CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208261Orig1s000

MICROBIOLOGY / VIROLOGY REVIEW(S)

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 208261 **SDN:** 000 Addendum **DATE REVIEWED:** 1/04/16

Clinical Virology Reviewers: Takashi E. Komatsu, Ph.D., RAC & Patrick R. Harrington, Ph.D.

NDA #: 208261 **Supporting Document Numbers:** 000

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Correspondence Date: May 28, 2015
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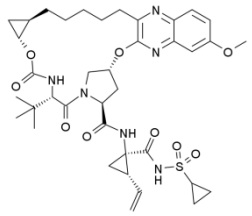
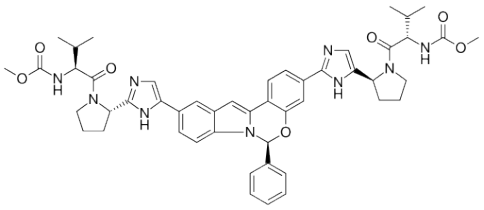
Reviewer Assignment Date: May 28, 2015
Original NDA Review Complete Date: October 21, 2015
PDUFA Date: January 28, 2016

Proprietary Name	**Zepatier®** **(combination product: grazoprevir and elbasvir)**	
Product Names [class]	grazoprevir, MK-5172 [NS3/4A protease inhibitor]	elbasvir, MK-8742 [NS5A inhibitor]
Individual IND #s	110261	114298
Chemical Name	(1ar,5s,8s,10r,22ar)-5-tert-butyl-n-((1r,2s)-1-{[-cyclopropylsulfonyl)amino] carbonyl}-2-vinylcyclopropyl)-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22, 22a-tetradecahydro-8h-7,10-methanocyclopropa [18,19][1,10,3,6]dioxadiazacyclononadecino[11, 12-b]quinoxaline-8-carboxamide	Dimethyl N,N′-([(6S)-6-phenylindolo[1,2-c][1,3]benzoxazine-3,10-diyl]bis{1H-imidazole-5,2-diyl-(2S)-pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})dicarbamate
Structure	 **MK-5172**	 **MK-8742**
Molecular Formula	$C_{38}H_{50}N_6O_9S$	$C_{49}H_{55}N_9O_7$
Molecular Weight	766.90	882.02

Amendments:

Response to labeling recommendations (SDN 035): October 20, 2015
Proposed PMR Dates (SDN 047): November 30, 2015
Response to labeling recommendations (SDN 048): November 30, 2015
Sponsor's minutes to the Late Cycle Meeting (SDN 049): December 3, 2015
Response to labeling recommendations (SDN 052): December 18, 2015
Response to proposed studies and dates for PMRs (SDN 056): January 7, 2016
Response to Clinical Virology request (SDN 057): January 7, 2016

Reference ID: 3876278

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 208261 **SDN:** 000 Addendum **DATE REVIEWED:** 1/04/16

Clinical Virology Reviewers: Takashi E. Komatsu, Ph.D., RAC & Patrick R. Harrington, Ph.D.

Response to labeling recommendations (SDN 058): January 12, 2016
Sponsor's PMR/PMC milestones (SDN 059): January 12, 2016
Response to labeling recommendations (SDN 060): January 14, 2016
Response to labeling recommendations (SDN 062): January 20, 2016

Related/Supporting Documents: IND 110261, IND 114298, DMF (b) (4), DMF (b) (4)
Indication(s): Treatment of chronic hepatitis C (CHC) genotypes 1, 4, or 6 infection in adults
Dosage Form(s): Fixed-dose combination product containing 100 mg of grazoprevir and 50 mg of elbasvir in a single tablet
Route(s) of Administration: Oral/tablet
Recommended Dosage: One tablet taken orally once daily with or without food
Dispensed: Rx _X_ **OTC** ___ **(Discipline relevant)**

Abbreviations: GT, genotype; HCV, hepatitis C virus; LDV, ledipasvir; PI, protease inhibitor; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response;

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CLINICAL VIROLOGY REVIEW ADDENDUM

1. Introduction and Background

The purpose of this review addendum is to document the following:

- Final agreed labeling for Section 2.1 Testing Prior to the Initiation of Therapy and Section 12.4 Microbiology
- Final agreed PMRs/PMCs related to Clinical Virology

2. Additional Analyses to Support Sections 2.1 Testing Prior to the Initiation of Therapy and 12.4 Microbiology of the Label

The sponsor did not initially accept the Division's recommendations, specifically concerning the need for screening NS5A polymorphisms in GT1a infected patients prior to initiation of MK-5172/MK-8742 using a commercially available assay. In the sponsor's response to the Division's labeling recommendation (dated 10/20/15, SDN 035), the sponsor stated that if the same methodology (next generation sequencing) and definitions were used to identify subjects harboring NS5A polymorphisms prior to initiating treatment, the efficacy of MK-5172/MK-8742 is comparable to that of Harvoni® (ledipasvir/sofosbuvir [LDV/SOF]). However, this approach was flawed as the sponsor in fact did *not* use the same methodology as used by Dr. Lisa K. Naeger for analyzing the Harvoni® baseline polymorphism data (please see the review of Dr. Lisa K. Naeger, Ph.D., NDA 205834 SDN 000; on pg. 14, Dr. Naeger states "consensus sequences were generated and used for analysis"). The sponsor used a 1% sensitivity threshold in their deep sequence analysis, which would identify subjects with viral populations with minor variants in addition to populations with predominant NS5A polymorphisms, while for the analysis of the Harvoni® baseline polymorphism data the consensus sequence derived from the next generation sequencing data was used (i.e., not including minor variants <15% in abundance). Based on the analyses that were conducted for Harvoni®, the sponsor's original analyses using population-based nucleotide sequencing would be the more relevant comparator.

In general based on Dr. Naeger's review of NDA 205834, Harvoni® regimens recommended in labeling appear to be only minimally impacted by baseline NS5A polymorphisms. The only subgroup of subjects in whom NS5A polymorphisms seemed to have a substantial impact on treatment efficacy in registrational trials were those in the ION-2 (treatment-experienced with or without cirrhosis) study who received Harvoni® for 12 weeks, who had a relapse rate of 22% (5/23). Looking more carefully at these 5 virologic relapsers (Dr. Naeger's NDA 205834 review, Appendix A), one subject had cirrhosis and therefore received a non-recommended regimen, and the other 4 subjects (3 GT1a, 1 GT1b) each had polymorphisms at two critical NS5A inhibitor resistance-associated positions (28, 30, 31 or 93). The presence of only one key NS5A polymorphism at a resistance-associated position had little impact on Harvoni® treatment efficacy, particularly for regimens dosed for ≥12 weeks (e.g., see Dr. Naeger's NDA 205834 review, Table 34, GT1 relapse rates based on number of baseline NS5A polymorphisms).

In contrast with MK-5172/MK-8742 for 12 weeks, even a single NS5A polymorphism had a substantial impact on efficacy for GT1a subjects (Table 1, FDA analysis, considering any amino acid polymorphism(s) at NS5A positions 28, 30, 31, 58, or 93). The impact of single baseline NS5A polymorphisms was observed regardless of the subject's cirrhotic status or previous Peg-IFN/ribavirin treatment experience. Therefore, these reviewers believe that screening NS5A polymorphisms prior to initiation of MK-5172/MK-8742 in GT1a patients is warranted to optimize treatment efficacy and to reduce the risk of virologic failure and the emergence of additional NS3 and NS5A resistance-associated substitutions that may reduce the efficacy of subsequent re-treatment. These concerns were

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relayed to the sponsor during the Late Cycle Meeting on 11/18/15 (see Appendix 1 for the Clinical Virology slides).

Table 1: GT1a Virologic Failure Rate for All Subjects Receiving MK-5172/MK-8742 for 12 Weeks (Any NS5A Polymorphisms at Positions 28, 30, 31, 58, or 93)

Regimen	Tx Experience	Cirrhosis	No PM	≥1 PM	1 Polymorphism	≥2 Polymorphisms
GZR/EBR 12 weeks	Naïve	N	2.2% (6/276)	17% (11/64)	13% (7/54)	40% (4/10)
GZR/EBR 12 weeks	Naïve	Y	1.6% (1/59)	5.8% (1/17)	8.3% (1/12)	0% (0/5)
GZR/EBR 12 weeks	Experienced	N	2.1% (1/48)	33% (3/9)	38% (3/8)	0% (0/1)
GZR/EBR 12 weeks	Experienced	Y	3.3% (1/28)	40% (2/5)	40% (2/5)	none
GZR/EBR	**All subjects**		**2.2% (9/411)**	**18% (17/95)**	**16% (13/79)**	**25% (4/16)**

In the sponsor's response to the Division's labeling recommendation (dated 11/30/15, SDN 048), the sponsor accepted the GT1a screening recommendations (b) (4) (b) (4) (b) (4) There were 33 subjects infected with HCV GT1a who had NS5A M28 polymorphisms at baseline in the recommended treatment arms, of whom 29 achieved SVR12 (88%; note: these numbers exclude subjects from study 048, the prior PI+ Peg-IFN/ribavirin failure study). Additionally, one of the subjects who achieved SVR12 but relapsed before SVR24 had the M28V polymorphism. While these reviewers agree that the NS5A M28 polymorphisms did not impact SVR12 rates to the same extent as the other positions (Table 2**Error! Reference source not found.**, FDA analysis), SVR12 rates below 95% for noncirrhotic or compensated cirrhotic GT1 patients are generally not acceptable in the current treatment era. Furthermore, these analyses are not powered to demonstrate a ~10% difference in SVR12 rates. Since the GT1a NS5A screening recommendation is not a limitation of use and an alternative, presumably more effective regimen is recommended for GT1a patients with NS5A polymorphisms (MK-5172/MK-8742 + RBV, 16 weeks; see below), data for subjects with M28 polymorphisms should be described in the label and position M28 should be considered in the screening algorithm to optimize treatment efficacy.

Table 2: Efficacy of MK-5172/MK-8742 with or without Ribavirin in HCV Genotype 1a-Infected Subjects with or without NS5A Resistance-associated Polymorphisms

	MK-5172/MK-8742 12 Weeks		MK-5172/MK-8742 + RBV 16 Weeks	
NS5A Polymorphism*	SVR12 with Polymorphism % (n/N)	SVR12 without Polymorphism % (n/N)	SVR12 with Polymorphism % (n/N)[5]	SVR12 without Polymorphism % (n/N)
M28	88% (29/33)[1]	95% (451/473)	100% (2/2)	100% (53/53)
Q30	40% (4/10)[2]	96% (476/496)	100% (1/1)	100% (54/54)
L31	38% (5/13)[3]	96% (475/493)	100% (2/2)	100% (53/53)
Y93	63% (5/8)[4]	95% (475/498)	100% (2/2)	100% (53/53)
M28, Q30, L31 or Y93	70% (39/56)	98% (441/450)	100% (6/6)	100% (49/49)

*Any change from GT1a reference.
[1]SVR12 rates for polymorphisms at M28: M28L (100%; 1/1), M28V (86%, 25/29), M28T (100%; 3/3)
[2]SVR12 rates for polymorphisms at Q30: Q30H (20%; 1/5), Q30L (50%, 1/2), Q30R (67%; 2/3)
[3]SVR12 rates for polymorphisms at L31: L31M (38%, 5/13)
[4]SVR12 rates for polymorphisms at Y93: Y93C (100%, 3/3), Y93H (33%; 1/3), Y93N (100%, 1/1), Y93S (0%; 0/1)
[5]SVR12 rates for 6 subjects with NS5A polymorphisms who received MK-5172/MK-8742+RBV for 16 weeks: M28V (100%; 2/2), Q30H (100%, 1/1), L31M (100%, 2/2), Y93C (100%, 1/1), Y93H (100%, 1/1)

After further consideration, these reviewers agreed with the sponsor that the available data do not warrant screening for NS5A H58 polymorphisms at this time. There were 49 subjects infected with HCV GT1a who had NS5A H58 polymorphisms at baseline in the recommended treatment arms, of whom 48

achieved SVR12 (98%; note: these numbers exclude subjects from study 048, the prior PI+ Peg-IFN/ribavirin failure study). However, these reviewers believe that this position should still be described in Section 12.4 of the label for the following reasons:

1. There was only one subject (5172-060_039600001) who had the NS5A H58D polymorphism and the subject did not achieve SVR12. Of note, this subject also had the NS5A M28V polymorphism at baseline and developed the NS5A Q30R substitution on-treatment.
2. NS5A H58D is a treatment-emergent resistance-associated substitution. In the sponsor's clinical studies, there were 3 virologic failures whose viral populations had treatment-emergent NS5A H58D substitution:
   - 5172-068_141300006: only NS5A H58D emergent
   - 5172-035_010200001: NS5A Q30R and H58D emergent
   - 5172-035_035500011: NS5A M28T, Q30H/Y, and H58D emergent
3. There was an additional subject (5172-048_001200002) in study 048 (prior PI+ Peg-IFN/ribavirin failure study) who had the NS5A H58D polymorphism at baseline. This subject did not achieve SVR12. However, this subject also had NS3 V36L and R155K substitutions at baseline, which confounds the interpretation of the data.
4. The NS5A H58D substitution alone confers a 6-fold reduction in susceptibility to MK-8742 in cell culture.

The GT1a virologic failure rate for all subjects excluding NS5A H58 polymorphisms are summarized in Table 3 (FDA analysis).

Table 3: GT1a Virologic Failure Rate for All Subjects Receiving MK-5172/MK-8742 for 12 Weeks (Any NS5A Polymorphisms at Positions 28, 30, 31, or 93)

Tx Experience	Cirrhosis	Regimen	All subjects	No PM	Any PM	1 Polymorphism	2+ Polymorphisms
Naïve	N	GZR/EBR 12 weeks	5% (17/340)	2% (6/303)	30% (11/37)	25% (8/32)	60% (3/5)
Naïve	Y	GZR/EBR 12 weeks	2.6% (2/76)	1.5% (1/68)	13% (1/8)	14% (1/7)	0% (0/1)
Experienced	N	GZR/EBR 12 weeks	7.0% (4/57)	2.0% (1/49)	38% (3/8)	38% (3/8)	none
Experienced	Y	GZR/EBR 12 weeks	9.1% (3/33)	3.3% (1/30)	67% (2/3)	67% (2/3)	none
All subjects			**5.1% (26/506)**	**2% (9/450)**	**30% (17/56)**	**28% (14/50)**	**50% (3/6)**

During the labeling negotiations, the Division's thinking with respect to the optimal approach to Section 2 of the label evolved. The Division was concerned that the approach to Sections 2.1 Testing Prior to the Initiation of Therapy and 2.2 Recommended Dosage in Adults (in the label submitted by the Sponsor on 12/18/2015, SDN 052) could lead to inadvertent, suboptimal treatment of some patients by HCV care providers. This concern was due to the lack of clear guidance in Sections 2.1 and 2.2 for the management of GT1a-infected patients with key NS5A polymorphisms (i.e., NS5A polymorphisms at positions 28, 30, 31, and 93). The Division was concerned that the dosing instructions may be misinterpreted by providers as recommending 12 weeks of MK-5172/MK-8742 for all GT1a-infected patients irrespective of the presence of NS5A polymorphisms if the footnote referencing Section 2.1 was overlooked. If providers referenced only the dosing table in the label highlights, the likelihood of selecting a suboptimal regimen is further compounded as there was no relevant footnote for this table. Given these concerns, the Division concluded that a clear direction in Section 2 should be provided for the management of GT1a-infected patients both with and without key baseline NS5A polymorphisms. As such, the Division was willing to leverage the available data from Study 068 to support a dosing recommendation of MK-5172/MK-8742 + RBV for 16 weeks in GT1a-infected patients with key NS5A polymorphisms. The addition of RBV and 16 weeks of treatment resulted in SVR12 in six out of six subjects whose GT1a virus had NS5A polymorphisms. While these results from Peg-IFN/ribavirin

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treatment-experienced subjects with NS5A polymorphisms are promising, these reviewers are concerned that the conclusion is based on a small number of subjects. Nevertheless, while there were only 6 subjects with the NS5A polymorphisms, two subjects had cirrhosis and there was a distribution of polymorphisms across the 4 NS5A positions, including one subject who had 2 key resistance-associated polymorphisms:

- 5172-068_143100003: Q30H, Y93H
- 5172-068_143500007: Y93C
- 5172-068_143700002: M28V
- 5172-068_143800018: M28V
- 5172-068_146200006: L31M
- 5172-068_151000006: L31M

All 6 of these subjects achieved SVR24.

Additionally, there is precedence where a small number of subjects have been used to recommend a dosing regimen. For example, the combination of simeprevir + sofosbuvir was recommended for 24 weeks treatment in treatment-naïve and treatment-experienced patients with cirrhosis (see label for Olysio®) based on an open label Phase 2 study (COSMOS Study). The overall SVR12 rates were 93% (26/28; both subjects who failed were relapsers) and 97% (30/31; subject who failed was not a virologic failure) in subjects who received simeprevir + sofosbuvir for 12 weeks and 24 weeks, respectively.

This recommendation is contingent on the provision of confirmatory data in this patient population in the form of a PMR. As dosing recommendations in Section 2.2 of the label are now based on the outcome of NS5A screening for GT1a-infected patients, the language in Section 2.1 with respect to baseline screening for NS5A polymorphisms in GT1a-infected patients has changed (b) (4) to a recommendation in order to determine the regimen and duration (see below).

3. Final Agreed Labeling for Highlights, Section 2.1 Testing Prior to the Initiation of Therapy, and Section 12.4 Microbiology

The final agreed Microbiology section of the label (Highlights, 2.1 Testing Prior to the Initiation of Therapy, and 12.4 Microbiology) is pasted below. Note that additional Clinical Virology-related edits have been suggested and incorporated into other sections of the label as appropriate.

HIGHLIGHTS OF PRESCRIBING INFORMATION
DOSAGE AND ADMINISTRATION

- Testing prior to initiation:
  - Genotype 1a: Testing for the presence of virus with NS5A resistance-associated polymorphisms is recommended. (2.1)

Dosage Regimens and Durations for ZEPATIER in Patients with Genotype 1 or 4 HCV with or without Cirrhosis

Patient Population	Treatment	Duration
Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced* without baseline NS5A polymorphisms†	ZEPATIER	12 weeks
Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced* with baseline NS5A polymorphisms†	ZEPATIER + ribavirin	16 weeks
Genotype 1b: Treatment-naïve or PegIFN/RBV-experienced*	ZEPATIER	12 weeks
Genotype 1a or 1b: PegIFN/RBV/PI-experienced‡	ZEPATIER + ribavirin	12 weeks
Genotype 4: Treatment-naïve	ZEPATIER	12 weeks

Genotype 4: PegIFN/RBV-experienced*	ZEPATIER + ribavirin	16 weeks

*Peginterferon alfa + r bavirin.
†Polymorphisms at amino acid positions 28, 30, 31, or 93.
‡Peginterferon alfa + ribavirin + HCV NS3/4A protease inh bitor.

2.1 Testing Prior to the Initiation of Therapy

NS5A Resistance Testing in HCV Genotype 1a-Infected Patients

Testing patients with HCV genotype 1a infection for the presence of virus with NS5A resistance-associated polymorphisms is recommended prior to initiation of treatment with ZEPATIER to determine dosage regimen and duration [see Dosage and Administration (2.2)], Table 1. In subjects receiving ZEPATIER for 12 weeks, sustained virologic response (SVR12) rates were lower in genotype 1a-infected patients with one or more baseline NS5A resistance-associated polymorphisms at amino acid positions 28, 30, 31, or 93 [see Microbiology (12.4)], Table 11.

12.4 Microbiology

Mechanism of Action

ZEPATIER combines two direct-acting antiviral agents with distinct mechanisms of action and non-overlapping resistance profiles to target HCV at multiple steps in the viral lifecycle.

Elbasvir is an inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly. The mechanism of action of elbasvir has been characterized based on cell culture antiviral activity and drug resistance mapping studies.

Grazoprevir is an inhibitor of the HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. In a biochemical assay, grazoprevir inhibited the proteolytic activity of the recombinant HCV genotype 1a, 1b, and 4a NS3/4A protease enzymes with IC_{50} values of 7 pM, 4 pM, and 62 pM, respectively.

Antiviral Activity

In HCV replicon assays, the EC_{50} values of elbasvir against full-length replicons from genotypes 1a, 1b, and 4, were 4 pM, 3 pM, and 0.3 pM, respectively. The median EC_{50} values of elbasvir against chimeric replicons encoding NS5A sequences from clinical isolates were 5 pM for genotype 1a (range 3-9 pM; N=5), 9 pM for genotype 1b (range 5-10 pM; N=4), 0.2 pM for genotype 4a (range 0.2-0.2 pM; N=2), 3,600 pM for genotype 4b (range 17 pM-34,000 pM; N=3), 0.45 pM for genotype 4d (range 0.4-0.5 pM; N=2), 1.9 pM for genotype 4f (N=1), 36.3 pM for genotype 4g (range 0.6-72 pM; N=2), 0.6 pM for genotype 4m (range 0.4-0.7 pM; N=2), 2.2 pM for genotype 4o (N=1), and 0.5 pM for genotype 4q (N=1).

In HCV replicon assays, the EC_{50} values of grazoprevir against full-length replicons from genotypes 1a, 1b, and 4, were 0.4 nM, 0.5 nM, and 0.3 nM, respectively. The median EC_{50} values of grazoprevir against chimeric replicons encoding NS3/4A sequences from clinical isolates were 0.8 nM for genotype 1a (range 0.4-5.1 nM; N=10), 0.3 nM for genotype 1b (range 0.2-5.9 nM; N=9), 0.3 nM for genotype 4a (N=1), 0.16 nM for genotype 4b (range 0.11-0.2 nM; N=2), and 0.24 nM for genotype 4g (range 0.15-0.33 nM; N=2).

Combination Antiviral Activity

Evaluation of elbasvir in combination with grazoprevir or ribavirin showed no antagonistic effect in reducing HCV RNA levels in replicon cells. Evaluation of grazoprevir in combination with ribavirin showed no antagonistic effect in reducing HCV RNA levels in replicon cells.

Resistance

In Cell Culture

HCV replicons with reduced susceptibility to elbasvir and grazoprevir have been selected in cell culture for genotypes 1a, 1b, and 4 which resulted in the emergence of resistance-associated amino acid substitutions in NS5A or NS3, respectively. The majority of amino acid substitutions in NS5A or NS3 selected in cell culture or identified in Phase 2b and 3 clinical trials were phenotypically characterized in genotype 1a, 1b, or 4 replicons.

For elbasvir, in HCV genotype 1a replicons, single NS5A substitutions M28A/G/T, Q30D/E/H/K/R, L31M/V, H58D, and Y93C/H/N reduced elbasvir antiviral activity by 1.5- to 2,000-fold. In genotype 1b replicons, single NS5A substitutions L28M, L31F and Y93H reduced elbasvir antiviral activity by 2- to 17-fold. In genotype 4 replicons, single NS5A substitutions L30S, M31V, and Y93H reduced elbasvir antiviral activity by 3- to 23-fold. In general, in HCV genotype 1a, 1b, or 4 replicons, combinations of elbasvir resistance-associated substitutions further reduced elbasvir antiviral activity.

For grazoprevir, in HCV genotype 1a replicons, single NS3 substitutions Y56H, R155K, A156G/T/V, D168A/E/G/N/S/V/Y reduced grazoprevir antiviral activity by 2- to 81-fold; V36L/M, Q80K/R, or V107I single substitutions had no impact on grazoprevir antiviral activity in cell culture. In genotype 1b replicons, single NS3 substitutions F43S, Y56F, V107I, A156S/T/V, D168A/G/V reduced grazoprevir antiviral activity by 1.5- to 375-fold. In genotype 4 replicons, single NS3 substitutions D168A/V reduced grazoprevir antiviral activity by 110- to 320-fold. In general, in HCV genotype 1a, 1b, or 4 replicons, combinations of grazoprevir resistance-associated substitutions further reduced grazoprevir antiviral activity.

In Clinical Studies

In a pooled analysis of subjects treated with regimens containing ZEPATIER or elbasvir + grazoprevir with or without ribavirin in Phase 2 and 3 clinical trials, resistance analyses of both drug targets were conducted for 50 subjects who experienced virologic failure and had sequence data available (6 with on-treatment virologic failure, 44 with post-treatment relapse). Treatment-emergent substitutions observed in the viral populations of these subjects based on HCV genotypes and subtypes are shown in Table 10. Treatment-emergent NS5A substitutions were detected in 30/37 (81%) genotype 1a, 7/8 (88%) genotype 1b, and 5/5 (100%) genotype 4 infected subjects. The most common treatment-emergent NS5A substitutions in genotype 1a were at position Q30 (n=22). Treatment-emergent NS3 substitutions were detected in 29/37 (78%) genotype 1a, 2/8 (25%) genotype 1b, and 2/5 (40%) genotype 4 infected subjects. The most common treatment-emergent NS3 substitutions in genotype 1a were at position D168 (n=18). Treatment-emergent substitutions were detected in both HCV drug targets in 23/37 (62%) genotype 1a, 1/8 (13%) genotype 1b, and 2/5 (40%) genotype 4 infected subjects.

Table 10: Treatment-Emergent Amino Acid Substitutions among Virologic Failures in the Pooled Analysis of ZEPATIER with and without Ribavirin Regimens in Phase 2 and Phase 3 Clinical Trials

Target	Genotype 1a N = 37	Genotype 1b N = 8	Genotype 4 N = 5
NS5A	M28A/G/T, Q30H/K/R/Y, L31F/M/V, H58D, Y93H/N/S	L28M, L31F/V, Y93H	L28S/T, M31I/V, P58D, Y93H
NS3	V36L/M, Y56H, V107I, R155I/K, A156G/T/V, V158A, D168A/G/N/V/Y	Y56F, V107I, A156T	A156M/T/V, D168A/G, V170I

Persistence of Resistance-Associated Substitutions

The persistence of elbasvir and grazoprevir treatment-emergent amino acid substitutions in NS5A, and NS3, respectively, was assessed in HCV genotype 1-infected subjects in Phase 2 and 3 trials whose virus had treatment-emergent resistance-associated substitutions in the drug target, and with available data through at least 24 weeks post-treatment using population nucleotide sequence analysis.

Viral populations with treatment-emergent NS5A resistance-associated substitutions were generally more persistent than those with NS3 resistance-associated substitutions. Among genotype 1a-infected subjects, NS5A resistance-associated substitutions persisted at detectable levels at follow-up week 12 in 95% (35/37) of subjects and 100% (9/9) of subjects with follow-up week 24 data. Among genotype 1b-infected subjects, NS5A resistance-associated substitutions persisted at detectable levels in 100% (7/7) of subjects at follow-up week 12 and in 100% (3/3) of subjects with follow-up week 24 data.

Among genotype 1a-infected subjects, NS3 resistance-associated substitutions persisted at detectable levels at follow-up week 24 in 31% (4/13) of subjects. Among genotype 1b-infected subjects, NS3 resistance-associated substitutions persisted at detectable levels at follow-up week 24 in 50% (1/2) of subjects.

Due to the limited number of genotype 4-infected subjects with treatment-emergent NS5A and NS3 resistance-associated substitutions, trends in persistence of treatment-emergent substitutions in this genotype could not be established.

The lack of detection of a virus containing a resistance-associated substitution does not necessarily indicate that viral populations carrying that substitution have declined to a background level that may have existed prior to treatment. The long-term clinical impact of the emergence or persistence of virus containing ZEPATIER-resistance-associated substitutions is unknown.

Effect of Baseline HCV Amino Acid Polymorphisms on Treatment Response in Genotype 1-Infected Subjects

Analyses using population nucleotide sequencing were conducted to explore the association between NS5A or NS3 amino acid polymorphisms and treatment response among treatment-naïve and treatment-experienced genotype 1 infected subjects. Baseline NS5A polymorphisms at resistance-associated positions (focusing on any change from subtype reference at NS5A amino acid positions 28, 30, 31, or 93) were evaluated. Baseline NS3 polymorphisms at positions 36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, or 175 were evaluated. Analyses of SVR12 rates pooled data from subjects naïve to direct-acting antivirals and who received ZEPATIER with or without ribavirin in Phase 3 clinical trials, and censored subjects who did not achieve SVR12 for reasons unrelated to virologic failure.

Genotype 1a
In genotype 1a-infected subjects, the presence of one or more HCV NS5A amino acid polymorphisms at position M28, Q30, L31 or Y93 was associated with reduced efficacy of ZEPATIER for 12 weeks (Table 11), regardless of prior treatment history or cirrhosis status. The prevalence of polymorphisms at any of these positions in genotype 1a-infected subjects was 11% (62/561) overall, and 12% (37/309) specifically for subjects in the U.S. across Phase 2 and Phase 3 clinical trials evaluating ZEPATIER for 12 weeks or ZEPATIER plus ribavirin for 16 weeks. The prevalence of polymorphisms at these positions in genotype 1a-infected subjects was 6% (35/561) at position M28, 2% (11/561) at position Q30, 3% (15/561) at position L31, and 2% (10/561) at position Y93. Polymorphisms at NS5A position H58 were common (10%) and were not associated with reduced ZEPATIER efficacy, except for a single virologic failure subject whose virus had baseline M28V and H58D polymorphisms.

The SVR12 rates for subjects treated with ZEPATIER for 12 weeks were 88% (29/33) for subjects with M28V/T/L polymorphisms (n=29, 3 and 1, respectively), 40% (4/10) for subjects with Q30H/R/L polymorphisms (n=5, 3 and 2, respectively), 38% (5/13) for subjects with an L31M polymorphism, and 63% (5/8) for subjects with Y93C/H/N/S polymorphisms (n=3, 3, 1 and 1, respectively). Although data are limited, among genotype among 1a-infected subjects with these NS5A polymorphisms who received ZEPATIER plus ribavirin for 16 weeks, six out of six subjects achieved SVR12. The specific NS5A polymorphisms observed in subjects treated with ZEPATIER plus ribavirin for 16 weeks included M28V (n=2), Q30H (n=1), L31M (n=2), or Y93C/H (n=1 each).

Table 11: SVR12 in HCV Genotype 1a-Infected Subjects without or with baseline NS5A Polymorphisms

NS5A polymorphism status	ZEPATIER 12 Weeks SVR12 % (n/N)	ZEPATIER + RBV 16 Weeks SVR12 % (n/N)
Without baseline NS5A polymorphism (M28, Q30, L31 or Y93)	98% (441/450)	100% (49/49)
With baseline NS5A polymorphism (M28*, Q30*, L31* or Y93*)	70% (39/56)	100% (6/6)

*Any change from GT1a reference.

There are insufficient data to determine the impact of HCV NS5A amino acid polymorphisms in treatment-experienced subjects who failed prior PegIFN + RBV + HCV protease inhibitor therapy and received ZEPATIER with ribavirin.

In genotype 1a-infected subjects, the NS3 Q80K polymorphism did not impact treatment response. Polymorphisms at other NS3 resistance-associated positions were uncommon and were not associated with reduced treatment efficacy.

Genotype 1b
In genotype 1b-infected subjects treated with ZEPATIER for 12 weeks, SVR12 rates (non-virologic failure-censored) were 94% (48/51) and 99% (247/248) for those with and without one or more NS5A polymorphisms at position 28, 30, 31 or 93.

In genotype 1b-infected subjects, baseline NS3 polymorphisms did not impact treatment response.

Effect of Baseline HCV Polymorphisms on Treatment Response in Genotype 4-Infected Subjects
Phylogenetic analysis of HCV sequences from genotype 4-infected subjects (n=71) in the pooled analyses of subjects (non-virologic failure-censored) treated with regimens containing ZEPATIER or elbasvir + grazoprevir with or without ribavirin in Phase 2 and 3 clinical trials identified 4 HCV genotype

4 subtypes (4a, 4d, 4k, 4o). Most subjects were infected with either subtype 4a (42%) or 4d (51%); 1 to 2 subjects were infected with each of the other genotype 4 subtypes. Among subjects enrolled at U.S. study sites, 11/13 (85%) were infected with HCV subtype 4a. There were two subjects infected with HCV subtype 4d who experienced virologic failure with the regimen containing grazoprevir and elbasvir.

In genotype 4-infected subjects, SVR12 rates for subjects with baseline NS5A polymorphisms (any change from reference at NS5A amino acid positions 28, 30, 31, 58 and 93 by population nucleotide sequencing) were 100% (28/28) and for subjects without baseline NS5A polymorphisms were 95% (41/43).

In genotype 4-infected subjects, SVR12 rates for subjects with baseline NS3 polymorphisms (any change from reference at NS3 amino acid positions 36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, and 175 by population nucleotide sequencing) were 100% (18/18) and for subjects without baseline NS3 polymorphisms were 96% (51/53).

Cross Resistance

Cross resistance is possible among NS5A inhibitors and NS3/4A protease inhibitors by class. Elbasvir and grazoprevir are fully active against viral populations with substitutions conferring resistance to NS5B inhibitors.

In the C-SALVAGE trial, subjects with genotype 1 infection who had failed prior treatment with boceprevir (n=28), simeprevir (n=8), or telaprevir (n=43) in combination with PegIFN + RBV received EBR 50 mg once daily + GZR 100 mg once daily + RBV for 12 weeks. There are limited data to determine the impact of HCV NS3 resistance-associated substitutions detected at baseline in treatment-experienced subjects who failed prior PegIFN + RBV + HCV protease inhibitor therapy and received ZEPATIER with ribavirin. SVR was achieved in 88% (21/24) of genotype 1a and genotype 1b infected subjects with NS3 resistance-associated substitutions detected at baseline. Specific NS3 substitutions observed at baseline included one or more of the following: V36L/M (n=8), T54S (n=4), S122G/T (n=9), R155K/T (n=9), A156S/T (n=1), and D168E/N (n=3). SVR was 100% (55/55) in subjects without baseline NS3 resistance substitutions. The 3 virologic failure subjects had the following NS3 or NS5A substitutions/polymorphisms at baseline: NS3 R155T/D168N, NS3 R155K plus NS5A H58D, and NS3 T54S plus NS5A L31M.

The efficacy of ZEPATIER has not been established in patients who have previously failed treatment of other regimens that included an NS5A inhibitor.

4. Final Agreed PMRs/PMCs

The sponsor has agreed to the following virology-related PMRs:

A. **Conduct a trial or study in hepatitis C virus genotype 1a infected subjects with at least one baseline NS5A polymorphism at amino acid position 28, 30, 31, or 93 to evaluate if (b) (4) treatment with elbasvir/grazoprevir and (b) (4) ribavirin reduces the rate of virologic failure and the rate of treatment-emergent drug resistant viral populations. The trial or study should have adequate representation of subjects with baseline NS5A polymorphisms that have been demonstrated to have the greatest impact on elbasvir/grazoprevir efficacy in clinical trials evaluating recommended regimens.**

Final Protocol Submission: 07/2016
Trial Completion: 07/2018
Final Report Submission: 12/2018

B. Please conduct site-directed mutant phenotype analyses of elbasvir against HCV replicons carrying the following NS5A substitutions: K24R (GT1a), H54Y (GT4d), E62D (GT1a), D427N (GT1a). Please include cross-resistance analyses with approved NS5A inhibitors.
Final Protocol Submission: 03/2016
Trial Completion: 12/2016
Final Report Submission: 01/2017

C. Please conduct site-directed mutant phenotype analyses of grazoprevir against HCV replicons carrying the following NS3 substitutions: I48A/V (GT1a), T185S (GT1a/GT1b), E357G/K (GT1a). Please include cross-resistance analyses with approved NS3/4A inhibitors.
Final Protocol Submission: 03/2016
Trial Completion: 12/2016
Final Report Submission: 01/2017

Additionally, the sponsor has agreed to the following PMC's:

D. Please submit the final report and datasets, including the SVR24 data, for Phase 2 Trial 048 (C-SALVAGE).
Final Protocol Submission: Completed
Trial Completion: May 2015
Final Report Submission: February 29, 2016

E. Please submit the final report and datasets, including the SVR24 data, for Phase 3 Trial 068 (C-EDGE TE).
Final Protocol Submission: Completed
Trial Completion: June 2015
Final Report Submission: February 29, 2016

F. Please submit the final report and datasets, including the SVR24 data, for Phase 3 Trial 061 (C-EDGE CO-INFECTION).
Final Protocol Submission: Completed
Trial Completion: May 2015
Final Report Submission: February 29, 2016

5. Administrative

5.1. Reviewers' Signatures

_____
Takashi E. Komatsu, Ph.D., RAC
Clinical Virology Reviewer

_____
Patrick R. Harrington, Ph.D.
Clinical Virology Reviewer

Reference ID: 3876278

5.2. Concurrence

_____
HFD-530/Clin.Virol.TL/J. O'Rear, Ph.D.

CC:
HFD-530/NDA # 208261
HFD-530/Division File
HFD-530/PM/Mani

Appendix 1: Slides used in Late Cycle Meeting

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Methodologies Used by Merck in the NS5A Polymorphism Analyses

(Table 2 from "MERCK RESPONSE TO FDA COMMENTS ON BASELINE NS5A RAV TESTING IN GT1 PATIENTS")

We have identified some concerns with the methodologies that were used:

Parameter	EBR/GZR NDA Submission	EBR/GZR New Analysis	LDV/SOF FDA Virology Report [3], USPI
Studies Included	Phase 2/3 Studies	Phase 2/3 Studies	Phase 2/3 Studies
Regimens Included	12, 16, 18 weeks, +RBV	12, 16, 18 weeks, +RBV	8, 12, 24 weeks
Patients Included	N, TE, treatment, +HIV, +CKD	TN, TE treatment, +HIV, +CKD	TN, TE treatment
Handling of non-virologic failures	RAV analyses considered only virologic failures	RAV analyses considered only relapse rates (matching the FDA review of LDV/SOF)	In the FDA review of RAVs, only relapses are considered [3]
Assay Methodology	100 % population sequencing	For GT1a: 99.4% had population sequencing, 89.0% had NGS at 1% ST; For GT1b: 99.3% had population sequencing, 72.1% had NGS at 1% ST	For TN: 100% NGS; For TN 12 Wk data: 11% NGS, 89 NGS at 15 ST; For TE patients with and without cirrhosis
RAVs evaluated	RAVs that result in > 5-fold decrease in EBR potency in vitro replicon assays	Any RAV at any of the NS5A positions (24, 28, 30, 31, 32, 58, 58, 92 and 93) associated with resistance to any NS5A as listed in the LED/SOF NDA virology review	Any RAV at any of the NS5A positions (24, 28, 30, 31, 32, 58, 58, 92 and 93) associated with resistance to any NS5A as listed in the LED/SOF NDA virology review

Focus should be on recommended regimens

Not a fair comparison:
- All failures w/recommended LDV/SOF regimens were relapsers
- On-treatment virologic failures with EBR/GZR should have been included

Apples vs Oranges:
- LDV/SOF Baseline analyses based on population or consensus NGS sequences
- Inclusion of minority variants detected by NGS dilutes impact with EBR/GZR

1

Tx-Experienced Subjects

(Table 5 from "MERCK RESPONSE TO FDA COMMENTS ON BASELINE NS5A RAV TESTING IN GT1 PATIENTS")

Much of Merck's argument hinges on this table, but this is not a fair comparison

LDV/SOF data are based on consensus or population sequences, while the EBR/GZR data include minority variants, which dilutes the impact

Pooling GT1a/GT1b dilutes impact in GT1a for EBR/GZR

All 4 VF subjects (3 GT1a, 1 GT1b) had 2 key NS5A PMs (positions 28, 30, 31, or 93)

There is not a comparable group of subjects who received EBV/GZR for 12 weeks.

