference) of the least squares means for logarithms.
c. Exponentiation of the endpoints of confidence intervals for the difference in the least squares means between the test and reference regimens for logarithms.
d. For dasabuvir and dasabuvir M1 from Regimen B, C_{max} comparisons shown are for C_{max} over 0 to 72 hours.

Source: Section 2.7.1. Summary of Biopharmaceutic Studies and Associated Analytical Methods; Page 63

Discussion and Conclusion

Comparison of the PK parameters of the various components of 3QD regimen with the 3-DAA regimen after single dose showed that there were no clinically relevant differences between the PK parameters. The mean C_{max} of ABT-450 decreased by 31 %, however, this decrease is not anticipated to be clinically relevant.

Comparison of the PK parameters of the various components of 3QD regimen with the 3-DAA regimen after multiple dose showed that there were no clinically relevant differences between the PK parameters. The mean C_{trough} of dasabuvir and dasabuvir M1 decreased by 29 % and 33 %, respectively and the mean C_{max} of dasabuvir M1, ABT-450 and ritonavir decreased by 21 %, 28 %, and 21 %, respectively. Based on the available exposure-response information, the aforementioned changes in PK parameters are not expected to be clinically relevant.

Food Effect Trial

M14-240

Title

A Phase 1 Study to Evaluate the Effect of Food on the Oral Bioavailability of Quad ER-12 Bi-Layer Tablets (Dasabuvir/Ombitasvir/ABT-450/r 600 mg/25 mg/150 mg/100 mg QD) and the Phase 3 Clinical Reference Regimen Under Fasting Conditions

Trial Period

December 23, 2014 to March 6, 2015
Final report date: August 5, 2015

Trial Objectives

The objectives of this study were:

- Evaluate the effect of food on dasabuvir, ombitasvir, paritaprevir and ritonavir from the 3QD regimen (Film-Coated Quad ER-12 formulation)
- Evaluate the bioavailability of dasabuvir, ombitasvir, paritaprevir and ritonavir from the 3QD regimen (Film-Coated Quad ER-12; dasabuvir/ombitasvir/paritaprevir/r 600 mg/25 mg/150 mg/100 mg QD) compared to the 3-DAA regimen (ombitasvir/paritaprevir/r 25/150/100 mg QD + dasabuvir 250 mg BID) after 1 day of dosing under fasted conditions.

Trial Design

This Phase 1, single-dose, open-label study was conducted according to a three-period, randomized, complete crossover design. Adult male and female subjects (N = 46) in general good health were selected to participate in the study according to the selection criteria.Enrolled subjects were randomly assigned in equal numbers to three sequences of Regimens A, B and C as shown in Table 1.

Table 1: Various Sequence Groups in the Trial

Sequence Group	Subject Numbers	N	Regimens Period 1	Period 2	Period 3
I	101, 103, 107, 110, 113, 115, 121, 124, 125, 130, 131, 133[a], 137, 142, 143[b] and 146	16	A	B	C
II	102, 106, 108, 112, 117, 118, 119, 122, 127, 129, 132, 134, 139, 140 and 145	15	B	C	A
III	104[c], 105, 109, 111, 114, 116, 120, 123, 126, 128, 135, 136, 138, 141[b] and 144	15	C	A	B

a. Subject 133 discontinued study drug due to an adverse event on Day 1 of Period 3 (Study Day 21).
b. Subjects 141 and 143 were prematurely discontinued from the study due to positive drug screens in Period 2, Day –1.
c. Subject 104 was prematurely discontinued from the study after dosing in Period 2 and was considered lost to follow-up.

Source: Final Study Report of Trial M14-240, page 29

The following regimens were administered on study day 1 of each period as follows:

Regimen A (3QD regimen under fed conditions): Three Quad ER-12 bi-layer tablets (total dose of dasabuvir/ombitasvir/paritaprevir/r was 600/25/150/100 mg) administered in the morning under non-fasted conditions **(high-fat meal).**

Regimen B (3QD regimen under fasting conditions): Three Quad ER-12 bi-layer tablets (total dose of dasabuvir/ombitasvir/paritaprevir/r was 600/25/150/100 mg) administered in the morning under **fasted conditions.**

Regimen C (3-DAA regimen under fasting conditions): Two ombitasvir/paritaprevir/r co-formulated tablets (total dose of 25/150/100 mg) QD with one dasabuvir immediate release (IR) tablet (250 mg) administered under **fasted conditions** in the morning and one dasabuvir IR tablet (250 mg) administered under **fasted conditions** in the evening.

The morning dose of Regimen A was administered with 240 mL of water approximately 30 minutes, and not more than 45 minutes, after the start of a high-fat breakfast. The morning doses of Regimens B and C were administered with 240 mL of water after a minimum 10-hour fast and approximately 4 hours before lunch. The evening dose of dasabuvir as part of Regimen C was administered with approximately 240 mL of water approximately 12 hours after the morning dose and approximately 4 hours before dinner. The sequences of regimens were such that each subject had received all three regimens upon completion of the study. A washout interval of at least 10 days separated the doses of the three study periods.

Table 2 shows the meal content for day 1 of each period.

Table 2: Meal content for day 1 of each period

Meal	Approximate Time	Regimen A	Regimen B	Regimen C
Breakfast	07:00	2 fried eggs, 2 bacon slices, 2 wheat bread slices (for subjects to toast), 2 pc butter, 4 oz (by wt) hashbrown potatoes, 8 oz whole milk	No Breakfast	No Breakfast
Lunch	11:30	1 chicken quesadilla, 1 oz sour cream, 4 oz salsa, 1 oz tortilla chips, 1 strawberry shortcake, 8 oz bottled water	1 lemon rosemary turkey sandwich, 6 oz cream of tomato soup, 1 pc whole wheat crackers, 1 oatmeal raisin cookie, 4 oz apple juice, 8 oz bottle water	5 baked chicken tenders, 2 oz BBQ sauce, 6 parmesan potato wedges, 3 pc ketchup, ¾ c green beans, 1 c fresh fruit cup, 8 oz milk, lowfat 2%
Dinner	16:30	4 oz roasted turkey breast, 2 oz gravy, ¾ c whipped potatoes, ¾ c steamed carrots, 1 italian ice, 8 oz bottled water	1 herb crusted tilapia, ½ c broccoli, ½ c roasted red potatoes, 1 slice cheesecake, 8 oz bottled water	Dinner at 23:30[a] 1 roast beef sandwich on whole wheat (2 sl bread), 1 sl cheddar cheese, 1 lettuce leaf, 2 tomato slices, 1 pc mayonnaise, 1 bag Lay's potato chips (1.5 oz), 1 c garden green salad, 1 pc ranch dressing (1.5 oz), ½ c apple crisp, ½ c vanilla ice cream, 8 oz bottled water
Evening Snack	19:30	½ c banana pudding w/ whip topping	¾ c traveling trail mix, 8 oz lemonade	No snack

Meal	Approximate Time	Regimen A	Regimen B	Regimen C
Nutritionals	NA	Breakfast: 753 Kcal; 55.3% calories from fat, 27.8% calories from carbohydrates, and 16.9% calories from protein Lunch: 784 Kcal; 38.4% calories from fat, 43.7% calories from carbohydrates, and 17.9% calories from protein Dinner: 458 Kcal; 10.1% calories from fat, 67.1% calories from carbohydrates, and 22.8% calories from protein Snack: 155 Kcal; 29.6% calories from fat, 66.3% calories from carbohydrates, and 4.1% calories from protein	Lunch: 871 Kcal; 27.9% calories from fat, 54.9% calories from carbohydrates, and 17.2% calories from protein Dinner: 819 Kcal; 48.1% calories from fat, 34.4% calories from carbohydrates, and 16.6% calories from protein Snack: 481 Kcal; 51.5% calories from fat, 38.6% calories from carbohydrates, and 9.9% calories from protein	Lunch: 1060 Kcal; 30.1% calories from fat, 47.1% calories from carbohydrates, and 22.8% calories from protein Dinner: 1197 Kcal; 48.8% calories from fat, 34.3% calories from carbohydrates, and 16.9% calories from protein

NA = Not Applicable

a. Subjects in Regimen C were served dinner approximately 4 hours after the evening dose of dasabuvir had been administered.