Not a recommended regimen

Table 5
Comparison EBR/GZR and LED/SOF:
Rates of Relapse among GT1-infected Treatment-Experienced Subjects

Treatment Group	Relapse Rate: All Patients	Non-cirrhotic With RAVs	Cirrhotics With RAVs
LED/SOF 12 Weeks	6.4% (7/109)	21.1% (4/19)	2/9 (22.2%)
EBR/GZR (no RBV) 12 Weeks	6.2% (9/146)	14.3% (5/35)	18.2% (2/11)
LED/SOF 24 Weeks	0% (0/109)	0% (0/19)	0% (0/3)
EBR/GZR (with RBV) 16/18 Weeks	0% (0/123)	0% (0/33)	0% (0/14)

NDA 208334 (ledipasvir/sofosbuvir) Division of Antiviral Products Microbiology/Virology Review. Lin 45.
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205834Orig1s000MicroR.pdf [3]
Group C RAVs (See Appendix 2): defined as any change from reference at NS5A amino acid positions 2 3
NGS at 1% ST or 20pop/seq when NGS not available
TE patients with and without cirrhosis

All 5 VF subjects (3 GT1a, 2 GT1b) had only 1 key NS5A PM (positions 30 [n=1] and 31 [n=4])

We agree that longer duration +RBV may reduce impact. However, there are insufficient data currently available to define a treatment regimen in this setting.

2

Virologic failure rate in Dr. L.Naeger's review of Harvoni

NS5A Polymorphisms		Any	1	2	3
LED/SOF 12 weeks		5.6% (8/144)	1.7% (2/115)	22% (6/27)	0% (0/2)

- Single NS5A polymorphisms (considering positions 24, 28, 30, 31, 32, 58, 92, 93) do not have a significant impact on LDV/SOF 12-week efficacy
- Pooled GT1a/GT1b

3

SVR Rates in TN/TE Subjects (NS5A) (GZR/EBR 12W)

TN (GT1a/1b)

TE (GT1a)

A = Has M/L28A/T, Q/R30H/K/R, L31F/M/V, H58D, Y93C/H/N at Baseline
B = Has M/L28A/T/V, Q/R30H/K/L/R, L31F/M/V, H58D, Y93C/H/N/S at Baseline

4

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TAKASHI E KOMATSU
01/21/2016

PATRICK R HARRINGTON
01/21/2016

JULIAN J O REAR
01/21/2016

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 208261 **SDN:** 000 **DATE REVIEWED:** 10/21/15

Clinical Virology Reviewers: Takashi E. Komatsu, Ph.D., RAC & Patrick R. Harrington, Ph.D.

NDA #: 208261 **Supporting Document Numbers:** 000

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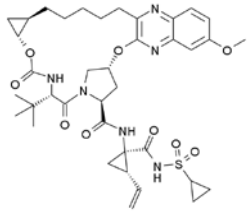
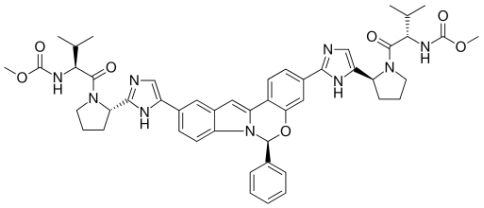
Reviewers: Takashi E. Komatsu, Ph.D., RAC
Patrick R. Harrington, Ph.D.

Initial Submission Dates:

Correspondence Date: May 28, 2015
CDER Receipt Date: May 28, 2015
Reviewer Receipt Date: May 28, 2015
Review Complete Date: October 21, 2015
PDUFA Date: January 28, 2016

Proprietary Name	**Zepatier®** **(combination product: grazoprevir and elbasvir)**	
Product Names [class]	grazoprevir, MK-5172 [NS3/4A protease inhibitor]	elbasvir, MK-8742 [NS5A inhibitor]
Individual IND #s	110261	114298
Chemical Name	(1ar,5s,8s,10r,22ar)-5-tert-butyl-n-((1r,2s)-1-{[-cyclopropylsulfonyl)amino] carbonyl}-2-vinylcyclopropyl)-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22, 22a-tetradecahydro-8h-7,10-methanocyclopropa [18,19][1,10,3,6]dioxadiazacyclononadecino[11, 12-b]quinoxaline-8-carboxamide	Dimethyl N,N′-([(6S)-6-phenylindolo[1,2-c][1,3]benzoxazine-3,10-diyl]bis{1H-imidazole-5,2-diyl-(2S)-pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})dicarbamate
Structure	 **MK-5172**	 **MK-8742**
Molecular Formula	$C_{38}H_{50}N_6O_9S$	$C_{49}H_{55}N_9O_7$
Molecular Weight	766.90	882.02

Reference ID: 3839313

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 208261 **SDN:** 000 **DATE REVIEWED:** 10/21/15

Clinical Virology Reviewers: Takashi E. Komatsu, Ph.D., RAC & Patrick R. Harrington, Ph.D.

Amendments:

Response to Information Request (SDN 007): June 25, 2015
Response to Information Request (SDN 012): July 6, 2015
Response to Information Request (SDN 014): July 7, 2015
Resubmission of revised nonclinical study reports (SDN 015): July 7, 2015
Request for proprietary name review (SDN 018): July 17, 2015
Resubmission of revised clinical study report 068 (SDN 027): August 25, 2015
Response to Information Request (SDN 029): September 1, 2015
Revised label (SDN 031): September 4, 2015
Response to labeling recommendations (SDN 035): October 20, 2015
Response to Information Request (SDN 037): October 21, 2015
Submission of Next Generation Sequencing Results (SDN 041): October 28, 2015

Related/Supporting Documents: IND 110261, IND 114298, DMF (b) (4) DMF (b) (4)
Indication(s): Treatment of chronic hepatitis C (CHC) genotypes 1, 4, or 6 infection in adults
Dosage Form(s): Fixed-dose combination product containing 100 mg of grazoprevir and 50 mg of elbasvir in a single tablet
Route(s) of Administration: Oral/tablet
Recommended Dosage: One tablet taken orally once daily with or without food
Dispensed: Rx _X_ **OTC** ___ **(Discipline relevant)**

Abbreviations: AE, adverse event; ARV, antiretroviral; BID, dose twice daily; BOC, boceprevir; CAT A; cathepsin A; CC, cytotoxic concentration; CES, carboxylesterase; CKD, chronic kidney disease; CLDN1, claudin-1; DAA, direct-acting antiviral; DMSO, dimethyl sulfoxide; DTG, delayed treatment group; EC, effective concentration; eGFR, estimated Glomerular Filtration Rate; ER, endoplasmic reticulum; FDC, fixed-dose combination; GT, genotype; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IC, inhibitory concentration; IFN, interferon; IRES, internal ribosomal entry site; ITG, immediate treatment group; ITT, intent-to-treat; LDL, low-density lipoproteins; LDV, ledipasvir; LiPA, line-probe assay; LLOQ, lower limit of quantification; LOD, limit of detection; mITT, modified intent-to-treat; NRTI, nucleos(t)ide reverse transcriptase inhibitor; NTR, non-translated region; OCLN, occludin; ORF, open reading frame; P/R, pegylated interferon alfa and ribavirin; PI, protease inhibitor; QD, dose once daily; RAV, resistance-associated variant; RBV, ribavirin; RT-PCR, reverse transcriptase-polymerase chain reaction; SEAP, secreted alkaline phosphatase; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response; TD, target detected; TN, treatment-naïve; TND, target not detected; TVR, telaprevir; TW, treatment week; VF, virologic failure; VLDL, very-low density lipoproteins;

Reference ID: 3839313

DIVISION OF ANTIVIRAL PRODUCTS (HFD-530)

VIROLOGY REVIEW

NDA: 208261 **SDN:** 000 **DATE REVIEWED:** 10/21/15

Clinical Virology Reviewers: Takashi E. Komatsu, Ph.D., RAC & Patrick R. Harrington, Ph.D.

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EXECUTIVE SUMMARY

1. Recommendations

1.1. Recommendation and Conclusion on Approvability:

This Original NDA is approvable from a Clinical Virology perspective for the treatment of chronic HCV genotype 1 or genotype 4 infected patients who are either naïve to prior anti-HCV therapy or who have failed prior therapy with Peg-IFNα/RBV, including patients with compensated cirrhosis. This Original NDA is also approvable for the treatment of chronic HCV genotype 1 infected patients who have failed prior therapy with Peg-IFNα/RBV plus boceprevir, simeprevir, or telaprevir, including patients with compensated cirrhosis.

However, both treatment-naïve and PR-treatment experienced subjects who were infected with HCV genotype 1a virus with one or more polymorphisms at amino acid positions associated with resistance to NS5A inhibitors were significantly less likely to benefit from a 12 week course of MK-5172/MK-8742 than subjects infected with HCV genotype 1a virus without key NS5A polymorphisms. A similar pattern with respect to impact of NS5A polymorphisms was noted for P/R-treatment experienced subjects infected with HCV genotype 1b virus. However, the impact of NS5A polymorphisms in P/R treatment experienced genotype 1b subjects was modest compared to what was observed in genotype 1a subjects. There are clinically significant consequences of virologic failure for subjects with NS5A polymorphisms in genotype 1a. Amongst subjects with genotype 1a virus with NS5A polymorphisms who failed treatment, 96% of subjects gained an NS3/4A resistance substitution or additional NS5A substitution(s), approximately 75% of subjects gained an additional NS5A resistance substitution(s), and approximately 60% of subjects gained an additional NS3/4A AND NS5A resistance substitution(s). The impact of NS5A polymorphisms was modest albeit the trend was still present for the PR-treatment experienced genotype 1b infected subjects. Treatment failure will therefore substantially impact retreatment options for these subjects. We therefore recommend screening all genotype 1a subjects and all P/R treatment experienced genotype 1b subjects for NS5A polymorphisms prior to initiation of MK-5172/MK-8742 using a commercially available assay. SVR rates were 98-100% when subjects with baseline NS5A polymorphisms were excluded from the analysis.

1.2. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, If Approvable:

This reviewer recommends the following post-marketing commitments or requirements, as appropriate:

1. Please conduct site-directed mutant phenotype analyses of MK-5172 against HCV replicons carrying the following NS3 substitutions: I48A/V (GT1a), T185S (GT1a/GT1b), E357G/K (GT1a). Please include cross-resistance analyses with approved NS3/4A inhibitors.
2. Please conduct site-directed mutant phenotype analyses of MK-8742 against HCV replicons carrying the following NS5A substitutions: K24R (GT1a), H54Y (GT4d), E62D (GT1a), D427N (GT1a). Please include cross-resistance analyses with approved NS5A inhibitors.

2. Summary of OND Virology Assessments

2.1. Nonclinical Virology

<u>MK-5172</u>

MK-5172 (grazoprevir) is an inhibitor of the HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. In a biochemical assay, MK-5172 inhibited the proteolytic activity of the recombinant HCV genotype 1a, 1b, and 4 NS3/4A protease enzymes with IC_{50} values of 7 pM, 4 pM, and 62 pM, respectively. In HCV replicon assays, the EC_{50} values of MK-5172 against full-length replicons from genotypes 1a, 1b, and 4, were 400 pM, 500 pM, and 300 pM, respectively. The median EC_{50} values of MK-5172 against chimeric replicons encoding NS3/4A sequences from clinical isolates were 800 pM for genotype 1a (range 400-5,100 pM; N=10), 450 pM for genotype 1b (range 200-5,900 pM; N=10), 300 pM for genotype 4a (N=1), 155 pM for genotype 4b (range 110-200 pM; N=2), 1,100 pM for genotype 4d (N=1), 240 pM for genotype 4g (range 150-330 pM; N=2), and 1,200 pM for genotype 40 (N=1). The median EC_{50} values of MK-5172 against replicons from genotypes 2, 3, 5, and 6 were 2,300 pM, 35,000 pM, 1,500 pM, and 900 pM. Combination of MK-5172 with MK-8742 (elbasvir) or ribavirin showed no antagonistic effect in replicon cells. Combination of MK-5172 with ribavirin showed no antagonistic effect in replicon cells.

Selection of HCV genotype 1a replicons with MK-5172 resulted in single NS3 substitutions D168A/E/G/S/V which reduced cell culture antiviral activity by 2- to 81-fold. Selection of HCV genotype 1b replicons resulted in single NS3 substitutions F43S, A156S/T/V, and D168A/G/V which reduced cell culture antiviral activity by 3- to 375-fold. Selection of HCV genotype 4 replicons resulted in single NS3 substitutions D168A/V which reduced cell culture antiviral activity by 110- to 320-fold.

<u>MK-8742</u>
MK-8742 (elbasvir) is an inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly. The mechanism of action of elbasvir has been characterized based on cell culture antiviral activity and drug resistance mapping studies. In HCV replicon assays, the EC_{50} values of MK-8742 against full-length replicons from genotypes 1a, 1b, and 4, were 4 pM, 3 pM, and 0.3 pM, respectively. The median EC_{50} values of MK-8742 against chimeric replicons encoding NS5A sequences from clinical isolates were 5 pM for genotype 1a (range 3-9 pM; N=5), 9 pM for genotype 1b (range 5-10 pM; N=5), 0.2 pM for genotype 4a (range 0.2-0.2 pM; N=2), 3,600 pM for genotype 4b (range 17 pM-34,000 pM; N=3), 0.45 pM for genotype 4d (range 0.4-0.5 pM; N=2), 1.9 pM for genotype 4f (N=1), 36.3 pM for genotype 4g (range 0.6-72 pM; N=2), 0.6 pM for genotype 4m (range 0.4-0.7 pM; N=2), 2.2 pM for genotype 4o (N=1), and 0.5 pM for genotype 4q (N=1). The median EC_{50} values of MK-8742 against replicons from genotypes 2a, 3a, 5 and 6 were 3 pM, 140 pM, 1 pM and 9 pM.

Selection of HCV genotype 1a replicons with MK-8742 resulted in single NS5A substitutions Q30D/E/H/R, L31M/V and Y93C/H/N which reduced cell culture antiviral activity by 6- to 2,000-fold. Selection of HCV genotype 1b replicons resulted in single NS5A substitutions L31F and Y93H which reduced cell culture antiviral activity by 17- to 67-fold. Selection of HCV genotype 4 replicons resulted in single NS5A substitutions L30S, M31V, and Y93H which reduced cell culture antiviral activity by 3- to 23-fold.

2.2. Clinical Virology

The clinical development to support the efficacy of MK-5172 + MK-8742 ± RBV includes 5 Phase 2 or 2/3 clinical trials, and 3 pivotal Phase 3 registration studies that enrolled a total of 1,969 subjects (note that subjects in the deferred treatment arms of Studies 052 and 060 are not included in this total as the current application contains only the safety findings in placebo-phase of these studies; subjects in these arms are undergoing active therapy currently). These studies enrolled a diverse population of subjects, including treatment-naïve and treatment-experienced, HCV mono- and HCV/HIV co-infected, and non-

cirrhotic and cirrhotic subjects. The sponsor also included a clinical study enrolling subjects with advanced chronic kidney disease (CKD), a population for which there is an unmet medical need for safe and effective anti-HCV therapy. Prior DAA experience was exclusionary for all of these studies except Study 048.

GT1:
Clinical Virology Review of Efficacy
Study 052 (Phase 3) was a randomized, parallel-group, multi-site, placebo controlled trial of MK-5172 + MK-8742, administered for 12 weeks without ribavirin, among HCV GT1-infected subjects with advanced chronic kidney disease (CKD). The overall ITT SVR12 rates were 61/63 (97%) and 54/60 (90%) for subjects infected with HCV GT1a and GT1b, respectively. The overall mITT SVR12 rates were 61/61 (100%) and 54/55 (98%) for subjects infected with HCV GT1a and GT1b, respectively. There was one subject (infected with HCV GT1b) who experienced relapse in this study by the SVR12 analysis timepoint.

Study 060 (Phase 3) was a randomized, parallel-group, double-blinded, placebo-controlled, multisite study that evaluated the efficacy and safety of MK-5172/MK-8742 (100mg/50mg FDC) among treatment-naïve GT 1-, 4-, or 6-infected, HCV-mono-infected subjects with or without cirrhosis. The overall ITT SVR12 rates were 144/157 (92%) and 129/131 (98%) for subjects infected with HCV GT1a and GT1b, respectively. There were more subjects who experienced virologic failure among those infected with GT1a compared to GT1b (10/157 [6%] vs. 1/131 [1%]).

Study 061 (Phase 3) was an open-label, multicenter study that evaluated the safety, tolerability, and efficacy of MK-5172/MK-8742 100mg/50mg FDC among treatment-naïve, HIV co-infected, HCV GT 1, 4 and 6 -infected subjects with or without cirrhosis. The overall ITT SVR12 rates were 136/144 (94%) and 42/44 (95%) for subjects infected with HCV GT1a and GT1b, respectively. All of the virologic failures were relapsers.

Among treatment-naïve, HCV GT1 infected subjects across all Phase 2/3 studies, the overall ITT SVR12 rates in MK-5172 100 mg + MK-8742 50 mg for 12 weeks treatment arms were 136/144 (94%) and 42/44 (95%) for subjects infected with HCV GT1a and GT1b, respectively. All of the virologic failures were relapsers. There was a trend towards more subjects who failed treatment having baseline HCV RNA >800,000 IU/mL. There were no clear differences between IL28B CC vs. IL28B non-CC subjects or between cirrhotic and non-cirrhotic subjects. These data support MK-5172+MK-8742 for 12 weeks in all treatment-naïve subjects with HCV GT1b regardless of cirrhosis, baseline viral load, or HIV-1 co-infection. The SVR12 rate in HCV GT1a is numerically lower relative to what was observed for Harvoni (label) or Viekira Pak (label) as recommended in prescribing information.

Study 068 (Phase 3) was a randomized, parallel-group, multi-site, open label trial of MK-5172/MK-8742 100 mg/50 mg fixed-dose combination (FDC) tablets administered once daily with or without RBV for 12 or 16 weeks among subjects with HCV GT 1, 4, or 6 infection who experienced virologic failure after prior treatment with pegylated recombinant human interferon α and ribavirin (P/R). The overall ITT SVR12 rates were 55/61 (92%) and 34/34 (100%) for subjects infected with HCV GT1a and GT1b, respectively in the MK-5172 100 mg + MK-8742 50 mg for 12 weeks arms. The overall ITT SVR12 rates were 56/60 (93%) and 28/29 (97%) for subjects infected with HCV GT1a and GT1b, respectively, for the 12 week MK-5172 100 mg + MK-8742 50 mg + RBV arms. The overall ITT SVR12 rates were 45/48 (94%) and 46/48 (96%) for subjects infected with HCV GT1a and GT1b, respectively, for the 16 week MK-5172 100 mg + MK-8742 50 mg arms. The overall ITT SVR12 rates were 55/58 (95%) and

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36/36 (100%) for subjects infected with HCV GT1a and GT1b, respectively, for the 16 week MK-5172 100 mg + MK-8742 50 mg + RBV arms. In P/R treatment-experienced subjects, MK-5172+MK-8742+RBV for 16 weeks minimizes relapse in GT1a P/R treatment-experienced subjects. There was no obvious benefit of adding RBV or extending treatment for GT1b in this study. These data support MK-5172+MK-8742 for 12 weeks in P/R-experienced subjects infected with HCV GT1b regardless of cirrhosis, baseline viral load, or HIV-1 co-infection. These data support MK-5172+MK-8742+RBV for 16 weeks in P/R-experienced subjects infected with HCV GT1a as the addition of RBV and longer treatment duration will minimize relapse.

Study 048 (Phase 2) was an open-label, single arm study of MK-5172 + MK-8742 + RBV in subjects with HCV genotype (GT) 1 infection who failed a prior approved NS3/4A protease inhibitor-containing regimen of boceprevir, simeprevir, or telaprevir taken concomitantly with peg-interferon α and RBV (P/R). The overall ITT SVR12 rates were 28/30 (93%) and 48/49 (98%) for subjects infected with HCV GT1a and GT1b, respectively. All of the virologic failures were relapsers. Numerically lower SVR12 rates were observed in subjects with PI resistance-associated substitutions at baseline. While the numbers are small, the overall SVR12 rates in these subjects are still reasonable (GT1a:12/14, 86%; GT1b: 8/9, 89%). For subjects infected with HCV GT1a, SVR12 was achieved in 4/4 (100%), 7/8 (88%), and 2/2 (100%) subjects with NS3 V36A/M, R155K, or V36M+R155K substitutions at baseline, respectively. These substitutions were the most common treatment-emergent substitutions for boceprevir, simeprevir, and telaprevir failures. These data support an indication for this GT1a population. For subjects infected with HCV GT1b, SVR12 was achieved in 2/2 (100%), 1/2 (50%), and 2/2 (100%) subjects with an NS3 V36A, T54A/S, or D168E/N substitution at baseline, respectively. There were no subjects with NS3 V55A, A156S/T, or I/V170A substitutions. The sponsor did not enroll enough subjects with key resistance-associated substitutions at baseline for GT1b to understand fully the impact of prior PI-based treatment failure on MK-5172 + MK-8742 + RBV efficacy. However, of the 49 GT1b subjects, 22 subjects were PI+P/R relapsers and an additional 12 subjects were breakthrough during the P/R tail. Of these 34 subjects, 33 subjects achieved SVR12 with MK-5172+MK-8742+RBV for 12 weeks treatment. Additionally, substitutions at position D168 generally do not persist as long as the R155K substitution, which may partially explain the difference in the number of subjects enrolled. Given these results, this reviewer also supports an indication for GT1b although the label should clearly describe all of the NS3 resistance-associated substitutions that were present at baseline.

<u>Drug Resistance</u>
For each HCV DAA/target, an analysis of treatment-emergent amino acid substitutions was conducted pooling data from treatment failure subjects who received MK-5172/MK-8742 +/- RBV regimen in Phase 2 and Phase 3 studies. Treatment-emergent substitutions included (most common substitutions in bold):

NS3/4A:
- GT1a subjects (n=70): NS3 V36L/M, I48V, Y56H, Q80K, V107I, R155K, **A156G/T/V**, **D168x** (including A, E, N, V, Y, with A most common), T185S, E357G/K
- GT1b subjects (n=15): NS3 **Y56F**, **V107I**, **A156T**, T185S

NS5A:
- GT1a subjects (n=70): NS5A K24R, **M28A/G/T/V**, **Q30H/K/R/Y**, L31F/M/V, H58D, E62D, Y93C/H/N/S, D427N
- GT1b subjects (n=15): NS5A L28M, L31F/V, **Y93H**

Overall, excluding the 4-, 6-, and 8-week treatment duration arms in studies 052 and 074, NS3/4A and NS5A resistance-associated substitutions emerged in viral populations from 29 (78%) and 30 (81%) GT1a virologic failure subjects, respectively, and in 2 (25%) and 7 (88%) GT1b virologic failure subjects, respectively.

The persistence of elbasvir and grazoprevir treatment-emergent amino acid substitutions in NS5A, and NS3, respectively, was assessed in HCV genotype 1-infected subjects in Phase 2 and 3 trials whose virus had treatment-emergent resistance-associated substitutions in the drug target, and with available data through at least 24 weeks post-treatment using population nucleotide sequence analysis.

- Viral populations with treatment-emergent NS5A resistance-associated substitutions were generally more persistent than those with NS3 resistance-associated substitutions. Among genotype 1a-infected subjects, NS5A resistance-associated substitutions persisted at detectable levels at follow-up Week 12 in 95% (35/37) of subjects and 100% (9/9) of subjects with follow-up Week 24 data. Among genotype 1b-infected subjects, NS5A resistance-associated substitutions persisted at detectable levels in 100% (7/7) of subjects at follow-up week 12 and in 100% (3/3) of subjects with follow-up Week 24 data.
- Among genotype 1a-infected subjects, NS3 resistance-associated substitutions persisted at detectable levels at follow-up Week 24 in 31% (4/13) of subjects. Among genotype 1b-infected subjects, NS3 resistance-associated substitutions persisted at detectable levels at follow-up week 24 in 50% (1/2) of subjects.

Collectively, these data indicate that NS5A resistance-associated substitutions persist long-term in nearly all subjects who experience virologic failure, and are likely to impact subsequent treatment with an NS5A inhibitor based regimen. The NS3/4A resistance-associated substitutions persist in a significant number of failures and may impact subsequent treatment with a PI-based regimen.

The impact of polymorphisms was evaluated using censored virologic failures. The analyses do not include non-virologic failures as well as subjects who did not have evaluable genotypic data.

In treatment-naïve subjects with GT1a, the SVR12 rates were substantially lower in subjects with NS5A resistance-associated polymorphisms (61% vs 97% or 73% vs 99%, depending on the polymorphisms analyzed). In GT1b, the impact of NS5A polymorphisms was minimal. In P/R treatment-experienced subjects with GT1a, the SVR12 rates were substantially lower in subjects with NS5A resistance-associated polymorphisms, similar to treatment-naïve subjects. If you exclude subjects with the polymorphisms, the SVR12 rate is 98%, even in the 12 week MK-5172+MK-8742 arm (and similar across all 4 arms). Addition of RBV and longer treatment duration (16 weeks) may be able to overcome impact of NS5A polymorphisms in GT1a, although this observation is based on a small number of subjects. In GT1b, the impact of NS5A polymorphisms was minimal albeit the trend was still present.

Collectively, in GT1a, NS5A resistance-associated polymorphisms had a substantial impact on efficacy for both treatment-naive and P/R treatment-experienced subjects. Prevalence of these substitutions was 8-12% in the US. Subjects with NS5A polymorphisms who fail treatment are likely to gain additional NS5A resistance substitutions and NS3/4A PI resistance substitutions. There was a modest impact in GT1b in TE subjects. NS5A polymorphisms are likely the biggest factor impacting efficacy in GT1a. Subjects with these polymorphisms should consider other therapies.

The impact of NS3 Q80K or other NS3 resistant-associated polymorphism is minimal in both treatment-naïve and P/R treatment-experienced subjects.

GT4

HCV GT4 is uncommon in the U.S. but is prevalent in other parts of the world. HCV GT4 is particularly prevalent in the Middle East and certain regions of Africa (Gower et al., 2014; Messina et al., 2015). In the U.S./North America, it is estimated that 1-6% of HCV infected subjects are infected with HCV GT4. However, HCV genotype 4 is extremely genetically diverse, with at least 18 subtypes described (Kamal and Nasser, 2008).

The overall ITT SVR12 rates in treatment-naïve subjects infected with HCV GT4 were 22/23 (96%), 28/29 (97%), 2/2 (100%), and 2/2 (100%) for subjects infected with HCV GT4a, GT4d, GT4k, and GT4-unknown, respectively. The SVR12 rates in P/R treatment-experienced subjects (study 068) based on the treatment arms were 77% (7/9), 93% (14/15), 60% (3/5), and 100% (8/8) for 12 weeks of MK-5172 + MK-8742, 12 weeks of MK-5172 + MK-8742 + RBV, 16 weeks of MK-5172 + MK-8742, and 16 weeks of MK-5172 + MK-8742 + RBV, respectively. The numbers are too small to make any conclusions regarding the relative efficacy of these different regimens, particularly for specific HCV GT4 subtypes. MK-5172 + MK-8742 + RBV for 16 weeks, is a conservative approach to maximize efficacy.

Based on paired Baseline/Post-Baseline analyses, the following NS3/4A substitutions emerged in the viruses from non-SVR subjects who received MK-5172/MK-8742 +/- RBV regimen:

NS3/4A:

- GT4a subjects (n=2): NS3 A156M/T/V, D168A/G, V170I

NS5A:

- GT4a subjects (n=2): NS5A L28T, P58D (note: these subjects had L28 and P58 polymorphisms, i.e., these substitutions were switches from L28M and P58Y, respectively).
- GT4d subjects (n=3): NS5A L28S, M31I/V, H54Y, Y93H

In summary, all 5 virologic failures had treatment-emergent resistance-associated substitutions in NS3/4A and/or NS5A.

Due to the limited number of genotype 4-infected subjects with treatment-emergent NS5A and NS3 resistance-associated substitutions, trends in persistence of treatment-emergent substitutions in these genotypes could not be established.

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3. Administrative

3.1. Reviewer's Signatures

_____
Takashi E. Komatsu, Ph.D., RAC
Clinical Virology Reviewer

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Patrick R. Harrington, Ph.D.
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3.2. Concurrence

_____
HFD-530/Clin.Virol.TL/J. O'Rear, Ph.D.

CC:
HFD-530/NDA # 208261
HFD-530/Division File
HFD-530/PM/Mani

OND VIROLOGY REVIEW

1. Introduction and Background

1.1. Important milestones in product development

MK-5172 (grazoprevir) is an HCV NS3/4A protease inhibitor. The Original IND 110261 for grazoprevir was submitted on November 22, 2010. The IND was placed on partial clinical hold on March 1, 2012 due to dose-related increases in transaminase levels observed in some subjects receiving MK-5172. The partial clinical hold was removed on August 24, 2012 provided that a daily MK-5172 dose of 100 mg was not exceeded.

MK-8742 (elbasvir) is an HCV NS5A inhibitor. The Original IND 114298 for elbasvir was submitted on April 21, 2012.

The combination of MK-5172 + MK-8742 was granted FDA Breakthrough Therapy Designation on October 18, 2013 for the treatment of HCV infection. The Breakthrough Therapy Designation was amended on February 28, 2014 to add the specific HCV genotype (HCV GT1) for which Breakthrough Therapy Designation was granted. On April 14, 2015, this Breakthrough Therapy Designation was rescinded due to the availability of new drugs, HARVONI® (NDA 205834, approved on October 10, 2014) and VIEKIRA PAK® (NDA 206619, approved on December 19, 2014). On April 1, 2015, the combination of MK-5172 + MK-8742 was granted FDA Breakthrough Therapy Designation for the treatment of HCV GT4 infection and for treatment of patients with HCV GT1 infection in patients with end stage renal disease on hemodialysis.

A pre-NDA teleconference to discuss the current application was held with the sponsor on February 20, 2015.

1.2. Overview of HCV

Hepatitis C virus (HCV) constitutes a significant health burden worldwide. Chronic hepatitis C virus infection is estimated in 130–170 million people (from CDC). Estimates of the infected population in the US range from 3-5 million people. In the long-term, the infection can lead to advanced liver fibrosis, cirrhosis and hepatocellular carcinoma. As a consequence, HCV is the most common indication for liver transplantation in developed countries (Thomas, 2013). For more than two decades, interferon has been the basis for HCV treatment. Responses to treatment were improved in 1998 by the addition of ribavirin and then in 2001–2002 by linking the interferon molecule to polyethylene glycol (Manns et al., 2001; McHutchison et al., 1998; Fried et al., 2002). Recently, there have been major advances in hepatitis C treatments with the licensing of the first direct-acting antivirals (DAAs) and large numbers of ongoing trials with various DAAs showing high efficacy, favorable tolerability profile, higher barrier to resistance, shortened treatment duration, and all oral regimen (Pawlotsky et al., 2014).

Discovered in 1989 (Choo et al., 1989), HCV is a ~9.6 kb, positive sense, single-stranded RNA virus of the *Flaviviridae* family, which also includes many arthropod-borne human pathogens of the Flavivirus genus such as yellow fever virus, West Nile virus and dengue virus. Together with the GBV-B virus and the recently identified non-primate, rodent and bat hepaciviruses, HCV has been grouped in the Hepacivirus genus (Drexler et al., 2013; Kapoor et al., 2011; Kapoor et al., 2013; Quan et al., 2013). HCV isolates have been grouped into seven genotypes and a number of subtypes (Simmonds 2013) with distinct geographic distributions and sensitivity to interferon-based treatment (Manns et al., 2006; Zein 2000). The only true HCV animal model is the chimpanzee, which has been crucial in studies of HCV immunity and pathogenesis (Bukh 2012). In addition, human-liver chimeric and genetically

modified HCV-permissive mouse models have also been developed (Billerbeck et al., 2013). For a long time, the lack of a cell culture system has been a major obstacle to study the HCV life cycle. However, selectable replicon systems (Lohmann et al., 1999) and retrovirus-based pseudotyped particles (Bartosch et al., 2003) have been major tools to understand HCV genomic replication and virus entry, respectively. Finally, since 2005, the full viral life cycle can be investigated with the help of complete viral replication systems (Lindenbach et al., 2005; Wakita et al., 2005; Zhong et al., 2005). It should be noted that these cell culture systems usually use Huh-7-derived hepatoma cells. However, this cell line lacks many features of hepatocytes (Meex et al., 2011). Primary human hepatocytes or human liver slices have therefore been developed to validate some experiments in more physiological models (Lagaye et al., 2012; Ploss et al., 2010; Podevin et al., 2010). In this review, we will discuss recent advances in the virology and cell biology of the HCV life cycle.

HCV is 50–80 nm in diameter (Catanese et al., 2013) and contains a single-stranded RNA genome, core and the envelope glycoproteins, E1 and E2 (Vieyres et al., 2014). The HCV genome interacts with the core protein to form the nucleocapsid that is surrounded by a lipid membrane, called the viral envelope, in which the envelope glycoproteins are anchored. Importantly, due to virion association with lipoproteins, apolipoproteins such as apoE, apoB, apoA1, apoC1, apoC2, and apoC3 can also be found in association with HCV particles (Andre et al., 2002; Catanese et al., 2013; Chang et al., 2007; Meunier et al., 2008; Nielsen et al., 2006). Furthermore, a characterization of cell culture-produced particles indicates that their lipid composition resembles very-low density lipoproteins (VLDL) and low-density lipoproteins (LDL) with cholesteryl esters accounting for almost half of the total HCV lipids (Merz et al., 2011). Electron microscopy analyses of purified infectious virions confirm the pleomorphic nature of HCV particles and show virions with a rather smooth and even surface (Catanese et al., 2013).

After the initial attachment to the cell surface, the following steps of HCV entry are only partially understood and they involve a series of specific cellular entry factors. They include SRB1 (Scarselli et al., 2002), CD81 tetraspanin (Pileri et al., 1998), tight-junction proteins claudin-1 (CLDN1) (Evans et al., 2007), and occludin (OCLN) (Ploss et al., 2009). Whether entry of HCV is restricted to hepatocytes still remains an unresolved issue. The CD81 tetraspanin is ubiquitously expressed and, in particular, is found in B-lymphocytes where it acts as a co-stimulatory molecule (Pileri et al., 1998). However, CD81 interaction with its partner EWI-2wint may also represent an important molecular determinant contributing to the restricted tropism of HCV, since EWI-2wint is expressed in several tissues or cell types (such as brain or immune cells) but not in hepatocytes (Rocha-Perugini et al., 2008). SRB1 is detected on many cell types, although it is highly expressed in the liver and steroidogenic tissues (Dao et al., 2011). The other entry factors, i.e., the tight junction proteins CLDN1 (Evans et al., 2007) and OCLN (Ploss et al., 2009) have more restricted expression profiles in epithelial tissues along with high-level expression in hepatocytes. Thus, in addition to the tissue-restricted expression of miR-122, which favors HCV genome expression (Jopling et al., 2005; Shimakami et al., 2012), the combined presence of these receptors and entry factors in hepatocytes, their expression rates, and their ability to interact is one element that may explain why the liver constitutes the main target for HCV particles (Reynolds et al., 2008).

RNA translation is initiated with the help of cellular factors (Niepmann 2013). The HCV genome contains a single open reading frame (ORF), which is flanked by 5′ and 3′ non-translated regions (NTRs). These NTRs contain highly structured RNA elements that are critical for genome translation and HCV RNA replication (Lohmann 2013). The 5 NTR contains an internal ribosomal entry site (IRES), which initiates translation of the HCV genome into a single polyprotein. Viral and host encoded

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proteases process the viral polyprotein into the 10 mature proteins: core, E1, E2, p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B (Moradpour et al., 2013). Signal peptidase and signal peptide peptidase mediate cleavage of the structural proteins, core, E1, E2, and the p7/NS2 junction. NS3 mediates cleavage of NS4A from itself and NS4B, after which NS4A associates with the N-terminus of NS3. The resulting NS3/4A protease complex can then cleave at the NS4B/5A and NS5A/5B junctions, whereas the cleavage between NS2 and NS3 is mediated by the NS2 cysteine protease whose function is strongly enhanced by the N-terminal one-third of NS3.