Source: Final Study Report of Trial M14-240, page 33-34

Identity of Investigational Products

Table 3 shows the identity of investigational products used in the trial

Table 3: Identity of investigational products used in the trial

	3-DAA Regimen		3QD Regimen
	Dasabuvir	Ombitasvir/Paritaprevir/ Ritonavir/	Dasabuvir/Ombitasvir/ Paritaprevir/Ritonavir
Dosage Form	Film-Coated IR Tablet	Film-Coated Co-Formulated Tablet	Film-Coated Quad ER-12 Bi-layer Tablet
Formulation (Material Master Identification Code)	[redacted] (b)(4)		
Strength (mg)	250	12.5/75/50	200/8.33/50/33.33
Mode of Administration	Oral	Oral	Oral
Bulk Product Lot Number	12-007842	13-001960	14-003856
Potency (% of Label Claim)	[redacted] (b)(4)		
Manufacturing Site	AbbVie Ireland NL B.V.	AbbVie Inc. Cork, Ireland	AbbVie Inc. Cork, Ireland
Manufacturing Date	[redacted] (b)(4)		
Batch Size			
Proposed Full-Scale Production Batch Size			
Units per bottle	[redacted] (b)(4)		
Finishing Lot Number	14-006946	14-006942	14-006940
Retest Date	[redacted] (b)(4)		

Source: Final Study Report of Trial M14-240, page 43

Sample Collection

Blood samples for ABT-450, ritonavir, ombitasvir, dasabuvir, and dasabuvir M1 were collected prior to dosing (0 hour) and at 1, 2, 3, 4,5, 6, 7, 8, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 22, 24, 36, 48, and 72 hours after dosing in each study period or upon subject discontinuation due to an adverse event.

Pharmacokinetic Analysis

The pharmacokinetic parameters of ABT-450, ritonavir, ombitasvir, dasabuvir, and dasabuvir M1 were calculated using non-compartmental methods.

Results

Bioanalytical methods

Table 4: Bioanalytical assay parameters

Analyte	Calibration Curve Range (ng/mL)	LLOQ (ng/mL)	QC Concentrations (ng/mL)	% CV	% Bias
ABT-267	0.464-316	0.464	1.16, 36.1, 246	2.9 % to 8.3 %	-2.8 to 5.2 %
ABT-450	0.601-409	0.601	1.55, 48.4, 329	2.7 % to 6.8 %	1.2 % to 4.5 %
Ritonavir	5.10-3470	5.10	13, 407, 2770	2.9 % to 5.7 %	1.8 % to 6.9 %
ABT-333	4.39-2990	4.39	11.1, 348,2370	5 % to 7.3 %	-2.1 % to 5.4 %
ABT-333 M1	4.68-3190	4.68	12.2, 380, 2580	2.9 % to 6.4 %	-0.4 % to 4.1%

The bioanalytical methods were acceptable.

Subject Disposition and Demographics

A total of 46 healthy volunteers (34 ault male subjects and 12 adult female subjects) were enrolled in the study and forty two subjects completed dosing. One subject (subject # 133) prematurely discontinued dosing after morning dosing on day 1 of period 3 (study day 21) due to an adverse event. Three subjects prematurely discontinued study drug: subject 104 discontinued after dosing in period 2 and was considered loss to follow up; subjects 141 and subject 143 were discontinued from the study in period 2, day -1 due to a positive drug screen and both subjects did not return for follow up visits.

Data from all 46 subjects were included in all the analysis.

Table 5 shows the demographic summary of subjects enrolled in the trial.

Table 5: Demographic Summary of All Subjects

	Mean ± SD (N = 46)	Min – Max
Age (years)	33.6 ± 9.0	22 – 56[a]
Weight (kg)	77.3 ± 12.0	54 – 108
Height (cm)	172 ± 9.5	152 – 195
Sex	34 Males (73.9%) and 12 Females (26.1%)	
Race	19 White (41.3%), 25 Black or African American (54.3%) and 2 Multi-Race (4.3%)	
Ethnicity	2 Hispanic or Latino (4.3%) and 44 None of the Above (95.7%)	

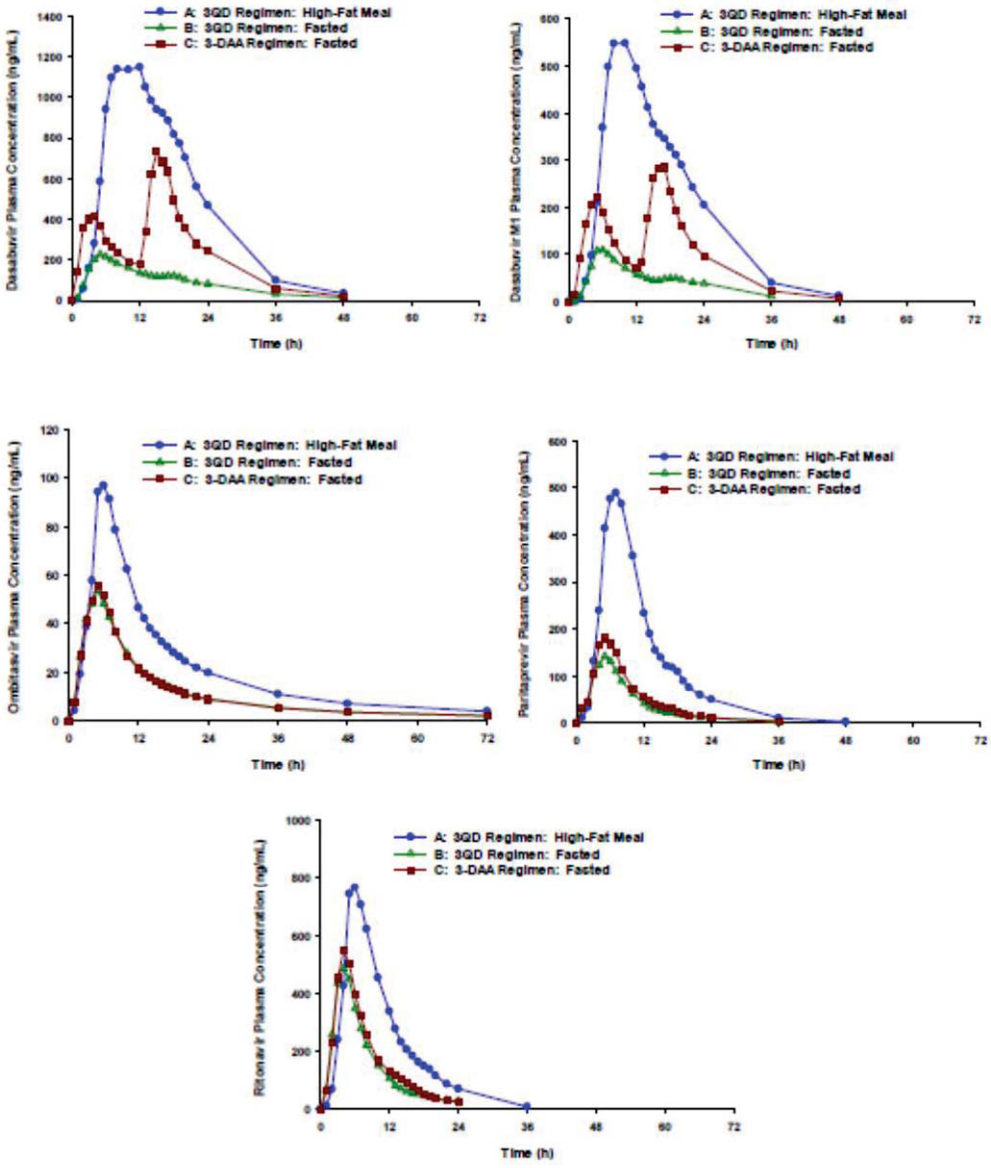
a. Subject 136 met the inclusion criteria (55 years of age on the day of enrollment).

Source: Final Study Report of Trial M14-566, page 74

Pharmacokinetics

Fig 1 shows the mean plasma concentration-time profiles of dasabuvir, dasabuvir M1, ombitasvir, paritaprevir, and ritonavir after various regimens.

Fig 1: Mean plasma concentration-time profiles of dasabuvir, dasabuvir M1, ombitasvir, paritaprevir, and ritonavir after various regimens



Source: Section 2.7.1. Summary of Biopharmaceutic Studies and Associated Analytical Methods; Page 68

Table 6 shows the geometric mean (arithmetic mean ± SD) pharmacokinetic parameters of dasabuvir, dasabuvir M1, ombitasvir, paritaprevir, and ritonavir after administration of various regimens.