After translation, the HCV proteins are associated with membranes derived from the endoplasmic reticulum (ER). Together, NS3/4A, NS4B, NS5A, and NS5B constitute the viral proteins of the replication machinery, which replicates the positive sense RNA genome through a negative strand intermediate (Lohmann 2013). The viral RNA-dependent RNA polymerase NS5B is the key enzyme of RNA synthesis. Nascent RNA genomes are translated to produce new viral proteins, serve as new/additional RNA templates for further RNA replication and are progressively assembled to form infectious virions. HCV replication is dependent on microRNA 122 (miR-122) (Jopling et al., 2005), a liver-specific microRNA that recruits Argonaute 2 to the 5′ end of the viral genome (Shimakami et al., 2012), stabilizing it and slowing its degradation by the 5′ exonuclease Xrn1 (Li et al., 2013).

Newly replicated viral genomes are transferred to the assembly sites via NS3/4A or NS5A, and NS2, and p7 connect replication complexes and core proteins to the glycoproteins. The next steps in HCV virion morphogenesis are tightly linked to the metabolism of very-low density lipoproteins (VLDL) (Gastaminza et al., 2008; Huang et al., 2007; Nahmias et al., 2008). However, the details of the intersection between HCV assembly and VLDL biogenesis remain poorly understood. It has been demonstrated that HCV particles contain apoE and neutral lipids, but how these components are acquired during HCV morphogenesis remains speculative.

HCV NS3 is a multifunctional protein (amino acids 1–631) with serine protease activity in the N-terminal amino acids (aa 1–180) and a nucleoside-triphosphatase- (NTPase-) dependent RNA helicase activity (NS3 NTPase/helicase) in the C-terminal amino acids (aa 181–631). Both enzyme activities have been well defined and high-resolution structures have been solved (Penin et al., 2004). The C-terminus of NS3 encodes a DExH/D-box RNA helicase. NS3 helicase hydrolyzed NTP as an energy source to unwind double-stranded RNA in a 3’ to 5’ direction during replication of viral genomic RNA (Tai et al., 1996). Structural analysis of NS3 revealed the unidirectional translocation and proposed a new function of NS3 as translocase, considering feasible strategies for developing specific inhibitors to block the action of NS3 helicase (Gu and Rice 2010). The activity of NS3 helicase can be regulated by interactions between the serine protease and helicase domains of NS3 (Frick et al., 2004; Pang et al., 2002), indicating that these two enzyme activities may be somehow coordinated during replication. The specific function of the HCV helicase is unknown; it has been shown that without functional helicase domains, HCV cannot replicate in cells. It may be involved in the initiation of RNA synthesis on the HCV genome RNA, which contains stable 3-terminal secondary structure in dissociation of nascent RNA strands from their template during RNA synthesis or in displacement of proteins or other trans-acting factors from the RNA genome. It has been now well recognized that both activities of NS3 protein are required for the replication of virus; they are considered as attractive target sites for the development of direct-acting antivirals (DAAs) therapies.

HCV NS5A is a phosphoprotein specifically (Tanji et al., 1995) capable of interacting with the 3'-NTR of the HCV genome (Huang et al., 2005), other nonstructural proteins (Shimakami et al., 2004), and numerous cellular proteins (Reiss et al., 2011; Tai and Salloum, 2011). NS5A is a 447 amino-acid phosphoprotein that is required for viral replication and also functions in virus assembly (Tellinghuisen et al., 2008; Appel et al., 2008). NS5A protein has been predicted to contain three domains: Domain I (aa 1-213), Domain II (aa 250-342) and Domain III (aa 356-447) (Tellinghuisen et al., 2004). The N-terminal region of Domain I (aa 1-30) consists of a well-characterized and highly conserved amphipathic α-helix (AH) with a hydrophobic side, and a polar, charged side (Penin et al., 2004). While Domains II and III have not been appreciably characterized and may not be well structured in isolation, the crystal structure of Domain I was determined at 2.5-Å resolution (Tellinghuisen et al., 2005), revealing a zinc-binding motif involving four cysteine residues (C39, C57, C59, and C80). NS5A has no known enzymatic activity, but forms homodimers, anchors to membrane, and binds RNA (Tellinghuisen et al., 2005; reviewed in Appel et al., 2006). Although the precise role of NS5A in HCV replication is unknown, it has been postulated that the membrane-bound protein may sequester RNA to the HCV replication complex. It has also been speculated that NS5A inhibitors may interfere with NS5A dimer association, thereby disrupting the protein's critical function (Gao et al., 2010). HCV NS5A exists in two phosphorylated forms, termed NS5A-p56 and NS5A-p58, according to their apparent molecular weight on SDS-PAGE gels (reviewed in Reyes 2002). NS5A-p56 is the basally phosphorylated form in which at least serine 222 (equivalent to S2194 when using genome numbering) is phosphorylated. NS5A-p58 is the hyperphosphorylated form in which several serine residues at the N-terminal region of Domain II are phosphorylated, including S225, S229 and S232 (genome numbering S2197, S2201, S2204) (Huang et al., 2007; Quintavalle et al., 2007; Gao et al., 2004). Recent studies indicate that differential phosphorylation of NS5A may serve as a switch to regulate HCV RNA replication by affecting its formation of complexes with other proteins (reviewed in Huang et al., 2007). An important clue was first provided by the finding that NS5A (as well as NS5B) can associate with hVAP-A via the region of NS5A involved in hyperphosphorylation. Subsequent studies showed hVAP-A, which is a widely expressed, ER/Golgi-localized protein involved in intracellular vesicle trafficking, to be essential for HCV replicon RNA replication (Gao et al., 2004), while NS5A amino acid substitutions that disrupt its interaction with hVAP-A strongly reduced HCV replicon RNA replication (Evans et al., 2004). Thus, hVAP-1 was proposed to function as a docking site for assembly and/or localization of HCV replication complex, also known as HCV replicase, on intracellular membranes. Intriguingly, a subset of adaptive amino acid substitutions previously identified in the HCV replicon system that are associated with loss of NS5A hyperphosphorylation displayed increased binding capacity to hVAP-A, indicating hyperphosphorylation of NS5A prevents its binding to hVAP-A, possibly disrupting the HCV replicase and hence preventing viral RNA replication (Evans et al., 2004). MK-8742, like the other NS5A DAAs, is a highly symmetrical molecule.

HCV NS4A is a cofactor for NS3 that directs the localization of NS3 and modulates its enzymatic activities (Failla et al., 1994). HCV NS4B is an integral membrane protein that is required for the assembly of the "membranous web," the organelle used for RNA replication (Egger et al., 2002; Konan et al., 2003). HCV NS5B is the viral RNA-dependent RNA polymerase (Behrens et al., 1996).

In the United States, approximately 70% of chronic HCV infections are caused by hepatitis C genotype 1, 15 to 20% by genotype 2, 10 to 12% genotype 3, 1% genotype 4, and less than 1% genotype 5 or 6. Among the genotype 1 infections, approximately 55% are genotype 1a and 35% 1b (Hepatitis C Online).

1.3. Current Antiviral Drugs for HCV

HCV NS3/4A protease inhibitors bind into the catalytic site of the enzyme and block post-translational processing of the viral polyprotein at the NS3/NS4A, NS4A/NS4B, NS4B/NS5A, and NS5A/NS5B cleavage sites, preventing the release of functional nonstructural proteins. Boceprevir (BOC, VICTRELIS®, NDA 202258, approved on 5/13/11) and telaprevir (TVR, INCIVEK®, NDA 201917, approved on 5/23/11; withdrawn 1/19/15) were the first wave of HCV direct-acting antivirals (DAA) that were approved in the US. These drugs were approved for use in combination with pegylated, recombinant human IFNα and ribavirin in patients infected with HCV genotype 1. They were given every 8 hours (TVR alternatively could be given every 12 hours), with a total treatment duration of 24 to 48 weeks. Furthermore, these drugs have low barriers to resistance and virologic failure was usually associated with resistance to BOC, TVR, and other HCV NS3/4A protease inhibitors in development. Telaprevir is no longer marketed in the U.S. due to the high SVR rates achieved with the interferon free direct-acting antiviral regimens. Additionally, Merck is planning to stop marketing boceprevir by the end of 2015 (HIV and Hepatitis.com).

The second wave of DAAs that were approved includes simeprevir (SMV, OLYSIO®, NDA 205123, approved on 11/22/13) and sofosbuvir (SOF, SOVALDI®, NDA 204671, approved on 12/6/13). SMV is a once-daily, oral HCV NS3/4A protease inhibitor approved for use in combination with pegylated IFNα and ribavirin in patients infected with HCV genotype 1. The treatment duration for SMV was 24 to 48 weeks. The presence of the HCV NS3 Q80K polymorphism (present in ~40% of HCV genotype 1a patients) was identified as an important predictor of SMV treatment outcomes in patients infected with genotype 1a HCV. Subsequently, SMV was approved for use with SOF in an IFN-free, all oral regimen.

SOF, a uridine nucleotide analog, is a once-daily, oral inhibitor of the HCV NS5B RNA-dependent RNA polymerase that acts by causing chain termination during replication of the HCV genome. It is the first FDA-approved HCV DAA for genotypes 2-4 (SOVALDI®). SOF is approved for use in combination with pegylated, recombinant human IFNα and ribavirin for patients infected with HCV genotypes 1 or 4 for a treatment duration of 12 weeks, and in combination with ribavirin for 24 weeks, can be considered for patients with HCV genotype 1 infection who are interferon ineligible, though this regimen is suboptimal (SVR rates of 76%, SOVALDI®). It is approved for use in combination with ribavirin for patients infected with HCV genotypes 2 or 3 for treatment durations of 12 weeks or 24 weeks, respectively. These SOF plus ribavirin regimens represent the first pegylated IFNα-free regimens for the treatment of chronic HCV infection. Despite the major advancement in the treatment of HCV infection by SOF, there was still a need for more efficacious, short duration, interferon-free regimens for HCV genotype 1.

Recently, other interferon-free combination HCV DAA regimens have been approved. SOF has been combined with ledipasvir (LDV), an HCV NS5A inhibitor, in a single fixed-dose once-daily tablet (HARVONI®, NDA 205834, approved on 10/10/14). HARVONI® is approved for most patients infected with HCV genotype 1 for a treatment duration of 12 weeks, and, for treatment-experienced patients with cirrhosis, 24 weeks. This regimen was found to be highly effective in HCV genotype 1 infected patients, including in populations that are generally considered difficult-to-treat such as genotype 1a infected patients, prior pegylated interferon alfa and ribavirin (P/R) treatment failure patients including those with prior NS3/4A protease inhibitor experience, and patients with compensated cirrhosis. VIEKIRA PAK® (NDA 206619, approved on 12/19/14) is approved for most patients infected with HCV genotype 1 for a treatment duration of 12 weeks, and, for HCV genotype 1a infected patients with cirrhosis, 24 weeks. VIEKIRA PAK® is a combination of paritaprevir (ABT-450), an HCV NS3/4a inhibitor, ombitasvir, an HCV NS5A inhibitor, and dasabuvir, an HCV non-nucleoside NS5B-palm polymerase inhibitor. Paritaprevir is given with the CYP3A inhibitor ritonavir, which has no direct anti-HCV activity, to allow

for higher drug levels and for once-daily dosing. This 3 DAA combination regimen, in some cases also dosed with ribavirin, was also found to be highly effective in HCV genotype 1 infected patients, including in populations that are generally considered difficult-to-treat such as genotype 1a infected patients, prior P/R treatment failure patients, and patients with compensated cirrhosis. DAKLINZA® (NDA 206843, approved on 7/24/15) in combination with SOF is approved for patients infected with HCV genotype 3. This regimen was found to be highly effective in HCV genotype 3 infected patients who are non-cirrhotic.

1.4. Methodology

This section summarizes clinical virology procedures that were used for the Phase 2 and Phase 3 studies.

HCV genotype/subtype determination

In all Phase 2/3 studies, samples were collected from subjects at screening and genotyped using the Abbott Real Time HCV Genotype II assay (Abbott Molecular) (PN060, PN061 and PN068), Versant 2.0 (INNO-LiPA) Line Probe assay (Siemens) (PN035 and PN047) or GenMark eSensor HCVg Direct assay (GenMark) (PN074). The Abbott Real Time HCV Genotype II assay is approved by the FDA. The Versant 2.0 (INNO-LiPA) Line Probe and GenMark eSensor HCVg Direct assays were not used in any of the sponsor's HCV GT1 pivotal studies. These assays can detect genotype (GT) 1a, 1b, 2, 3, 4, 5 and 6, but subtype determination other than 1a and 1b is either not feasible or not fully validated. In some samples, vendors also performed phylogenetic analysis on NS5B regions to confirm ambiguous genotype/subtype information. To determine subtypes in non-GT1-infected subjects, the sponsor has conducted an independent phylogenetic analysis, and BLAST search using the HCV NS3 and NS5A sequences derived from subject samples and compared them with reference sequences obtained from Genbank (summarized in study report 044sth).

HCV viral load assessments

Plasma HCV RNA levels were determined using the FDA-approved Roche COBAS™ Taqman™ HCV Test v2.0 (Roche COBAS™ Taqman) (PN035 and PN047) or Roche COBAS™ Taqman™ HCV Test v2.0 (High Pure System) (Roche COBAS™ Taqman HPS) on blood samples drawn from each subject at various time points prior to, during, and after dosing. The Roche COBAS™ Taqman™ HCV Test v2.0 assay has a LLOQ of 25 IU/mL and LOD of 15 IU/mL. The Roche COBAS™ Taqman™ HCV Test v2.0 (High Pure System) assay has a LLOQ of 15 IU/mL and LOD of 9.3 IU/mL. (Note that the LOD is defined as the 95% positive hit concentration.) All critical study endpoints and trial decisions were based on the LLOQ cutoff.

HCV sequence analysis

Plasma samples from all subjects who participated in the study were collected prior to dosing to generate baseline sequence information. Additional samples were collected from subjects who met the criteria for virologic failure and follow-up visits whenever available. Due to assay limitations, only samples with viral titers above 1,000 IU/mL were sequenced. The HCV NS3/4A and NS5A regions from subject plasma samples were amplified using reverse transcription polymerase chain reaction (RT-PCR) followed by Sanger population nucleotide sequence analysis. The limit of variant detection in the population was approximately 25% of the viral population.

1.5. Prior FDA Virology reviews

This is the original NDA submission and the Clinical Virology review of MK-5172 + MK8742. The sponsor has not requested regulatory approval of the individual components of this combination

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product. Clinical Virology reviews of IND submissions for MK-5172 (IND 110261) and MK-8742 (IND 114298) were conducted by Takashi Komatsu, Ph.D.

2. Nonclinical Virology

2.1. MK-5172 (grazoprevir)

2.1.1. Mechanism of Action (Study Reports MK-5172-PD001, MK-5172-PD006, MK-5172-PD007, MK-5172-PD012)

MK-5172 is an inhibitor of HCV NS3/4A protease. Full length recombinant HCV NS3/4A enzyme (genotype 1b, BK strain expressed in and purified from *E. coli*) was used in biochemical reactions catalyzing the cleavage of a substrate peptide in a time-resolved fluorescence format. Reactions were conducted over 60 minutes at room temperature following a 30-minute pre-incubation of enzyme and inhibitor. The peptide sequence is Ac-C(Eu)DDMEEAbu[COO]ASK(QSY7)-amide, where Eu represents a europium cryptate modification, Abu is amino butyric acid, [COO] is an ester bond that is the site of cleavage, and QSY7 is a fluorescence quencher modification. Enzyme catalyzed cleavage of the ester bond results in separation of the fluorescent europium cryptate from the quencher and an increase in fluorescence (Ex λ = 340 nM, Em λ = 615 nM). The long-lived fluorescence of the europium allows for use of time-resolved measurements which reduces background fluorescence, and increases the sensitivity of the assay so that NS3/4A concentrations as low as 15 pM can be used. Enzymes of additional genotypes were similarly constructed and prepared using the following strains: GT1a H77 (GenBank Ac. #AF009606); GT2a JFH1 (GenBank Ac. #AB047639); GT2b J8 (GenBank Ac. #D10988); GT3a NZL1 (GenBank Ac. #D17763); GT4a (GenBank Ac. #GU814265.1), GT5a (patient sequence identifier 1209A014, sequence on internal file), and GT6a (GenBank Ac. #DQ480512). The IC_{50} values for MK-5172 were 7 pM, 4 pM, 67 pM, 135 pM, 690 pM, 62 pM, 67 pM, and 34 pM against GT1a, GT1b, GT2a, GT2b, GT3a, GT4a, GT5a, and GT6a, respectively (Table 1, study report MK-5172 PD006, pg. 8). Of note, there was a reduced antiviral activity (relative to GT1a/1b) for GT2b and especially for GT3a. A possible explanation for the reduced antiviral activity could be that different amino acids are found at certain key positions (e.g., 168) in GTs 1, 2 and 3 (Thibeault et al., 2004)..

Table 1: Activity of MK-5172 in Enzyme Assays Catalyzed by NS3/4A from Different Genotypes of HCV.

Enzyme	MK-5172 IC_{50} (nM)
1a	0.007 ± 0.001
1b	0.004 ± 0.001
2a	0.067 ± 0.024
2b	0.135 ± 0.051
	(b) (4)
4a	0.062 ± 0.031
5a	0.067 ± 0.022
	(b) (4)
1b R155K	0.021 ± 0.010
1b A156T	3.917 ± 0.695
1b A156V	5.511 ± 1.574
1b D168Y	0.105 ± 0.024

To further characterize NS3 proteinase activity in a cellular context, a deoxyribonucleic acid (DNA) transfection-based ProSEAP phenotype assay was performed that measured protease cleavage activity via processing of a reporter gene product that is secreted from cells (secreted alkaline phosphatase); addition of a protease inhibitor would reduce the amount of secreted reporter protein (Study report MK-5172-PD001). The EC_{50} values for MK-5172 in this assay were 2.3 nM, 1.2 nM, (b) (4) (b) (4) (b) (4) 1.2 nM, (b) (4) GT1a, GT1b, GT2a, GT2b, GT3a, GT4a, and GT6a, respectively. Consistent with the results from the biochemical assay, there was reduced activity against HCV GT2a, GT2b, and GT3a.

HCV NS3/4A is a serine protease; therefore, the off-target activity of MK-5172 was determined in reactions catalyzed by human serine proteases. In a panel of enzyme and receptor binding displacement assays (b) (4) a total of 11 targets were evaluated (Study report MK-5172 PD007). The IC_{50} values were all >1 μM, yielding in all cases a selectivity index relative to the HCV GT1b enzyme greater than 1,000,000-fold.

MK-5172-mediated carboxylesterase (CES) inhibition was assessed in the CES1/2 enzyme assays with 4-NPA substrate (Study report MK-5172 PD012). The IC_{50} value for MK-5172-mediated inhibition of CES1/2 was >100 μM. Given the low (sub-μM) plasma levels of MK-5172, the sponsor predicts insignificant (<10%) inhibition of CES1/2 under *in vivo* conditions. Cathepsin A (Cat A)-mediated hydrolysis of MK-5172 substrate was assessed using a LC-TOF/MS detection setup. The IC_{50} value for MK-5172-mediated inhibition of Cat A was >200 μM. These results indicate that MK-5172, which is not a prodrug metabolized by either enzyme, does not inhibit CES1/2 or Cat A-mediated processing of pro-drugs such as sofosbuvir and other therapeutics agents.

2.1.2. Antiviral Activity in Cell Culture (Study Reports MK-5172-PD001, MK-5172-PD005, MK-5172-PD011, MK-5172-PD014)

The EC_{50} values of MK-5172 were 0.4 nM, 0.5 nM, (b) (4) (b) (4) and 0.3 nM against full-length replicons from GT1a, GT1b, GT2a, GT3a, and GT4a, respectively (Table 4). The activity of MK-5172 was also evaluated against HCV replicons representing several clinical isolates. These studies were conducted using chimeric replicons. The median EC_{50} values of MK-5172 were 0.8 nM (range 0.4-5.1 nM; N=10), 0.45 nM (range 0.2-5.9 nM; N=10), (b) (4) for GT1a, GT1b, GT2a. and GT2b, respectively (Tables 2, 3, and 4, study report MK-5172 PD001, pg. 8 & 11, study report MK-5172 PD005, pg. 7-8). The activity of MK-5172 was also evaluated against chimeric replicons bearing the protease gene from several patient isolates from GTs 3-6 (Table 4, study report MK-5172 PD005, pg. 7-8). The median EC_{50} values were (b) (4) and (b) (4)) against GT3a and GT5a, respectively. The range of EC_{50} values against GT6 (b) (4) The median EC_{50} values were 0.3 nM (n=1), 0.15 nM (n=2, range 0.11-0.2 nM), 1.1 nM (n=1), 0.24 nM (n=2, range 0.15-0.33 nM), and 1.2 nM (n=1) against subtypes 4a, 4b, 4d, 4g, and 4o, respectively. Of note, the EC_{50} value of MK-5172 against the 4a isolate shifted ~10-fold (3.7 nM) when the NS3 G162R adaptive substitution to enhance replication in tissue culture was introduced. Of note, there was a reduced antiviral activity (relative to GT1a/1b) for GT2a, GT2b, and especially for GT3a, consistent with the biochemical results.

Table 2: Activity of MK-5172 against HCV GT1a in Cell Culture.

Patient Sequence	MK-5172 EC_{50} (nM)	Fold-Shift H77
H77	2.3 ± 1.4	1
ps25	0.7 ± 0.2	0.3
ps26	0.6 ± 0.3	0.3

Patient Sequence	MK-5172 EC_{50} (nM)	Fold-Shift H77
ps27	0.7 ± 0.4	0.3
ps28	0.4 ± 0.3	0.2
ps29	0.4 ± 0.3	0.2
ps35	5.1 ± 1.3	2.2
ps36	1.1 ± 0.4	0.5
ps38	2.8 ± 0.7	1.2
ps40	0.8 ± 0.1	0.3
ps41	1.4 ± 0.2	0.6

Table 3: Activity of MK-5172 against HCV GT1b in Cell Culture.

Patient Sequence	MK-5172 EC_{50} (nM)	Fold-Shift con1
con1	1.2 ± 0.8	1
ps19	0.2 ± 1	0.2
ps20	1.8 ± 0.2	1.5
ps30	5.9 ± 1.4	4.9
ps31	0.3 ± 0.1	0.3
ps32	0.6 ± 0.3	0.5
ps33	4.9 ± 0.4	4.1
ps34	0.3 ± 0.2	0.3
ps42	0.2 ± 0.1	0.2
ps43	0.2 ± 0.1	0.2

Table 4: Activity of MK-5172 against Various HCV Genotypes/Subtypes in Cell Culture.

Replicon	EC_{50} (nM)	EC_{90} (nM)
1a H77	0.4 ± 0.3	0.9 ± 0.5
1b con1	0.5 ± 0.3	1.1 ± 0.6
(b) (4)		
GT4b (FJ025854)[a]	0.2 ± 0.04	0.3 ± 0.05
GT4b (FJ0025855)[a]	0.11 ± 0.04	0.32 ± 0.13
GT4g (JX227963)[a]	0.15 ± 0.09	0.71 ± 0.78
GT4g (JX227971)[a]	0.33 ± 0.1	0.6 ± 0.16
(b) (4)		
(b) (4)		
GT1b (40% NHS)	**1.1 ± 0.4**	**3.1 ± 0.7**

a. The chimeric replicon has NS3 residues (1-181) and 4A sequences in the background of JFH1.

b. The chimeric replicon has NS3 residues (1-181) and 4A sequences in the background of GT1b N strain.
* GenBank accession numbers are indicated in parenthesis.
** Internal nomenclature. NS3 GenBank accession number GU945457.1; NS4A GenBank accession number GU945457.1.

MK-5172 had no measurable antiviral activity against HIV-1 or HBV in cell culture assays (study reports MK-5172-PD011 and MK-5172-PD014).

2.1.3. Antiviral Activity in Cell Culture in the Presence of Serum and Serum Proteins (Study Report MK-5172-PD005)

Serum proteins have been found to bind and sequester many drugs. The EC_{50} value of MK-5172 shifted 2.2-fold in the presence of 40% normal human serum.

2.1.4. Cytotoxicity/Therapeutic Index (Study Report MK-5172-PD003)

A caveat to using a cell culture system to measure anti-viral activity is the possibility that the agent kills the host cells resulting in an artifactual inhibition of virus replication. Therefore, it is important to determine the cytotoxicity of the test compound to the host cells. Cytotoxicity evaluations can also give insight into the possible toxicity of the agent on stationary and dividing cells, and on human cells. The sponsor evaluated the cytotoxicity of MK-5172 using the Promega Cell Titer 96 Aqueous One Solution (MTS assay). The CC_{50} value was 69 µM in Huh-7 cells, representing a therapeutic index for the HCV 1b replicon of 137,800 (Table 5, study report MK-5172 PD003, pg. 7).

Table 5: Toxicity of MK-5172 in Cell Culture.

Cell line	CC_{50}, µM
Huh-7 gt1b (HB-1)	68.9
HeLa	70.4

2.1.5. Combination Antiviral Activity in Cell Culture (Study Reports MK-5172-PD003, MK5172-PD008, MK-2248A-PD001, MK-5172-PD015, MK-5172-PD017)

Drug interactions can result in an antagonistic, additive, or synergistic effect upon their antiviral activity in cell culture. In these studies, HCV replicons were exposed to combinations of test compounds at concentrations that spanned the EC_{50} values of the individual compounds, and antagonism, additivity and synergy were calculated according to the Prichard and Shipman method (1990; MacSynergy™). In cell culture HCV replicon assays, MK-5172 had non-antagonistic combination anti-HCV activity relationships with MK-8742, RBV, and interferon-α at the intersection of the EC_{50} values. In another set of studies, MK-5172 had non-antagonistic anti-HCV activity with an investigational HCV NS5A inhibitor, MK-8408, sofosbuvir (HCV NS5B nucleotide inhibitor), and investigational HCV NS5B nucleotide inhibitors MK-2248, IDX20617 and IDX20963. (Note: No cytotoxic effects were observed at any of the combination doses tested.)

MK-5172 was added to dose response titrations of each of the HIV-1 drugs. The HIV drugs investigated in this study were emtricitabine/tenofovir disoproxil (NRTI), efavirenz/rilpivirine (NNRTI), dolutegravir/raltegravir (INSTI), atazanavir/darunavir (PI), enfuvirtide (fusion inhibitor) and maraviroc (CCR5 receptor antagonist). The concentrations of MK-5172 added to the assays were 0, 15, 100 and 500 nM, corresponding to approximately 0, C_{min}, C_{max}, and 5 times the C_{max} concentration in human plasma observed at a 100 mg dose of MK-5172 administered once daily in Phase I clinical studies. A concentration of 100 nM increased maraviroc EC_{50} value 1.2-fold from 0.38 to 0.45 nM (p value = 0.03). There were no significant changes in the EC_{50} values for the other HIV-1 drugs in the presence of any

concentration of MK-5172 tested (p values >0.05). The concentrations of HIV-1 drugs added to the dose response titrations of the HCV compounds in replicon cells corresponded to approximately C_{min}, C_{max}, and 5 times the C_{max} concentration in human plasma observed in Phase I clinical studies; where necessary, the concentration of the HIV drugs was capped at 20 µM to avoid potential cytotoxicity effects. The presence of the HIV-1 drugs did not affect the EC_{50} value of MK-5172 in HCV genotype (GT) 1a replicon cells.

2.1.6. Resistance Development in Cell Culture (Study Report MK-5172-PD002)

Selection in cell culture of virus resistant to the candidate agent can provide insight into whether the genetic threshold for the development of resistance is high or low and provides *in vivo* validation of the mechanism of action. Resistant colony selections for MK-5172 were performed with replicons bearing the NS3 proteases of GT1-6. In initial studies with the GT1b (Con1) replicon, 26 colonies were obtained under MK-5172 selection at 6 nM MK-5172 (10x EC_{50} value), while only 6 colonies were isolated at 30 nM (50x EC_{50} value). Amino acid substitutions Q41H, F43S, A156S/T/V, and D168A/V/G were identified (Table 6, study report MK-5172 PD002, pg. 6). Substitutions at positions A156 and D168 have been shown to be associated with resistance to other HCV NS3/4A protease inhibitors.

Table 6: MK-5172 Selection in HCV GT1b Replicon.

Drug, Fold EC_{50}	F43	A156	D168	Q41, A156	A156, D168	None
MK-7009 10X	0	0	2V, 2H, 7Y	0	0	1
MK-5172 10X	1S	1T, 2S	1A, 1V, 1G	0	1 156V, 168V 1 156S, 168A	0
MK-5172 50X	1S, 2F/S	1T, 1T/S/A	0	1 Q41H,A156V	0	1

Additional selections were conducted against GT1a, GT2a, GT3a, GT4a, GT5a, and GT6a replicons (Table **7**, study report MK-5172 PD002, pg. 7). Selections were conducted at approximately 0-, 2.5-, 5-, 10-, or 25-fold the respective EC_{50} values. For each selection, colonies were pooled and sequenced as a population, which as opposed to analysis of individual drug-resistant colonies/clones, limits the ability to detect multiple independent resistance pathways.

For the GT1a replicon selections, substitutions at D168 were observed at all concentrations, with substitutions such as D168V or D168A, which confer greater reduction in susceptibility, observed at the higher drug concentrations. Although Q41R arose in several of the selections, it also arose in the absence of drug, and conferred a <3-fold reduction in GT1a replicon susceptibility to MK-5712. Substitutions A39V and I48A have not previously been described and are under evaluation for effects on antiviral activity. Of note, an NS3 I48V substitution was observed in the sponsor's clinical studies (see Section 5.2). (b) (4)

For the GT2a selections, Y56H and A156T/V were the most frequently observed substitutions. T27I, Q41R, and L175F were also observed. For the GT3a selections Q168R was observed at all drug concentrations. According to the sponsor, this substitution has been observed in clinical studies of MK-5172 in GT3a subjects; in cell culture Q168R confers ~4-fold reduction in susceptibility to MK-5172. It is unclear at this time whether the Q168R substitution was observed in the absence of other NS3 substitutions. Given that this substitution was observed in treatment failure subjects, a ~4-fold reduction in susceptibility to MK-5172 may be clinically significant. Additional substitutions that were observed include N77S, V163I, and Q178R. The effect of these newly described substitutions identified in the

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GT2a or GT3a selections on MK-5172 antiviral activity is under evaluation. As noted above, in the absence of any drug selection GT3 is already naturally less susceptible to MK-5172 relative to other genotypes, likely due in part to the natural presence of the Q168 sequence in GT3. (b) (4)

For the GT4a selections, substitutions at D168 were observed at the higher MK-5172 drug concentrations. D168G and D168V emerged at 11 nM MK-5172 (10x EC_{50} value), while D168V and D168A emerged at 33 nM (30x EC_{50} value). D168 substitutions were not observed at lower drug concentrations. A61T and G90R emerged in a number of the selections (A61T quite prominently) including in the no drug control. G162R was observed as a minor population at one of the low concentrations of MK-5172. (b) (4)

Substitutions at D168 also commonly arose in both GT5a and GT6a selections. With GT5a, D168N was detected at the lowest drug concentration tested of (b) (4) and was more prominent in the (b) (4) and (b) (4) selections. D168A was first detected at (b) (4) selection, and was prominent at the highest drug concentration tested of (b) (4). D168V was also detected at higher drug concentrations. (b) (4)

(b) (4)

Table 7: MK-5172 Selection in HCV GT1a, 2a, 3a, 4a, 5a, and 6a Replicons.

Genotype	MK-5172, nM	Treatment Fold EC_{50} Value	Substitutions (% Population)
gt1a	no drug	0	Q41R (10)
	2.5	2.5	Q41R (50); **D168E** (35)
	5.0	5	A39V (100); Q41R (90); **D168V** (90)
	10.0	10	**I48A** (40); **D168A** (30); **D168G** (30);
gt4a	no drug	0	A61T (100%); G90R (5%)
	1.1	1	A61T (100%); G90R (5%)
	3.3	3	A61T (100%) G90R (5%); G162R (5%)
	11	10	A61T (70%); G90R (5%); **D168V** (30%); **D168G** (30%)
	33	30	A61T (95%); G90R (5%); **D168V** (50%); **D168A** (50%)

(b) (4)

(b) (4)

(b) (4)

Genotype	MK-5172, nM	Treatment Fold EC_{50} Value	Substitutions (% Population)
	37.5	25	D168N (5%); D168A (90%); D168V (10%)

(b) (4)

[redacted]

2.1.7. Cross-resistance (Study Reports MK-5172-PD005, MK-5172-PD010)

The antiviral activity of MK-5172 was evaluated using a panel of GT1a, GT1b, GT2a, GT3a, GT4a, or GT5a replicon cell lines engineered to encode substitutions reported in pre-clinical or clinical studies of protease inhibitors, including those that were identified in the MK-5172 cell culture selection studies (Table 8, study report MK-5172 PD005, pg. 10-15).

Table 8: Activity of MK-5172 against GT1a, 1b, 2a, 3a, 4a, 5a, and 6a Replicons Expressing NS3 Resistance-Associated Substitutions.

Genotype/Mutant	EC_{50} (nM) ± SD	Fold-shift EC_{50} Value (relative to Wild-Type)	EC_{90} (nM) ± SD	Fold-shift EC_{90} Value (relative to Wild-Type)
GT1a WT (H77)	0.4 ± 0.2	1.0	0.9 ± 0.5	1.0
GT1a V36A	0.5 ± 0.3	1.5	1.1 ± 0.5	1.2
GT1a V36I	0.4 ± 0.2	1.0	0.7 ± 0.4	0.8
GT1a V36L	0.5 ± 0.3	1.4	1.2 ± 0.6	1.3
GT1a V36M	0.3 ± 0.2	1.0	0.9 ± 0.3	0.9
GT1a A39V	0.1 ± 0.03	0.3	0.3 ± 0.1	0.3
GT1a Q41R	0.8 ± 0.2	2.2	1.9 ± 0.3	2.1
GT1a F43L	0.7 ± 0.1	1.9	2.9 ± 0.6	3.1
GT1a T54A	0.3 ± 0.1	0.7	0.5 ± 0.3	0.6
GT1a T54S	0.3 ± 0.2	0.9	1.0 ± 0.7	1.1
GT1a V55A	0.5 ± 0.3	1.4	0.9 ± 0.4	0.9
GT1a V55I	0.2 ± 0.1	0.6	0.6 ± 0.1	0.6
GT1a Y56H	5.7 ± 4.3	16.1	42.6 ± 26.4	46.0
GT1a Q80K	0.3 ± 0.3	0.9	1.0 ± 0.6	1.1
GT1a Q80R	0.4 ± 0.2	1.1	1.7 ± 0.7	1.8
GT1a V107I	0.2 ± 0.1	0.7	0.7 ± 0.4	0.7
GT1a I132V/T	0.5 ± 0.3	0.8	1.5 ± 0.7	0.8
GT1a P146S	0.8 ± 1.2	2.4	1.1 ± 0.3	1.2
GT1a R155K	1.3 ± 0.7	3.7	2.8 ± 2.2	3.0
GT1a R155T	3.4 ± 1.7	9.7	7.1 ± 2.5	7.7
GT1a A156G	1.7 ± 0.1	4.8	4.1 ± 0.9	4.4
GT1a A156L	918*	2295	1820*	2022
GT1a A156S	0.9 ± 0.4	2.5	2.3 ± 0.8	2.5
GT1a V158I	0.1*	0.3	0.4*	0.4
GT1a D168A	28.6 ± 13.0	80.7	105.8 ± 80.5	114.2
GT1a D168E	4.9 ± 4.2	13.9	11.6 ± 5.1	12.5
GT1a D168F	8.4 ± 4.8	21.0	30 ± 15	33.3
GT1a D168G	9.6 ± 6.9	27.2	46.4 ± 34.1	50.1
GT1a D168H	4.9 ± 2.7	12.3	18 ± 8	20.0
GT1a D168I	14.3 ± 5.2	40.5	68.5 ± 8.3	74.0
GT1a D168K	75.1 ± 32.1	212.2	280.7 ± 18.5	303.1
GT1a D168L	4.3 ± 2.4	10.8	18 ± 10	20.0

Genotype/Mutant	EC_{50} (nM) ± SD	Fold-shift EC_{50} Value (relative to Wild-Type)	EC_{90} (nM) ± SD	Fold-shift EC_{90} Value (relative to Wild-Type)
GT1a D168N	0.9 ± 0.4	2.5	2.7 ± 1.1	2.9
GT1a D168S	0.7 ± 0.3	2.3	6.4 ± 4.8	7.6
GT1a D168T	34.7 ± 8.0	97.9	85.9 ± 22.8	92.7
GT1a D168V	10.5 ± 5.0	29.7	54.5 ± 40.3	58.8
GT1a D168Y	6.9 ± 5.2	21	24 ± 16	27
GT1a I170T	0.7 ± 0.3	2.0	1.8 ± 1.0	2.0
GT1a I170V	0.1*	0.3	0.4*	0.4
GT1a V36L_Q80K	0.5 ± 0.2	1.4	2.6 ± 1.4	2.8
GT1a V36L_Q80K_R155S	14.2 ± 9.4	40.1	62.2 ± 35.6	67.1
GT1a V36M_R155K	3.5 ± 2.4	9.9	10.1 ± 4.8	10.9
GT1a V36M_A156T	151 ± 20	481.0	480 ± 82	573.0
GT1a T54S_R155K	2.0 ± 1.0	5.7	5.4 ± 2.0	5.8
GT1a Y56H_D168N	19.3 ± 15.2	61.4	53.2 ± 30.8	63.3
GT1a R155K_D168N	2.7 ± 1.4	7.6	7.5 ± 3.4	8.1
GT1a R155T_D168N	4.1 ± 0.8	11.7	10.6 ± 1.9	11.4
GT1a V36M_V107I_R155K	3.8 ± 2.5	10.6	8.0 ± 2.8	8.6
GT1a WT (Huh 7.5)	0.14 ± 0.07	1.0	0.4 ± 0.3	1.0
GT1a Y56H_D168A	655 ± 437	4679	2160*	5400
GT1a Y56H_A156T_D168N	2420*	17000	> 5000	>12500
GT1a A156T_D168N	1250*	8929	2870*	7175
GT1a NS3 Q41R_NS5A M28K	0.5 ± 0.1	1.5	2.4 ± 1.3	2.9
GT1a NS3 Q41R NS5A M28T	0.5 ± 0.1	1.6	1.3 ± 0.4	1.6
GT1b WT (Con1)	0.5 ± 0.3	1.0	1.0 ± 0.6	1.1
GT1b V36A	1.0 ± 0.4	2.0	2.2 ± 0.6	2.4
GT1b V36I	0.2 ± 0.1	0.4	0.6 ± 0.3	0.6
GT1b V36L	0.5 ± 0.2	0.9	1.6 ± 0.6	1.7
GT1b V36M	0.9 ± 0.6	1.7	1.8 ± 1.1	2.0
GT1b Q41L	0.1 ± 0.05	0.2	0.3 ± 0.1	0.3
GT1b Q41R	1.1 ± 0.2	2.2	2.2 ± 0.7	2.3
GT1b F43S	1.3 ± 1.4	2.6	4.7 ± 5.3	5.0
GT1b T54A	0.6 ± 0.2	1.2	1.6 ± 0.6	1.7
GT1b T54C	0.8 ± 0.3	1.6	1.6 ± 0.6	1.7
GT1b T54G	0.8 ± 0.4	1.7	2.1 ± 0.6	2.2
GT1b T54S	0.6 ± 0.3	1.2	2.0 ± 1.2	2.1
GT1b V55A	0.7 ± 0.2	1.4	1.4 ± 0.4	1.5
GT1b V55I	0.7 ± 0.3	1.5	1.8 ± 0.8	2.0
GT1b Y56F	0.7 ± 0.4	1.5	2.0 ± 1.2	2.2
GT1b Y56H	6.3 ± 2.8	12.6	18.0 ± 7.6	19.4
GT1b Q80L	1.1 ± 0.8	2.1	2.8 ± 2.4	3.0
GT1b Q80R	0.9 ± 0.5	1.9	2.3 ± 1.3	2.5
GT1b Q86R	0.1 ± 0.1	0.2	0.3 ± 0.2	0.3
GT1b V107I	0.5 ± 0.2	1.0	1.1 ± 0.5	1.2
GT1b S122A	0.4 ± 0.2	0.8	1.1 ± 0.7	1.0
GT1b S122G	0.3 ± 0.1	0.5	1.0 ± 0.3	1.0
GT1b S122R	0.3 ± 0.1	0.5	1.5 ± 1.1	1.4
GT1b R155E	1.4 ± 0.7	2.7	3.8 ± 1.8	4.1
GT1b R155G	14.2 ± 5.4	28.3	29.6 ± 3.8	32.0
GT1b R155K	1.1 ± 0.4	2.2	2.4 ± 1.0	2.6
GT1b R155N	0.9 ± 0.9	1.9	2.3 ± 1.6	2.5
GT1b R155Q	1.2 ± 0.6	2.4	2.9 ± 0.6	3.2
GT1b R155S	1.7 ± 1.2	3.4	5.6 ± 4.6	6.0

Genotype/Mutant	EC_{50} (nM) ± SD	Fold-shift EC_{50} Value (relative to Wild-Type)	EC_{90} (nM) ± SD	Fold-shift EC_{90} Value (relative to Wild-Type)
GT1b R155T	6.7 ± 2.8	13.3	24.7 ± 3.1	26.6
GT1b R155W	13.4 ± 2.2	26.7	36.1 ± 7.6	38.9
GT1b A156G	0.7 ± 0.4	1.4	1.4 ± 0.8	1.5
GT1b A156S	1.1 ± 0.6	2.1	3.4 ± 1.5	3.7
GT1b A156T	140.1 ± 59.1	279.5	365.3 ± 176.8	394.5
GT1b A156V	187.7 ± 100.1	374.6	578.4 ± 197.6	624.6
GT1b D168A	6.8 ± 3.2	13.6	21.1 ± 9.3	22.8
GT1b D168E	1.6 ± 0.7	3.2	6.1 ± 3.2	6.6
GT1b D168F	38.0 ± 15.2	75.9	102.6 ± 31.4	110.8
GT1b D168G	5.7 ± 4.0	11.3	18.8 ± 6.5	20.2
GT1b D168H	25.6 ± 9.3	51.0	78.2 ± 17.5	84.4
GT1b D168I	6.6 ± 1.6	13.2	37.2 ± 14.7	40.1
GT1b D168K	60.6 ± 44.1	120.9	247.0 ± 104.5	266.7
GT1b D168L	7.6 ± 2.6	15.1	36.3 ± 3.7	39.2
GT1b D168N	0.4 ± 0.2	0.7	1.6 ± 1.0	1.8
GT1b D168S	2.0 ± 1.1	4.1	7.2 ± 4.2	6.9
GT1b D168T	13.0 ± 7.7	26.0	31.2 ± 15.0	33.7
GT1b D168V	7.2 ± 4.5	14.4	25.8 ± 16.3	27.8
GT1b D168Y	4.2 ± 1.9	8.4	13.4 ± 5.4	14.5
GT1b V170A	0.7 ± 0.2	1.4	2.4 ± 0.8	2.6
GT1b V170I	0.4 ± 0.3	0.9	1.5 ± 1.2	1.7
GT1b V170T	0.5 ± 0.2	0.9	1.3 ± 0.4	1.4
GT1b Y56H_D168A	303 ± 55	758	847 ± 373	941
GT1b Q80R_D168E	17.1 ± 8.9	34.2	74.0 ± 23.4	79.9
GT1b R155W_A156G	1540*	3080	>2000	>2000
GT1b R155W_A156G_D168N	278*	555.0	902*	974.0
GT1b T54S_Q80L_V170I	0.47 ± 0.2	0.9	1.9 ± 0.9	1.9
GT1b A156G_D168N	9.0 ± 4.0	18.2	42.5 ± 13.6	41.2
[redacted] (b) (4)				
[redacted] (b) (4)				
GT4a (ED43) WT	0.3 ± 0.2	1.0	0.8 ± 0.4	1.0
GT4a G162R	0.7 ± 0.5	2.3	1.6 ± 1.0	2.0
GT4a G162R_D168A	96 ± 12	320	216 ± 40	270
GT4a G162R_D168V	33 ± 20	110	97 ± 31	121

Genotype/Mutant	EC_{50} (nM) ± SD	Fold-shift EC_{50} Value (relative to Wild-Type)	EC_{90} (nM) ± SD	Fold-shift EC_{90} Value (relative to Wild-Type)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Red: Amino acid substitutions that were observed to emerge in clinical studies.
Orange: Amino acid substitutions with fold change equal to or greater than the lowest fold change seen clinically.

The following substitutions conferred the same cut-off of the lowest fold change seen clinically (note: A cut-off of 1.0-fold, 1.0-fold, and 1.9-fold were used for GT1a, GT1b, and GT6, respectively. An arbitrary cut-off of 2-fold was used for GT2, GT3, GT4, and GT5 as there were insufficient clinical data to support a clinical cut-off.) (FDA analysis):

- GT1a: V36A/I/L/M, Q41R, F43L, V55A, Y56H, Q80K/R, V107I, P146S, R155K/T, A156G/L/S, D168A/E/F/G/H/I/K/L/N/S/T/V/Y, I170T, V36L + Q80K, V36L + Q80K + R155S, V36M + R155K, V36M + A156T, T54S + R155K, Y56H + D168N, R155K + D168N, R155T + D168N, Y56H + D168A, Y56H + A156T+D168N
- GT1b: V36A/M, Q41R, F43S, T54A/C/G/S, V55A/I, Y56F/H, Q80L/R, V107I, R155E/G/K/N/Q/S/T/W, A156G/S/T/V, D168A/E/F/G/H/I/K/L/S/T/V/Y, V170A, Y56H + D168A, Q80R + D168E, R155W + A156G, R155W + A156G + D168N, A156G + D168N

(b) (4)

(b) (4)

- GT4a: G162R, G162R + D168A/V

(b) (4)

(b) (4)

The sponsor also conducted a transient transfection assay in GT1a to facilitate the analysis of additional resistance-associated substitutions. The EC_{50} value of MK-5172 for the WT replicons measured in the transiently expressed replicon assay are within 3-fold of those measured in the stable replicon cells (Table 9, pharmacol-written-summary, pg. 33-34).

Table 9: Activity of MK-5172 in GT1a Transient Transfection Assay of Replicons Expressing NS5A Resistance-Associated Substitutions.

Substitution	EC_{50} ± SD (nM)[1]	Fold-Shift (vs. WT)	Relative Fitness (vs. WT)[2]
1a WT	0.27 ± 0.1	1.0	1.0
V55A Q80R	3.5 ± 1.7	13.0	0.3
Y56F	0.3 ± 0.06	1.1	0.8
Y56H D168A	263 ± 215	974	0.02
Q80K	2.2 ± 1.3	8.1	1.0
Q80K R155K	11.2 ± 4.7	41.5	0.8

Substitution	EC_{50} ± SD (nM)[1]	Fold-Shift (vs. WT)	Relative Fitness (vs. WT)[2]
Q80L	4.5 ± 1.7	17	0.9
R109K	0.6 ± 0.11	2.0	2.4
S122A	0.2 ± 0.1	0.7	0.7
S122G	0.3 ± 0.1	1.1	0.9
S122R	0.8 ± 0.6	3.0	0.4
S122T	0.6 ± 0.2	2.2	0.8
S122A R155K	2.0 ± 0.4	7.4	0.5
S122G R155K	2.9 ± 0.5	10.7	0.8
S122N R155K	1.5 ± 0.2	5.6	0.9
S122R R155K	1.9 ±1.1	7.0	0.1
S122T R155K	1.8 ± 0.6	6.7	1.0
I132V	0.4 ± 0.2	1.3	0.7
R155K	2.5 ± 1.4	9.3	0.4
R155K D168A	1.9 ± 0.7	7.0	0.7
R155K D168E	1.0 ± 0.7	3.7	0.7
R155K D168V	2.0 ± 1.2	7.4	1.3
R155W	5.9 ± 4.3	21.9	0.1
R155W A156G	8.8 ± 1.1	32.6	0.006
R155W A156G D168N	1286 ± 905	4763	0.9
R155Q A156S D168G	30 ± 10	111.1	0.4
A156G	1.2 ± 1.0	4.4	1
A156L	2732*	10119	0.02
A156T D168N	1074 ± 1151	3978	0.05
D168A	82 ± 12	304	0.5
D168E	11 ± 1.3	41	0.4
D168N	2.4 ± 1.6	37	0.6
D168V	46 ± 20	170	0.3
I170V	0.7 ± 0.3	2.3	1.3

1. Average ± SD, N≥3.
2. Fitness range: ≤0.02 = unfit; 0.03-0.5 = moderate; >0.5 = fit.

Red: Amino acid substitutions that were observed to emerge in clinical studies.
Orange: Amino acid substitutions with the same cut-off of the lowest fold change seen clinically.

The following substitutions conferred the same cut-off of the lowest fold change seen clinically (note: A cut-off of 1.0-fold was used (FDA analysis):

- GT1a: V55A + Q80R, Y56F, Y56H + D168A, Q80K/L, Q80K + R155K, R109K, S122G/R/T, S122A/N/R + R155K, S122G + R155K, I132V, R155K/W, R155W + A156G, R155K + D168A/V, R155W + A156G + D168N, A156G/L, A156T + D168N, D168A/E/N/V, I170V

Certain results in the transient transfection assays were not entirely consistent with those observed with the stable cell line assays. For example, in the transient assay, the GT1a Q80K substitution conferred a 8.1-fold reduced susceptibility, compared to a 0.9-fold in the stable cell-line (see Table 8). The clinical significance of these differences is unknown. Of note, the sponsor's clinical data demonstrate that the NS3 Q80K polymorphism at baseline does not impact SVR rates (see Section 4.5.1).

2.1.8. Activity of MK-5172 in HCV-infected Chimpanzees (Study Report MK-5172-PD004)

The activity of MK-5172 was probed by administering the compound orally to 3 HCV-infected chimpanzees (2 with HCV GT1a and 1 with HCV GT1b) at a dose of 1 mg/kg b.i.d. for 7 days (Study report PD004). The plasma viral load in the GT1b-infected chimpanzee decreased 4-5 $\log_{10}$ IU/mL on oral administration of MK-5172. The plasma viral load in the GT1a wild-type-infected chimpanzee decreased by ~3.5 $\log_{10}$ IU/mL following administration of MK-5172. The R155K mutant virus was the only resistant virus to arise during dosing in the GT1a wild-type infected chimpanzee, and quickly reverted to wild-type following cessation of dosing. The plasma viral load in another GT1a-infected

Reference ID: 3839313

chimpanzee, which entered the study harboring R155K virus as the primary circulating species, exhibited a ~2 $\log_{10}$ IU/mL decrease in viral load at the end of the dosing duration. Viral loads rebounded rapidly after the end of dosing. A novel R119Q substitution was also detected as a mixed R/Q population in the GT1a-infected chimpanzees. Of note, the Division does not require or request studies in chimpanzees for HCV drug development.

2.2. MK-8742 (elbasvir)

2.2.1. Mechanism of Action (Study Report MK-5172-PD012)

MK-8742 is an HCV NS5A inhibitor. The mechanism of action of MK-8742 has been characterized in HCV replicon activity and drug resistance selection studies.

2.2.2. Antiviral Activity in Cell Culture (Study Reports MK-8742-PD002, MK-8742-PD009, MK-5172-PD011, MK-5172-PD014)

The activity of MK-8742 was evaluated against a panel of HCV replicons. The EC_{50} values for MK-8742 were 4 pM, 3 pM [redacted] (b) (4) [redacted] (b) (4) 0.3 pM, [redacted] (b) (4) and [redacted] (b) (4) against replicons with reference sequences for GT1a, GT1b, GT2a, GT2b, GT3a, GT4a, GT5a, and GT6 respectively (Table 10, study report MK-8742 PD002, pg. 6). The reduced activity in GT2b could be a concern for MK-8742. The loss in activity in genotype 2b is largely due to the M31 polymorphism within the NS5A sequence (Study Report MK-8742-PD009). Of note, the GT1a, GT1b, GT2a, GT3a, and GT4a isolates used complete replicons while the rest were chimeric replicons.

Table 10: Activity of MK-8742 against Various HCV Genotypes/Subtypes in Cell Culture.

Replicon	$EC_{50} \pm SD^a$ (nM)	$EC_{90} \pm SD$ (nM)
1a_H77	0.004 ± 0.002	0.006 ± 0.002
1a_H77 (40% NHS)	0.040 ± 0.013	0.082 ± 0.027
1b_con1	0.003 ± 0.001	0.006 ± 0.004
[redacted] (b) (4) [redacted] (b) (4)		
4a_ED43_GU814265	0.0003 ± 0.0001	0.0005 ± 0.0001
4a_DQ418782/con1[c]	0.003 ± 0.001	0.016 ± 0.009
[redacted] (b) (4) [redacted] (b) (4)		

a SD was calculated from N ≥3 independent experiments.
b This replicon has the gt2b, gt5a, [redacted] (b) (4) NS5A sequences in JFH1 background.
c These replicons have the gt3a and gt4a NS5A sequences in con1 background.

The median EC_{50} values of MK-8742 were 4.5 pM (n=6, range 3 pM-9 pM), 8 pM (n=5, range 3 pM – 10 pM), [redacted] (b) (4) against GT1a, GT1b, GT3a, and GT5a clinical isolates. For genotype 4, the median EC_{50} values of MK-8742 were 0.2 pM (n=2, range 0.2-0.2 pM), 3,600 pM (n=3, range 17 pM-34,000 pM), 0.45 pM (n=2, range 0.4-0.5 pM), 1.9 pM (n=1), 36.3 pM (n=2, range 0.6-72 pM), 0.6 pM (n=2, range 0.4-0.7 pM), 2.2 pM (n=1), and 0.5 pM (n=1) against clinical isolates of subtypes 4a, 4b, 4d, 4f, 4g, 4m, 4o, and 4q, respectively.

MK-8742 had no measurable antiviral activity against HIV-1 or HBV in cell culture assays (Study Reports MK-5172-PD011 and MK-5172-PD014).

2.2.3. Antiviral Activity in Cell Culture in the Presence of Serum and Serum Proteins (Study Report MK-8742-PD002)

The EC_{50} value of MK-8742 shifted 10-fold in the presence of 40% normal human serum.

2.2.4. Cytotoxicity/Therapeutic Index (Study Report MK-5172-PD011, MK-5172-PD012)

The sponsor evaluated the cytotoxicity using 3 independent and complementary assays (MTS, ^{14}C thymidine incorporation into DNA and analysis of house-keeping gene GAPDH mRNA) that monitor different aspects of cellular cytotoxicity in a number of cell lines to assess the compound's potential to elicit cytotoxic effect. The CC_{50} value was >25 µM in Huh-7 cells representing a therapeutic index for the HCV 1b replicon of >8,300,000 (Table 11, Study Report MK-5172 PD011, pg. 7).

Table 11: Toxicity of MK-8742 in Cell Culture.

Cell Line	MTS Assay	^{14}C Thymidine DNA Synthesis Assay	GAPDH qPCR Assay
	CC_{50} (µM)		
Huh7	>25	>25	>25
HepG2	>25	>25	>25
HEK293T	>25	>25	>25
Hep3B	>25	>25	>25
MT4	>25	NT[a]	NT

MK-8742-mediated carboxylesterase (CES) inhibition was assessed in the CES1/2 enzyme assays with 4-NPA substrate (Study Report MK-5172 PD012). The IC_{50} value for MK-8742-mediated inhibition of CES1/2 was >50 µM. Cathepsin A (Cat A)-mediated hydrolysis of MK-8742 substrate was assessed using a LC-TOF/MS detection setup. The IC_{50} value for MK-8742-mediated inhibition of Cat A was >50 µM. These results indicate that MK-8742, which is not a prodrug metabolized by either enzyme, does not inhibit CES1/2 or Cat A-mediated processing of pro-drugs such as sofosbuvir and other therapeutics agents.

2.2.5. Combination Antiviral Activity in Cell Culture (Study Reports MK5172-PD008, MK-2248A-PD001, MK-5172-PD015)

In these studies, HCV replicons were exposed to combinations of test compounds at concentrations that spanned the EC_{50} values of the individual compounds, and antagonism, additivity and synergy were calculated according to the Prichard and Shipman method (1990; MacSynergy™). In cell culture HCV replicon assays, MK-8742 had non-antagonistic combination anti-HCV activity relationships with MK-5172, RBV, and interferon-α at the intersection of the EC_{50} values. In another set of studies, MK-8742 had non-antagonistic anti-HCV activity with HCV NS5B nucleotide inhibitors MK-2248, IDX20617 and IDX20963. (Note: No cytotoxic effects were observed at any of the combination doses tested.)

MK-8742 was added to dose response titrations of each of the HIV-1 drugs. The HIV drugs investigated in this study were emtricitabine/tenofovir disoproxil (NRTI), efavirenz/rilpivirine (NNRTI), dolutegravir/raltegravir (INSTI), atazanavir/darunavir (PI), enfuvirtide (fusion inhibitor) and maraviroc (CCR5 receptor antagonist). The concentrations of MK-8742 added to the assays were 0, 30, 100 and 500 nM, corresponding to approximately 0, C_{min}, C_{max}, and 5 times the C_{max} concentration in human plasma observed at a 50 mg dose of MK-8742 administered once daily in Phase I clinical studies. There was no significant impact on the EC_{50} values for any of the HIV-1 drugs at any concentration of MK-8742 tested. The concentrations of HIV-1 drugs added to the dose response titrations of the HCV compounds in replicon cells corresponded to approximately C_{min}, C_{max}, and 5 times the C_{max} concentration in human plasma observed in Phase I clinical studies; where necessary, the concentration of the HIV drugs was capped at 20 µM to avoid potential cytotoxicity effects. The

presence of the HIV-1 drugs did not affect the EC_{50} value of MK-8742 in HCV genotype (GT) 1a replicon cells.

2.2.6. Resistance Development in Cell Culture (MK-8742-PD002, MK-8742-PD003, MK-8742-PD009)

Selection in cell culture of virus resistant to the candidate agent can provide insight into whether the genetic threshold for the development of resistance is high or low and provides a validation of the mechanism of action. Resistance selections were conducted at up to 10,000-fold multiples of the EC_{90} value against GT1-6 replicons.

A dose-dependent reduction in the number of resistant colonies was observed in GT1a. Clonal sequencing of NS5A derived from resistant colonies demonstrated that MK-8742 at 1,000X EC_{90} value selected for Q30D and Q30D+Y93N substitutions (Table 12, study report MK-8742 PD002, pg. 13). A dose-dependent reduction in the number of resistant colonies was observed in GT1b although fewer colonies were selected compared to GT1a replicon cells treated with comparable doses. Single, double, and triple-linked substitutions involving L31F and Y93H were evident, and a novel variant V121I was identified. The V121I substitution was not phenotypically characterized (note: this substitution was not observed in any of the isolates from virologic failures in the sponsor's clinical studies). The sponsor should evaluate the phenotype of the V121I substitution. (b) (4)

Table 12: Summary of Resistance Selections in GT1a, 1b, and 3a Replicon Cells.

Replicon Cell Type	Treatment Fold EC_{90}	Recovered # Colonies	EC_{50} nM	EC_{90} nM	EC_{90} Fold Shift[a]	Mutations Observed
gt1a-H77	1000X	4	135	526	90000	Q30D, Q30D-Y93N
	100X	56	5	15	3000	Y93N
	10X	204	2	11	2000	not detected
	1X	TMTC[b]	<2	<2	<300	not detected
	DMSO	n/a	0.008	0.015	<3	n/a
gt1b-con1	1000X	3	27	120	20000	Y93H, L31F-Y93H-V121I
	100X	5	n/a[c]	n/a[c]	n/a[c]	n/a[c]
	10X	38	0.6	12	2000	Y93H, V121I, Y93H-V121I
	1X	122	0.2	1	200	Y93H
	DMSO	n/a[c]	0.008	0.011	<3	n/a[c]

(b) (4)

[a] EC_{90} shift: EC_{90} from selected cell/ EC_{90} from gt1a_H77 or gt1b_con1.
[b] TMTC: too many to count as the result of a lawn of cells.
[c] n/a = cell failed to expand.
[d] Replicons have the gt3a NS5A sequences in con1 background.

In GT2a_JFH (31L), a dose-dependent reduction in the number of colonies was observed (Table 13, study report PD009, pg. 9). Population nucleotide sequence analysis detected F28S and F28Y amino acid substitutions in resistant colonies that emerged from MK-8742 treatment. Treatment of GT2b_0907 ((b) (4) with up to (b) (4) EC_{90} value did not yield countable individual colonies. The treated cells were highly resistant to MK-8742 as measured with an EC_{90} value (b) (4) Population nucleotide sequence analysis showed that Y93H was present at (b) (4) or higher in resistant colonies. The Y93H resistance-associated substitution in linkage with the pre-existing (b) (4) resistance polymorphism account for the significant reduction in susceptibility of MK-8742 in the resistant colonies. (b) (4)

(b) (4)

(b) (4)

MK-8742 significantly reduced the number of resistant colonies at 100-fold and 1,000-fold EC_{90} value selections in GT3a. Two main amino acid substitutions, E92K and Y93H, were identified. The antiviral activity of MK-8742 is significantly reduced (~4,400-fold less potent) against GT3a Y93H compared to the wild-type (Table 12). Attempts to propagate cells harboring the E92K variant for phenotypic analysis have been unsuccessful indicating a low replication fitness in these cell culture assays. (b) (4)

(b) (4)

In GT4 replicon cells, MK-8742 showed a dose-dependent reduction in the number of resistant colonies up to 30X EC_{90} value (Table 14, study report MK-8742 PD003, pg. 14). Population nucleotide sequence analysis revealed that amino acid substitutions L30F/S, M31V, and Y93H were most prevalent. In addition to these changes, a novel N69K substitution was also observed. The N69K substitution confers ~2-fold reduced susceptibility to MK-8742 and was not detected as a treatment-emergent substitution in the limited number of virologic failures in the sponsor's clinical studies (Table 17). At the highest dose tested, all colonies retained a single amino acid substitution: L30S. The L30S change caused a 6-fold reduced susceptibility to MK-8742. The pooled resistant colonies selected at the highest dose were 40-fold more resistant relative to cells treated with DMSO.

Table 14: Summary of Resistance Selections in GT4a Replicon Cells.

Cell Line	Treatment (multiple of EC_{90})	Number of Resistant Colonies Selected	Activity in Pooled Resistant Colonies, EC_{90} (nM)	Fold Shift (Relative to DMSO)	Resistant Variants[b]
GT4a (ED43)	1X	TMTC[a]	0.0004	0.8	ND
	3X	TMTC	0.003	6	L30F (30%), M31V (5%), Y93H (5%)
	10X	144	0.017	34	L30F (30%), L30P (10%), M31V (5%), N69K (50%), Y93H (70%)
	30X	35	0.020	40	L30S (100%)

a TMTC = Too many to count.
b Key amino acid substitutions deduced from population sequencing of resistant colonies and quantified based on peaks from the electropherogram.
ND = No variant detected.

In a chimeric GT5a_SA13 replicon (in the background of JFH-1), similar numbers of resistant colonies were observed at [redacted] (b) (4) EC_{90} value. Population nucleotide sequence analysis of colonies revealed 2 amino acid substitutions: L28F and L31F at these doses (Table 15, study report MK-8742 PD003, pg. 15). The resistant colonies selected at the highest dose that bear primarily the L31F amino acid substitution caused [redacted] (b) (4) reduced susceptibility to MK-8742. The reduction in antiviral activity of MK-8742 against the L28F variant was [redacted] (b) (4) [redacted] (b) (4) [redacted] (b) (4)

Table 15: Summary of Resistance Selections in GT5a Replicon Cells.

Cell Line	Treatment (multiple of EC_{90})	Number of Resistant Colonies Selected	Resistant Variants[b]
[redacted] (b) (4)			

Resistance selection studies in a chimeric GT6a replicon (in the background of JFH-1) showed a reduction in the number of resistant colonies with increasing concentrations of MK-8742. Population nucleotide sequence analysis of pooled colonies identified 2 amino acid substitutions: F28S and L31F (Table 16, study report MK-8742 PD003, pg. 17). The reduction in potency of MK-8742 in the pooled resistant colonies selected with the highest dose of the compound was [redacted] (b) (4). Replicons bearing the substitution encoding for F28S fail to grow likely due to low replication fitness. When engineered into replicons, the L31F substitution caused [redacted] (b) (4) reduction in susceptibility to MK-8742. Resistance information with respect to GT6 will not be included in the label as Zepatier® will not be approved for this genotype.

Table 16: Summary of Resistance Selections in GT6a Replicon Cells.

Cell Line	Concentration (multiple of EC90)	Number of Resistant Colonies Selected	Activity in pooled resistant Colonies, EC90 (nM)	Fold shift (Relative to DMS0)	Resistant Variants[b]
[redacted] (b) (4)					

In summary, resistance emerged easily and most occurred at positions previously shown to be associated with resistance to other NS5A inhibitors. The following substitutions emerged for each genotype:

- GT1a: Q30D, Y93N
- GT1b: L31F, Y93H, V121I
  (b) (4)
  (b) (4)
- GT4a: L30F/P/S, M31V, N69K, Y93H
  (b) (4)
  (b) (4) (b) (4)

2.2.7. Cross-resistance (Study Reports MK-8742-PD003, MK-5172-PD010)

The antiviral activity of MK-8742 was evaluated using a panel of GT1a, GT1b, GT2a, GT3a, GT4a, GT5a, or GT6a replicon cell lines engineered to encode substitutions reported in pre-clinical or clinical studies of NS5A inhibitors, including those that were identified in the MK-8742 cell culture selection studies (Table 17, pharmacol-written-summary, pg. 62-63).

Table 17: Activity of MK-8742 against GT1a, 1b, 2a, 3a, 4a, 5a, and 6a Replicons Expressing NS5A Resistance-Associated Substitutions.

Replicon	EC_{50} ± SD (nM)	Fold Shift (vs. WT)	EC_{90} ± SD (nM)	Fold Shift (vs. WT)
1a H77 (WT)	0.004 ± 0.002	1.0	0.006 ± 0.002	1.0
1a M28V	0.008 ± 0.002	2.0	0.013 ± 0.007	2.2
1a Q30D	3.7 ± 1.7	925	8 ± 3.5	1333.0
1a Q30E	0.1 ± 0.07	25.0	0. 15 ± 0.03	25.0
1a Q30H	0.03 ± 0.002	7.5	0.2 ± 0.09	33.3
1a Q30K	0.006 ± 0.003	2	0.059 ± 0.014	9.8
1a Q30R	0.5 ± 0.5	125.0	2.5 ± 1.6	417.0
1a L31F	0.08 ± 0.04	20.0	0.6 ± 0.4	100.0
1a L31M	0.002± 0.001	0.5	0.009 ± 0.004	1.5
1a L31V	0.5 + 0.3	125.0	1.0 ± 0.6	167.0
1a Y93C	0.2 ± 0.07	50.0	1.1 ± 0.3	183.0
1a Y93H	2.4 ± 1.3	600.0	28 ± 26	4667.0
1a Y93N	8	2000.0	18.0	3000.0
1a Q30D/Y93N	180	45000.0	371.0	61833.0
1b con1 (WT)	0.003 ± 0.001	1.0	0.006 ± 0.004	1.0
1b L28M	0.006 + 0.003	2.0	0.02 ± 0.006	3.3
1b L28V	0.004 + 0.001	1.3	0.01 ± 0.004	1.7
1b R30Q	0.009 ± 0.003	3.0	0.02 ± 0.007	3.3
1b L31F	0.05 ± 0.02	16.7	0.2	33.3
1b L31V	0.01 ± 0.01	3.3	0.07 + 0.03	11.7
1b Q62E	0.007	2.3	0.0	2
1b L31V/Q62E	0.01	3.3	0.0	5.0
1b Y93C	0.005 ± 0.001	1.7	0.01 ± 0.002	1.7
1b Y93H	0.05 ± 0.03	17	0.4 ± 0.2	66.7
1b Q62E/Y93H	0.04	13.3	0.2	33.3

(b) (4)

Replicon	EC_{50} + SD (nM)	Fold Shift (vs. WT)	EC_{90} + SD (nM)	Fold Shift (vs. WT)
[redacted] (b) (4)				
4a_DQ418782	0.003	1.0	0.016	1.0
4a L30H	0.72 ± 0.28	240.0	2.39 ± 0.97	149.0
4a M31V	0.01	3.3	0.06	3.8
4a P32L	0.014 ± 0.01	4.7	0.045 ± 0.01	2.6
4a Y93H	0.069	23.0	0.25	15.6
4a_ED43	0.0002 ± 0.0001	1.0	0.0008 ± 0.0001	1.0
4a_ED43 L30F	0.003 ± 0.002	15.0	0.015 ± 0.011	19.0
4a_ED43 L30P	0.0002± 0.0001	1.0	0.0004 ± 0.0002	0.5
4a_ED43 L30S	0.0008± 0.0005	4.0	0.0043 ± 0.0036	5.4
4a_ED43 M31V	0.0005± 0.0004	2.5	0.0009 ± 0.0007	1.1
4a_ED43 N69K	0.0003 ± 0.0003	2	0.0003 ± 0.0001	0
4a_ED43 Y93H	0.0015 ± 0.0020	8	0.0032 ± 0.0030	4

[redacted] (b) (4)

Red: Amino acid substitutions that were observed to emerge in clinical studies.
Orange: Amino acid substitutions with the same cut-off of the lowest fold change seen clinically.

The following substitutions conferred the same cut-off of the lowest fold change seen clinically (Note: Cut-offs of 0.5-fold, 1.3-fold, and 1.0-fold were used for GT1a, GT1b, and GT4, respectively. (b) (4) [redacted]

- GT1a: M28V, Q30D/E/H/K/R, L31F/M/V, Y93C/H/N. Q30D+Y93N
- GT 1b: L28M/V, R30Q, L31F/V, Q62E, L31V + Q62E, Y93C/H, Q62E+Y93H (b) (4) [redacted] (b) (4) [redacted] (b) (4)
- GT 4a: L30F/H/P/S, M31V, P32L, N69K, Y93H (b) (4) [redacted] (b) (4) [redacted]

The sponsor also conducted a transient transfection assay in GT1a to facilitate the analysis of additional resistance-associated substitutions. The EC_{50} value of MK-8742 for the WT replicons measured in the transiently expressed replicon assay are within 3-fold of those measured in the stable replicon cells (Table 18, pharmacol-written-summary, pg. 65-66).

Table 18: Activity of MK-8742 in GT1a Transient Transfection Assay of Replicons Expressing NS5A Resistance-Associated Substitutions.

Variant	EC_{50} ± SD (nM)[1]	Fold-Shift (*vs.* WT)	Relative Fitness[2]
WT	0.007 ± 0.004	1	1
M28A	0.427 ± 0.22	61	0.16
M28G	500 ± 54	71429	0.17
M28T	0.108 ± 0.03	15	0.78
M28V	0.01 ± 0.01	1	1.03
Q30D	NT	NT	Unfit
Q30E	0.394 ± 0.02	56	0.85

Variant	EC_{50} ± SD (nM)[1]	Fold-Shift (*vs.* WT)	Relative Fitness[2]
Q30G	0.067	10	0.85
Q30H	0.044 ± 0.03	6	1.3
Q30K	0.432 ± 0.13	62	0.81
Q30L	0.006 ± 0.002	1	0.17
Q30R	0.114 ± 0.009	16	0.80
L31F	0.67 ± 0.38	96	0.8
L31M	0.07 ± 0.03	10	1.5
L31V	0.43 ± 0.13	61	0.85
H58D	0.041 ± 0.02	6	0.86
R81M	0.005 ± 0.005	1	1.28
R81S	0.005 ± 0.004	1	0.44
R81W	0.008 ± 0.005	1	0.66
A92P	0.008 ± 0.003	1	0.75
Y93C	0.08 ± 0.004	11	0.3
Y93F	0.012 ± 0.012	2	0.45
Y93H	1.54 ± 0.78	220	0.2
Y93N	6.5 ± 1.25	929	0.5
M28A_Q30H	10 ± 1	1429	0.40
M28T_Q30H	16 ± 1	2286	0.70
Q30H_L31V	10 ± 1	1429	1.10
Q30R_L31F	39 ± 2	5571	0.93
Q30R_L31V	50 ± 10	7143	1.1
Q30R_A92P	0.2 ± 0.14	29	0.53
L31V_Y93H	272 ± 115	38857	0.50
L31V_Y93N	375 ± 145	53571	0.51
K24T_M28T_Q30R	49	7000	1.15
K24Q_M28T_L31M	0.06	9	0.41
K24M_Q30R_R81M	0.48 ± 0.01	69	1.0
M28A_Q30H_L31V	154 ± 7	22000	0.25
M28T_Q30H_L31V	392 ± 34	56000	0.16
M28T_Q30R_L31V	624 ± 97	89143	0.69
M28V_Q30H_L31V	17 ± 5	2429	0.83
M28T_Q30R_L31V_Y93H	5000	714286	0.22

1. Average (N = 1-3).
2. Fitness range: ≤0.02 = unfit; 0.03-0.5 = moderate; >0.5 = fit.

Red: Amino acid substitutions that were observed to emerge in clinical studies.
Orange: Amino acid substitutions with the same cut-off of the lowest fold change seen clinically.

The following substitutions conferred the same cut-off of the lowest fold change seen clinically (Note: A cut-off of 1.0-fold was used.) (FDA analysis):

- GT1a: M28A/G/T/V, Q30E/G/H/K/L/R, L31F/M/V, H58D, R81M/S/W, A92P, Y93C/F/H/N, M28A/T+Q30H, Q30H+L31V, Q30R+L31F/V, Q30R+A92P, L31V+Y93H/N, K24T+M28T+Q30R, K24Q+M28T+L31M, K24M+Q30R+R81M, M28A/T/V+Q30H+L31V, M28T+Q30R+L31V, M28T+Q30R+L31V+Y93H).

3. Clinical Virology Review of Efficacy (GT1)

3.1. Summary of Key Efficacy Studies

The clinical development to support the efficacy of MK-5172 + MK-8742 ± RBV includes 5 Phase 2 or 2/3 clinical trials, and 3 pivotal Phase 3 registration studies that enrolled a total of 1969 subjects (note that subjects in the deferred treatment arms of Studies 052 and 060 are not included in this total as the current application contains only the safety findings in placebo-phase of these studies; subjects in these arms are undergoing active therapy currently). These studies enrolled a diverse population of subjects, including treatment-naïve and treatment-experienced, HCV mono- and HCV/HIV co-infected, and non-

cirrhotic and cirrhotic subjects. The sponsor also included a clinical study enrolling subjects with advanced chronic kidney disease (CKD), a population for which there is an unmet medical need for safe and effective anti-HCV therapy. Table 19 briefly summarizes the key design aspects of these studies. Prior DAA experience was exclusionary for all of these studies except Study 048. Of note this section covers only GT1 and not other GTs, which are described in subsequent sections (GT4: Section 5, GT6: Section 6, GT3: Appendix A8).

Table 19: Overview of Key Phase 2 and Phase 3 Studies.

Phase	Study	Genotype	Regimen	Population(s)	N
2/3	52	1	12 weeks, MK-5172 + MK-8742 (ITG vs. DTG)	CKD Stages 4-5, including dialysis	235 (122 ITG/PK) (113 DTG)
3	60	1, 4, 6	12 weeks, MK-5172 + MK-8742 (ITG vs. DTG)	Treatment naive (± cirrhosis)	421 (316 ITG) (105 DTG)
3	61	1, 4, 6	12 weeks, MK-5172 + MK-8742	HIV co-infected (TN, ± cirrhosis)	218
3	68	1, 4, 6	12 or 16 weeks MK-5172 + MK-8742 ± RBV	P/R treatment-experienced, ± cirrhosis, ±	420
2	35	1, 3	8, 12, or 18 weeks MK-5172 + MK-8742 ± RBV	TN (± cirrhosis) Prior P/R null- responders (± cirrhosis) HIV co-infected (TN, non-cirrhotic)	573
2	47	2, 4, 5, 6	GT2: MK-5172 + MK-8742 + RBV; MK-5172 + RBV For GT4, 5, 6: 12 weeks MK-5172 + MK-8742 ± RBV	TN (non-cirrhotic)	98
2	48	1	12 weeks MK-5172 + MK-8742 + RBV	Prior DAA/P/R failures (± cirrhosis)	79
2	74	1, 3	4, 6, 8, or 12 weeks MK-5172 + MK-8742 + SOF	TN (± cirrhosis)	143

Note: Delayed Treatment Group (DTG) serves as placebo in Studies 052 and 060.
ITG = Immediate Treatment Group.