Table 6: Geometric mean (arithmetic mean ± SD) pharmacokinetic parameters of dasabuvir, dasabuvir M1, ombitasvir, paritaprevir, and ritonavir after administration of various regimens

Pharmacokinetic Parameters	(Units)	Regimen A 3QD Regimen (N = 45)	Regimen B 3QD Regimen (N = 43)	Regimen C 3-DAA Regimen (N = 45)
		Dasabuvir		
C_{max}[a]	(ng/mL)	1390 (1530 ± 673)	212 (281 ± 267)	799 (841 ± 268)
T_{max}[b]	(h)	12.0 (5.0 – 20.0)	4.0 (3.0 – 24.0)	4.0 (2.0 – 8.0)
$t_{1/2}$[c]	(h)	6.76 ± 1.25	10.2 ± 3.94	7.07 ± 1.65
AUC_t	(ng•h/mL)	19800 (22300 ± 10300)	3110 (4170 ± 4310)	10400 (10900 ± 3570)
AUC_∞	(ng•h/mL)	19900 (22500 ± 10300)	3380 (4400 ± 4310)	10500 (11100 ± 3590)
		Dasabuvir M1 Metabolite		
C_{max}[a]	(ng/mL)	624 (692 ± 345)	97.5 (137 ± 143)	315 (335 ± 114)
T_{max}[b]	(h)	10.0 (6.0 – 20.0)	5.0 (4.0 – 24.0)	5.0 (3.0 – 7.0)
$t_{1/2}$[c]	(h)	5.92 ± 0.73	9.55 ± 3.99[d]	6.01 ± 1.17
AUC_t	(ng•h/mL)	8300 (9380 ± 4540)	1140 (1720 ± 2360)	4180 (4480 ± 1710)
AUC_∞	(ng•h/mL)	8440 (9510 ± 4570)	1330 (1890 ± 2390)[d]	4280 (4580 ± 1720)
		Ombitasvir		
C_{max}	(ng/mL)	104 (110 ± 35.2)	51.0 (54.7 ± 21.5)	53.7 (57.7 ± 22.0)
T_{max}[b]	(h)	6.0 (4.0 – 22.0)	5.0 (3.0 – 6.0)	5.0 (3.0 – 7.0)
$t_{1/2}$[c]	(h)	20.6 ± 5.54	22.7 ± 6.62	22.4 ± 6.96
AUC_t	(ng•h/mL)	1430 (1470 ± 357)	716 (769 ± 306)	718 (773 ± 288)
AUC_∞	(ng•h/mL)	1560 (1610 ± 435)	787 (853 ± 359)	788 (857 ± 344)
		Paritaprevir		
C_{max}	(ng/mL)	484 (699 ± 646)	80.8 (156 ± 271)	114 (215 ± 311)
T_{max}[b]	(h)	7.0 (4.0 – 19.0)	5.0 (1.0 – 12.0)	5.0 (1.0 – 7.0)
$t_{1/2}$[c]	(h)	5.21 ± 1.33	6.44 ± 2.07	5.17 ± 1.52
AUC_t	(ng•h/mL)	3950 (5170 ± 4220)	838 (1300 ± 1670)	1050 (1610 ± 1790)
AUC_∞	(ng•h/mL)	3970 (5190 ± 4220)	860 (1310 ± 1670)	1070 (1630 ± 1790)

Pharmacokinetic Parameters	(Units)	Regimen A 3QD Regimen (N = 45)	Regimen B 3QD Regimen (N = 43)	Regimen C 3-DAA Regimen (N = 45)
		Ritonavir		
C_{max}	(ng/mL)	837 (944 ± 479)	403 (531 ± 425)	445 (589 ± 432)
T_{max}[b]	(h)	6.0 (4.0 - 19.0)	4.0 (2.0 - 5.0)	4.0 (2.0 - 7.0)
$t_{1/2}$[c]	(h)	4.59 ± 0.97	6.07 ± 1.53	5.16 ± 1.52
AUC_t	(ng•h/mL)	6560 (7470 ± 4000)	3030 (3820 ± 2530)	3300 (4250 ± 3030)
AUC_∞	(ng•h/mL)	6720 (7590 ± 3980)	3150 (3930 ± 2540)	3420 (4350 ± 3040)

Regimen A = 3QD Regimen: three ER-12 bi-layer tablets (total dose of dasabuvir/ombitasvir/paritaprevir/r was 600/25/150/100 mg) administered in the morning under non-fasted conditions (high-fat breakfast).

Regimen B = 3QD Regimen: three ER-12 bi-layer tablets (total dose of dasabuvir/ombitasvir/paritaprevir/r was 600/25/150/100 mg) administered in the morning under fasted conditions.

Regimen C = 3-DAA Regimen: two ombitasvir/paritaprevir/r co-formulated tablets (total dose of 25/150/100 mg) QD with one dasabuvir IR tablet (250 mg) administered under fasted conditions in the morning and one dasabuvir IR tablet (250 mg) administered under fasted conditions in the evening.

a. C_{max} was calculated based on data from 0 to 72 hours post-morning dose for Regimen C.

b. Median (range). For Regimen C, dasabuvir and dasabuvir M1 T_{max} was determined after first dose (morning dose).

c. Harmonic mean ± pseudo-standard deviation.

d. N = 42.

Source: Section 2.7.1. Summary of Biopharmaceutic Studies and Associated Analytical Methods; Page 69-70

Table 7 shows the C_{max} and AUC ratios of central values and 90 % confidence intervals for dasabuvir, dasabuvir M1, ombitasvir, paritaprevir, and ritonavir.

Table 7: C_{max} and AUC ratios of central values and 90 % confidence intervals for dasabuvir, dasabuvir M1, ombitasvir, paritaprevir, and ritonavir

Regimens Test vs. Reference	Pharmacokinetic Parameter (units)	Central Value[a]		Relative Bioavailability	
		Test	Reference	Point Estimate[b]	90% Confidence Interval[c]
		Dasabuvir			
A vs. B Food Effect	C_{max} (ng/mL)	1377	208	6.625	5.547 – 7.911
	AUC_t (ng•h/mL)	19624	3083	6.366	5.419 – 7.478
	AUC_∞ (ng•h/mL)	19798	3347	5.915	5.059 – 6.916
B vs. C Relative Bioavailability in Fasted Condition	C_{max} (ng/mL)[d]	208	800	0.260	0.218 – 0.309
	AUC_t (ng•h/mL)	3083	10394	0.297	0.253 – 0.348
	AUC_∞ (ng•h/mL)	3347	10551	0.317	0.272 – 0.370
		Dasabuvir M1 Metabolite			
A vs. B Food Effect	C_{max} (ng/mL)	621	95.1	6.529	5.398 – 7.896
	AUC_t (ng•h/mL)	8272	1111	7.445	6.201 – 8.938
	AUC_∞ (ng•h/mL)	8407	1277	6.585	5.552 – 7.809
B vs. C Relative Bioavailability in Fasted Condition	C_{max} (ng/mL)[d]	95.1	315	0.302	0.250 – 0.363
	AUC_t (ng•h/mL)	1111	4206	0.264	0.220 – 0.317
	AUC_∞ (ng•h/mL)	1277	4303	0.297	0.250 – 0.352
		Ombitasvir			
A vs. B Food Effect	C_{max} (ng/mL)	104	50.9	2.055	1.828 – 2.310
	AUC_t (ng•h/mL)	1430	716	1.997	1.841 – 2.167
	AUC_∞ (ng•h/mL)	1558	785	1.985	1.829 – 2.154
B vs. C Relative Bioavailability in Fasted Condition	C_{max} (ng/mL)	50.9	53.6	0.948	0.844 – 1.066
	AUC_t (ng•h/mL)	716	720	0.994	0.901 – 1.096
	AUC_∞ (ng•h/mL)	785	790	0.994	0.903 – 1.094

Regimens Test vs. Reference	Pharmacokinetic Parameter (units)	Central Value[a]		Relative Bioavailability	
		Test	Reference	Point Estimate[b]	90% Confidence Interval[c]
		Paritaprevir			
A vs. B Food Effect	C_{max} (ng/mL)	481	80.5	5.967	4.623 – 7.702
	AUC_t (ng•h/mL)	3918	835	4.693	3.862 – 5.704
	AUC_∞ (ng•h/mL)	3944	857	4.600	3.800 – 5.569
B vs. C Relative Bioavailability in Fasted Condition	C_{max} (ng/mL)	80.5	115	0.701	0.543 – 0.904
	AUC_t (ng•h/mL)	835	1060	0.787	0.648 – 0.957
	AUC_∞ (ng•h/mL)	857	1083	0.792	0.654 – 0.958
		Ritonavir			
A vs. B Food Effect	C_{max} (ng/mL)	837	401	2.088	1.754 – 2.486
	AUC_t (ng•h/mL)	6545	3022	2.166	1.885 – 2.488
	AUC_∞ (ng•h/mL)	6702	3150	2.128	1.862 – 2.432
B vs. C Relative Bioavailability in Fasted Condition	C_{max} (ng/mL)	401	445	0.901	0.735 – 1.103
	AUC_t (ng•h/mL)	3022	3312	0.913	0.781 – 1.066
	AUC_∞ (ng•h/mL)	3150	3433	0.917	0.790 – 1.066

Regimen A = 3QD Regimen: three ER-12 bi-layer tablets (total dose of dasabuvir/ombitasvir/paritaprevir/r was 600/25/150/100 mg) administered in the morning under non-fasted conditions (high-fat breakfast).

Regimen B = 3QD Regimen: three ER-12 bi-layer tablets (total dose of dasabuvir/ombitasvir/paritaprevir/r was 600/25/150/100 mg) administered in the morning under fasted conditions.

Regimen C: 3-DAA Regimen: two ombitasvir/paritaprevir/r co-formulated tablets (total dose of 25/150/100 mg) QD with one dasabuvir IR tablet (250 mg) administered under fasted conditions in the morning and one dasabuvir IR tablet (250 mg) administered under fasted conditions in the evening.

a. Exponentiation of the least squares means for logarithms.

b. Exponentiation of the difference (test minus reference) in the least squares means between the test and reference regimens for logarithms.

c. Exponentiation of the endpoints of confidence intervals for the difference in the least squares means between the test and reference regimens for logarithms.

d. C_{max} was calculated from 0 to 72 hours post-morning dose for Regimen C.

Source: Section 2.7.1. Summary of Biopharmaceutic Studies and Associated Analytical Methods; Page 71-72

Conclusion

- Relative to administration of the 3-QD regimen under fasting conditions, administration of the 3-QD regimen under fed (high fat conditions) showed increase in mean dasabuvir, paritaprevir, ombitasvir, and ritonavir exposure by approximately 5. 9 fold, 4.6 fold, 2-fold and 2-fold, respectively.
- In the fasted state, dasabuvir and paritaprevir exposures were lower (approximately 70% lower for dasabuvir and approximately 21% to 30% lower for paritaprevir) with the 3QD regimen compared to the approved 3-DAA regimen. Ritonavir and ombitasvir exposures with the 3QD regimen were comparable (≤ 10% change in exposures) to the 3-DAA regimen.
- The greater magnitude of food effect on dasabuvir and paritaprevir from the 3-QD regimen as compared to the 3-DAA regimen appears to be primarily driven by the lower exposures of dasabuvir and paritaprevir in the fasted state from the 3-QD regimen.

Pharmacometric Review

1 SUMMARY OF FINDNGS

AbbVie has developed a fixed-dose combination tablet composed of a once daily preparation of dasabuvir (200 mg) with immediate release (IR) ombitasvir, paritaprevir and ritonavir (8.33/50/33.33 mg). This formulation is intended to replace the existing direct-acting antiviral (3-DAA) regimen of two ombitasvir/paritaprevir/ritonavir (12.5/ 75/50 mg) tablets QD plus one dasabuvir (250 mg) tablet BID. For adults, the new fixed dose combination is comprised of 3 tablets taken orally QD, for a total daily dosage of 600 mg of dasabuvir, 25 mg of ombitasvir, 150 mg of paritaprevir, and 100 mg of ritonavir (3QD) with or without ribavirin. No efficacy or safety studies were conducted with the 3QD regimen. Determination of the acceptability of the 3QD regimen is based on: i) bioavailability comparisons between the 3QD and 3-DAA regimens under fasting and fed conditions; ii) efficacy and safety observations using the 3-DAA regimen from the original NDA 206619 submission; and iii) impact assessment of ombitasvir, paritaprevir, and dasabuvir PK differences based on exposure-response modeling.

To compare the exposures of each component of the 3-DAAs and 3QD regimens under non-fasting conditions, Phase 1 Study (Study M14-566) was conducted. The results are listed in Table 1.

Table 1 Relative Bioavailability for the 3QD Regimen versus the 3-DAA Reference Regimen for Dasabuvir, Ombitasvir, Paritaprevir and Ritonavir after Multiple Dose Administration in Study M14-566

	Geometric Mean Ratio and 90% CI		
Drug	$C_{max,ss}$	$AUC_{24,ss}$	C_{trough}
Dasabuvir	0.905 (0.823 – 0.995)	0.892 (0.809 – 0.985)	0.710 (0.622 – 0.812)
Paritaprevir	0.722 (0.638 – 0.818)	0.900 (0.814 – 0.994)	1.055 (0.970 – 1.147)
Ombitasvir	1.040 (1.005 – 1.077)	1.090 (1.063 – 1.117)	1.098 (1.064 – 1.132)
Ritonavir	0.793 (0.746 – 0.842)	0.893 (0.846 – 0.943)	1.009 (0.946 – 1.075)

Source: Applicant's exposure-SVR_{12} analysis report, Page 20, Table 3.

The results indicate that the 3QD regimen yielded comparable exposures to the 3-DAA reference regimen following multiple dose administration under non-fasting conditions for most of the PK parameters and compounds. Exceptions to this were steady-state dasabuvir C_{trough}, paritaprevir C_{max}, and ritonavir C_{max}, which were lower for the 3QD tablet regimen compared to the 3-DAA reference regimen by 29%, 28% and 21% respectively. The maximum decrease in dasabuvir C_{trough}, based on the lower bound of 90% CI of the geometric mean ratio (0.710 [0.622, 0.812]) was 38%.

A separate Phase 1 study (Study M14-240) evaluated the bioavailability of the 3QD regimen relative to the 3-DAA reference regimen after single dose administration under fasting conditions. The results from this study are described in Table 2.

Table 2 Relative Bioavailability for the 3QD Regimen versus the 3-DAA Reference Regimen for Dasabuvir, Ombitasvir, Paritaprevir, and Ritonavir after Single Dose Administration under Fasting Conditions in Study M14-240

	Geometric Mean Ratio[a] and 90% CI[b]	
Drug	C_{max}	AUC_{∞}
Dasabuvir	0.260 (0.218 – 0.309)	0.317 (0.272 – 0.370)
Paritaprevir	0.701 (0.543 – 0.904)	0.792 (0.654 – 0.958)
Ombitasvir	0.948 (0.844 – 1.066)	0.994 (0.903 – 1.094)
Ritonavir	0.901 (0.735 – 1.103)	0.917 (0.790 – 1.066)

Source: Applicant's exposure-SVR_{12} analysis report, Page 22, Table 4.

These data suggest that under fasting conditions, dasabuvir AUC_{∞} was 68% lower and a maximum of 73% lower based on the lower bound of 90% CI for the geometric mean ratio (0.317 [0.272, 0.370]). Paritaprevir AUC_{∞} was 21% lower and a maximum of 35% lower based on the lower bound of 90% CI for the geometric mean ratio (0.792 [0.654, 0.958]) for the 3QD regimen, compared to the 3-DAA regimen.

1.1 Key Review Questions

Based on the results from these two bioavailability studies, the following key review questions were identified:

1.1.1 What is the impact of lower dasabuvir C_{trough} under fed conditions from the 3QD regimen on SVR_{12} in patients infected with HCV genotype 1a?

The impact of a 38% decrease in dasabuvir C_{trough} under fed conditions with the 3QD regimen on SVR_{12} in HCV genotype 1a patients is predicted to be not clinically relevant. In all genotype 1a patients and genotype 1a patients with multiple patient factors (male, cirrhosis, IL28B non-CC genotype) indicative of poorer response, a decrease in SVR_{12} of 0.6% and 1.0%, respectively, is predicted for the 3QD regimen compared to the 3-DAA regimen. This conclusion is based on: i) observations from M11-652 treatment arms that did not include dasabuvir (only paritaprevir, ombitasvir, ritonavir, and ribavirin); ii) safety and efficacy data from the 3-DAA regimen in genotype 1a patients; and iii) exposure-response analyses assessing the impact of changes in exposure on SVR_{12}.

Observed results from treatment arms with no dasabuvir (lower bound) show that the SVR_{12} of genotype 1a patients could be as low as 86%, around 10% reduction compared to that of 250 BID dosing. Higher dose of dasabuvir would not result in higher response rate (Table 3). The predicted response

rates based on the exposure-SVR_{12} analysis submitted by the Applicant was comparable with observations, further confirming the exposure-SRV_{12} relationship could be well described by the model.