(b) (4)

3.2. Study 052 (C-SURFER)

Study 052 was a randomized, parallel-group, multi-site, placebo controlled trial of MK-5172 + MK-8742, administered for 12 weeks without ribavirin, among HCV GT1-infected subjects with advanced chronic kidney disease (CKD). Ribavirin was not included in the regimen since it is contraindicated in subjects with advanced CKD. Cirrhotics and non-cirrhotics, as well as subjects who were treatment-naïve or had failed prior P/R HCV therapy, were eligible for enrollment (note: prior DAA experience was exclusionary). The critical feature of this study was the enrollment of only subjects with CKD Stages 4 and 5, including hemodialysis dependent subjects. CKD 4 is defined as estimated Glomerular Filtration Rate (eGFR) of 15-29 mL/min/1.73m^2. CKD 5 is defined as an eGFR <15 mL/min/1.73m^2, including dialysis dependence. The majority of the subjects were to be on maintenance hemodialysis (including subjects awaiting renal transplant and subjects with a previous failed kidney transplant no longer on immunosuppressant therapy).

The study had 3 arms:

1. A total of 11 subjects (6 on hemodialysis and 5 not on hemodialysis) were enrolled in an open label intensive PK arm.

2. A total of 224 subjects were randomized in a 1:1 ratio into one of two blinded arms:
   a. 111 subjects were enrolled in the immediate treatment group: these subjects received MK-5172 100 mg QD + MK-8742 50 mg QD for 12 weeks with 24 weeks of follow-up once dosing was completed.
   b. 113 subjects were enrolled in a deferred treatment group: these subjects received placebo for 12 weeks, followed by a 4-week unblinding period, then 12 weeks of open-label MK-5172/MK-8742 100 mg/50 mg QD, then an additional 24 weeks of follow-up once study medication was completed.

The primary efficacy endpoint of this study was the SVR12 rate (defined as HCV RNA <LLOQ [either TD[u] or TND] 12 weeks following therapy) for the subjects in the combined immediate treatment and intensive PK arms. The primary analysis population was the mITT population. Compared to the ITT population, the mITT population excluded subjects with missing efficacy data due to death or early discontinuation from the study for reasons unrelated to their responses to the HCV treatment. This analysis population was selected because subjects with CKD Grades 4/5 have a high incidence of major cardiovascular events that may lead to study discontinuation.

This reviewer conducted the analysis on both the ITT and mITT population. The overall ITT SVR12 rates were 61/63 (97%) and 54/60 (90%) for subjects infected with HCV GT1a and GT1b, respectively (Table 20, FDA analysis). Of note, genotypic data for non-SVR12 subjects were available for 1 and 4 subjects infected with HCV GT1a and GT1b, respectively; none had NS5A resistance-associated polymorphisms. Two subjects relapsed between follow-up week 12 and week 24; both subjects had NS5A resistance-associated polymorphisms. The overall mITT SVR12 rates were 61/61 (100%) and 54/55 (98%) for subjects infected with HCV GT1a and GT1b, respectively. There was one subject (infected with HCV GT1b) who experienced relapse in this study by the SVR12 analysis timepoint. The median baseline HCV RNA levels were 1.6 x 10^6 IU/ml (n=61) and 6.2 x 10^5 IU/ml (n=55) for subjects infected with HCV GT1a and GT1b, respectively. Of note, there were 2 subjects infected with HCV GT1a who achieved SVR12 but relapsed by SVR24 (subjects 5172-052_054100001 & 5172-052_061000002). Both of these subjects were non-cirrhotic and had baseline HCV RNA >800,000 IU/mL (please see section 4.5.2. for more details).

Table 20: SVR12 Rates in Study 052.

	HCV GT1a		HCV GT1b	
	ITT (n=63)	**mITT (n=61)**	**ITT (n=60)**	**mITT (n=55)**
SVR12	61/63 (97%)[1]	61/61 (100%)	54/60 (90%)	54/55 (98%)
Any VF	0/63 (0%)	0/61 (0%)	1/60 (2%)	1/55 (2%)
Breakthrough	0/63 (0%)	0/61 (0%)	0/60 (0%)	0/55 (0%)
Relapse	0/63 (0%)	0/61 (0%)	1/60 (2%)	1/55 (2%)
Others	2/63 (3%)	0/61 (0%)	5/60 (8%)	0/55 (0%)
Treatment Naïve	52/53 (98%)	52/52 (100%)	44/49 (90%)	44/44 (100%)
P/R Experienced	9/10 (90%)	9/9 (100%)	10/11 (91%)	10/11 (90%)
IL28B CC	13/13 (100%)	13/13 (100%)	15/19 (79%)	15/15 (100%)
IL28B CT	25/25 (100%)	25/25 (100%)	28/29 (97%)	28/29 (97%)
IL28B TT	23/24 (96%)	23/23 (100%)	10/10 (100%)	10/10 (100%)
IL28B Unknown	0/1 (0%)	0/0 (100%)	1/2 (50%)	1/1 (100%)
≤800,000 IU/mL	21/22 (95%)	21/21 (100%)	29/32 (91%)	29/29 (100%)
>800,000 IU/mL	40/41 (98%)	40/40 (100%)	25/28 (89%)	25/26 (96%)
Cirrhotic	5/6 (83%)	5/5 (100%)	1/1 (100%)	1/1 (100%)
Non-Cirrhotic	56/57 (98%)	56/56 (100%)	53/59 (90%)	53/54 (98%)

1. Two subjects with GT1a achieved SVR12 but relapsed by SVR24.

3.3. Study 060 (C-EDGE Treatment Naive)

Study 060 was a randomized, parallel-group, double-blinded, placebo-controlled, multisite study that evaluated the efficacy and safety of MK-5172/MK-8742 (100mg/50mg FDC) among treatment-naïve GT 1-, 4-, or 6-infected, HCV-mono-infected subjects with or without cirrhosis. Subjects were randomized in a 3:1 ratio to one of two arms:

- Immediate treatment arm: MK-5172/MK-8742 for 12 weeks, then 24 weeks of follow-up.
- Deferred treatment arm: placebo for 12 weeks, then a 4 week pause, then MK-5172/MK-8742 for 12 weeks (open-label), with 24 weeks of follow-up once dosing had been completed.

Randomization was stratified by fibrosis stage (Metavir F0-F3 vs. F4) and HCV genotype/subtype (GT1a vs. GT1b vs. GT4/6).

A total of 421 subjects enrolled: 105 in the deferred treatment arm and 316 in the immediate treatment arm. Efficacy was evaluated in the immediate treatment arm. Safety was evaluated by comparing adverse experience profiles of the immediate and deferred treatment arms.

The primary objective of the study was to evaluate the efficacy of MK-5172/MK-8742 as assessed by the proportion of subjects in the immediate treatment arm achieving SVR12, defined as HCV RNA <LLOQ (either TD[u] or TND) 12 weeks after the end of all study therapy.

The overall ITT SVR12 rates were 144/157 (92%) and 129/131 (98%) for subjects infected with HCV GT1a and GT1b, respectively (Table 21, FDA analysis). There were more subjects who experienced virologic failure in subjects infected with GT1a than GT1b (10/157 [6%] vs. 1/131 [1%]). All of the subjects who failed treatment had baseline HCV RNA >800,000 IU/mL. There were no clear differences between IL28B CC vs. IL28B non-CC subjects or between cirrhotic and non-cirrhotic subjects. The median baseline HCV RNA levels were 1.5 x 10^6 IU/ml (n=157) and 1.5 x 10^6 IU/ml (n=131) for subjects infected with HCV GT1a and GT1b, respectively.

Table 21: SVR12 Rates in Study 060 (HCV GT1).

	HCV GT1a (n=157)	HCV GT1b (n=131)
SVR12	144/157 (92%)	129/131 (98%)
Any VF	10/157 (6%)	1/131 (1%)
Breakthrough	1/157 (1%)	0/131 (0%)
Relapse	9/157 (6%)	1/131 (1%)
Others	3/157 (2%)	1/131 (1%)
IL28B CC	41/46 (89%)	47/48 (98%)
IL28B CT	79/87 (91%)	62/62 (100%)
IL28B TT	23/23 (100%)	20/20 (100%)
IL28 Unknown	1/1 (100%)	0/1 (0%)
≤800,000 IU/mL	43/43 (100%)	38/38 (100%)
>800,000 IU/mL	101/114 (89%)	91/93 (98%)
<6 Million IU/mL	133/144 (92%)	118/120 (98%)
>6 Million IU/mL	11/13 (85%)	11/11 (100%)
Cirrhotic	32/34 (94%)	34/34 (100%)
Non-Cirrhotic	112/123 (91%)	95/97 (98%)

3.4. Study 061 (C-EDGE Treatment-Naïve HIV Co-infected)

Study 061 was an open-label, multicenter study that evaluated the safety, tolerability, and efficacy of MK-5172/MK-8742 100mg/50mg FDC among treatment-naïve, HIV co-infected, HCV GT 1, 4 and 6 - infected subjects with or without cirrhosis. A total of 218 subjects were enrolled. All subjects were dosed with MK-5172/MK-8742 100 mg/50 mg QD for 12 weeks, with 24 weeks of follow-up once dosing had been completed. With respect to HIV-related eligibility criteria, eligible subjects were to have unquantifiable plasma HIV-1 RNA (HIV-1 RNA <20 copies/mL) based on the Roche COBAS

Ampliprep/Taqman v 2.0® assay and a $CD4^+$ T-cell count ≥200 cells/mm^3 while on a stable antiretroviral (ARV) treatment regimen. Because of drug interaction concerns with the anti-HCV regimen, the only eligible HIV-1 ARV regimens in the original protocol included dual NRTI backbone of tenofovir/emtricitabine or abacavir/lamivudine PLUS raltegravir [or dolutegravir or rilpivirine].

The primary efficacy endpoint of the study was to evaluate the efficacy of MK-5172/MK-8742 as assessed by the proportion of subjects achieving SVR12, defined as HCV RNA <LLOQ (either TD[u] or TND) 12 weeks after the end of all study therapy.

The overall ITT SVR12 rates were 136/144 (94%) and 42/44 (95%) for subjects infected with HCV GT1a and GT1b, respectively (Table 22, FDA analysis). All of the virologic failures were relapsers. There was a trend towards more subjects who failed treatment having baseline HCV RNA >800,000 IU/mL. There were no clear differences between IL28B CC vs. IL28B non-CC subjects or between cirrhotic and non-cirrhotic subjects. The median baseline HCV RNA levels were 1.8 x 10^6 IU/ml (n=144) and 6.6 x 10^5 IU/ml (n=44) for subjects infected with HCV GT1a and GT1b, respectively.

Table 22: SVR12 Rates in Study 061 (HCV GT1).

	HCV GT1a (n=144)	HCV GT1b (n=44)
SVR12	136/144 (94%)	42/44 (95%)
Any VF	5/144 (3%)	1/44 (2%)
Breakthrough	0/144 (0%)	0/44 (0%)
Relapse	5/144 (3%)	1/44 (2%)
Others	3/144 (2%)	1/44 (2%)
IL28B CC	56/59 (95%)	8/8 (100%)
IL28B CT	63/67 (94%)	26/27 (96%)
IL28B TT	17/18 (94%)	8/9 (89%)
≤800,000 IU/mL	50/52 (96%)	25/26 (96%)
>800,000 IU/mL	86/92 (93%)	17/18 (94%)
<6 Million IU/mL	127/135 (94%)	42/44 (95%)
>6 Million IU/mL	9/9 (100%)	0
Cirrhotic	19/19 (100%)	12/12 (100%)
Non-Cirrhotic	117/125 (94%)	30/32 (94%)

All subjects had HIV-1 RNA <20 copies/mL at the last available on anti-HCV treatment visit or at the last available post-treatment follow-up visit. However, two subjects on ARV experienced transient HIV-1 viremia during the treatment period, defined as HIV-1 RNA >200 copies on 2 consecutive visits measured at least 2 weeks apart.

- Subject AN191524 is a non-cirrhotic, HIV-1 co-infected, GT1a-infected subject previously on an ARV regimen of abacavir, lamivudine and ritonavir boosted atazanavir, and an additional dose of abacavir for the diagnosis of neurocognitive impairment. The ARV regimen was changed to abacavir, lamivudine and dolutegravir. The subject's HIV-1 viral load was undetectable at screening. Scheduled laboratory monitoring at Day 1 revealed HIV viral load of 361 copies/mL. Repeat laboratory evaluation at TW4 revealed HIV viral load on 9,638 copies/mL. According to the sponsor, the subject had been erroneously taking an alternate ARV regimen consisting of dolutegravir, abacavir, and ritonavir. The subject was educated and counseled regarding the appropriate ARV regimen of abacavir, lamivudine and dolutegravir. The subject was continued in the study without any missed study drug. Repeat labs at TW8 and TW12 revealed an undetectable HIV viral load.
- Subject AN191550 is a non-cirrhotic, HIV-1 co-infected, GT1a-infected subject on an ARV regimen of abacavir, lamivudine, and raltegravir. Routine laboratory evaluation at TW4 showed HIV-1 viral load of 304 copies/mL. Repeat testing at TW8 showed HIV-1 viral load of 3,810 copies/mL. The site was contacted and provided additional history. The site reports that while

the subject takes the medication every day, sometimes the subject takes both raltegravir tablets at the same time, in order not to forget the second dose. The site performed additional education with the subject regarding the ARV regimen. Repeat evaluation showed HIV viral load of 30 copies/mL performed at the central lab, and 23 copies/mL performed at the local lab. This subject was compliant with the prescribed ARV, was continued on the same regimen, and was undetectable at follow-up testing.

Both of these subjects were not considered to be virologic failures so HIV-1 resistance analyses were not conducted.

$CD3^+$ $CD4^+$ cells were monitored for any change from baseline. Overall, there were no clinically meaningful changes in $CD3^+$ $CD4^+$ cell counts during the study and through FW12 (mean/median chance from baseline at FW12 were 34.92 $CD3^+$ $CD4^+$/µL and 32 $CD3^+$ $CD4^+$/µL, respectively). Of note, Viekira Pak treatment resulted in decrease in lymphocyte levels (see review from Dr. Patrick R. Harrington for NDA 206619). AbbVie speculated that the decrease is due to the inclusion of RBV in the treatment regimen. Given that MK-5172/MK-8742 does not include RBV in this population, decrease in lymphocyte levels was not expected.

3.5. Study 068 (C-EDGE P/R Treatment Experienced)

Study 068 was a randomized, parallel-group, multi-site, open label trial of MK-5172/MK-8742 100 mg/50 mg fixed-dose combination (FDC) tablets administered once daily with or without RBV for 12 or 16 weeks among subjects with HCV GT 1, 4, or 6 infection who experienced virologic failure after prior treatment with pegylated interferon α and ribavirin (P/R). HIV-1 infected subjects were eligible for enrollment. The trial randomized 420 subjects in a 1:1:1:1 ratio to treatment with MK-5172/MK-8742 QD for 12 weeks ± RBV or for 16 weeks ± RBV. Randomization was stratified by the presence or absence of cirrhosis and by prior P/R treatment response (relapser, partial responder or null responder).

The primary efficacy endpoint was the proportion of subjects achieving SVR12, which is defined as HCV RNA <LLOQ (either TD[u] or TND) 12 weeks after the end of all study therapy.

<u>MK-5172 100 mg + MK-8742 50 mg for 12 Weeks</u>
The overall ITT SVR12 rates were 55/61 (92%) and 34/34 (100%) for subjects infected with HCV GT1a and GT1b, respectively (Table 23 & Table 24, FDA analysis). There were more subjects who experienced virologic failure in subjects infected with GT1a than GT1b. All of the subjects who failed treatment had baseline HCV RNA >800,000 IU/mL. There were no clear differences between IL28B CC vs. IL28B non-CC subjects or between cirrhotic and non-cirrhotic subjects. The median baseline HCV RNA levels were 2.1 x 10^6 IU/ml (n=61) and 1.9 x 10^6 IU/ml (n=34) for subjects infected with HCV GT1a and GT1b, respectively.

<u>MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks</u>
The overall ITT SVR12 rates were 56/60 (93%) and 28/29 (97%) for subjects infected with HCV GT1a and GT1b, respectively (Table 23 & Table 24, FDA analysis). There were more subjects who experienced virologic failure in subjects infected with GT1a than GT1b. Most of the subjects who failed treatment had baseline HCV RNA >800,000 IU/mL. There were no clear differences between IL28B CC vs. IL28B non-CC subjects or between cirrhotic and non-cirrhotic subjects. The median baseline HCV RNA levels were 2.1 x 10^6 IU/ml (n=61) and 1.9 x 10^6 IU/ml (n=34) for subjects infected with HCV GT1a and GT1b, respectively.

MK-5172 100 mg + MK-8742 50 mg for 16 Weeks

The overall ITT SVR12 rates were 45/48 (94%) and 46/48 (96%) for subjects infected with HCV GT1a and GT1b, respectively (Table 23 & Table 24, FDA analysis). There were more subjects who experienced virologic failure in subjects infected with GT1a than GT1b. All of the subjects who failed treatment had baseline HCV RNA >800,000 IU/mL. There were no clear differences between IL28B CC vs. IL28B non-CC subjects or between cirrhotic and non-cirrhotic subjects. The median baseline HCV RNA levels were 2.7 x 10^6 IU/ml (n=48) and 1.8 x 10^6 IU/ml (n=48) for subjects infected with HCV GT1a and GT1b, respectively.

MK-5172 100 mg + MK-8742 50 mg + RBV for 16 Weeks

The overall ITT SVR12 rates were 55/58 (95%) and 36/36 (100%) for subjects infected with HCV GT1a and GT1b, respectively (Table 23 & Table 24, FDA analysis). All of the failures were non-virologic failures, likely due to the toxicities of longer treatment with RBV. All of the subjects who failed treatment had baseline HCV RNA >800,000 IU/mL. There were no clear differences between IL28B CC vs. IL28B non-CC subjects or between cirrhotic and non-cirrhotic subjects. The median baseline HCV RNA levels were 1.9 x 10^6 IU/ml (n=58) and 1.2 x 10^6 IU/ml (n=36) for subjects infected with HCV GT1a and GT1b, respectively.

Table 23: SVR12 Rates in Study 068 (HCV GT1a; P/R Treatment-Experienced Subjects).

	MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	MK-5172 100 mg + MK-8742 50 mg for 16 Weeks	MK-5172 100 mg + MK-8742 50 mg + RBV for 16 Weeks
SVR12	55/61 (90%)	56/60 (93%)	45/48 (94%)	55/58 (95%)
Any VF	5/61 (8%)	4/60 (7%)	3/48 (6%)	0/58 (0%)
Breakthrough	0/61 (0%)	0/60 (0%)	0/48 (0%)	0/58 (0%)
Relapse	5/61 (8%)	4/60 (7%)	3/48 (6%)	0/58 (0%)
Others	1/61 (2%)	0/60 (0%)	0/48 (0%)	3/58[1] (5%)
≤800,000 IU/mL	11/11 (100%)	15/15 (100%)	7/7 (100%)	9/9 (100%)
>800,000 IU/mL	44/50 (88%)	41/45 (91%)	38/41 (93%)	46/49 (94%)
Cirrhotic	19/21 (90%)	14/16 (88%)	17/18 (94%)	22/22 (100%)
Non-Cirrhotic	36/40 (90%)	42/44 (95%)	28/30 (93%)	33/36 (92%)

1. Two of the subjects achieved SVR4.

Table 24: SVR12 Rates in Study 068 (HCV GT1b; P/R Treatment-Experienced Subjects).

	MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	MK-5172 100 mg + MK-8742 50 mg for 16 Weeks	MK-5172 100 mg + MK-8742 50 mg + RBV for 16 Weeks
SVR12	34/34 (100%)	28/29 (97%)	46/48 (96%)	36/36 (100%)
Any VF	0/34 (0%)	1/29 (3%)	1/48 (2%)	0/36 (0%)
Breakthrough	0/34 (0%)	0/29 (0%)	0/48 (0%)	0/36 (0%)
Relapse	0/34 (0%)	1/29 (3%)	1/48 (2%)	0/36 (0%)
Others	0/34 (0%)	0/29 (0%)	1/48 (2%)	0/36 (0%)
≤800,000 IU/mL	8/8 (100%)	4/5 (80%)	10/10 (100%)	15/15 (100%)
>800,000 IU/mL	26/26 (100%)	24/24 (100%)	36/38 (95%)	21/21 (100%)
Cirrhotic	9/9 (100%)	14/14 (100%)	16/16 (100%)	9/9 (100%)
Non-Cirrhotic	25/25 (100%)	14/15 (93%)	30/32 (94%)	27/27 (100%)

In P/R treatment-experienced subjects, MK-5172+MK-8742+RBV for 16 Weeks minimizes relapse in GT1a P/R treatment-experienced subjects. There was no obvious benefit of adding RBV or extending treatment for GT1b in this study. **These data support MK-5172+MK-8742 for 12 weeks in P/R-experienced subjects infected with HCV GT1b regardless of cirrhosis, baseline viral load, or HIV-1 co-infection. These data support MK-5172+MK-8742+RBV for 16 Weeks in P/R-experienced subjects infected with HCV GT1a as the addition of RBV and longer treatment duration will minimize relapse.**

3.6. Study 035 (C-WORTHy)

Study 035 was a multicenter, randomized, parallel-group trial that evaluated MK-5172 with MK-8742 ± RBV for treatment of hepatitis C. The protocol was conducted in 4 parts as follows:

Part A

Part A was a dose-response evaluation of MK-5172 + MK-8742 ± RBV for 12 weeks in subjects who were treatment-naïve (TN), non-cirrhotic with genotype (GT)1 infection. Fifty-two (52) subjects were randomized in a 1:1 ratio to 2 treatment arms (A1 and A2) in which open label MK-5172 100 mg once daily (QD) was administered with double-blind MK-8742 doses of either 20 or 50 mg QD and twice daily (BID) with RBV. A third arm (A3) of 13 GT1b-infected subjects received MK-5172 100 mg QD + MK-8742 50 mg, (no RBV). In all arms, subjects were treated for 12 weeks.

Part B

Part B was an open label evaluation of MK-5172 100 mg QD + MK-8742 50 mg QD ± RBV for 8, 12, or 18 weeks in diverse study populations, including subjects with or without cirrhosis, HCV/HIV co-infection, or prior null treatment response to P/R. Part B was open label with respect to the dose of therapy administered, but the investigators and subjects were blinded to the assigned treatment duration through Week 8 or Week 12. A total of 406 subjects, who had screening HCV GT1 and HCV RNA ≥10,000 IU/mL, were randomized to 13 arms. Enrollment in treatment arms that included evaluations of both HCV GT1a- and GT1b-infected subjects were managed such that at least 40% of subjects enrolled in each arm had GT1a infection. Additionally, in the subject population of prior null responders, enrollment was stratified by the presence or absence of cirrhosis. The population of prior null responders included at least 70% who had experienced <2-log reduction in HCV RNA at TW 12 of a peg-IFN/RBV regimen, while the remainder (up to 30%) were allowed to fulfill the definition of null responder as a subject with <1-log reduction in HCV RNA at TW4.

Part C

An additional 61 treatment-naïve, non-cirrhotic subjects with HCV GT1b were randomized into 2 arms (C1 and C2). These subjects were treated for 8 weeks with MK-5172 100 mg + MK-8742 50 mg ± RBV.

Overall efficacy and virologic failure rates in HCV GT1 are summarized in Table 25 (FDA analysis). Administration of a 12 week regimen of once daily administration of MK-5172 100 mg + MK-8742 50 mg, without ribavirin, results in high efficacy among:

- Treatment-naïve, non-cirrhotic, GT1 HCV mono-infected subjects (Arms A1-A3, B1-B3)
- Treatment-naïve, non-cirrhotic, GT1 HCV/HIV co-infected subjects (Arms B12-B13)
- Treatment-naïve, cirrhotic, GT1 HCV infected subjects (Arms B4-B7)
- Prior Peg-interferon/ribavirin null-responder, GT1 HCV infected subjects with or without cirrhosis (Arms B8-B11)

Lengthening the duration of therapy to 18 weeks, adding RBV, or both numerically increased the proportion of subjects who achieve SVR12 (note: based on small number of subjects). Administration of an 8-week regimen of once-daily administration of MK-5172 100 mg + MK-8742 50 mg, with or without ribavirin, results in high efficacy among HCV treatment-naïve, non-cirrhotic, HCV GT1b-infected subjects; an 8-week duration of therapy is suboptimal for treatment of HCV GT1a infection. The most common form of virologic failure following treatment with MK-5172 + MK-8742 is relapse. Of note, there were two subjects infected with HCV GT1a (subjects 5172-035_020200014 & 5172-035_037200004) who achieved SVR12 but relapsed by SVR24 (Please see Section 5.5.2. for more details).

Table 25: SVR12 and Virologic Failure Results in Study 035 (GT1).

		HCV GT1a					HCV GT1b					HCV GT1-Other				
Arm	**Dur. (Wks)**	**N**	**SVR12**	**Breakthrough**	**Relapse**	**Other**	**N**	**SVR12**	**Breakthrough**	**Relapse**	**Other**	**N**	**SVR12**	**Breakthrough**	**Relapse**	**Other**
A1	12	19	18/19 (95%)	0/19 (0%)	0/19 (0%)	1/19 (5%)	6	6/6 (100%)	0/6 (0%)	0/6 (0%)	0/6 (0%)					
A2	12	19	16/19 (84%)	0/19 (0%)	1/19 (5%)	2/19 (11%)	9	9/9 (100%)	0/9 (0%)	0/9 (0%)	0/9 (0%)					
A3	12						12	12/12 (100%)	0/12 (0%)	0/12 (0%)	0/12 (0%)					
B1	8	30	23/30 (77%)	0/30 (0%)	6/30 (20%)	1/30 (3%)										
B2	12	14	14/14 (100%)	0/14 (0%)	0/14 (0%)	0/14 (0%)	17	14/17 (82%)	1/17 (6%)	1/17 (6%)	1/17 (6%)	2	2/2 (100%)	0/2 (0%)	0/2 (0%)	0/2 (0%)
B3	12	30	29/30 (97%)	0/30 (0%)	1/30 (3%)	0/30 (0%)	1	1/1 (100%)	0/1 (0%)	0/1 (0%)	0/1 (0%)					
B4	12	20	18/20 (90%)	0/20 (0%)	2/20 (10%)	0/20 (0%)	10	10/10 (100%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	1	0/1 (0%)	1/1 (100%)	0/1 (0%)	0/1 (0%)
B5	12	20	19/20 (95%)	0/20 (0%)	1/20 (5%)	0/20 (0%)	7	7/7 (100%)	0/7 (0%)	0/7 (0%)	0/7 (0%)	2	2/2 (100%)	0/2 (0%)	0/2 (0%)	0/2 (0%)
B6	18	24	23/24 (96%)	0/24 (0%)	0/24 (0%)	1/24 (4%)	8	8/8 (100%)	0/8 (0%)	0/8 (0%)	0/8 (0%)					
B7	18	23	20/23 (87%)	0/23 (0%)	2/23 (9%)	1/23 (4%)	8	8/8 (100%)	0/8 (0%)	0/8 (0%)	0/8 (0%)					
B8	12	18	16/18 (89%)	0/18 (0%)	0/18 (0%)	2/18 (11%)	14	14/14 (100%)	0/14 (0%)	0/14 (0%)	0/14 (0%)					
B9	12	22	20/22 (91%)	0/22 (0%)	2/22 (9%)	0/22 (0%)	11	10/11 (91%)	0/11 (0%)	1/11 (9%)	0/11 (0%)					
B10	18	19	19/19 (100%)	0/19 (0%)	0/19 (0%)	0/19 (0%)	14	14/14 (100%)	0/14 (0%)	0/14 (0%)	0/14 (0%)					
B11	18	17	16/17 (94%)	1/17 (5%)	0/17 (0%)	0/17 (0%)	15	15/15 (100%)	0/15 (0%)	0/15 (0%)	0/15 (0%)					
B12	12	24	23/24 (96%)	0/24 (0%)	1/24 (4%)	0/24 (0%)	5	5/5 (100%)	0/5 (0%)	0/5 (0%)	0/5 (0%)					
B13	12	22	19/22 (86%)	2/22 (9%)	0/22 (0%)	1/22 (5%)	8	7/8 (88%)	0/8 (0%)	0/8 (0%)	1/8 (13%)					
C1	8						30	27/30 (90%)	0/30 (0%)	2/30 (7%)	0/30 (0%)					
C2	8						31	29/31 (94%)	0/31 (0%)	2/31 (6%)	0/31 (0%)					

A1: TN NC: MK-5172 100 mg + MK-8742 20 mg + RBV for 12 Weeks
A2: TN NC: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks
A3: TN NC/GT1b: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks
B1: TN NC/GT1a: MK-5172 100 mg + MK-8742 50 mg + RBV for 8 Weeks
B2: TN NC: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks
B3: TN NC/GT1a: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks
B4: TN C: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks
B5: TN C: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks
B6: TN C: MK-5172 100 mg + MK-8742 50 mg + RBV for 18 Weeks
B7: TN C: MK-5172 100 mg + MK-8742 50 mg for 18 Weeks
B8: NR: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks
B9: NR: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks
B10: NR: MK-5172 100 mg + MK-8742 50 mg + RBV for 18 Weeks
B11: NR: MK-5172 100 mg + MK-8742 50 mg for 18 Weeks
B12: TN HIV NC: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks
B13: TN HIV NC: MK-5172 100 mg + MK-8742 50 mg for 12 Weeks
C1: TN NC/GT1b: MK-5172 100 mg + MK-8742 50 mg + RBV for 8 Weeks
C2: TN NC/GT1b: MK-5172 100 mg + MK-8742 50 mg for 8 Weeks

Reference ID: 3839313

3.7. Pooled Analysis (GT1)

Among treatment-naïve, HCV GT1 infected subjects, the overall ITT SVR12 rates in MK-5172 100 mg + MK-8742 50 mg for 12 weeks treatment arms were 136/144 (94%) and 42/44 (95%) for subjects infected with HCV GT1a and GT1b, respectively (Table 26, FDA analysis). All of the virologic failures were relapsers. There was a trend towards more subjects who failed treatment having baseline HCV RNA >800,000 IU/mL. There were no clear differences between IL28B CC vs. IL28B non-CC subjects or between cirrhotic and non-cirrhotic subjects. **These data support MK-5172+MK-8742 for 12 weeks in all treatment-naïve subjects with HCV GT1b regardless of cirrhosis, baseline viral load, or HIV-1 co-infection. The SVR12 rate in HCV GT1a is numerically lower relative to what was observed for Harvoni (label) or Viekira Pak (label).**

Table 26: SVR12 Rates in Studies 035, 060, 061 (HCV GT1; Treatment-naïve subjects).

	HCV GT1a (n=373)	HCV GT1b (n=203)
SVR12	347/373 (93%)	198/203 (98%)
Any VF	20/373 (5%)	2/203 (1%)
Breakthrough	3/373 (1%)	0/203 (0%)
Relapse	17/373 (5%)	2/203 (1%)
Others	6/373 (2%)	3/203 (1%)
IL28B CC	118/126 (94%)	60/61 (98%)
IL28B CT	185/202 (92%)	105/107 (98%)
IL28B TT	43/44 (98%)	33/34 (97%)
IL28 Unknown	1/1 (100%)	0/1 (0%)
≤800,000 IU/mL	103/105 (98%)	71/72 (99%)
>800,000 IU/mL	244/268 (91%)	127/131 (97%)
≤ 6 Million IU/mL	306/327 (94%)	182/186 (98%)
>6 Million IU/mL	41/46 (89%)	16/17 (94%)
Cirrhotic	70/73 (96%)	53/53 (100%)
Non-Cirrhotic	277/300 (92%)	145/150 (97%)
HCV Monoinfected	192/207 (93%)	149/151 (99%)
HIV coinfected	155/166 (93%)	49/52 (94%)

3.8. Study 048 (C-SALVAGE)

Study 048 was an open-label, single arm study of MK-5172 + MK-8742 + RBV in subjects with HCV genotype (GT) 1 infection who failed a prior approved NS3/4A protease inhibitor-containing regimen of boceprevir, simeprevir, or telaprevir taken concomitantly with peg-interferon α and RBV (P/R). A total of 79 subjects with HCV GT1 infection, of whom 43% were cirrhotic, received open label MK-5172 100 mg QD + MK-8742 50 mg QD + RBV (weight-based, twice daily) for 12 weeks and were followed up for an additional 24 weeks.

For inclusion, all subjects must have received at least 4 weeks of treatment with a DAA on the prior regimen, and approximately 80% of subjects must have met criteria for virologic failure (with or without resistance-associated substitutions) on the prior regimen. Other subjects may have failed a prior regimen for reasons such as adverse events (AEs) or administrative reasons (such as withdrawal of consent or non-compliance). There were 23/30 (77%) subjects infected with HCV GT1a and 11/49 (22%) subjects infected with HCV GT1b who had identifiable PI-resistance associated polymorphisms or substitutions that were selected by their previous treatment. There were 8/30 (27%) subjects infected with HCV GT1a and 1/49 (2%) subjects infected with HCV GT1b who had the NS3 R155K or A156S/T (most common resistance pathways for boceprevir) substitutions at baseline. There were 8/30 (27%) subjects infected with HCV GT1a and 3/49 (6%) subjects infected with HCV GT1b who had the NS3 R155K or D168E/N/V (most common resistance pathways for simeprevir) substitutions at baseline. There were 8/30 (27%) subjects infected with HCV GT1a and 1/49 (2%) subjects infected with HCV GT1b who had the NS3 R155K or A156S/T (most common resistance pathways for telaprevir) substitutions at baseline.

The primary efficacy endpoint was the proportion of subjects achieving SVR12, defined as HCV RNA <15 IU/mL (either TD[u] or TND) 12 weeks after the end of study therapy.

The overall ITT SVR12 rates were 28/30 (93%) and 48/49 (98%) for subjects infected with HCV GT1a and GT1b, respectively (Table 27, FDA analysis). All of the virologic failures were relapsers. There was a trend towards that more subjects who failed treatment had baseline HCV RNA >800,000 IU/mL. There were no clear differences between IL28B CC vs. IL28B non-CC subjects or between cirrhotic and non-cirrhotic subjects.

Table 27: SVR12 Rates in Study 048.

	HCV GT1a (n=30)	HCV GT1b (n=49)
SVR12	28/30 (93%)	48/49 (97%)
Any VF	2/30 (7%)	1/49 (2%)
Breakthrough	0/30 (0%)	0/49 (0%)
Relapse	2/30 (7%)	1/49 (2%)
Others	0/30 (0%)	0/49 (0%)
IL28B CC	1/1 (100%)	1/1 (100%)
IL28B CT	18/19 (95%)	34/34 (100%)
IL28B TT	9/10 (90%)	13/14 (93%)
≤800,000 IU/mL	6/7 (86%)	20/20 (100%)
>800,000 IU/mL	22/23 (96%)	28/29 (97%)
Cirrhotic	9/10 (90%)	23/24 (96%)
Non-Cirrhotic	19/20 (95%)	25/25 (100%)

Numerically lower SVR12 rates were observed in subjects with PI resistance-associated substitutions at baseline (Table 28, FDA analysis). While the numbers are small, the overall SVR12 rates in these subjects are still reasonable (GT1a:12/14, 86%; GT1b: 8/9, 89%). All 3 subjects who failed treatment were relapsers. Subject 480035 was infected with GT1a and was a boceprevir + P/R relapser. The subject had NS3 R155T and D168N boceprevir resistance-associated substitutions at baseline. The subject developed an additional NS3 A156T substitution on-treatment. Subject 480048 was infected with GT1a and was a telaprevir + P/R failure who experienced breakthrough during the P/R-tail. The subject had NS3 V36L and R155K telaprevir resistance-associated substitutions as well as NS5A H58D polymorphism. The subject developed the NS3 A156T and D168N substitutions on-treatment. Subject 480043 was infected with GT1b and was a telaprevir + P/R who experienced breakthrough during the P/R-tail. The subject had NS3 T54S telaprevir resistance-associated substitution as well as an NS5A L31M polymorphism. The subject developed the NS3 A156T substitution on-treatment. There were 7/28 (25%), 5/8 (63%), and 11/43 (26%) subjects with detectable boceprevir, simeprevir, and telaprevir resistance-associated substitutions at baseline, respectively. For boceprevir, NS3 V36A/G/I/L/M, T54A/C/G/S, V55A/I, V107I, R155C/G/K/M/Q/T, A156F/N/S/T/V, V158I, D168A/E/F/H/V/N, I/V170A/F/T/V, and M175L were considered. For simeprevir, NS3 Q80K, S122A/G/R, R155C/G/K/M/Q/T, D168A/E/F/H/V/N, and I/V170T were considered. For telaprevir, NS3 V36A/G/I/L/M, T54A/S, V55A/I, I132V, R155C/G/K/M/Q/T, A156F/N/S/T/V, and D168A/E/F/H/V/N were considered. However, if all of the above resistance-associated substitutions are considered regardless of the prior PI treatment, there were 10/28 (36%), 5/8 (63%), and 19/43 (44%) with detectable resistance-associated substitutions at baseline in the boceprevir, simeprevir, and telaprevir treatment-experienced subgroups, respectively.

Table 28: SVR12 Rates in Study 048 by Prior Mode of Failure.