Table 3 Observed and predicted response rates for genotype 1a patients in clinical trials with different dose regimens of dasabuvir (Predicted based on C_{trough})

Dasabuvir Dose	No. of Subjects	Observed SVR_{12}	Predicted SVR_{12}
0	N=77	85.7%	88.6% (85.7%-90.9%)
250 mg BID	N=1021	96.1%	97.5% (97.2%-97.7%)
400 mg BID	N=155	91.6%	94.8% (93.5-95.8)

Source: Reviewer's analysis

The impact of lower dasabuvir C_{trough} of under fed conditions are expecting to be less than 1% based on the exposure-SVR_{12} analysis submitted by the Applicant. The reviewer performed an independent exposure-response analysis and confirmed the Applicant's results. The lower bound of C_{trough} ratio (62%) was used in the analysis. The effect of the lower dasabuvir C_{trough} on SVR_{12} was predicted for the whole population and a subpopulation representing the hard-to-treat population (Cirrhotic, male, IL28B non-CC patients) based on the exposure-response relationship as presented in Table 4.

Table 4 Predicted Effects of 38% Lower Dasabuvir C_{trough} on SVR_{12}

Population	No. of patients	Observed SVR_{12}%	Predicted SVR_{12}% for 3-DAA (95%CI)	Predicted SVR_{12}% for 3QD (95%CI)	Decrease in SVR_{12}%
All patients	1253	95.0	96.8 (96.6-97.1)	96.2 (95.9-96.5)	0.6
Cirrhotic, male, IL28B non-CC patients	118	92.4	94.5 (93.6-95.4)	93.5 (92.4-94.5)	1.0

Source: Reviewer's analysis

1.1.2 What is the impact of lower dasabuvir and paritaprevir AUC under fasting conditions from the 3QD regimen on SVR_{12} in patients infected with HCV genotype 1a?

The combined impact of a 73% and 35% decrease in dasabuvir and paritaprevir AUC, respectively, under fasting conditions with the 3QD regimen on SVR_{12} in HCV genotype 1a patients is predicted to be larger than those under fed conditions. This conclusion is based on: i) observations from M11-652 treatment arms that did not include dasabuvir (only paritaprevir, ombitasvir, ritonavir, and ribavirin); ii) dose ranging for paritaprevir from M11-652; iii) safety and efficacy data from the 3-DAA regimen in genotype 1a patients; and iv) exposure-response analyses assessing the impact of changes in exposure on SVR_{12}. Based on these differences in SVR_{12}, the 3QD regimen should be administered under fed conditions, similar to labeling for the 3-DAA regimen.

Observed results from treatment arms with 100 mg paritaprevir show that the SVR_{12} of genotype 1a patients was 5% lower compared to that of 150 mg dosing. Higher dose of paritaprevir would not result in higher response rate (Table 5). The predicted response rates based on the exposure-SVR_{12} analysis submitted by the Applicant was comparable with observations with a little bit overestimated response rate for dasabuvir with 400 mg BID and paritaprevir with 100 mg QD (Table 5).

Table 5 Observed response rates for genotype 1a patients in clinical trials with different dose regimens of dasabuvir and paritaprevir (Predicted based on AUC)

Drug	Dose	No. of Subjects	Observed SVR_{12}	Predicted SVR_{12}
Dasabuvir	0	N=77	85.7%	87.1% (84.1%-89.6%)
	250 mg BID	N=1021	96.1%	97.2% (97.0%-97.4%)
	400 mg BID	N=155	91.6%	96.6% (95.8-97.3)
Paritaprevir	100 mg QD	N=67	91.0%	95.0% (92.6%-96.6%)
	150 mg QD	N=1135	95.6%	97.1% (96.8%-97.3%)
	200 mg QD	N=51	86.3%	89.0% (85.8%-91.5%)

Source: Reviewer's analysis

In all genotype 1a patients and genotype 1a patients with multiple patient factors (male, cirrhosis, IL28B non-CC genotype) indicative of poorer response, a decrease in SVR_{12} of 2.3% and 3.8%, respectively, is predicted for the 3QD regimen compared to the 3-DAA regimen under fasting conditions (Table 6). However, it is worth noting that the predictions are based on exposure-SVR_{12} analysis using data under fed conditions.

Table 6 Predicted Combined Effects of 73% Lower Dasabuvir AUC and 35% Lower Paritaprevir AUC on SVR_{12}

Population	No. of patients	Observed SVR_{12}%	Predicted SVR_{12}% for 3-DAA (95%CI)	Predicted SVR_{12}% for 3QD (95%CI)	Decrease in SVR_{12}%
All patients	1253	95.0	96.7 (96.5-97.0)	94.4(94.0-94.8)	2.3
Cirrhotic, male, IL28B non-CC patients	118	92.4	94.3 (93.4-95.0)	90.5(89.1-91.7)	3.8

Source: Reviewer's analysis

1.1.3 What is the impact of lower exposures under fasting or fed conditions with the 3QD regimen on SVR_{12} in patients infected with HCV genotype 1b?

The SVR_{12} rate for genotype 1b patients was higher than 99% across the studies, much higher than the response rate for genotype 1a patients. Therefore, genotype 1b patients were not included in the exposure-SVR_{12} analysis. Due to the high observed response rate in these populations, even smaller effects of lower exposures on response rate are expected under fasting or fed conditions with the 3QD regimens.

1.2 Recommendations

The Division of Pharmacometrics (Office of Clinical Pharmacology) has reviewed this application and recommends approval of the fixed-dose combination composed of dasabuvir, ombitasvir, paritaprevir and ritonavir (200/8.33/50/33.33 mg) administered three tablets once daily. The reviewer agrees with the Applicant's conclusion from the exposure-SVR_{12} analysis that the fixed-dose combination is predicted to have similar efficacy profile under the proposed dosing recommendation in HCV GT1a- and GT1b-infected subjects. Based on the bioavailability studies with the 3QD regimen under fasting conditions, the reviewer agrees that the 3QD regimen should be administered with food. This

recommendation is similar to the recommendation for the 3-DAA regimen, which also was to be administered with food.

2 PERTINENT REGULATORY BACKGROUND

AbbVie's 3-DAA was approved on 12/19/2014 and is indicated for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis with or without ribavirin. The approved regimen, available in a co-packaged configuration, consists of two tablets of the fixed dose combination (FDC) of ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg) given once daily (QD) with dasabuvir (250 mg) given twice daily (BID). When specified as a component of the treatment, ribavirin co-administered with the regimen is intended to be administered BID based on patient weight. AbbVie has now developed an alternative FDC, denoted as 3QD, to provide QD dosing regimen for all of dasabuvir/ombitasvir/paritaprevir/ritonavir (200/8.33/50/33.33 mg per tablet) given three tablets orally QD for a total dosage of dasabuvir 600 mg, ombitasvir 25 mg, paritaprevir 150 mg, and ritonavir 100 mg, plus a patient weight based dosing of ribavirin. The new NDA application was submitted on 9/28/2015 with two bioavailability studies, one population PK study and two exposure-response analysis studies.

3 RESULT OF APPLICANT's ANALYSIS

3.1 Exposure-response Analysis

3.1.1 Objectives

- To develop two separate relationships between 3-DAA and ribavirin steady-state C_{trough} or AUC and SVR_{12} following administration of the 3-DAA regimen with and without ribavirin in GT1a-infected subjects in four Phase 3 studies and two Phase 2 studies.
- To predict the impact on SVR12 of a 29% lower dasabuvir C_{trough} (maximum of 38% lower) with the 3QD regimen relative to the approved 3-DAA regimen in GT1a-infected subjects under fed conditions.
- To determine the impact on SVR_{12} of a 68% lower dasabuvir steady state AUC (maximum of 73% lower) and a 21% lower paritaprevir steady state AUC (maximum of 35% lower) for the 3QD regimen in subjects under fasting conditions.

3.1.2 Trial included in the exposure-response analysis

The data for the exposure-SVR_{12} analysis was collected from HCV GT1a-infected subjects following treatment with the 3-DAA regimen of paritaprevir/ritonavir/ombitasvir and dasabuvir or 2-DAA regimen (in the absence of either dasabuvir or ombitasvir) with and without ribavirin in four Phase 3 studies and two Phase 2 studies. A list of Phase 2/3 studies is provided in Table 7. In these studies, the treatment regimen was administered under non-fasting conditions.