	HCV GT1a	HCV GT1b
P/R+BOC Breakthrough	4/4 (100%)	1/1 (100%)
P/R+BOC Relapser	0/1 (0%)	10/10 (100%)

	HCV GT1a	HCV GT1b
P/R+BOC Nonresponder	2/2 (100%)	3/3 (100%)
P/R+BOC Other	3/3 (100%)	4/4 (100%)
With Any BOC Resistance at BL	3/4 (75%)	3/3 (100%)
With BOC Resistance at BL at position 56, 155, 156, or 168	0/1 (0%)	0/0 (0%)
P/R+SMV Relapser	1/1 (100%)	2/2 (100%)
P/R+SMV Nonresponder	2/2 (100%)	1/1 (100%)
P/R+SMV P/R Tail Breakthrough	0/0 (0%)	1/1 (100%)
P/R+SMV Other	1/1 (100%)	0/0 (0%)
With Any SIM Resistance at BL	3/3 (100%)	2/2 (100%)
With SMV Resistance at BL at position 56, 155, 156, or 168	3/3 (100%)	1/1 (100%)
P/R+TPV Breakthrough	3/3 (100%)	0/0 (0%)
P/R+TPV Relapser	2/2 (100%)	10/10 (100%)
P/R+TPV Nonresponder	5/5 (100%)	3/3 (100%)
P/R+TPV P/R Tail Breakthrough	3/4 (75%)	10/11 (91%)
P/R+TPV Other	2/2 (100%)	3/3 (100%)
With Any TPV Resistance at BL	6/7 (86%)	3/4 (75%)
With TPV Resistance at BL at position 56, 155, 156, or 168	5/6 (83%)	1/1 (100%)

For subjects infected with HCV GT1a, SVR12 was achieved in 4/4 (100%), 7/8 (88%), and 2/2 (100%) subjects with NS3 V36A/M, R155K, and V36M+R155K substitution at baseline, respectively (Table 29). These substitutions were the most common treatment-emergent substitutions for boceprevir, simeprevir, and telaprevir failures for GT1a. These data support an indication for GT1a. For subjects infected with HCV GT1b, SVR12 was achieved in 2/2 (100%), 1/2 (50%), and 2/2 (100%) subjects with NS3 V36A, T54A/S, and D168E/N substitution at baseline, respectively. There were no subjects with NS3 V55A, A156S/T, or I/V170A substitutions. The sponsor did not enroll enough subjects with key resistance-associated substitution at baseline for GT1b to understand fully the impact of prior PI-based treatment failure on MK-5172 + MK-8742 + RBV efficacy. However, of the 49 GT1b subjects, 22 subjects were PI+P/R relapsers and an additional 12 subjects were breakthrough during the P/R tail. Of these 34 subjects, 33 subjects achieved SVR12 with MK-5172+MK-8742+RBV for 12 weeks treatment. Additionally, substitutions at position D168 generally do not persist as long as the R155K substitution, which may partially explain the difference in the number of subjects enrolled. Given these results, this reviewer also supports an indication for GT1b although the label should clearly state all of the NS3 resistance-associated substitutions that were present at baseline.

Table 29: SVR12 Rates in Subjects with Resistance-Associated Substitutions at Key NS3 Positions

	HCV GT1a	HCV GT1b
V36A/M	4/4 (100%)	2/2 (100%)
T54A/S	2/2 (100%)	1/2 (50%)
V55A	0/0 (0%)	0/0 (0%)
R155K	7/8 (87%)	0/0 (0%)
A156S/T	1/1 (100%)	0/0 (0%)
D168E/N/V	0/1 (0%)	2/2 (100%)
I/V170A	0/0 (0%)	0/0 (0%)
V36M+R155K	2/2 (100%)	0/0 (0%)

boceprevir resistance substitution frequencies (GT1a; 1b): V36M (40%), R155K (45%), T54S (13%); T54A/S (47%), I/V170A (19%), A156S (16%), V55A (13%)
simeprevir resistance substitution frequencies (GT1a; 1b): R155K (77%); D168V/E (78%)
telaprevir resistance substitution frequencies (GT1a; 1b): V36M (49%), R155K (56%), V36M+R155K (40%); V36A, T54A/S, A156T (6-15%)

In GT1a, there were 28/29 (97%) vs 0/1 (0%) subjects without/with NS5A M/L28A/T, Q/R30H/K/R, L31F/M/V, H58D, Y93C/H/N polymorphisms who achieved SVR12. There were 25/26 (96%) vs 3/4

(75%) subjects without/with NS5A M/L28A/G/T/V, Q/R30H/K/L/R, L31F/M/V, H58D, Y93C/H/N/S polymorphisms who achieved SVR12. In GT1b, there were 45/45 (100%) vs 3/4 (75%) subjects without/with NS5A M/L28A/T, Q/R30H/K/R, L31F/M/V, H58D, Y93C/H/N polymorphisms who achieved SVR12. There were 44/44 (100%) vs 4/5 (80%) subjects without/with NS5A M/L28A/G/T/V, Q/R30H/K/L/R, L31F/M/V, H58D, Y93C/H/N/S polymorphisms who achieved SVR12.

These data support MK-5172+MK-8742+RBV for 12 weeks in boceprevir/simeprevir/telaprevir + P/R experienced subjects. However, this reviewer recommends prescreening for NS5A polymorphisms and 16 weeks of treatment for subjects with the NS5A polymorphisms (assuming similar or greater impact as in PI-treatment-naïve subjects). Additionally, the label should state the number of subjects who were enrolled for each key resistance-substitution and that only a few subjects with SMV experience were evaluated in this study. It should also be clear that these data do not constitute an evaluation of efficacy for prior SMV/SOF treatment failures, which is an important distinction as subjects who failed SMV/SOF may be particularly difficult to treat and are also more likely (compared to BOC or TVR experienced subjects) to have D168 resistance-associated substitutions that are key MK-5172 resistance pathways.

4. Clinical Virology Review of Drug Resistance (GT1)

4.1. Overview of Treatment-Emergent Resistance Analyses

For each HCV DAA target, an analysis of treatment-emergent amino acid substitutions was conducted pooling data from non-SVR subjects who received the MK-5172/MK-8742 +/- RBV regimen in the Phase 2 and Phase 3 studies. Baseline and Post-Baseline NS3/4A and NS5A population nucleotide sequence analysis data were available from 85 subjects (70 GT1a and 15 GT1b). Of these 85 subjects, 4 experienced on-treatment virologic failure and 81 experienced virologic relapse. Paired Baseline/Post-Baseline analyses were conducted to identify treatment-emergent substitutions. All amino acid positions across the 2 drug targets were analyzed and potentially novel resistance-associated substitutions were flagged if they emerged in Post-Baseline samples from at least 2 subjects. The following positions were considered as “known” resistance-associated positions based on previous analyses conducted by the sponsor or others (see reviews by Dr. Patrick R. Harrington for NDA 206619 SDN 000 and Lisa K. Naeger for NDA 205834 SDN 000):

- NS3/4A (1a/1b): NS3 V36, F43, T54, V55, Y56, Q80, I/V132, R155, A156, D168, I/V170, E357, and NS4A V23
- NS5A (1a/1b): K24, M/L28, P29, Q/R30, L31, P32, H/Q54, H/P58, E/Q62, A92 and Y93

(Note: The sponsor’s site-directed mutant phenotype data for MK-5172 variants observed in subjects who experienced virologic failure during the Phase 1, 2 and early phase 3 studies can be found in the Appendix A6. For substitutions that were first observed in the Phase 3 studies, replicon cell lines will need to be established before drug resistance evaluation can be performed. The data for these variants will be provided as soon as they are available after the NDA submission.)

4.2. NS3/4A (MK-5172) Treatment-Emergent Substitutions

Based on paired Baseline/Post-Baseline analyses, the following NS3/4A substitutions emerged in the viruses from non-SVR subjects who received MK-5172/MK-8742 +/- RBV regimen in the Phase 2/3 studies (Table 30, FDA analysis) (Yellow=not listed in sponsor’s draft label; *of these, only Q80K and E357K are known NS3/4A inhibitor resistance-associated substitutions*):

- GT1a subjects (n=70): NS3 V36L/M, I48V, Y56H, Q80K, V107I, R155K, A156G/T/V, D168x (including A, E, N, V, Y, with A most common), T185S, E357G/K
- GT1b subjects (n=15): NS3 Y56F, V107I, A156T, T185S

Table 30: Treatment-Emergent NS3/4A Substitutions.

	All Virologic Failures with Available Data		≥12 Wk Duration Arms	
Substitution	**GT1a (n=70)**	**GT1b (n=15)**	**GT1a (n=37)**	**GT1b (n=8)**
V36L/M	6 (9%)	0 (0%)	4 (11%)	0 (0%)
I48V	2 (3%)	0 (0%)	1 (3%)	0 (0%)
Y56H	6 (9%)	0 (0%)	5 (14%)	0 (0%)
Y56F/H	6 (9%)	1 (7%)	5 (14%)	1 (13%)
Q80K	2 (3%)	0 (0%)	0 (0%)	0 (0%)
V107I	2 (3%)	1 (7%)	1 (3%)	1 (13%)
R155I/K	3 (4%)	0 (0%)	2 (5%)	0 (0%)
A156G/T/V	13 (19%)	1 (7%)	13 (35%)	1 (13%)
V158A	2 (3%)	0 (0%)	2 (5%)	0 (0%)
D168A	15 (21%)	0 (0%)	13 (35%)	0 (0%)
D168A/E/N/V/Y	20 (29%)	0 (0%)	18 (49%)	0 (0%)
T185S	1 (1%)	1 (7%)	1 (3%)	1 (13%)
E357G/K	3 (4%)	0 (0%)	3 (8%)	0 (0%)
Any substitution at the above positions (excluding those highlighted in yellow)	35 (50%)	2 (13%)	29 (78%)	2 (25%)
Any substitution at the above positions detected at the time of virologic failure, including those that were detected at baseline (excluding those highlighted in yellow)	36 (51%)	4 (27%)	29 (78%)	4 (50%)
≥2 Tx Emergent Substitutions (excluding those highlighted in yellow)	13 (19%)	1 (7%)	11 (30%)	1 (13%)

Yellow=not listed in sponsor's draft label.

The most commonly observed treatment-emergent substitutions in NS3/4A were A156G/T/V (mostly T) and D168A/E/N/V/Y (mostly A) in subjects infected with GT1a. In subjects infected with GT1b treatment-emergent substitutions in NS3/4A included Y56F, V107I, A156T and T185S, but none of these were observed in more than 1 GT1b infected subject. Overall, 51% of GT1a virologic failures and 13% of GT1b virologic failures had viral populations with at least 1 treatment-emergent resistance-associated substitution in NS3/4A. Excluding the 4-, 6-, and 8-week treatment duration arms in studies 035 and 074, treatment-emergent NS3/4A resistance-associated substitutions were detected in 78% and 25% of GT1a and GT1b virologic failure subjects' viruses, respectively.

(b) (4)

(b) (4)

[redacted]

4.3. NS5A (MK-8742) Treatment-Emergent Substitutions

Based on paired Baseline/Post-Baseline analyses, the following NS5A substitutions emerged in the viruses from non-SVR subjects who received MK-5172/MK-8742 +/- RBV regimen in the Phase 2/3 studies (Table 31, FDA analysis) (Yellow=not listed in sponsor's draft label; *K24R and E62D are known although likely minor NS5A inhibitor resistance-associated substitutions*):

- GT1a subjects (n=70): NS5A K24R, M28A/G/T/V, Q30H/K/R/Y, L31F/M/V, H58D, E62D, Y93C/H/N/S, D427N
- GT1b subjects (n=15): NS5A L28M, L31F/V, Y93H

(Note: The sponsor's site-directed mutant phenotype data for MK-8742 of variants observed in subjects who experienced virologic failure during the Phase 1, 2 and early phase 3 studies can be found in the Appendix A7. For substitutions that were first observed in the Phase 3 studies, replicon cell lines will need to be established before drug resistance evaluation can be performed. The data for these variants will be provided as soon as they are available after the NDA submission.)

Table 31: Treatment-Emergent NS5A Substitutions.

	All Virologic Failures with Available Data		≥12 Wk Duration Arms	
Substitution	**GT1a (n=70)**	**GT1b (n=15)**	**GT1a (n=37)**	**GT1b (n=8)**
K24R	2 (3%)	0 (0%)	2 (5%)	0 (0%)
M/L28A/G/M(1b)/T/V	14 (20%)	1 (7%)	7 (19%)	1 (13%)
Q/R30R	24 (34%)	0 (0%)	17 (46%)	0 (0%)
Q/R30H/K/R/Y	28 (40%)	0 (0%)	22 (59%)	0 (0%)
L31M	6 (9%)	0 (0%)	4 (11%)	0 (0%)
L31F/M/V	7 (10%)	2 (13%)	4 (11%)	2 (25%)
H58D	4 (6%)	0 (0%)	3 (8%)	0 (0%)
E62D	2 (3%)	0 (0%)	0 (0%)	0 (0%)
Y93C/H/N/S	9 (13%)	6 (40%)	5 (14%)	5 (63%)
D427N	2 (3%)	0 (0%)	1 (3%)	0 (0%)
Any substitution at the above positions (excluding those highlighted in yellow)	47 (67%)	8 (53%)	30 (81%)	7 (88%)
Any substitution at the above positions detected at the time of virologic failure, including those that were detected at baseline (excluding those highlighted in yellow)	56 (80%)	8 (53%)	37 (100%)	7 (88%)
≥2 Tx Emergent Substitutions	12 (17%)	1 (7%)	7 (19%)	1 (13%)

Yellow=not listed in sponsor's draft label.

The most commonly observed treatment-emergent substitutions in NS5A were M28A/G/T/V (mostly G and T) and Q30H/K/R/Y (mostly R) in subjects infected with GT1a. The most commonly observed treatment-emergent substitution in NS5A was Y93H in subjects infected with GT1b. Overall, 67% of GT1a virologic failures and 53% of GT1b virologic failures had viral populations with at least 1 treatment-emergent resistance-associated substitution in NS5A. Excluding the 4-, 6-, and 8-week treatment duration arms in studies 035 and 074, treatment-emergent NS3/4A resistance-associated substitutions were detected in 81% and 88% of GT1a and GT1b virologic failure subjects' viruses, respectively.

Several of the substitutions listed above (highlighted in yellow) are not presented in the sponsor's draft prescribing information. There were 2 virologic failures whose virus developed the NS5A K24R substitution. One of the subjects had NS5A resistance-associated polymorphisms Q30R and L31M. The other subject also developed NS5A Y93N resistance-associated substitution along with the K24R substitution at time of failure. The K24R substitution confers ~2.5-10-fold reduction in susceptibility to ledipasvir in GT1a (see review of Dr. Lisa K. Naeger for NDA 205834, SDN 000). However, there were 7 subjects infected with GT1a virus harboring this polymorphism. SVR12 was achieved in 7 (100%) of the subjects. Additionally, of the 2 virologic failures with treatment-emergent K24R, this substitution emerged late in one subject (subject 5172-060_025200006: on Day 168, virologic failure on Day 113). The NS5A E62 position is possibly associated with resistance to both daclatasvir and ombitasvir. While there were 2 virologic failures whose virus developed the NS5A E62D substitution, there were 2 virologic failures whose virus developed an NS5A D62E substitution, indicating that drug pressure did not preferentially select for the D62 variant. Furthermore, there were 58 subjects infected with GT1a virus harboring this polymorphism. SVR12 was achieved in 54 (93%) of the subjects. The NS5A D427N substitution developed in virus of 2 subjects infected with GT1a virus. Both of these subjects' viruses also developed the NS5A H58D substitution (note: NS5A H58D confers a 6-fold reduced susceptibility to MK-8742). There was one subject infected with GT1a virus harboring a D427N polymorphism. This subject achieved SVR12. There are no available phenotype data of the impact of any of these substitutions on MK-8742 antiviral activity. Substitution D427N is a MK-8742 unique resistance-associated substitution. This reviewer will request the sponsor to phenotype K24R and D427N (with and without NS5A H58D) as a PMR.

There were no examples of emergent substitutions at NS5A V121. The NS5A V121I substitution emerged in cell culture selection studies.

4.4. Overall Summary of Treatment-Emergent Resistance

The numbers of subjects with viral populations that had treatment-emergent resistance-associated substitutions across both drug targets are summarized in Table 32 (FDA analysis). Overall, excluding the 4-, 6-, and 8-week treatment duration arms in studies 052 and 074, NS3/4A and NS5A resistance-associated substitutions emerged in viral populations from 29 (78%) and 30 (81%) GT1a virologic failure subjects, respectively, and in 2 (25%) and 7 (88%) GT1b virologic failure subjects, respectively. Among GT1a virologic failure subjects (4-, 6-, 8-week duration excluded), viral populations with treatment-emergent substitutions in at least one or both drug targets were detected in 36 (97%) and 23 (62%) subjects, respectively. Among GT1b virologic failure subjects (4-, 6-, 8- week duration excluded), viral populations with treatment-emergent substitutions at least one or both drug targets were detected in 8 (100%) and 1 (12%) subjects, respectively.

The detection of resistance was less frequent, at least based on population nucleotide sequence analysis, for the shorter duration arms. A possible explanation for this observation could be that wild-type virus was not completely cleared in many of these subjects and likely outgrew drug resistant virus following cessation of dosing. Additionally, this observation indicates that true virologic failure with the MK-5172/MK-8742 +/- RBV regimen is more likely to be associated with the emergence of resistance-associated substitutions than failure due to non-virologic reasons or a sub-optimal treatment duration.

Table 32: Summary of Treatment-Emergent Resistance-Associated Substitutions.

Target	Substitution	All Virologic Failures with Available Data	≥12 Wk Duration Arms	All Virologic Failures with Available Data	≥12 Wk Duration Arms
		GT1a (n=70)	GT1a (n=37)	GT1b (n=15)	GT1b (n=8)
NS3/4A	Any Tx-Emergent Substitution	36 (51%)	29 (78%)	2 (13%)	2 (25%)
NS5A	Any Tx-Emergent Substitution	47 (67%)	30 (81%)	8 (53%)	7 (88%)
≥1 Tx-Emergent Substitution in NS3/4A or NS5A		54 (77%)	36 (97%)	9 (60%)	8 (100%)
≥1 Tx-Emergent Substitution in NS3/4A and NS5A		28 (40%)	23 (62%)	1 (7%)	1 (12%)
Resistance-associated substitution at time of failure in NS3/4A or NS5A		57 (81%)	37 (100%)	9 (60%)	8 (100%)

4.5 Impact of HCV Polymorphisms (GT1)

The impact of polymorphisms was evaluated using censored virologic failures. The analyses do not include non-virologic failures as well as subjects who did not have evaluable genotypic data. **Of note, SVR12 data were used as SVR24 data are not available for all of the subjects at the time of this review.**

4.5.1. NS3/4A (MK-5172) Polymorphisms at Resistance-Associated Positions

The impact of NS3/4A resistance-associated polymorphism on SVR12 rates was evaluated. The analyses also included NS3 Q80K substitution, which has been shown to impact the efficacy of certain other NS3/4A protease inhibitors, most notably SMV (OLYSIO®, NDA 205123). The polymorphisms detected in the viruses from these subjects include the following (expressed relative to the "wild-type" genotype 1a consensus):

- NS3: V36L/M, Y56F/H, Q80K, V107I, R155I/K, A156G/T/V, V158A, D168A/E/N/V/Y

The impact of NS3 Q80K or other NS3 resistant-associated polymorphism is minimal in both treatment-naïve and P/R treatment-experienced subjects (Table 33 & Table 34; FDA analysis). As expected, NS3 Q80K was a common polymorphism in this group of GT1a subjects. Note that these analyses excluded study 048, which included subjects who previously were exposed to an NS3/4A protease inhibitor (see section 3.8 above), as natural polymorphisms cannot be distinguished from previous drug-selected substitutions in this population.

Table 33: SVR12 Rates in Treatment-Naïve Subjects.

	GT1a		GT1b		GT1a		GT1b	
	Without NS3 Q80K	With NS3 Q80K	Without NS3 Q80K	With NS3 Q80K	Without NS3 RAV (Q80K-excluded)	With NS3 RAV (Q80K-excluded)	Without NS3 RAV (Q80K-excluded)	With NS3 RAV (Q80K-excluded)
Study 052 (TN)	29/29 (100%)	23/23 (100%)	43/43 (100%)	0/0 (0%)	51/51 (100%)	1/1 (100%)	34/34 (100%)	9/10 (90%)
Study 060	85/93 (91%)	59/61 (97%)	127/128 (99%)	2/2 (100%)	134/144 (93%)	10/10 (100%)	96/97 (99%)	33/33 (100%)
Study 061	88/91 (97%)	47/49 (96%)	42/43 (98%)	0/0 (0%)	131/135 (98%)	4/5 (80%)	32/33 (96%)	10/10 (100%)
Study 035 (TN)	48/52	20/20	27/27	0/0 (0%)	65/69	3/3	25/25	2/2

	(92%)	(100%)	(100%)		(94%)	(100%)	(100%)	(100%)
Total (TN)	**250/265 (94%)**	**149/153 (97%)**	**239/241 (99%)**	**2/2 (100%)**	**381/399 (95%)**	**18/19 (95%)**	**187/189 (99%)**	**54/55 (98%)**

Q80K-excluded = NS3 V36L/M, Y56F/H, V107I, R155I/K, A156G/T/V, V158A, D168A/E/N/V/Y

Table 34: SVR12 Rates in P/R Treatment-Experienced Subjects.

	GT1a		GT1b		GT1a		GT1b	
	Without NS3 Q80K	**With NS3 Q80K**	**Without NS3 Q80K**	**With NS3 Q80K**	**Without NS3 RAV (Q80K-excluded)**	**With NS3 RAV (Q80K-excluded)**	**Without NS3 RAV (Q80K-excluded)**	**With NS3 RAV (Q80K-excluded)**
Study 052 (TE): MK-5172+MK-8742 for 12 Wks	4/4 (100%)	5/5 (100%)	10/11 (91%)	0/0 (0%)	9/9 (100%)	0/0 (0%)	6/6 (100%)	4/5 (80%)
Study 068: MK-5172+MK-8742 for 12 Wks	37/39 (95%)	18/21 (86%)	34/34 (100%)	0/0 (0%)	54/59 (92%)	1/1 (100%)	24/24 (100%)	10/10 (100%)
Study 068: MK-5172+MK-8742+RBV for 12 Wks	15/16 (94%)	5/6 (83%)	10/11 (91%)	0/0 (0%)	20/22 (91%)	4/4 (100%)	6/7 (86%)	0/0 (0%)
Study 068: MK-5172+MK-8742 for 16 Wks	30/32 (94%)	15/16 (94%)	46/47 (98%)	0/0 (0%)	43/46 (93%)	2/2 (100%)	30/31 (97%)	16/16 (100%)
Study 068: MK-5172+MK-8742+RBV for 16 Wks	34/34 (100%)	21/21 (100%)	36/36 (100%)	0/0 (0%)	53/53 (100%)	2/2 (100%)	25/25 (100%)	11/11 (100%)
Study 035: MK-5172+MK-8742 for 12 Wks	15/16 (94%)	5/6 (83%)	10/11 (91%)	0/0 (0%)	20/22 (91%)	4/4 (100%)	6/7 (86%)	0/0 (0%)
Study 035: MK-5172+MK-8742+RBV for 12 Wks	14/14 (100%)	2/2 (100%)	14/14 (100%)	0/0 (0%)	15/15 (100%)	1/1 (100%)	9/9 (100%)	5/5 (100%)
Study 035: MK-5172+MK-8742 for 18 Wks	11/12 (92%)	5/5 (100%)	15/15 (100%)	0/0 (0%)	16/17 (94%)	3/3 (100%)	12/12 (100%)	0/0 (0%)
Study 035: MK-5172+MK-8742+RBV for 18 Wks	16/16 (100%)	3/3 (100%)	14/14 (100%)	0/0 (0%)	19/19 (100%)	3/3 (100%)	11/11 (100%)	0/0 (0%)
Total (TE)								
MK-5172+MK-8742 for 12 Wks	**55/57 (96%)**	**25/28 (89%)**	**58/59 (98%)**	**0/0 (0%)**	**78/83 (94%)**	**2/2 (100%)**	**39/39 (100%)**	**19/20 (95%)**
MK-5172+MK-8742+RBV for 12 Wks	**51/54 (94%)**	**20/21 (95%)**	**42/43 (97%)**	**0/0 (0%)**	**67/71 (94%)**	**4/4 (100%)**	**28/28 (100%)**	**14/15 (93%)**
MK-5172+MK-8742 for 16 or 18 Wks	**41/44 (93%)**	**20/21 (95%)**	**61/62 (98%)**	**0/0 (0%)**	**59/63 (94%)**	**5/5 (100%)**	**42/43 (98%)**	**16/16 (100%)**
MK-5172+MK-874+RBV2 for 16 or 18 Wks	**50/50 (100%)**	**24/24 (100%)**	**50/50 (100%)**	**0/0 (0%)**	**72/72 (100%)**	**5/5 (100%)**	**36/36 (100%)**	**11/11 (100%)**

Q80K-excluded = NS3 V36L/M, Y56F/H, V107I, R155I/K, A156G/T/V, V158A, D168A/E/N/V/Y

4.5.2. NS5A (MK-8742) Polymorphisms at Resistance-Associated Positions

The impact of NS5A resistance-associated polymorphisms on SVR12 rates was evaluated. The polymorphisms detected in the viruses from these subjects include the following (expressed relative to the "wild-type" genotype 1a or 1b consensus):

- NS5A (1a/1b reference differences indicated before position number): M/L28A/G/T/V, Q/R30H/K/L/R, L31M/V, H58D, Y93C/H/N/S

In treatment-naïve subjects with GT1a, the SVR12 rates were substantially lower in subjects with NS5A resistance-associated polymorphisms (61% vs 97% or 73% vs 99%, depending on the polymorphisms analyzed) (Table 35, FDA analysis). Note that 'List B' includes all of the polymorphisms in 'List A' but also considers a few additional polymorphisms at these same positions. If you exclude subjects with polymorphisms, the SVR12 rate is 99% compared to overall rates of 95%. As illustrated in Figure 1 (FDA analysis), these differences are statistically significant. In GT1b, the impact of NS5A polymorphisms was minimal. As stated above, there were 2 subjects each in studies 035 & 052 who were infected with HCV GT1a and who achieved SVR12 but relapsed by SVR24. Three of the 4 subjects had NS5A resistance-associated polymorphisms described in list 'A' (subjects 5172-035_037200004, 5172-052_054100001, and 5172-052_061000002). The remaining subject (5172-035_020200014) developed the NS5A Q30R resistance-associated substitution (as well as the NS3 T185S, highlighted in yellow above). In the current analysis, all of these subjects were not considered

virologic failures as they achieved SVR12. If considering the 3 subjects with NS5A polymorphisms who experienced virologic relapse between Post-Treatment Weeks 12 and 24, the SVR rates for those with polymorphisms in List A or List B drop to 11/23 (48%) and 29/44 (66%), respectively. **Therefore, the impact of NS5A resistance-associated polymorphisms is greater when this analysis is conducted using SVR24 rates, and may be even greater if more subjects with NS5A resistance-associated polymorphisms experience late relapse. A careful analysis needs to be conducted when all of the SVR24 data are submitted to this NDA.**

Table 35: SVR12 Rates in Treatment-Naïve Subjects.

	GT1a	GT1b	GT1a		GT1b		GT1a		GT1b	
	Overall		Without 'A'	With 'A'	Without 'A'	With 'A'	Without 'B'	With 'B'	Without 'B'	With 'B'
Study 052 (TN)	52/52 (100%)	43/43 (100%)	46/46 (100%)	6/6 (100%)	36/36 (100%)	7/7 (100%)	45/45 (100%)	7/7 (100%)	35/35 (100%)	8/8 (100%)
Study 060	144/154 (94%)	129/130 (99%)	142/145 (98%)	2/9 (22%)	113/113 (100%)	16/17 (94%)	133/135 (99%)	11/19 (58%)	111/111 (100%)	18/19 (95%)
Study 061	133/138 (96%)	42/43 (98%)	130/134 (97%)	3/4 (75%)	37/38 (97%)	5/5 (100%)	125/128 (98%)	8/10 (80%)	36/37 (97%)	6/6 (100%)
Study 035 (TN)	68/72 (94%)	27/27 (100%)	65/68 (95%)	3/4 (75%)	25/25 (100%)	2/2 (100%)	62/64 (96%)	6/8 (75%)	25/25 (100%)	2/2 (100%)
Total (TN)	**397/416 (95%)**	**241/243 (99%)**	**383/393 (97%)**	**14/23 (61%)**	**211/212 (99%)**	**30/31 (97%)**	**365/372 (99%)**	**32/44 (73%)**	**207/208 (99%)**	**34/35 (97%)**

A = Has an M/L28A/T, Q/R30H/K/R, L31M/V, H58D, or Y93C/H/N polymorphism
B = Has an M/L28A/G/T/V, Q/R30H/K/L/R, L31M/V, H58D, or Y93C/H/N/S polymorphism
For Study 035, only the 12 week w/o RBV arms were considered for this analysis.

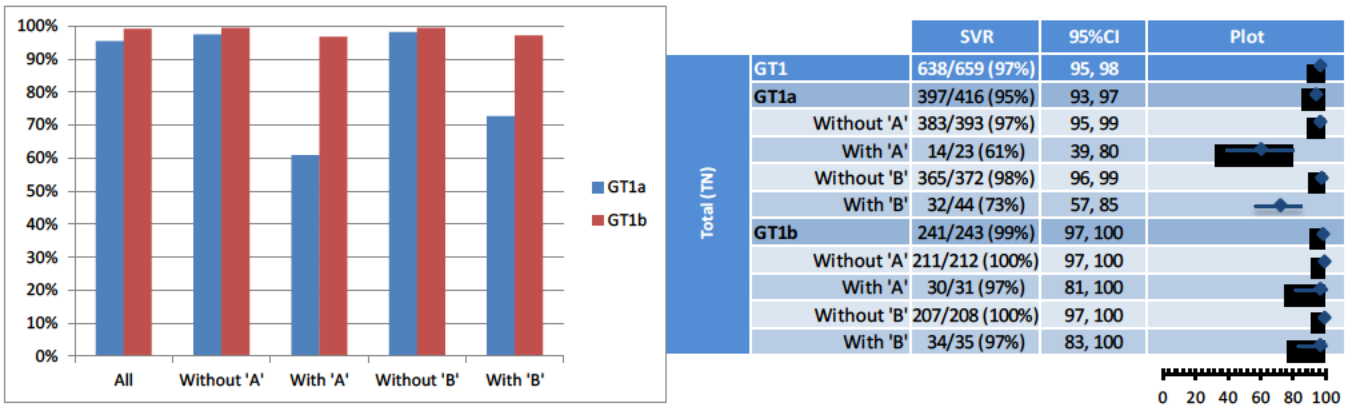


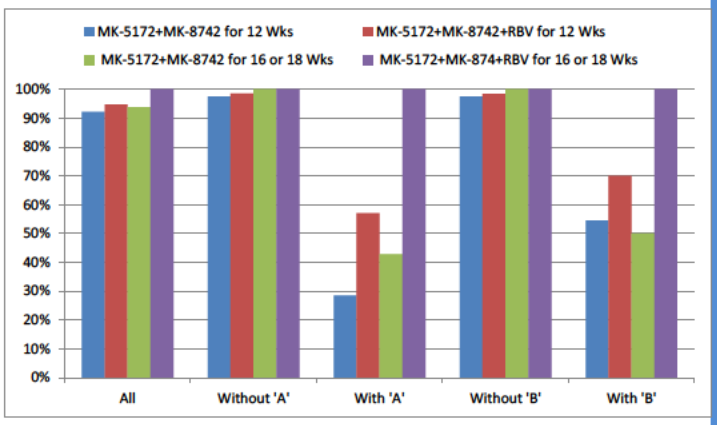
Figure 1: SVR12 Rates in Treatment-Naïve Subjects.
A = Has an M/L28A/T, Q/R30H/K/R, L31M/V, H58D, or Y93C/H/N polymorphism
B = Has an M/L28A/G/T/V, Q/R30H/K/L/R, L31M/V, H58D, or Y93C/H/N/S polymorphism

In P/R treatment-experienced subjects with GT1a, the SVR12 rates were substantially lower in subjects with NS5A resistance-associated polymorphisms, similar to treatment-naïve subjects (Table 36, FDA analysis). If you exclude subjects with the polymorphisms, the SVR12 rate is 98%, even in the MK-5172+MK-8742 for 12 weeks arm (and similar across all 4 arms). Addition of RBV and longer treatment duration (16 wk) may be able to overcome impact of NS5A polymorphisms in GT1a, although this observation is based on small number of subjects. As illustrated in Figure 2 (FDA analysis), these differences are statistically significant in the treatment arms without RBV. In GT1b, the impact of NS5A polymorphisms was minimal albeit the trend was still present (Figure 3, FDA analysis).

Table 36: SVR12 Rates in P/R Treatment-Experienced Subjects.

	GT1a	GT1b	GT1a		GT1b		GT1a		GT1b	
	Overall		Without 'A'	With 'A'	Without 'A'	With 'A'	Without 'B'	With 'B'	Without 'B'	With 'B'
Study 052 (TE): MK-5172+MK-8742 for 12 Wks	9/9 (100%)	10/11 (91%)	9/9 (100%)	0/0 (0%)	8/8 (100%)	2/3 (67%)	9/9 (100%)	0/0 (0%)	8/8 (100%)	2/3 (67%)
Study 068: MK-5172+MK-8742 for 12 Wks	54/59 (92%)	34/34 (100%)	52/53 (99%)	2/6 (33%)	32/32 (100%)	2/2 (100%)	48/49 (98%)	6/10 (60%)	32/32 (100%)	2/2 (100%)
Study 068: MK-5172+MK-8742+RBV for 12 Wks	20/22 (91%)	10/11 (91%)	20/21 (95%)	0/1 (0%)	8/8 (100%)	2/3 (67%)	20/21 (95%)	0/1 (0%)	8/8 (100%)	2/3 (67%)
Study 068: MK-5172+MK-8742 for 16 Wks	45/48 (94%)	46/47 (98%)	43/43 (100%)	2/5 (40%)	39/39 (100%)	7/8 (88%)	42/42 (100%)	3/6 (50%)	38/38 (100%)	8/9 (89%)
Study 068: MK-5172+MK-8742+RBV for 16 Wks	55/55 (100%)	36/36 (100%)	51/51 (100%)	4/4 (100%)	33/33 (100%)	3/3 (100%)	49/49 (100%)	6/6 (100%)	33/33 (100%)	3/3 (100%)
Study 035: MK-5172+MK-8742 for 12 Wks	20/22 (91%)	10/11 (91%)	20/21 (95%)	0/1 (0%)	8/8 (100%)	2/3 (67%)	20/21 (95%)	0/1 (0%)	8/8 (100%)	2/3 (67%)
Study 035: MK-5172+MK-8742+RBV for 12 Wks	16/16 (100%)	14/14 (100%)	15/15 (100%)	1/1 (100%)	12/12 (100%)	2/2 (100%)	15/15 (100%)	1/1 (100%)	12/12 (100%)	2/2 (100%)
Study 035: MK-5172+MK-8742 for 18 Wks	16/17 (94%)	15/15 (100%)	15/15 (100%)	1/2 (50%)	14/14 (100%)	1/1 (100%)	15/15 (100%)	1/2 (50%)	14/14 (100%)	1/1 (7%)
Study 035: MK-5172+MK-8742+RBV for 18 Wks	19/19 (100%)	14/14 (100%)	19/19 (100%)	0/0 (0%)	9/9 (100%)	5/5 (100%)	19/19 (100%)	0/0 (0%)	9/9 (100%)	5/5 (100%)
Total (TE)										
MK-5172+MK-8742 for 12 Wks	**83/90 (92%)**	**54/56 (96%)**	**81/83 (98%)**	**2/7 (29%)**	**48/48 (100%)**	**6/8 (75%)**	**77/79 (98%)**	**6/11 (55%)**	**48/48 (100%)**	**6/8 (75%)**
MK-5172+MK-8742+RBV for 12 Wks	**72/76 (95%)**	**42/43 (98%)**	**68/69 (99%)**	**4/7 (57%)**	**37/37 (100%)**	**5/6 (83%)**	**65/66 (98%)**	**7/10 (70%)**	**37/37 (100%)**	**5/6 (83%)**
MK-5172+MK-8742 for 16 or 18 Wks	**61/65 (94%)**	**61/62 (98%)**	**58/58 (100%)**	**3/7 (43%)**	**53/53 (100%)**	**8/9 (89%)**	**57/57 (100%)**	**4/8 (50%)**	**52/52 (100%)**	**9/10 (90%)**
MK-5172+MK-874+RBV for 16 or 18 Wks	**74/74 (100%)**	**50/50 (100%)**	**70/70 (100%)**	**4/4 (100%)**	**42/42 (100%)**	**8/8 (100%)**	**68/68 (100%)**	**6/6 (100%)**	**42/42 (100%)**	**8/8 (100%)**

A = Has an M/L28A/T, Q/R30H/K/R, L31M/V, H58D, or Y93C/H/N polymorphism
B = Has an M/L28A/G/T/V, Q/R30H/K/L/R, L31M/V, H58D, or Y93C/H/N/S polymorphism



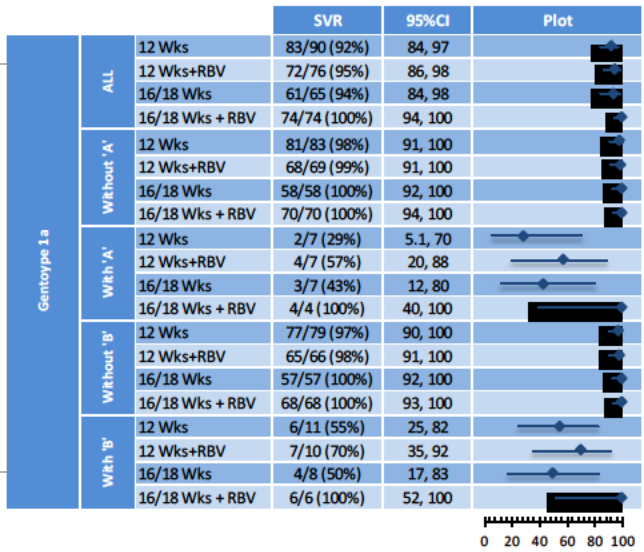
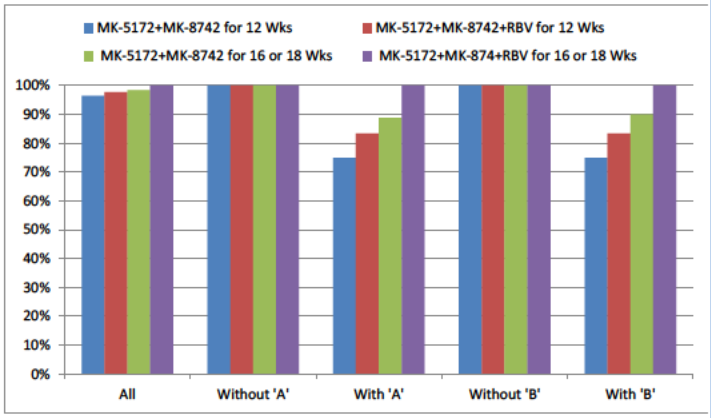


Figure 2: SVR12 Rates in P/R Treatment-Experienced Subjects (GT1a).
A = Has an M28A/T, Q30H/R, L31M, H58D, or Y93C/H/N polymorphism
B = Has an M28A/G/T/V, Q30H/L/R, L31M, H58D, or Y93C/H/N/S polymorphism



			SVR	95%CI	Plot
Gentoype 1b	ALL	12 Wks	54/56 (96%)	87, 99	
		12 Wks+RBV	42/43 (98%)	86, 100	
		16/18 Wks	61/62 (98%)	90, 100	
		16/18 Wks + RBV	50/50 (100%)	91, 100	
	Without 'A'	12 Wks	48/48 (100%)	91, 100	
		12 Wks+RBV	37/37 (100%)	88, 100	
		16/18 Wks	53/53 (100%)	92, 100	
		16/18 Wks + RBV	42/42 (100%)	90, 100	
	With 'A'	12 Wks	6/8 (75%)	36, 96	
		12 Wks+RBV	5/6 (83%)	36, 99	
		16/18 Wks	8/9 (89%)	51, 99	
		16/18 Wks + RBV	8/8 (100%)	60, 100	
	Without 'B'	12 Wks	48/48 (100%)	91, 100	
		12 Wks+RBV	37/37 (100%)	88, 100	
		16/18 Wks	52/52 (100%)	91, 100	
		16/18 Wks + RBV	42/42 (100%)	90, 100	
	With 'B'	12 Wks	6/8 (75%)	36, 96	
		12 Wks+RBV	5/6 (83%)	36, 99	
		16/18 Wks	9/10 (90%)	54, 99	
		16/18 Wks + RBV	8/8 (100%)	60, 100	

0 20 40 60 80 100

Figure 3: SVR12 Rates in P/R Treatment-Experienced Subjects (GT1b).
A = Has an L28M, R30H/K, L31M/V, or Y93H polymorphism
B = Has an L28M/V, R30H/K/L, L31M/V, or Y93H/S polymorphism

The SVR12 rates for subjects with polymorphisms were compared to the baseline HCV RNA levels (Table 37, FDA analysis). The impact of NS5A polymorphisms is greater with higher baseline HCV RNA levels.