Table 7 Study Drug Regimens Used in Phase 2/3 Studies

Regimens	Studies	DAA Doses
paritaprevir/ritonavir/ombitasvir + dasabuvir + ribavirin	M11-646, M13-098, M13-099, M14-103	150 mg/100 mg/25 mg once daily (QD) 400 mg or 250 mg twice daily (BID)
paritaprevir/ritonavir/ombitasvir + dasabuvir ± ribavirin	M14-002	
paritaprevir/ritonavir ± ombitasvir ± dasabuvir ± ribavirin	M11-652	150 mg/100 mg QD, 25 mg QD, 400 mg BID

Source: Applicant's exposure-SVR_{12} analysis report, Page 25, Table 5.

Reviewer's comments: The studies included in the exposure-response analysis involved different formulations with different bioavailability for the drugs. In addition, M11-652 included paritaprevir dosing of 100, 150 or 200 mg, not just 100 or 150 mg. All the 400 mg BID dosing for dasabuvir included in the analysis was from in M11-652, none of them from other study as listed from the table.

3.1.3 Data analysis plan

Data analysis was performed using logistic regression procedure in SAS version 9.2 with SVR_{12}, a binary response (Yes or No) as the dependent variable and 3-DAA and ribavirin steady state C_{trough} or AUC as predictor and subject or study specific variables as covariates.

The covariates investigated in the exposure-response analysis included:

- Demographics (age, weight, body mass index [BMI], body surface area [BSA], sex, ethnicity [Hispanic/Latino versus Non-Hispanic/Latino] and race [Black versus Non-Black]),
- Baseline HCV RNA,
- IL28B genotype (CC, Non-CC [CT, TT]),
- Prior pegIFN/ribavirin treatment experience (naïve and pegIFN/ribavirin treatment experienced), and
- Compensated liver cirrhosis (Child-Pugh A).

The empirical Bayes post-hoc estimates of the pharmacokinetic parameters of the 3-DAAs for each subject-estimated using the respective population pharmacokinetic models were used to provide the steady state 3-DAA and ribavirin exposure variable (C_{trough} or AUC). Relevant details are presented in reports R&D/14/0047 (Studies M11-646, M13-098, M14-002, M13-099 and M14-103) and R&D/13/1098 (Study M11-652).

Only data from GT1a-infected subjects were included in the current analysis as > 99% of GT1b-infected subjects who completed assigned treatment achieved SVR_{12}. Continuous covariates including log10 baseline viral load (BSVL or HCV RNA), sex, age, BMI and categorical covariates including IL28B genotype, prior pegIFN/ribavirin treatment experience, race, ethnicity and cirrhosis were evaluated in the multiple linear logistic regression models. The association between SVR_{12} and covariates was evaluated in the model at the alpha level of 0.05.

The backward elimination procedure and clinical relevance were used for selecting the appropriate covariates in the logistic regression model of SVR_{12} with covariates including log-transformed steady state C_{trough} for the 3-DAAs and ribavirin. The same approach was utilized when log-transformed steady state AUC was used for the 3-DAAs and ribavirin in the analysis.

Reviewer comments: The population PK analyses were previously reviewed and found acceptable in the original NDA 206619 submission. No additional assessments of the population PK analyses were conducted during this submission.

3.1.4 Prediction and simulation methodology

The impact of a dasabuvir C_{trough} (29% and a maximum of 38% lower) reduction from the 3QD regimen on percent SVR_{12} in comparison to that of the reference 3-DAA regimen was determined for various sub-populations based on statistically significant covariates and clinical relevance. Four sub-populations were selected and are listed below:

- Non-cirrhotic females with IL28B CC genotype
- Non-cirrhotic males with IL28B CC genotype
- Cirrhotic females with IL28B non-CC genotype
- Cirrhotic males with IL28B non-CC genotype

For the 3-DAA regimen and 3QD regimens, SVR_{12} rates, differences in SVR_{12} rates (delta SVR_{12}), and the pharmacodynamic equivalence ratio (the ratio of SVR_{12} rates between the 3QD and 3-DAA regimens as well as the 90% CI of the ratio) between the 2 regimens were estimated for the following scenarios for each sub-population.

a. Geometric mean of dasabuvir C_{trough} (representing the 3-DAA regimen as reference)
b. 29% reduction in dasabuvir C_{trough} (representing a point estimate of 0.71 for the 3QD regimen as test)
c. 38% reduction in dasabuvir C_{trough} (representing the lower bound of the 90% CI 0.62 for the 3QD regimen as test, conservative scenario)

A similar approach was utilized for evaluating the impact of lower dasabuvir and paritaprevir AUC_{∞} on SVR_{12} under fasting conditions, using the relationship with steady state AUC as the exposure variable for 3-DAAs and ribavirin and covariates based on clinical relevance. The following test scenarios were selected to predict the impact of reduction in dasabuvir and paritaprevir AUC_{∞} on SVR_{12} for the 3QD regimen under fasting conditions for the sub-populations listed above.

a. Geometric mean of dasabuvir and paritaprevir AUC (representing the 3-DAA regimen as reference)
b. 68% and 21% lower dasabuvir and paritaprevir steady state AUC, respectively (representing point estimates of 0.317 and 0.792 for the 3QD regimen as test).
c. 73% and 35% lower dasabuvir and paritaprevir steady state AUC, respectively (representing the lower bound of the 90% CI of 0.272 and 0.654 for the 3QD regimen as test, (conservative scenario).

3.1.5 Result of exposure-response logistic regression analyses

Two separate multiple linear logistic regression analyses were performed to explore the relationships between steady-state DAAs and ribavirin C_{trough} values (to evaluate impact on SVR_{12} under non-fasting conditions) or AUC values (to evaluate impact on SVR_{12} corresponding to lower exposures under fasting conditions) and SVR_{12} rate in HCV GT1a-infected subjects.

C_{trough} was selected as the primary exposure variable for assessing the impact of PK differences from the 3QD regimen under fed conditions (intended label instruction). In bioavailability study M14-566, the steady state AUC values for the 3-DAAs were comparable (90% CI for the geometric mean ratios were within 0.8 and 1.25) while dasabuvir C_{trough} was 29% lower (maximum of 38% lower, representing the lower bound of the 90% CI 0.62 for 3-QD regimen, as shown in Table 1.

In summary, C_{trough} for all 3-DAAs and ribavirin were statistically significant predictors of SVR_{12} ($p < 0.05$) such that an increase in Ln C_{trough} was positively correlated with percent SVR_{12} (Table 8). Amongst the demographic covariates, baseline viral load and subject age were negatively correlated with SVR_{12} ($p < 0.01$). Subjects with IL28B non-CC genotype (CT or TT) were predicted to achieve lower SVR_{12} rates in comparison to subjects with IL28B CC genotype. Sex was a marginally non-significant covariate ($p = 0.067$) and hence was retained in the final model. Although the presence of cirrhosis was statistically non-significant ($p = 0.2$), based on clinical relevance of cirrhosis it was retained in the model. Prior treatment experience and Black race were also considered to be clinically important covariates but were not retained in the model as they were highly non-significant (p-values of > 0.75).

Table 8 Summary of Predictor Variables (3-DAA or 2-DAA ± Ribavirin Regimens; Based on C_{trough})

Predictor Variable (unit)	β	SE	p-value
Intercept	18.2256	2.4833	< 0.0001
Baseline VL (log_{10} IU/mL)	–0.8424	0.3088	0.0064
Age (year)	–0.0547	0.0181	0.0026
Ln Ombitasvir C_{trough} (mg/L)	0.6615	0.1909	0.0005
Ln Dasabuvir C_{trough} (mg/L)	0.3390	0.0843	< 0.0001
Ln Paritaprevir C_{trough} (mg/L)	0.3697	0.1367	0.0068
Ln Ribavirin C_{trough} (mg/L)	0.2132	0.0490	< 0.0001
Sex (Male)	–0.7413	0.4046	0.0669
Presence of Cirrhosis	–0.5589	0.4361	0.2000
IL28B (non-CC)	–1.0844	0.4048	0.0074

Source: Applicant's exposure-SVR_{12} analysis report, Page 58, Table 10.

To evaluate the impact on SVR_{12} of lower dasabuvir and paritaprevir steady state AUC under fasting conditions (contrary to the proposed labeling that recommend administration under fed conditions), similar analyses were performed using steady state AUC as the exposure variable. Potential baseline and

demographic covariates were also evaluated in both approaches to determine the relationship to SVR_{12}. Summary of the estimates for the predictor variables and odds ratios are presented in Table 9.

Table 9 Summary of Predictor Variables (3-DAA or 2-DAA ± Ribavirin Regimens; Based on AUC)

Predictor Variable (unit)	β	SE	p-value
Intercept	12.2412	2.2075	<0.0001
Baseline VL (log10 IU/mL)	-0.8206	0.3022	0.0066
Age (year)	-0.0493	0.0178	0.0058
Ln Ombitasvir AUC(mg·hr/L)	0.4009	0.0925	<0.0001
Ln Dasabuvir AUC (mg·hr /L)	0.2727	0.0502	<0.0001
Ln Paritaprevir AUC (mg·hr /L)	0.3556	0.1240	0.0041
Ln Ribavirin AUC(mg·hr /L)	0.1506	0.0337	<0.0001
Sex (Male)	-0.9899	0.4021	0.0138
Presence of Cirrhosis	-0.5456	0.4357	0.2105
IL28B (non-CC)	-1.0940	0.4014	0.0064

Source: Applicant's exposure-SVR_{12} analysis report, Page 130, Appendix 14.5_2.1.

3.1.6 Prediction of impact of C_{trough}/AUC reduction on SVR_{12} for different populations

As summarized in Table 10, the mean baseline viral load and age in each sub-population along with the geometric mean values for the DAAs and ribavirin C_{trough} values (from the dataset comprised of Phase 2 and 3 studies used to develop the model) were used to predict SVR_{12} for the reference 3-DAA regimen. For the 3QD regimen, dasabuvir exposures were reduced by 29% and 38% for predictions.

Table 10 Geometric Mean and Variability (% CV) for Variables Used in Simulations with C_{trough} as the Exposure Variable

Sub-Population	Number of Subjects (N)	C_{trough} Dasabuvir (mg/L)	C_{trough} Paritaprevir (mg/L)	C_{trough} Ombitasvir (mg/L)	C_{trough} Ribavirin (mg/L)	Age[a] (Years)	Baseline Viral Load[a] (log_{10} IU/mL)
Non-cirrhotic, female, IL28B CC	85	0.263 (65)	0.0403 (117)	0.0396 (43)	1.54 (26)	49.5 (23)	6.68 (10)
Non-cirrhotic, male, IL28B CC	147	0.167 (65)	0.0207 (119)	0.0206 (47)	1.24 (28)	50.8 (20)	6.62 (10)
Cirrhotic, female, IL28B non-CC	42	0.301 (65)	0.0889 (111)	0.0309 (44)	1.27 (30)	55.5 (17)	6.31 (9)
Cirrhotic, male, IL28B non-CC	118	0.244 (64)	0.051 (120)	0.0178 (48)	1.09 (27)	57.1 (10)	6.48 (9)

Source: Applicant's exposure-SVR_{12} analysis report, Page 61, Table 12.

3.1.6.1 Predicted effect of lower dasabuvir C_{trough} for the 3QD regimen on SVR_{12}

The effect of lower dasabuvir C_{trough} from the 3QD regimen compared to the 3-DAA regimen on model predicted SVR12 are summarized in Table 11.

Table 11 Predicted Effect of Lower Dasabuvir C_{trough} on SVR_{12}

Population	Observed SVR_{12} %	Predicted SVR_{12} % (95% CI)		Decrease in SVR_{12} for 3QD vs. 3-DAA (Delta SVR_{12} %) (95% CI)	Pharmacodynamic Equivalence (Ratio and 90% CI)
		3 DAA (Reference)	3 QD		
Effect of 29% Lower Dasabuvir C_{trough}[a]					
Non-cirrhotic, female, IL28B CC	100	99.80 (99.56 to 100.03)	99.77 (99.52 to 100.03)	0.02 (0.00 to 0.05)	1.00 (1.00 to 1.00)
Non-cirrhotic, male, IL28B CC	96.6	99.0 (98.1 to 99.9)	98.9 (97.9 to 99.8)	0.13 (0.02 to 0.23)	0.999 (0.998 to 1.00)
Cirrhotic, female, IL28B non-CC	100	99.1 (98.1 to 100)	99.0 (97.9 to 100)	0.11 (–0.01 to 0.24)	0.999 (0.998 to 1.00)
Cirrhotic, male, IL28B non-CC	92.4	95.4 (92.2 to 98.6)	94.9 (91.3 to 98.4)	0.54 (0.10 to 0.97)	0.994 (0.990 to 0.998)
Effect of 38% Lower Dasabuvir C_{trough}[b]					
Non-cirrhotic, female, IL28B CC	100	99.80 (99.56 to 100.03)	99.76 (99.49 to 100.03)	0.04 (0.00 to 0.07)	1.00 (0.999 to 1.00)
Non-cirrhotic, male, IL28B CC	96.6	99.0 (98.1 to 99.9)	98.8 (97.8 to 99.8)	0.18 (0.03 to 0.33)	0.998 (0.997 to 1.00)
Cirrhotic, female, IL28B non-CC	100	99.1 (98.1 to 100)	98.9 (97.8 to 100)	0.16 (–0.02 to 0.34)	0.998 (0.997 to 1.00)
Cirrhotic, male, IL28B non-CC	92.4	95.4 (92.2 to 98.6)	94.6 (90.9 to 98.4)	0.77 (0.14 to 1.39)	0.992 (0.986 to 0.998)

Source: Applicant's exposure-SVR_{12} analysis report, Page 63, Table 14.

As shown in Table 11, a 29% lower dasabuvir C_{trough} for the 3QD regimen is expected to have a minimal impact on SVR12 rates (0.02% to 0.54% lower SVR_{12}) compared to the current 3-DAA regimen as the reference. A conservative scenario of a 38% lower mean dasabuvir C_{trough} level, based on the lower bound of the 90% CI for the geometric mean ratio of the 3QD regimen obtained in Study M14-566 [0.710 (90% CI; 0.622, 0.812)], may lead to 0.04% to 0.77% lower SVR_{12}. Even for the most difficult to treat sub-population (patients with multiple factors identified as reducing the likelihood of achieving SVR_{12} such as cirrhosis, male gender, and IL28B non-CC genotype), the difference in SVR_{12} was predicted to be 0.77 (95% CI 0.14, 1.34) for 38% lower dasabuvir C_{trough} for the 3QD regimen.

Reviewer's comments: The Reviewer conducted an independent prediction for effect of 38% lower dasabuvir C_{trough} on SVR12 as shown in Table 4. The Reviewer used actual covariates values for each patient instead of mean baseline viral load, 3-DAA and ribavirin C_{trough} value to predict the response rate for all patients and hard-to-treat population. The results seem to be consistent between the Applicant's and the Reviewer analyses.

3.1.6.2 Predicted effect of lower dasabuvir and paritaprevir steady state AUC for the 3QD regimen under fasting conditions on SVR_{12}

The mean baseline viral load and age in each sub-population along with the geometric mean values for the DAAs and ribavirin AUC (from the dataset comprised of Phase 2 and 3 studies used to develop the model) that was used to predict SVR_{12} for the reference 3-DAA regimen under fasting conditions are summarized in Table 12.

Table 12 Geometric Mean and Variability (% CV) for Variables Used in Predicting SVR_{12} Using AUC as Exposure Variable

Sub-Population	Number of Subjects (N)	AUC Dasabuvir (mg/L)	AUC Paritaprevir (mg/L)	AUC Ombitasvir (mg/L)	AUC Ribavirin (mg/L)	Age[a] (years)	Baseline Viral Load[a] (log_{10} IU/mL)
Non-cirrhotic, female, IL28B CC	85	12.0 (47)	2.44 (109)	1.46 (39)	44.1 (26)	49.5 (23)	6.68 (10)
Non-cirrhotic, male, IL28B CC	147	8.52 (47)	1.28 (115)	0.809 (44)	35.0 (28)	50.8 (20)	6.62 (10)
Cirrhotic, female, IL28B non-CC	42	13.5 (46)	5.19 (104)	1.19 (40)	37.2 (28)	55.5 (17)	6.31 (9)
Cirrhotic, male, IL28B non-CC	118	11.4 (45)	3.06 (114)	0.713 (45)	30.9 (27)	57.1 (10)	6.48 (9)

Source: Applicant's exposure-SVR_{12} analysis report, Page 71, Table 18.