Table 37: SVR12 Rates of Subjects with Polymorphisms Stratified by Baseline HCV RNA Levels.

	≤800,000 IU/mL		>800,000 IU/mL	
	GT1a	GT1b	GT1a	GT1b
With List 'A'	6/6 (100%)	15/16 (94%)	21/42 (50%)	42/46 (91%)
With List 'B'	11/11 (100%)	17/18 (94%)	44/68 (65%)	45/49 (92%)
	≤1M IU/mL		>1M IU/mL	
	GT1a	GT1b	GT1a	GT1b
With List 'A'	7/8 (88%)	15/16 (94%)	20/40 (50%)	42/46 (91%)
With List 'B'	13/14 (93%)	17/18 (94%)	42/65 (65%)	45/49 (92%)
	≤1.2M IU/mL		>1.2M IU/mL	
	GT1a	GT1b	GT1a	GT1b
With List 'A'	8/11 (73%)	18/19 (95%)	19/37 (51%)	39/43 (91%)
With List 'B'	16/19 (84%)	21/22 (95%)	39/60 (65%)	41/45 (91%)

A = Has an M/L28A/T, Q/R30H/K/R, L31M/V, H58D, Y93C/H/N polymorphism
B = Has an M/L28A/G/T/V, Q/R30H/K/L/R, L31M/V, H58D, Y93C/H/N/S polymorphism

Of the 24 VFs with BL NS5A resistance-associated polymorphisms (considering the cumulative list in 'List B' and excluding VFs in the <12 week treatment arms), 19 had only one, 4 had two, and 1 had three polymorphisms at baseline. All resistance-associated amino acid positions were associated with reduced SVR12 rates in GT1a (Table 38, FDA analysis). All positions are associated with both phenotypic and treatment-emergent resistance for NS5A inhibitors. Trying to parse out specific resistance-associated polymorphism is challenging given the small numbers of subjects with certain individual polymorphisms. For example, subjects with NS5A M28A or Y93C polymorphism achieved an SVR12 rate of 1/1 (100%) and 5/5 (100%), respectively. However, given the small numbers of subjects and the fact that both of these were also detected as treatment-emergent substitutions in virologic failure subjects and confer >50-fold reductions in susceptibility to MK-8742 in cell culture, it is not possible to conclude these specific polymorphisms have no impact on efficacy when other polymorphisms at the same position are associated with reduced efficacy. Additionally, all of the

virologic failures with NS5A Q30R or Y93H polymorphisms had other polymorphisms (M28V, L31M, or Q30L) which may indicate that these are linked. Finally, there were other NS5A resistance-associated polymorphisms such as NS5A L31F and L31V that were not present in any of the subjects in the sponsor's studies. However, there were subjects in the studies that were conducted for Harvoni® who had an NS5A L31F resistance-associated polymorphism. It is likely that there would be an impact in efficacy for NS5A L31F and L31V polymorphisms given that both also confer >50-fold reduced susceptibility to MK-8742 in cell culture. **Given these challenges, this reviewer believes that all NS5A resistance-associated polymorphisms should be screened at these 5 positions, regardless of whether there were any such subjects in the sponsor's studies or whether SVR12 was achieved in a small number of subjects with a specific variant. These 5 positions are established as clear MK-8742 resistance-associated positions where polymorphisms are demonstrated to reduce MK-5172 + MK-8742 treatment efficacy in HCV GT1a infected patients, with significant resistance-related consequences of virologic failure (as described below). Therefore, with respect to the impact of any particular individual amino acid polymorphism at these positions, the burden of proof should now be on demonstrating the regimen is *not* impacted by that amino acid, which requires sufficient data to make such a claim.** Similar results were observed in GT1b (Table 39, FDA analysis), although as noted above the impact of NS5A polymorphisms on treatment efficacy is clearly less in GT1b compared to GT1a.

Table 38: SVR12 Rates by Position (GT1a).

NS5A Polymorphism at BL	SVR12	Any other polymorphisms for VFs with indicated polymorphism	Fold Shift in Cell Culture
W/O M28A	686/720 (95%)		~60
With M28A	1/1 (100%)		
W/O M28T	684/717 (95%)		~15
With M28T	3/4 (75%)	No other substitution	
W/O M28V	656/686 (96%)		~2
With M28V	31/35 (89%)	1 failure had Q30L, 1 failure H58D; 5 were in RBV arms, all achieved SVR12 i.e. SVR12 87% in non-RBV arms	
W/O Q30H	684/714 (96%)		~7.5
With Q30H	3/7 (43%)	1 had Y93H	
W/O Q30L	686/719 (96%)		~1
With Q30L	1/2 (50%)	Had M28V and Y93H	
W/O Q30R	685/717 (96%)		~125
With Q30R	2/4 (50%)	Both had L31M	
W/O L31M	676/698 (97%)		~0.2 (~10 in transient transfection assay)
With L31M	11/23 (48%)	2 had Q30R	
W/O H58D	687/720 (96%)		~6
With H58D	0/1 (0%)	Had M28V	
W/O Y93C	682/716 (95%)		~50
With Y93C	5/5 (100%)		
W/O Y93H	684/716 (96%)		~600
With Y93H	3/5 (60%)	2 had Q30H, 1 had M28V and Q30L	
W/O Y93N	686/718 (96%)		~929
With Y93N	1/3 (33%)	No other substitution	
W/O Y93S	687/720 (96%)		n/a
With Y93S	0/1 (0%)	No other substitution	

Table 39: SVR12 Rates by Position (GT1b).

NS5A Polymorphism at BL	SVR12	Any other polymorphisms for VFs with indicated polymorphism	Fold Shift in Cell Culture
W/O L28M	444/449 (98%)		~2
With L28M	4/5 (80%)	Has Y93H	
W/O R30H	447/453 (98%)		
With R30H	1/1 (100%)		
W/O R30K	444/450 (98%)		

NS5A Polymorphism at BL	SVR12	Any other polymorphisms for VFs with indicated polymorphism	Fold Shift in Cell Culture
With R30K	4/4 (100%)		
W/O R30L	447/453 (98%)		
With R30L	1/1 (100%)		
W/O L31M	430/433 (99%)		~1
With L31M	18/21 (85%)	No other substitution	
W/O L31V	447/453 (98%)		~3
With L31V	1/1 (100%)		
W/O Y93H	413/417 (99%)		~16
With Y93H	35/37 (94%)	One has L31M	
W/O Y93S	447/453 (98%)		
With Y93S	1/1 (100%)		

The prevalence of the NS5A polymorphisms in GT1a was 7-11% (8-12% in US) (Table 40, FDA analysis). The prevalence of the NS5A polymorphisms in GT1b was 14-15% (11-12% in US). These rates were similar to what were observed in other NS5A inhibitor programs (Table 41, FDA analysis). The prevalence of the NS5A polymorphisms was similar between gender and various ethnic backgrounds (Table 42, FDA analysis). These data indicate that the NS5A polymorphisms are present in a significant proportion of the HCV-infected US population.

Table 40: Prevalence of NS5A Resistance-Associated Polymorphisms.

		Total - GT1a	US - GT1a	Total-GT1b	US-GT1b
TN	Prevalence of 'A'	23/416 (6%)	17/229 (8%)	31/243 (13%)	9/83 (11%)
	Prevalence of 'B'	44/416 (11%)	25/229 (11%)	35/243 (15%)	10/83 (13%)
TE	Prevalence of 'A'	25/305 (8%)	14/162 (8%)	31/211 (15%)	7/59 (11%)
	Prevalence of 'B'	35/305 (12%)	23/162 (14%)	32/211 (15%)	7/59 (11%)
Total	Prevalence of 'A'	48/721 (7%)	31/391 (8%)	62/454 (14%)	16/142 (11%)
	Prevalence of 'B'	79/721 (11%)	48/391 (12%)	67/454 (15%)	17/142 (12%)

A = Has an M/L28A/T, Q/R30H/K/R, L31M/V, H58D, or Y93C/H/N polymorphism
B = Has an M/L28A/G/T/V, Q/R30H/K/L/R, L31M/V, H58D, or Y93C/H/N/S polymorphism

Table 41: Comparison of the Frequencies of the Polymorphisms to other Registration Studies (or pooled datasets).

	MK-5172-MK-8742		Harvoni		Viekira Pak		Asunaprevir*/Daclatasvir	
	GT1a (n=721)	GT1b (n=454)	GT1a (n=863)	GT1b (n=414)	GT1a (n=330)	GT1b (n=185)	GT1a (n=168)	GT1b (n=817)
M/L28A/G/T	1%	0%	2%	0.3%	1%	0%	1%	0%
Q/R30H/K/R	2%	1%	5%	0.3%	2%	1%	1%	2%
L31M/V	3%	5%	4%	5%	1%	5%	1%	4%
H58D	0.1%	0%	0.3%	0%	0%	0%	0%	0%
Y93C/H/N	2%	8%	5%	9%	2%	6%	1%	9%
Total (List A)	**7%**	**14%**	**7%**	**11%**	**5%**	**12%**	**4%**	**15%**
M/L28A/G/T/V	6%	1%	9%	0.3%	8%	0%	5%	0.4%
Q/R30H/K/L/R	2%	1%	5%	0.3%	2%	1%	1%	2%
L31M/V	3%	5%	4%	5%	1%	5%	1%	4%
H58D	0.1%	0%	0.3%	0%	0%	0%	0%	0%
Y93C/H/N/S	2%	8%	5%	15%	2%	6%	1%	10%
Total (List B)	**11%**	**15%**	**14%**	**12%**	**11%**	**12%**	**8%**	**15%**

*not approved

Table 42: Prevalence of NS5A resistance-associated polymorphisms by gender and race.

	Male	Female	White	Black	Hispanic	Asian	Race-Other
GT1a							
Has 'A'	36/507 (7%)	12/214 (5%)	28/472 (6%)	12/150 (8%)	7/62 (11%)	1/26 (4%)	0/11 (0%)
Has 'B'	59/507 (12%)	20/214 (9%)	45/472 (10%)	21/150 (14%)	11/62 (18%)	2/26 (8%)	0/11 (0%)
GT1b							

Has 'A'	37/264 (14%)	25/190 (13%)	44/271 (16%)	4/68 (5%)	4/29 (13%)	10/83 (12%)	0/3 (0%)
Has 'B'	39/264 (15%)	28/190 (15%)	44/271 (16%)	6/68 (9%)	4/29 (14%)	13/83 (16%)	0/3 (0%)

A = Has an M/L28A/T, Q/R30H/K/R, L31M/V, H58D, or Y93C/H/N polymorphism
B = Has an M/L28A/G/T/V, Q/R30H/K/L/R, L31M/V, H58D, or Y93C/H/N/S polymorphism

In GT1a subjects with NS5A polymorphisms who failed treatment, there were 19/26 (73%) subjects who gained an additional NS5A resistance substitution(s) (Table 43, FDA analysis). There were 25/26 (96%) or 15/26 (58%) subjects who gained an NS3 resistance substitution OR an additional NS5A substitution(s), or, gained an NS3 resistance substitution AND an additional NS5A substitution(s), respectively. In GT1b subjects with NS5A polymorphisms who failed treatment, there were 6/6 (100%) subjects who gained an additional NS5A resistance substitution(s). There were 6/6 (100%) or 1/6 (17%) subjects who gained an NS3 resistance substitution OR an additional NS5A substitution(s), or, gained an NS3 resistance substitution AND an additional NS5A substitution(s), respectively. Treatment failure most likely will impact retreatment with Harvoni®, Viekira Pak™, and SIM/SOF.

Table 43: Treatment-Emergent Substitutions amongst Virologic Failures with NS5A Polymorphisms.

	All Virologic Failures with Available Data		Virologic Failure ≥12 Wk Duration	
	GT1a	**GT1b**	**GT1a**	**GT1b**
Has 'A' at baseline and NS5A Tx Emerge	23/32 (72%)	6/6 (100%)	19/26 (73%)	6/6 (100%)
Has 'B' at baseline and NS5A Tx Emerge	28/37 (76%)	6/6 (100%)	22/29 (76%)	6/6 (100%)
Has 'A' at baseline and either NS3 or NS5A Tx Emerge	29/32 (91%)	6/6 (100%)	25/26 (96%)	6/6 (100%)
Has 'B' at baseline and either NS3 or NS5A Tx Emerge	34/37 (92%)	6/6 (100%)	28/29 (97%)	6/6 (100%)
Has 'A' at baseline and either NS3 and NS5A Tx Emerge	16/32 (50%)	1/6 (17%)	15/26 (58%)	1/6 (17%)
Has 'B' at baseline and either NS3 and NS5A Tx Emerge	18/37 (49%)	1/6 (17%)	17/29 (59%)	1/6 (17%)

A = Has an M/L28A/T, Q/R30H/K/R, L31M/V, H58D, or Y93C/H/N polymorphism
B = Has an M/L28A/G/T/V, Q/R30H/K/L/R, L31M/V, H58D, or Y93C/H/N/S polymorphism

4.6. Overall Summary of Polymorphisms

In GT1a, NS5A resistance-associated polymorphisms had a substantial impact on efficacy for both treatment-naive and P/R treatment-experienced subjects. Prevalence of these substitutions was 8-12%. Subjects with NS5A polymorphisms who fail treatment are likely to gain additional NS5A resistance substitutions and NS3/4A PI resistance substitutions. There was a modest impact in GT1b in TE subjects. NS5A polymorphisms are likely the biggest factor impacting efficacy in GT1a. Subjects with these polymorphisms should consider other therapies. Addition of RBV and longer treatment duration (16 wk) may be able to overcome impact of NS5A polymorphisms in GT1a, although this conclusion is based on a small number of subjects. The possible solutions to this issue include:

- Screen for NS5A polymorphisms and consider alternative therapy (i.e., recommend in the label under Limitations of Use or Dosage and Administration). Alternatively, baseline screening could be considered only in patients with baseline viral load >800,000 IU/mL, though this conclusion is based on a small number of subjects.
- Give RBV (and possibly 16 weeks treatment) for all GT1a infected patients. However, up to ~90% of patients will be treated unnecessarily with RBV (and possibly longer duration with all 3 drugs).
- Screen for NS5A polymorphisms (in patients with baseline viral load >800,000 IU/mL) and patients with NS5A polymorphisms can either use alternative therapy or consider adding RBV (and possibly 16 weeks).
- Leave it to AASLD Guidelines (note: AASLD currently recommends SIM/SOF for 24 weeks in GT1a subjects with cirrhosis WITHOUT the NS3 Q80K polymorphism (AASLD Guidelines) even though this was not stated in the drug label).

Several issues were considered for recommending screening for NS5A resistance-associated polymorphisms in the label (Table 44, FDA analysis). There were two other programs (Olysio® and Daklinza®) that considered recommending baseline screening in labels. Unlike what was the situation of these other programs, there are currently two commercially available assays for NS5A testing. Both (b) (4) have NS5A testing now for GT1a and GT1b. There are also better alternatives for subjects with the NS5A polymorphisms. Harvoni®, Viekira Pak™, and SIM/SOF have SVR rates >>90% in the same population. Furthermore, subjects who fail Zepatier® will gain additional NS3/4A and NS5A resistance substitutions, impacting future treatment options. Given these considerations, this reviewer believes that screening for NS5A resistance-associated polymorphisms should be recommended in labeling, or otherwise described prominently in the prescribing information and used for treatment decision making.

Table 44: Comparisons with Other Programs That Considered Baseline Screening.

	Olysio (GT1a)	Daklinza (GT3)	MK-5172+MK-8742 (GT1a)
Are there commercially available assays for NS5A testing at time of NDA approval?	No	No	Yes
Are there better IFN-free alternatives for subjects w/ polymorphisms?	No (only BOC/TPV+P/R was approved)	No (only SOF+RBV for 24wks approved)	Yes (Harvoni®, Viekira Pak™, SIM/SOF approved)
Resistance-related consequence to failure?	Additional PI substitutions that impact PI class (note: next generation PI's like MK-5172 possibility)	No emergence of additional major NS5A resistance substitutions	Will gain additional NS3 and NS5A substitutions (impacting both drug classes)
Impact a significant number of population	Up to 40% of the most common subtype in US (~40%)	Up to 10% of GT3 (~12% in US)	Up to 12% of the most common subtype in US
Baseline Screening Recommendation in Label	Yes	No	Yes (Reviewer's recommendation)

5. Clinical Virology Review of Subjects infected with HCV GT4

5.1. Overview of GT4

HCV GT4 is uncommon in the U.S. but is prevalent in other parts of the world. HCV GT4 is particularly prevalent in the Middle East and certain regions of Africa (Gower et al., 2014; Messina et al., 2015). In the U.S./North America, it is estimated that 1-6% of HCV infected subjects are infected with HCV GT4. However, HCV genotype 4 is extremely genetically diverse, with at least 18 subtypes described (Kamal and Nasser, 2008; Smith et al., 2013). According to a review by Kamal and Nasser (2008), most HCV genotype 4 cases reported from the U.S. have been clustered among intravenous drug users or immigrants from countries where HCV genotype 4 is known to be most prevalent, or among individuals who acquired the infection in these countries, and the prevalence of HCV subtypes may vary due to introduction and spread of new or rare subtypes. The authors reported that subtype 4a is most prevalent in Egypt, subtypes 4c/4d are most prevalent in Saudi Arabia, and the major subtypes reported in Europe include 4a and 4d. Taken together, these observations further emphasize the desire for a regimen with demonstrated efficacy against diverse HCV genotype 4 subtypes that could potentially be represented in the U.S. HCV genotype 4 population.

The sponsor summarized the distribution of HCV GT4 subtypes in the HCV-infected population in the US as follows:

- In a retrospective review of a database of 4,026 consecutive specimens collected between 2007 and 2010 at a Veterans Administration Hospital in Southwest Florida, there were 53 cases of GT4 infection; of these half were GT4a, c, or d; the rest were GT4 (unspecified) (Thomas et al., 2012).

- Among a cohort of 60 GT4 subjects enrolled in a clinical trial of sofosbuvir in Los Angeles in 2012/3, 48 (80%), 6 (10%), 3 (5%), 2 (3%) and 1 (2%) had GT4a, GT4o, GT4n, GT4l, or GT4m infection, respectively (Ruane et al., 2014).
- The Sponsor has access to a database of 56,917 commercially insured HCV patients in the US with laboratory data collected between 2000 and 2009. HCV genotype was available for 8,741 subjects. Of these, 53 subjects were infected with GT4: 33 subjects with GT4 (not otherwise specified) and 20 subjects with GT4a.
- Of the 14 sequences deposited in the [redacted] (b) (4) from American subjects, 13 were identified as GT4a and 1 was identified GT4d (HCV Sequence Database).

Taking these disparate sources of data together, along with the cohort of US subjects enrolled in the clinical program for MK-5172/MK-8742, it appears that the predominant HCV GT4 subtype in the US is GT4a, with GT4o and GT4d representing the next most common GT4 subtypes.

The sponsor has conducted an independent phylogenetic analysis, and BLAST search using the HCV NS3 and NS5A sequences derived from subject samples and compared them with reference sequences obtained from Genbank (summarized in study report 044sth). As summarized in Table 45 (FDA analysis), the most commonly observed GT4 subtypes were 4a and 4d. In the U.S., 19/22 (86%) subjects with available data were infected with HCV subtype 4a.

Table 45: HCV GT4 Subtypes Based on Phylogenetic Analysis.

GT4 Subtypes (Total)	Number of Subjects
4a	54 (48%)
4d	47 (42%)
4k	3 (2%)
4l	1 (<1%)
4o	2 (1%)
4 (analyzed but not determined)	3 (2%)
GT4 Subtypes (U.S.)	**Number of Subjects**
4a	19 (86%)
4d	1 (5%)
4 (analyzed but not determined)	2 (9%)

5.2. Clinical Efficacy in GT4

Table 46 (FDA analysis) summarizes SVR12 rates according to GT4 subtype based on phylogenetic analysis for the pooled analysis across studies 047, 060, and 061 (data on the individual studies are summarized in the Appendix). The overall ITT SVR12 rates in treatment-naïve subjects infected with HCV GT4 were 22/23 (96%), 28/29 (97%), 2/2 (100%), and 2/2 (100%) for subjects infected with HCV GT4a, GT4d, GT4k, and GT4-unknown, respectively. There were no clear differences between IL28B CC vs. IL28B non-CC subjects. There was also not a clear difference between cirrhotic and non-cirrhotic subjects, although results are available for only 6 cirrhotic subjects (all achieved SVR). The median baseline HCV RNA levels were 7.3 x 10^5 IU/ml (n=23), 1.2 x 10^6 IU/ml (n=29), 2.5 x 10^6 IU/ml (n=2), and 6.8 x 10^5 IU/ml (n=2) for subjects infected with HCV GT4a, GT4d, GT4k, and GT4-unknown, respectively.

Table 46: SVR12 Rates in Studies 047, 060, 061 (HCV GT4: treatment naïve; MK+5172+MK-8742 12W).

	HCV GT4-all	HCV GT4a	HCV GT4d	HCV GT4k	HCV GT4-unknown
SVR12	54/56 (96%)	22/23 (96%)	28/29 (97%)	2/2 (100%)	2/2 (100%)
Any VF	1/56 (2%)	0/23 (0%)	1/29 (4%)	0/2 (0%)	0/2 (0%)
Breakthrough	0/56 (0%)	0/23 (0%)	0/29 (0%)	0/2 (0%)	0/2 (0%)
Relapse	1/56 (2%)	0/23 (0%)	1/29 (4%)	0/2 (0%)	0/2 (0%)
Others	1/56 (2%)	1/23 (4%)	0/29 (0%)	0/2 (0%)	0/2 (0%)

	HCV GT4-all	HCV GT4a	HCV GT4d	HCV GT4k	HCV GT4-unknown
IL28B CC	17/17 (100%)	5/5 (100%)	11/11 (100%)	1/1 (100%)	0/0 (0%)
IL28B CT	27/29 (93%)	12/13 (92%)	12/13 (92%)	1/1 (100%)	2/2 (100%)
IL28B TT	10/10 (100%)	5/5 (100%)	5/5 (100%)	0/0 (0%)	0/0 (0%)
≤800,000 IU/mL	25/26 (96%)	12/13 (92%)	12/12 (100%)	0/0 (0%)	1/1 (100%)
>800,000 IU/mL	29/30 (97%)	10/10 (100%)	17/17 (100%)	2/2 (100%)	1/1 (100%)
Cirrhotic	6/6 (100%)	2/2 (100%)	4/4 (100%)	0/0 (0%)	0/0 (0%)
Non-Cirrhotic	48/50 (96%)	20/21 (95%)	24/25 (96%)	2/2 (100%)	2/2 (100%)
HCV Monoinfected	27/28 (96%)	13/14 (93%)	11/11 (100%)	2/2 (100%)	1/1 (100%)
HIV coinfected	27/28 (96%)	9/9 (100%)	17/18 (94%)	0/0 (0%)	1/1 (100%)

Table 47 (FDA analysis) summarizes the SVR12 rates in P/R treatment-experienced subjects (study 068) based on the treatment arms (details of the individual arms are summarized in the Appendix). The numbers are too small to make any conclusions. **The sponsor's proposal, MK-5172 100 mg + MK-8742 50 mg + RBV for 16 Weeks, is a conservative approach to maximize efficacy.**

Table 47: SVR12 Rates in Study 068 (HCV GT4: P/R treatment experienced; MK+5172+MK-8742±RBV 12 or 16W).

	MK-5172 100 mg + MK-8742 50 mg for 12 Weeks	MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks	MK-5172 100 mg + MK-8742 50 mg for 16 Weeks	MK-5172 100 mg + MK-8742 50 mg + RBV for 16 Weeks
GT4-all				
SVR12	7/9 (77%)	14/15 (93%)	3/5 (60%)	8/8 (100%)
Any VF	1/9 (11%)	1/15 (7%)	2/5 (40%)	0/8 (0%)
Breakthrough	0/9 (0%)	0/15 (0%)	2/5 (40%)	0/8 (0%)
Relapse	1/9 (11%)	1/15 (7%)	0/5 (0%)	0/8 (0%)
Others	1/9 (11%)	0/15 (0%)	0/5 (0%)	0/8 (0%)
Cirrhotic	4/6 (67%)	4/5 (80%)	1/2 (50%)	4/4 (100%)
Non-Cirrhotic	3/3 (100%)	10/10 (100%)	2/3 (67%)	4/4 (100%)
GT4a				
SVR12	4/4 (100%)	7/7 (100%)	1/3 (33%)	4/4 (100%)
Any VF	0/4 (0%)	0/7 (0%)	2/3 (67%)	0/4 (0%)
Breakthrough	0/4 (0%)	0/7 (0%)	2/3 (67%)	0/4 (0%)
Relapse	0/4 (0%)	0/7 (0%)	0/3 (0%)	0/4 (0%)
Others	0/4 (0%)	0/7 (0%)	0/3 (0%)	0/4 (0%)
Cirrhotic	2/2 (100%)	3/3 (100%)	1/2 (50%)	3/3 (100%)
Non-Cirrhotic	2/2 (100%)	4/4 (100%)	0/1 (0%)	1/1 (100%)

GT4: 4a (n=18), 4d (n=15), 4k (n=1), 4l (n=1), 4o (n=2)

5.3. Analysis of Polymorphisms at NS3 Resistance-Associated Amino Acid Positions

Baseline NS3 amino acid sequences at positions associated with resistance to NS3/4A protease inhibitors were relatively conserved across HCV GT4 subtypes (Table 48, FDA analysis). There were insufficient numbers of subjects with polymorphisms at NS3 positions of interest to detect a substantial difference in polymorphism frequency between U.S. and non-U.S. study subjects. Of note, a Q80K polymorphism is common in GT1a and is associated with reduced efficacy for some NS3/4A protease inhibitors, but position Q80 was 100% conserved in HCV GT4a and GT4d infected subjects.

Table 48: Frequency of Polymorphisms at NS3/4A Positions Associated with Resistance.

GT4 Subtype	Reference Sequence	N	36	43	54	55	56	80	132	155	156	168	170
4a	ED43	47			S (1)				L (1)				I (6)
4d	ED43	47										E (2)	
4k	ED43	3							L (1)				
4l	ED43	1											
4o	ED43	2											
4	ED43	2											
4a (U.S.)	ED43	16			S (1)				L (1)				I (5)
4a (non-U.S.)	ED43	31											I (1)

4a-ED43 Reference	L	F	T	V	Y	Q	I	R	A	D	V
1a-H77 Reference	V	F	T	V	Y	Q	I	R	A	D	I
1b-Con1 Reference	V	F	T	V	Y	Q	V	R	A	D	V

Numbers in parentheses indicate the total number of subjects with the indicated polymorphisms.

As was observed in GT1, variability in GT4 NS5A amino acid sequences was observed at multiple positions previously described as being associated with resistance to NS5A inhibitors (Table 49, FDA analysis). The "wild-type" consensus sequences at certain positions (e.g., 30, 62) appear to differ across certain subtypes. Importantly, the detection frequencies for NS5A polymorphisms in GT4a sequences did not differ significantly by geographic location (U.S. versus non-U.S.), supporting the pooling of efficacy results for subjects infected with HCV GT4a independent of geographic location.

Table 49: Frequency of Polymorphisms at NS5A Positions Associated with Resistance.

GT4 Subtype	Reference Sequence	N	24	28	29	30	31	32	54	58	62	92	93
4a	ED43	47	S (1)	M (8)		R (6)				S (2), L (1), Y (1)	E (43), M (1), Q (2)		H (1)
4d	PS2	47					L (1)			L (2), S (3), T (19)	A (1), G (1), Q (3)		
4k	QC383	3					L (2)						
4l	QC274	1											
4o	BID-G2038	2											
4	PS2	2											
4a (U.S.)	ED43	16	S (1)	M (6)		R (3)				S (1), Y (1)	E (14), M (1), Q (1)		H (1)
4a (non-U.S.)	ED43	31		M (2)		R (3)				S (1), L (1)	E (29), Q (1)		
4a-ED43 Reference			K	L	P	L	M	P	H	P	D	A	Y
4d-PS2 Reference			K	L	P	R	M	P	H	P	E	A	Y
4k-QC383 Reference			K	L	P	R	M	P	H	P	E	A	Y
4l-QC274 Reference			K	L	P	R	M	P	H	P	E	A	Y
4o-BID-G2038 Reference			K	M	P	T	M	P	H	P	N	A	Y
1a-H77 Reference			K	M	P	Q	L	P	H	H	E	A	Y
1b-Con1 Reference			Q	L	P	R	L	P	Q	P	Q	A	Y

Numbers in parentheses indicate the total number of subjects with the indicated polymorphisms.

Based on paired Baseline/Post-Baseline analyses, the following NS3/4A substitutions emerged in the viruses from non-SVR subjects who received MK-5172/MK-8742 +/- RBV regimen (Table 50, FDA analysis):

- GT4a subjects (n=2): NS3 A156M/T/V, D168A/G, V170I

Based on paired Baseline/Post-Baseline analyses, the following NS5A substitutions emerged in the viruses from non-SVR subjects who received MK-5172/MK-8742 +/- RBV regimen (Yellow=not listed in sponsor's draft label; *H54 is a known position although likely minor NS5A inhibitor resistance-associated substitutions*):

- GT4a subjects (n=2): NS5A L28T, P58D (note: these subjects had L28 and P58 polymorphisms, i.e., these substitutions were switches from L28M and P58Y, respectively).
- GT4d subjects (n=3): NS5A L28S, M31I/V, H54Y, Y93H

In summary, all 5 virologic failures had treatment-emergent resistance-associated substitutions in the NS3/4A and/or NS5A.

Table 50: Treatment-Emergent Amino Acid Substitutions.

USUBJID	Subtype	Virologic Failure Category	NS3/4A	NS5A	NS5A Polymorphism
5172-061_072200004	4d	Relapse		L28S	
5172-068_141400005	4a	Virologic Breakthrough	A156M	L28T	L28M, Y93H
5172-068_141400007	4a	Virologic Breakthrough	A156M/T/V, D168A/G, V170I	P58D	L28M, P58Y
5172-068_158000007	4d	Relapse		L28S, M31I, H54Y	
5172-068_158300004	4d	Relapse		M31V, Y93H	P58T

Yellow: Not included in the sponsor's proposed package insert.
5172-068_141400005 was a switch from NS5A L28M to L28T (i.e., had polymorphism).
5172-068_141400007 was a switch from P58Y to P58D (i.e., had polymorphism).

The impact of baseline NS5A resistance-associated polymorphisms on SVR12 rates was evaluated (Table 51, FDA analysis). The numbers were too small to make any conclusions. However, there was a numerical trend towards more subjects not achieving SVR12 in subjects with NS5A resistance-associated polymorphisms in both treatment-naïve and P/R treatment-experienced subjects. These (b) (

Table 51: Impact of NS5A Polymorphisms on SVR12 Rates.

	5172-047 (TN)		5172-060 (TN)		5172-061 (TN)		Total - TN		5172-068 (TE)	
	W/O	With	W/O	With	W/O	With	W/O	With	W/O	With
GT4a	8/8 (100%)	2/3 (66%)	5/5 (100%)	4/4 (100%)	5/5 (100%)	4/4 (100%)	18/18 (100%)	10/11 (90%)	13/13 (100%)	3/5 (60%)
GT4d	4/4 (100%)	3/3 (100%)	3/3 (100%)	4/4 (100%)	10/11 (90%)	7/7 (100%)	17/18 (94%)	14/14 (100%)	3/4 (75%)	9/11 (81%)
GT4-Other	1/1 (100%)	0/0 (0%)	1/1 (100%)	1/1 (100%)	1/1 (100%)	0/0 (0%)	3/3 (100%)	1/1 (100%)	3/3 (100%)	1/1 (100%)

With or without NS5A L28M/T/V, L/R/T30R(4a), M31L, P58L/S/T/Y, Y93H

The sponsor has determined the frequency of polymorphisms in clinical isolates at amino acid positions 28, 30, 31, 58, and 93 that may confer resistance to NS5A inhibitors in available GT4 subtype sequences. NS5A nucleotide sequences (68 in total) with known GT 4 and subtype designation were retrieved from the HCV database at the (b) (4) In addition, the sub-types of 116 GT4 subjects in the sponsor's clinical database were determined with the aid of the ML phylogenetics software (PhyML) and included in the analysis. All 184 unique sequences were codon aligned and translated into amino acids. The most prevalent subtypes accounting for >70% of all sequences were 4a and 4d (Table 52, efficacy-information-amendment-31aug2015, pg. 2).

Table 52: NS5A GT4 Subtype Sequences Used in Analysis

Sub-type	# of sequences	% of total
4a	75	41
4b	4	2
4c	1	<1
4d	58	32
4f	7	4
4g	3	2
4k	7	4
4l	4	2
4m	3	2
4n	3	2

4o	6	3
4p	1	<1
4q	1	<1
4r	4	2
4t	1	<1
4v	5	3
4*	1	<1

*Subtype unknown.

The frequency of amino acids at positions 28, 30, 31, 58, and 93 in NS5A for each subtype is summarized in Table 53 (efficacy-information-amendment-31aug2015, pg. 3-4). In a few cases, the sequences deposited in the public database contained an ambiguous base call which did not allow determination of the encoded amino acid. Among the 2 most prevalent subtypes, 4a and 4d, the most frequently observed amino acid at the key positions accounted for >75% of the population with one exception at position 58 in subtype 4d where P and T were observed at 50% and 40%, respectively. The most frequent polymorphisms observed in subtype 4a at positions 28, 30, 58 and 93 were M (15%), R (9%), S (3%) and H (3%) respectively; no polymorphisms were observed at position 31(100% M). The most frequent polymorphisms observed in subtype 4d at positions 28, 31, 58 and 93 were S (3%), L/V (2% each), and T (40%) respectively; no polymorphisms were observed at position 30 (100% R). In subtype 4b, positions 28, 30, and 93 had the most frequently observed polymorphisms and account for ≤75% of the population. In subtype 4f, position 30 had the most frequently observed polymorphisms and account for ≤75% of the population. In subtypes 4k and 4n, position 31 had the most frequently observed polymorphisms and account for ≤75% of the population. In subtype 4r, position 28 had the most frequently observed polymorphisms and account for ≤75% of the population.