The test scenarios were based on geometric mean ratios and the 90% CI obtained for dasabuvir AUC_{∞} (0.317 [90% CI; 0.272, 0.370]) and paritaprevir AUC_{∞} (0.792 [90% CI; 0.654, 0.958]), from the relative bioavailability study (Study M14-240, Table 2). The predicted results are summarized in Table 13.

As shown in Table 13, a 68% lower dasabuvir and 21% lower paritaprevir steady state AUC for the 3QD regimen is expected to decrease SVR12 rates by 0.17% to 3.3% compared to the current 3-DAA regimen under fasting conditions. A conservative scenario of a maximum of 73% dasabuvir and 35% lower paritaprevir steady state AUC (based on the lower bound of the 90% CI for the geometric mean ratio of the 3QD regimen obtained in Study M14-240, dasabuvir AUC_{∞} (0.317 [90% CI; 0.272, 0.370]) and paritaprevir AUC_{∞} (0.792 [90% CI; 0.654, 0.958]), is predicted to lower SVR12 by 0.24% to 4.5%. Even for the most difficult to treat sub-population (cirrhotic males with IL28B non-CC genotype), the reduction in SVR_{12} was predicted to be 4.50 (95% CI 1.04, 7.97) for 73% lower dasabuvir AUC (35% lower paritaprevir for the 3QD regimen.

Table 13 Predicted Effect of Lower Dasabuvir and Paritaprevir Steady-State AUC for the 3QD Regimen Compared to the 3-DAA Regimen on SVR_{12} under Fasting Conditions

Population	Predicted SVR_{12} % (95% CI)		Decrease in SVR_{12} for 3QD vs 3-DAA (Delta SVR_{12} %) (95% CI)	Pharmacodynamic Equivalence (Ratio and 90% CI)
	3-DAA (Reference)	3QD		
Effect of 68% Lower Dasabuvir and 21% Lower Paritaprevir AUC[a]				
Non-cirrhotic, female, IL28B CC	99.6 (99.2 to 100)	99.5 (98.9 to 100)	0.17 (–0.02 to 0.37)	0.998 (0.997 to 1.00)
Non-cirrhotic, male, IL28B, CC	98.2 (96.7 to 99.8)	97.4 (95.2 to 99.6)	0.83 (0.09 to 1.57)	0.992 (0.985 to 0.998)
Cirrhotic, female, IL28B Non-CC	98.5 (97.0 to 100)	97.8 (95.5 to 100)	0.72 (–0.05 to 1.49)	0.993 (0.986 to 0.999)
Cirrhotic, male, IL28B, Non-CC	92.5 (87.5 to 97.4)	89.2 (82.1 to 96.3)	3.27 (0.83 to 5.71)	0.965 (0.941 to 0.988)
Effect of 73% Lower Dasabuvir and 35% Lower Paritaprevir AUC[b]				
Non-cirrhotic, female, IL28B CC	99.6 (99.2 to 100)	99.4 (98.7 to 100)	0.24 (–0.04 to 0.53)	0.998 (0.995 to 1.00)
Non-cirrhotic, male, IL28B, CC	98.2 (96.7 to 99.8)	97.1 (94.6 to 99.6)	1.16 (0.08 to 2.24)	0.988 (0.979 to 0.998)
Cirrhotic, female, IL28B Non-CC	98.5 (97.0 to 100)	97.5 (94.9 to 100)	1.00 (–0.10 to 2.10)	0.990 (0.980 to 0.999)
Cirrhotic, male, IL28B, Non-CC	92.5 (87.5 to 97.4)	88.0 (79.9 to 96.0)	4.50 (1.04 to 7.97)	0.951 (0.918 to 0.985)

Source: Applicant's exposure-SVR_{12} analysis report, Page 72, Table 19.

Reviewer's comments: The Reviewer conducted an independent prediction for effect of 73% lower dasabuvir AUC and 35% lower paritaprevir AUC on SVR12 as shown in Table 6. The Reviewer used actual covariates values for each patient instead of mean baseline viral load, 3-DAA and ribavirin AUC value to predict the response rate for all patients and hard-to-treat population. The results seem to be consistent between the Applicant's and the Reviewer analyses.

3.1.7 Applicant's conclusion

Data from the Phase 2 and Phase 3 studies with paritaprevir/ritonavir with ombitasvir and/or dasabuvir regimen with and without ribavirin were used to develop an exposure-response relationship using logistic regression in HCV GT1a subjects.

The relationship was used to predict the impact of lower dasabuvir C_{trough} from the 3QD regimen on SVR_{12} rates compared to the 3-DAA + ribavirin regimen in HCV GT1a subjects. In addition, simulations were conducted to predict the impact of lower dasabuvir C_{trough} on SVR_{12} rates. Results from these predictions as well as simulations indicated that:

- Under non-fasting conditions 38% lower dasabuvir C_{trough} from the 3QD regimen will result in a minimal impact on SVR_{12} rates compared to SVR_{12} rates with the 3-DAA regimen. The decrease in SVR_{12} rates was predicted to range from 0.02% to 0.5% across the various populations for a 38% decrease in dasabuvir C_{trough} values in HCV GT1a subjects. With an even shallower exposure-SVR_{12} relationship than HCV GT1a subjects, negligible impact of this change on SVR_{12} is expected in HCV GT1b-infected subjects.
- If the 3QD regimen is administered under fasting conditions throughout the entire dosing period contrary to the label proposed non-fasting conditions, 0.2% to 0.8% lower SVR_{12} and 0.7 to 3.3% lower SVR_{12} is anticipated in non-cirrhotic and cirrhotic HCV GT1a subjects respectively.

Overall, considering the differences in the plasma concentration-time profiles between the two regimens, the two products are predicted to have similar efficacy profiles under the proposed dosing recommendations in HCV GT1a- and GT1b-infected subjects.

Reviewer's comments: The reviewer verified the Applicant's exposure-SVR_{12} analyses for dasabuvir, ombitasvir, paritaprevir and ribavirin. The covariates for the logistic model include concentrations of the four drugs, baseline viral load, age, sex, presence of cirrhosis and IL28B non-CC genotype, which are in a good agreement with the Applicant's analyses. The reviewer performed the independent simulation based on the exposure-SVR_{12} relationships for genotype 1a patients regardless of covariates and with covariates representative of the most difficult-to-treat patients. Overall, the results are consistent with the Applicant's predictions. Although there was a statistically significant correlation between dasabuvir C_{trough} and SVR_{12}, the relationship is flat (Figure 1) and minimum impact on SVR_{12} is predicted in GT1a patients. Independent analyses were not conducted for GT1b patients. However, given that such patients have higher response rates than GT1a patients with the 3-DAA regimen, the predicted impact of the PK differences is expected to be even less.

It is noteworthy that both the 3-DAA regimen and the 3QD regimen have considerably lower 3-DAA exposures under fasting conditions and the magnitude of food effect is even greater for the 3QD regimen compared to 3-DAA regimen. Hence it is expected that under fasting conditions the SVR_{12} for the 3QD regimen would be slightly lower compared to 3-DAA regimen. Similar to the 3-DAA regimen, the 3QD regimen should therefore be administered with food.

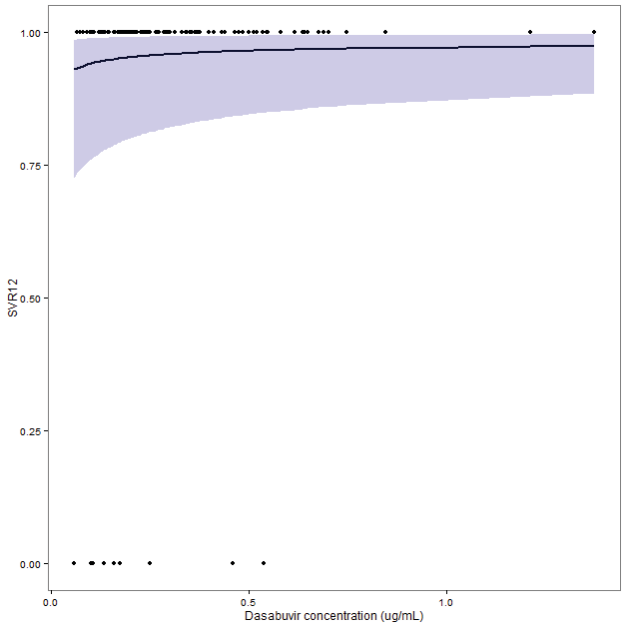


Figure 1 Relationship between Dasabuvir C_{trough} and SVR_{12} in male, cirrhotic and IL28B non-CC patients

Source: Reviewer's analysis

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/s/

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