Table 53: Prevalence of Substitutions at Amino Acid Positions 28, 30, 31, 58, and 93 in NS5A among GT4 Subtypes

	28			30			31			58			93		
Sub-type	AA†	Count‡	%T	AA†	Count‡	%T	AA†	Count‡	%T	AA†	Count‡	%T	AA†	Count‡	%T
4a	L	57	76	L	66	88	M	75	100	P	68	91	Y	73	97
	M	11	15	R	7	9				S	2	3	H	2	3
	X	5	7	X	2	3				X	2	3			
	T	1	1							D	1	1			
	V	1	1							Y	1	1			
										L	1	1			
4b	L	2	50	S	3	75	M	4	100	P	4	100	S	2	50
	M	2	50	A	1	25							H	1	25
													T	1	25
4c	L	1	100	R	1	100	M	1	100	P	1	100	Y	1	100
4d	L	55	95	R	58	100	M	55	95	P	29	50	Y	57	98
	S	2	3				L	1	2	T	23	40	H	1	2
	X	1	2				V	1	2	S	3	5			
							X	1	2	L	2	3			
										X	1	2			
4f	L	7	100	R	4	57	M	6	86	P	7	100	Y	7	100
				Q	2	29	V	1	14						
				X	1	14									
4g	L	3	100	L	2	67	M	3	100	P	3	100	H	1	33.3
				R	1	33							R	1	33.3
													Y	1	33.3
4k	L	6	86	R	6	86	L	5	71	P	7	100	Y	7	100
	-	1	14	-	1	14	M	1	14						
							-	1	14						
4l	L	4	100	R	4	100	M	4	100	P	4	100	Y	4	100
4m	L	3	100	S	3	100	M	3	100	P	2	67	Y	3	100
										R	1	33			
4n	L	3	100	R	3	100	M	2	67	T	3	100	Y	3	100

	28			30			31			58			93		
Sub-type	AA†	Count‡	%⊤	AA†	Count‡	%⊤	AA†	Count‡	%⊤	AA†	Count‡	%⊤	AA†	Count‡	%⊤
							L	1	33						
4o	M	6	100	T	6	100	M	6	100	P	6	100	Y	6	100
4p	L	1	100	R	1	100	M	1	100	P	1	100	Y	1	100
4q	L	1	100	R	1	100	M	1	100	P	1	100	Y	1	100
4r	M	2	50	R	4	100	L	4	100	P	4	100	Y	4	100
	I	1	25												
	V	1	25												
4t	L	1	100	R	1	100	M	1	100	P	1	100	Y	1	100
4v	L	5	100	R	5	100	M	5	100	P	5	100	Y	5	100
4*	L	1	ni	R	1	ni	M	1	ni	P	1	ni	Y	1	ni

ni = not included in calculations.
*sub-type is unknown.
† single letter designation of amino acid observed at indicated position in NS5A. X=ambiguous residue. "-" = missing residue.
‡ number of unique occurrences of amino acid at indicated position in the subtype.
⊤ number of unique occurrences of amino acid at indicated position in the subtype expressed as a percentage (rounded up).

Overall, these data support MK-5172+MK-8742 for 12 weeks in treatment-naïve subjects infected and MK-5172+MK-8742+RBV for 16 weeks in P/R treatment-experienced subjects with GT4. However, insufficient data are available for non-GT4a or GT4d subtypes with respect to NS5A polymorphisms that might impact efficacy.

(b) (4)

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(b) (4)

7. Persistence of resistance-associated substitutions

7.1. NS3/4A resistance-associated substitutions

Of the 70 GT1a subjects for whom sequence information was available, 35 subjects had treatment-emergent NS3 resistance-associated substitutions after MK-5172 and MK-8742 therapy. At FUW12, 17/27 (63%) of the subjects had detectable NS3 resistance-associated substitutions (Table 61, FDA analysis). By FUW24, 3/13 (23%) of the subjects who had sequence data had detectable treatment-emergent NS3 resistance-associated substitutions.

Of the 15 GT1b subjects for whom sequence information was available, 2 subjects had treatment-emergent NS3 resistance-associated substitutions after MK-5172 and MK-8742 therapy. At FUW12, 1/1 (100%) of the subjects with available data had detectable NS3 resistance-associated substitutions. There were no subjects who had sequence data had available at FUWK24.

Of the 5 GT4 subjects for whom sequence information was available, 2 subjects had treatment-emergent NS3 resistance-associated substitutions after MK-5172 and MK-8742 therapy. At FUW12, 1/2 (50%) of the subjects with FUW12 data had detectable NS3 resistance-associated substitutions. There were no subjects who had sequence data had available at FUWK24.

(b) (4)

Table 61: Persistence of Treatment-Emergent Substitutions in NS3/4A.

	Number of Virologic Failures	Number of subjects with Tx-emergent substitutions	Number of with Tx-emergent substitutions at FUWK12	Resistance-associated substitutions observed at FUWK12	Number with Tx-emergent substitutions at FUWK24	Resistance-associated substitutions observed at FUWK24
GT1a	70	35	17/27 (63%)	V36L/M (n=2), Y56H (n=2), V107I (n=2), A156G (n=1), D168A/E/N/V/Y (n=13)	3/13 (23%)	A156G (n=1), D168A/V (n=2)
GT1b	15	2	1/1 (100%)	Y56F (n=1), V107I (n=1)	0/0 (0%)	
GT4	5	2	1/2 (50%)	A156M (n=1)	0/0 (0%)	

(b) (4)

Collectively, these data indicate that NS3/4A resistance-associated substitutions persist in a significant number of failures and may impact subsequent treatment with a PI-based regimen.

7.2. NS5A resistance-associated substitutions

Of the 70 GT1a subjects for whom sequence information was available, 47 subjects had treatment-emergent NS5A resistance-associated substitutions after MK-5172 and MK-8742 therapy. At FUW12, 36/38 (95%) of the subjects with available data had detectable NS5A resistance-associated

substitutions (Table 62, FDA Analysis). By FUW24, 9/9 (100%) of the subjects who had sequence data had detectable treatment-emergent NS5A resistance-associated substitutions.

Of the 15 GT1b subjects for whom sequence information was available, 8 subjects had treatment-emergent NS5A resistance-associated substitutions after MK-5172 and MK-8742 therapy. At FUW12, 7/7 (100%) of the subjects with available data had detectable NS5A resistance-associated substitutions. By FUW24, 3/3 (100%) of the subjects who had sequence data had detectable treatment-emergent NS5A resistance-associated substitutions.

Of the 5 GT4 subjects for whom sequence information was available, 5 subjects had treatment-emergent NS5A resistance-associated substitutions after MK-5172 and MK-8742 therapy. At FUW12, 4/5 (80%) of the subjects with available data had detectable NS5A resistance-associated substitutions. By FUW24, 3/3 (100%) of the subjects who had sequence data had detectable treatment-emergent NS5A resistance-associated substitutions. There were no subjects who had available sequence data at FUWK24.

(b) (4)

Collectively, these data indicate that NS5A resistance-associated substitutions persist long-term in nearly all subjects who experience virologic failure, and are likely to impact subsequent treatment with an NS5A inhibitor based regimen.

Table 62: Persistence of Treatment-Emergent Substitutions in NS5A.

	Number of Virologic Failures	Number of subjects with Tx-emergent substitutions	Number of with Tx-emergent substitutions at FUWK12	Resistance-associated substitutions observed at FUWK12	Number of with Tx-emergent substitutions at FUWK24	Resistance-associated substitutions observed at FUWK24
GT1a	70	47	36/38 (95%)	M28A/G/T/V (n=10), Q30R (n=18), L31M/V (n=6), H58D (n=3), Y93C/H/N/S (n=7)	9/9 (100%)	M28G/T (n=3), Q30R (n=5), L31M/V (n=2), H58D (n=1), Y93H/N (n=2)
GT1b	15	8	7/7 (100%)	L28M (n=1), L31F/V (n=2), Y93H (n=5)	3/3 (100%)	L31V (n=1), Y93H (3)
GT4	5	5	4/5 (80%)	L28S/T (n=2), M31I/V (n=2), H54Y (n=2), Y93H (n=1)	0/0 (0%)	

(b) (4)

8. Viral Kinetics

The sponsor is seeking an indication for 8 week treatment with MK-5172+MK-8742 in treatment-naïve genotype 1b patients without significant fibrosis or cirrhosis. The sponsor studied this regimen in only 31 subjects in study 035 (Table 63, FDA Analysis). SVR12 was achieved in 29/31 (94%) of subjects. To determine whether the HCV viral kinetics can support the 8 week treatment duration, the HCV RNA levels were determined at each treatment week. At TW4 in non-cirrhotic subjects infected with GT1b, there were 172/176 (98%) and 135/176 (77%) who achieved <LLOQ and TND, respectively (Table 63 & Table 64, FDA Analysis, FDA Analysis). These rates are worse than those of other regiments such as HARVONI® and Viekira Pak™ (reviewed in Harrington et al., 2015). Given that much greater than 90%

of subjects did not achieve TND at TW4, this regimen does not support an 8-week treatment for all subjects infected with GT1b. The vast majority (much greater than 90 percent) of subjects should be less than the TND at a time point that is half the treatment length. However, for non-cirrhotic subjects infected with GT1b with baseline HCV RNA level ≤800,000 IU/mL, 57/57 (100%) and 51/57 (89%) subjects achieved <LLOQ and TND at TW4, respectively. These rates are not far from the rates for the overall population at TW8 (177/177 [100%] and 177/177 [100%] for LLOQ and TND< respectively). Therefore, non-cirrhotic subjects infected with GT1b with baseline HCV RNA level ≤800,000 IU/mL may be considered for the 8-week treatment duration. Indeed, in study 035 for the 8 week treatment duration arm in GT1b, 29/31 (94%) achieved SVR12. Both subjects who failed were relapsers and had baseline HCV RNA >800,000 IU/mL. However, this option should be considered *ONLY* if there is a serious clinical signal *AFTER* week 8 of treatment and warrants the shorter treatment duration (i.e., otherwise, everyone should get 12 weeks as a conservative approach to maximize treatment efficacy which minimizes the risk of treatment-emergent drug resistance). Of note, MK-5172 was placed on partial hold due to toxicity. This toxicity appears to be related to both dose and duration of drug exposure.

Table 63: Subjects Achieving <LLOQ by Treatment Week in Treatment-Naïve Subjects Treated with MK-5172+MK-8742 (GT1b, studies P035, P060, P061).

	Total		≤800,000 IU/mL		>800,000 IU/mL	
	Non-cirrhotic	Cirrhotic	Non-cirrhotic	Cirrhotic	Non-cirrhotic	Cirrhotic
TW2	126/179 (70%)	37/61 (61%)	52/59 (88%)	14/18 (78%)	74/120 (62%)	23/43 (53%)
TW4	172/176 (98%)	60/61 (98%)	57/57 (100%)	17/18 (94%)	115/119 (97%)	43/43 (100%)
TW6	137/139 (99%)	45/45 (100%)	53/53 (100%)	16/16 (100%)	84/86 (98%)	29/29 (100%)
TW8	177/177 (100%)	59/60 (98%)	58/58 (100%)	18/18 (100%)	119/119 (100%)	41/42 (98%)
TW12	148/148 (100%)	61/61 (100%)	55/55 (100%)	18/18 (100%)	93/93 (100%)	43/43 (100%)

Table 64: Subjects Achieving TND by Treatment Week in Treatment-Naïve Subjects Treated with MK-5172+MK-8742 (GT1b, studies P035, P060, P061).

	Total		≤800,000 IU/mL		>800,000 IU/mL	
	Non-cirrhotic	Cirrhotic	Non-cirrhotic	Cirrhotic	Non-cirrhotic	Cirrhotic
TW2	68/179 (38%)	12/61 (20%)	37/59 (63%)	6/18 (33%)	31/120 (26%)	6/43 (13%)
TW4	135/176 (77%)	47/61 (77%)	51/57 (89%)	15/18 (83%)	84/119 (71%)	32/43 (74%)
TW6	132/139 (95%)	39/45 (87%)	53/53 (100%)	15/16 (94%)	79/86 (92%)	24/29 (83%)
TW8	177/177 (100%)	59/60 (98%)	58/58 (100%)	18/18 (100%)	118/119 (99%)	41/42 (98%)
TW12	148/148 (100%)	61/61 (100%)	55/55 (100%)	18/18 (100%)	93/93 (100%)	43/43 (100%)

For comparison, the HCV viral kinetics was evaluated for subjects infected with GT1a (Table 65 & Table 66, FDA Analysis). At TW4 in non-cirrhotic subjects infected with GT1a there were 279/295 (95%) and 217/295 (74%) who achieved <LLOQ and TND, respectively. Indeed, this regimen was dropped for the 8-week treatment duration in GT1a due to achieving the virologic futility criteria (≥3 of first 10 subjects are virologic failures) but achieved SVR12 rates >95% in GT1b, which is consistent with the TW4 results.

Table 65: Subjects Achieving <LLOQ by Treatment Week in Treatment-Naïve Subjects Treated with MK-5172+MK-8742 (GT1a, studies P035, P060, P061).

	Total		≤800,000 IU/mL		>800,000 IU/mL	
	Non-cirrhotic	Cirrhotic	Non-cirrhotic	Cirrhotic	Non-cirrhotic	Cirrhotic
TW2	196/291 (67%)	53/95 (56%)	72/88 (82%)	9/15 (60%)	124/203 (61%)	44/80 (55%)
TW4	279/295 (95%)	78/94 (83%)	85/88 (97%)	14/15 (93%)	194/207 (94%)	64/79 (81%)
TW6	239/243 (98%)	48/52 (92%)	84/85 (99%)	10/10 (100%)	155/158 (98%)	38/42 (90%)
TW8	288/291 (99%)	93/94 (99%)	87/87 (100%)	14/14 (100%)	201/204 (99%)	79/80 (99%)
TW12	293/293 (100%)	94/95 (99%)	90/90 (100%)	15/15 (100%)	203/203 (100%)	79/80 (99%)

Table 66: Subjects Achieving TND by Treatment Week in Treatment-Naïve Subjects Treated with MK-5172+MK-8742 (GT1a, studies P035, P060, P061).

	Total		≤800,000 IU/mL		>800,000 IU/mL	
	Non-cirrhotic	Cirrhotic	Non-cirrhotic	Non-cirrhotic	Cirrhotic	Non-cirrhotic
TW2	95/291 (33%)	18/95 (19%)	50/88 (57%)	6/15 (40%)	45/203 (22%)	12/80 (15%)
TW4	217/295 (74%)	59/94 (63%)	78/88 (89%)	11/15 (73%)	139/207 (67%)	48/79 (61%)
TW6	222/243 (91%)	45/52 (87%)	76/85 (89%)	9/10 (90%)	146/158 (92%)	36/42 (86%)
TW8	280/291 (96%)	89/94 (95%)	85/87 (98%)	14/14 (100%)	195/204 (96%)	75/80 (94%)
TW12	292/293 (99%)	93/95 (98%)	90/90 (100%)	15/15 (100%)	202/203 (99%)	78/80 (98%)

9. Conclusion

This Original NDA is approvable from a Clinical Virology perspective for the treatment of chronic HCV genotype 1 or genotype 4 infected patients who are either naïve to prior anti-HCV therapy or who have failed prior therapy with Peg-IFNα/RBV, including patients with compensated cirrhosis. This Original NDA is also approvable for the treatment of chronic HCV genotype 1 infected patients who have failed prior therapy with Peg-IFNα/RBV plus boceprevir, simeprevir, or telaprevir, including patients with compensated cirrhosis. However, we recommend screening all genotype 1a subjects and all P/R treatment-experienced genotype 1b subjects for NS5A polymorphisms prior to initiation of MK-5172/MK-8742 using a commercially available assay. Both treatment-naïve and PR-treatment experienced subjects who were infected with HCV genotype 1a virus with one or more polymorphisms at amino acid positions associated with resistance to NS5A inhibitors were significantly less likely to benefit from a 12 week course of MK-5172/MK-8742 than subjects infected with HCV genotype 1a virus without key NS5A polymorphisms. A similar pattern with respect to impact of NS5A polymorphisms was noted for P/R-treatment experienced subjects infected with HCV genotype 1b virus. There are clinically significant consequences of virologic failure for subjects with NS5A polymorphisms in genotype 1a. Amongst subjects with genotype 1a virus with NS5A polymorphisms who failed treatment, 96% of subjects gained an NS3/4A resistance substitution or additional NS5A substitution(s), approximately 75% of subjects gained an additional NS5A resistance substitution(s), and approximately 60% of subjects gained an additional NS3/4A AND NS5A resistance substitution(s). Similar impacts were noted for genotype 1b infected subjects. Treatment failure will therefore substantially impact retreatment options for these subjects.

Microbiology Package Insert

Clinical virology-related sections of the proposed drug label and suggested edits are shown below. The words with strikethroughs are the text the sponsor was requested to delete and the words in yellow are recommended insertions. At the time of this review the review team was still negotiating labeling and comparing analysis results with the sponsor so the edits shown below should be considered preliminary. Of note, the sponsor has not accepted the Division's recommendations, specifically concerning the need for screening NS5A polymorphisms prior to initiation of MK-5172/MK-8742 using a commercially available assay. In the sponsor's response to the Division's labeling recommendation (dated 10/20/15), the sponsor states that if the same methodology (next generation sequencing) and definitions are used to identify subjects harboring NS5A polymorphisms prior to initiating treatment, the efficacy of MK-5172/MK-8742 is comparable to that of Harvoni®. However, the sponsor did not use the same methodology as used by Dr. Lisa K. Naeger for analyzing the Harvoni® data (please see the review of Dr. Lisa K. Naeger, Ph.D., NDA 205834, SDN 000; on pg. 14 Dr. Naeger states "consensus sequences were generated and used for analysis"). The sponsor used a 1% sensitivity threshold in their deep sequence analysis which would identify subjects with viral populations with minor variants in addition to populations with NS5A polymorphisms. However, the consensus sequence derived from the next generation sequencing data (i.e., not including minor variants) was used for the analysis of the Harvoni® data. Based on the analyses that were conducted for the Harvoni® data, the sponsor's original analyses using population sequencing would be the more appropriate comparator. Furthermore, all 4 subjects who failed Harvoni® in the P/R-treatment experienced, non-cirrhotic arm and had received 12 weeks of the drug had two NS5A resistance-associated polymorphisms. With MK-5172/MK-8742, even a single NS5A polymorphism had a substantial impact on efficacy (of the 24 VFs with NS5A polymorphisms, 19 subjects had only 1, 4 subjects had 2, and 1 subject had 3 polymorphisms at baseline; see Section 4.5.2). Using this comparison, the efficacy observed between MK-5172/MK-8742 and Harvoni® is different (see section 4.5.2. above). Therefore, this reviewer believes that screening NS5A polymorphisms prior to initiation of MK-5172/MK-8742 using a commercially available assay is warranted. The following response (draft communication) was communicated to the sponsor in response to the sponsor's labeling comments of 10/20/15:

> *We appreciate the new NGS data that you have submitted and the amount of work put into preparing the submission, and we agree that your analyses indicate that low minority HCV variants with changes at NS5A inhibitor resistance-associated amino acid positions likely have less of an impact on clinical outcome relative to those that predominate in the viral population.*
>
> *However, to make the comparison with ledipasvir/sofosbuvir, please note that the NS5A polymorphism analyses that were conducted by Dr. Lisa K. Naeger for the HarvoniTM virology review used population sequences or consensus amino acid sequences derived from the NGS data. As described in Dr. Naeger's NDA 205834 review, please see pg. 14: "For baseline samples where population sequencing only or both population and deep sequencing data were available, analyses using the population sequence were reported. For baseline samples that only had deep sequencing data, consensus sequences were generated and used for analysis." Therefore, your original data using population sequencing are the more relevant for comparison, and your additional analyses using NGS data to include minor variants present at ≥1% of the viral population do not change our previous position.*
>
> *Furthermore, all 4 of the ledipasvir/sofosbuvir relapsers in the 12 week non-cirrhotic arm you have cited in Table 5 (pg. 15) of your document had two critical NS5A resistance-associated polymorphisms at baseline (see Dr. Naeger's review pg. 65-67 Subjects 79378, 79303, 79214*

and 79179). Your data indicate that a single NS5A resistance-associated polymorphism can impact efficacy of GZR/EBR (of the 24 VF's with NS5A polymorphisms, 19 subjects had only 1).

We also refer you to our midcycle communication where we have outlined our concerns about the resistance consequences of virologic failure. Patients with NS5A polymorphisms who fail GZR/EBR would likely gain additional NS3/4A and NS5A resistance substitution(s), which may severely limit the efficacy of subsequent re-treatment. This risk of virologic failure and multiple-class DAA resistance with GZR/EBR can be minimized almost entirely if HCV GT1a patients are screened for the presence of NS5A resistance-associated polymorphisms.

Therefore, with respect to labeling, the Division does not agree with placement of information related to the impact of baseline NS5A polymorphisms on treatment response solely in Section 12.4 of the label. We recognize that there may be some situations in which GZR/EBR could be a reasonable treatment even in those with NS5A polymorphisms (e.g., patients with renal disease), (b) (4) *An acceptable alternative* (b) (4) *is to include a recommendation for testing for baseline NS5A polymorphisms in Section 2 under a subsection entitled "Testing Prior to Initiation of GZR/EBR". The Division is also amenable to stating that the optimal treatment regimen and duration for GT 1a infected patients with baseline NS5A polymorphisms is unknown, rather than the original proposal* (b) (4). (b) (4)

(b) (4)

For the reasons outlined above, the Division believes that screening recommendations for baseline NS5A polymorphisms for HCV GT1a infected patients should be displayed prominently in the label. If the Sponsor and the Division are unable to reach agreement on this issue, the Division will need to consider other regulatory steps to address this matter, which may include convening an Advisory Committee. The Sponsor should be aware that such steps may delay the approval of this product.

12.1 Mechanism of Action

TRADEMARK is a fixed-dose combination of elbasvir and grazoprevir which are direct-acting antiviral agents against the hepatitis C virus [see Microbiology (12.4)].

12.4 Microbiology

Mechanism of Action

TRADEMARK combines two direct-acting antiviral agents with distinct mechanisms of action and non-overlapping resistance profiles to target HCV at multiple steps in the viral lifecycle.

Elbasvir is an inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly. The mechanism of action of elbasvir has been characterized based on cell culture antiviral activity and drug resistance mapping studies.

Grazoprevir is an inhibitor of the HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. In a biochemical assay, grazoprevir inhibited the proteolytic activity of the recombinant HCV genotype 1a, 1b, and 4 NS3/4A protease enzymes with IC_{50} values of 7 pM, 4 pM, and 62 pM, respectively ~~from~~ (b) (4)

Antiviral Activity

In HCV replicon assays, the EC_{50} values of elbasvir against full-length replicons from genotypes 1a, 1b, (b) (4) and 4~~,~~ (b) (4) respectively. The median EC_{50} values of elbasvir against chimeric replicons encoding NS5A sequences from clinical isolates were ~~0.00~~5 nM for genotype 1a (range (b) (4) p(b)M; N=5), (b) (4) p(b)M for genotype 1b (range (b) (4) 10 p(b)M; N=5), 0.2 pM for genotype 4a (range 0.2-0.2 pM; N=2), 3,600 pM for genotype 4b (range 17 pM-34,000 pM; N=3), 0.45 pM for genotype 4d (range 0.4-0.5 pM; N=2), 1.9 pM for genotype 4f (N=1), 36.3 pM for genotype 4g (range 0.6-72 pM; N=2), 0.6 pM for genotype 4m (range 0.4-0.7 pM; N=2), 2.2 pM for genotype 4o (N=1), and 0.5 pM for genotype 4q (N=1). The median EC_{50} values of elbasvir against replicons from genotypes 2a, 3a, 5 and 6 were 3 pM, 140 pM, 1 pM and 9 (b) (4)

In HCV replicon assays, the EC_{50} values of grazoprevir against full-length replicons from genotypes 1a, 1b, (b) (4) and 4~~,~~ (b) (4) were 0.4 nM, 0.5 nM, (b) (4) and 0.3 nM, (b) (4) respectively.

The median EC_{50} values of grazoprevir against chimeric replicons encoding NS3/4A sequences from clinical isolates were 0.8 nM for genotype 1a (range 0.4-5.1 nM; N=10), 0.45 nM for genotype 1b (range 0.2-5.9 nM; N=10), and 0.3 nM for genotype 4a (N=1), 0.16 nM for genotype 4b (range 0.11-0.2 nM; N=2), 1.1 nM, for genotype 4d (N=1), 0.24 nM for genotype 4g (range 0.15-0.33 nM; N=2), and 1.2 nM, for genotype 4o0 (N=1).~~-~~ (b) (4)

Combination Antiviral Activity

Evaluation of elbasvir in combination with grazoprevir or ribavirin showed no antagonistic effect in reducing HCV RNA levels in replicon cells. Evaluation of grazoprevir in combination with ribavirin showed no antagonistic effect in reducing HCV RNA levels in replicon cells.

Resistance

In Cell Culture

HCV replicons with reduced susceptibility to elbasvir and grazoprevir have been selected in cell culture for genotypes 1a, 1b, and 4, (b) (4) which resulted in the emergence of drug resistance-associated amino acid substitutions in NS5A or NS3, respectively. Amino acid substitutions in NS5A or NS3 selected in cell culture or identified in Phase 2b and 3 clinical trials were phenotypically characterized in genotype 1a, 1b, or 4 replicons.

For elbasvir, in HCV genotype 1a replicons, single NS5A substitutions M28A/G/T, Q30D/E/H/K/R, L31M/V, H58D, and Y93C/H/N reduced elbasvir antiviral activity by 1.5 (b) (4) to 2000-fold. In genotype 1b replicons, single NS5A substitutions L28M, L31F and Y93H reduced elbasvir antiviral activity by (b) (4) to 67-fold. In genotype 4 replicons, single NS5A substitutions L30S, M31V, and Y93H reduced elbasvir antiviral activity by 3- to 23-fold. (b) (4) In general, in HCV genotype 1a, 1b, or (b) (4) replicons, combinations of elbasvir resistance-associated substitutions further reduced elbasvir antiviral activity.

For grazoprevir, in HCV genotype 1a replicons, single NS3 substitutions V36L/M, Y56H, V107I, R155K, A156G/T/V, D168A/E/G/N/S/V/Y reduced grazoprevir antiviral activity by 1 (b) (4) to 81-fold. In genotype 1b replicons, single NS3 substitutions F43S, Y56F, V107I, A156S/T/V, and D168A/G/V reduced grazoprevir antiviral activity by 1.5 (b) (4) to 375-fold. In genotype 4 replicons, single NS3 substitutions D168A/V reduced grazoprevir antiviral activity by 110- to 320-fold. (b) (4) In general, in HCV genotype 1a, 1b, or 4- (b) (4) replicons, combinations of grazoprevir resistance-associated substitutions further reduced grazoprevir antiviral activity.

In Clinical Studies

In a pooled analysis of (b) (4) subjects treated with regimens containing TRADEMARK or elbasvir + grazoprevir with or without ribavirin in Phase 2 and 3 clinical trials, resistance analyses were conducted for 504 subjects who experienced virologic failure and had sequence data available (6 (b) (4) with on-treatment virologic failure, 44 (b) (4) with post-treatment relapse).

Treatment-emergent substitutions observed in the viral populations of these subjects based on genotypes are shown in Table 8. Treatment-emergent substitutions were detected in both HCV drug targets in 23/37 (62%) genotype 1a, 1/8 (13%) genotype 1b, and 2/5 (40%) genotype 4, (b) (4)

(b) (4)

(b) (4)

[redacted]

Persistence of Resistance-Associated Substitutions

The persistence of elbasvir and grazoprevir treatment-emergent amino acid substitutions in NS5A, and NS3, respectively, was assessed in HCV genotype 1-infected subjects in Phase 2 and 3 trials whose virus had treatment-emergent resistance-associated substitutions in the drug target, and with available data through at least 24 weeks post-treatment using population nucleotide sequence analysis.

Viral populations with t~~T~~reatment-emergent NS5A resistance-associated substitutions were generally more persistent than those with NS3 resistance-associated substitutions. Among genotype 1a-infected subjects, [redacted] (b) (4) NS5A resistance-associated substitutions~~,~~ [redacted] (b) (4) persisted at detectable levels at follow-up week 12 in [redacted] (b) (4) 95% (b) (4) 35/37~~44~~) of subjects and 100% (b) (4) 9/9 [redacted] (b) (4) of subjects with follow-up week 24 data. Among genotype 1b-infected subjects, NS5A resistance-associated substitutions persisted at detectable levels in 100% (7/7) of subjects at follow-up week 12 and in 100% (3/3) of subjects with follow-up week 24 data.

Among genotype 1a-infected subjects, NS3 resistance-associated substitutions~~,~~ [redacted] (b) (4) persisted at detectable levels at follow-up week 24 in 31 (b) (4) % (4 (b) (4) 13 (b) (4) of subjects [redacted] (b) (4) Among genotype 1b-infected subjects, NS3 resistance-associated substitutions persisted at detectable levels at follow-up week 24 in 50% (1/2) of subjects.

Due to the limited number of genotype 4~~-~~ [redacted] (b) (4) infected subjects with treatment-emergent NS5A and NS3 resistance-associated substitutions, trends in persistence of treatment-emergent substitutions in [redacted] (b) (4) this genotype~~s~~ could not be established.

The lack of detection of virus containing a resistance-associated substitution does not indicate that the resistant virus is no longer present at clinically significant levels. The long-term clinical impact of the emergence or persistence of virus containing TRADEMARK-resistance-associated substitutions is unknown.

Effect of Baseline HCV Polymorphisms on Treatment Response

Analyses were conducted to explore the association between [redacted] (b) (4) NS5A and/or NS3 polymorphisms and treatment response among HCV direct-acting antiviral-naïve subjects [redacted] (b) (4) (b) (4)

(b) (4)

Genotype 1a

(b) (4)

Genotype 1b

(b) (4)

(b) (4)

(b) (4)

(b) (4) Cross Resistance

Cross-resistance is expected among NS5A inhibitors and NS3/4A protease inhibitors by class. Elbasvir and grazoprevir are fully active against viral populations with substitutions conferring resistance to NS5B inhibitors.- (b) (4)

(b) (4)

(b) (4)

The efficacy of TRADEMARK has not been established in patients who have previously failed treatment of other regimens that included an NS5A inhibitor. (b) (4)

APPENDICES

Appendix A1: Study 060 (C-EDGE Treatment Naive) – GT4 & GT6

The overall ITT SVR12 rates were 9/9 (100%), 7/7 (100%), 1/1 (100%), and 1/1 (100%) for subjects infected with HCV GT4a, GT4d, GT4k, and unknown, respectively (Table A1-1, FDA Analysis). There were no clear differences between IL28B CC vs. IL28B non-CC subjects, between cirrhotic and non-cirrhotic subjects, or between subjects with baseline HCV RNA ≤800,000 IU/ml vs. >800,000 IU/mL. The median baseline HCV RNA levels were 4.0 x 10^5 IU/ml (n=9), 1.3 x 10^6 IU/ml (n=7), and 3.0 x 10^6 IU/ml (n=1) for subjects infected with HCV GT4a, GT4d, and GT4k, respectively.

Table A1-1: SVR12 Rates in Study 060 (HCV GT4).

	All HCV GT4	HCV GT4a	HCV GT4d	HCV GT4k	Unknown
SVR12	18/18 (100%)	9/9 (100%)	7/7 (100%)	1/1 (100%)	1/1 (100%)
Any VF	0/18 (0%)	0/9 (0%)	0/7 (0%)	0/1 (0%)	0/1 (0%)
Breakthrough	0/18 (0%)	0/9 (0%)	0/7 (0%)	0/1 (0%)	0/1 (0%)
Relapse	0/18 (0%)	0/9 (0%)	0/7 (0%)	0/1 (0%)	0/1 (0%)
Others	0/18 (0%)	0/9 (0%)	0/7 (0%)	0/1 (0%)	0/1 (0%)
IL28B CC	4/4 (100%)	2/2 (100%)	2/2 (100%)	0/0 (0%)	0/0 (0%)
IL28B CT	11/11 (100%)	5/5 (100%)	4/4 (100%)	1/1 (100%)	1/1 (100%)
IL28B TT	3/3 (100%)	2/2 (100%)	1/1 (100%)	0/0 (0%)	0/0 (0%)
IL28 Unknown	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
≤800,000 IU/mL	10/10 (100%)	7/7 (100%)	3/3 (100%)	0/0 (0%)	0/0 (0%)
>800,000 IU/mL	8/8 (100%)	2/2 (100%)	4/4 (100%)	1/1 (100%)	1/1 (100%)
Cirrhotic	2/2 (100%)	1/1 (100%)	1/1 (100%)	0/0 (0%)	0/0 (0%)
Non-Cirrhotic	16/16 (100%)	8/8 (100%)	6/6 (100%)	1/1 (100%)	1/1 (100%)

(b) (4)

(b) (4)

Appendix A2: Study 061 (C-EDGE Treatment-Naïve HIV Co-infected) – GT4 & GT6

The overall ITT SVR12 rates were 9/9 (100%), 17/18 (94%), and 1/1 (100%) for subjects infected with HCV GT4a, GT4d, and unknown, respectively (Table A2-1, FDA Analysis). The one subject who failed treatment was a relapse had baseline HCV RNA >800,000 IU/mL. There were no clear differences between IL28B CC vs. IL28B non-CC subjects, between cirrhotic and non-cirrhotic subjects, or between subjects with baseline HCV RNA ≤800,000 IU/ml vs. >800,000 IU/mL. The median baseline HCV RNA levels were 9.0 x 10^5 IU/ml (n=9) and 9.6 x 10^5 IU/ml (n=18) for subjects infected with HCV GT4a and GT4d, respectively.

Table A2-1: SVR12 Rates in Study 061 (HCV GT4).

	All HCV GT4	HCV GT4a	HCV GT4d	Unknown
SVR12	27/28 (96%)	9/9 (100%)	17/18 (94%)	1/1 (100%)
Any VF	1/28 (4%)	0/9 (0%)	0/18 (0%)	0/1 (0%)
Breakthrough	0/28 (0%)	0/9 (0%)	0/18 (0%)	0/1 (0%)
Relapse	1/28 (4%)	0/9 (0%)	1/18 (6%)	0/1 (0%)
Others	0/28 (0%)	0/9 (0%)	0/18 (0%)	0/1 (0%)
IL28B CC	10/10 (100%)	2/2 (100%)	8/8 (100%)	0/0 (0%)
IL28B CT	11/12 (92%)	5/5 (100%)	5/6 (83%)	1/1 (100%)
IL28B TT	6/6 (100%)	2/2 (100%)	4/4 (100%)	0/0 (0%)
IL28 Unknown	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
≤800,000 IU/mL	12/12 (100%)	3/3 (100%)	8/8 (100%)	1/1 (0%)
>800,000 IU/mL	15/16 (94%)	6/6 (100%)	9/10 (90%)	0/0 (0%)
Cirrhotic	4/4 (100%)	1/1 (100%)	3/3 (100%)	0/0 (0%)
Non-Cirrhotic	23/24 (96%)	8/8 (100%)	14/15 (93%)	1/1 (100%)

(b) (4)

Appendix A3: Study 068 (C-EDGE Treatment Experienced)

MK-5172 100 mg + MK-8742 50 mg for 12 Weeks

The overall ITT SVR12 rates were 4/4 (100%), 2/4 (50%), and 1/1 (100%) for subjects infected with HCV GT4a, GT4d, and GT4o, respectively (Table A3-1, FDA Analysis). There were no clear differences between IL28B CC vs. IL28B non-CC subjects, between cirrhotic and non-cirrhotic subjects, or between subjects with baseline HCV RNA ≤800,000 IU/ml vs. >800,000 IU/mL. The median baseline HCV RNA levels were 1.5 x 10^7 IU/ml (n=4), 1.7 x 10^7 IU/ml (n=4), and 5.4 x 10^5 IU/ml (n=1) for subjects infected with HCV GT4a, GT4d, and GT4o, respectively.

Table A3-1: SVR12 Rates in Study 068 (HCV GT4, MK-5172 100 mg + MK-8742 50 mg for 12 Weeks).

	All HCV GT4	HCV GT4a	HCV GT4d	HCV GT4o
SVR12	7/9 (77%)	4/4 (100%)	2/4 (50%)	1/1 (100%)
Any VF	1/9 (11%)	0/4 (0%)	1/4 (25%)	0/1 (0%)
Breakthrough	0/9 (0%)	0/4 (0%)	0/4 (0%)	0/1 (0%)
Relapse	1/9 (11%)	0/4 (0%)	1/4 (25%)	0/1 (0%)
Others	1/9 (11%)	0/4 (0%)	1/4 (25%)	0/1 (0%)
IL28B CC	1/1 (100%)	0/0 (0%)	0/0 (0%)	1/1 (100%)
IL28B CT	5/7 (71%)	3/3 (100%)	2/4 (50%)	0/0 (0%)
IL28B TT	1/1 (100%)	1/1 (100%)	0/0 (0%)	0/0 (0%)
IL28 Unknown	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
≤800,000 IU/mL	3/4 (75%)	1/1 (100%)	1/2 (50%)	1/1 (100%)
>800,000 IU/mL	4/5 (80%)	3/3 (100%)	1/2 (50%)	0/0 (0%)
Cirrhotic	4/6 (67%)	2/2 (100%)	1/3 (33%)	1/1 (100%)
Non-Cirrhotic	3/3 (100%)	2/2 (100%)	1/1 (100%)	0/0 (0%)
HCV monoinfected	7/9 (78%)	4/4 (100%)	2/4 (50%)	1/1 (100%)
HIV coinfected	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
P/R RELAPSER	2/2 (100%)	0/0 (0%)	1/1 (100%)	1/1 (100%)
P/R PARTIAL RESPONDER	0/1 (0%)	0/0 (0%)	0/1 (0%)	0/0 (0%)
P/R NULL RESPONDER	5/6 (83%)	4/4 (100%)	1/2 (50%)	0/0 (0%)

MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks

The overall ITT SVR12 rates were 7/7 (100%), 4/5 (80%), 1/1 (100%), 1/1 (100%), and 1/1 (100%) for subjects infected with HCV GT4a, GT4d, GT4k, GT4l, and GT4o, respectively (Table A3-2, FDA Analysis). There were no clear differences between IL28B CC vs. IL28B non-CC subjects, between cirrhotic and non-cirrhotic subjects, or between subjects with baseline HCV RNA ≤800,000 IU/ml vs. >800,000 IU/mL. The median baseline HCV RNA levels were 1.4 x 10^6 IU/ml (n=7), 3.2 x 10^6 IU/ml (n=5), 1.1 x 10^6 IU/ml (n=1), 9.1 x 10^6 IU/ml (n=1), and 8.8 x 10^5 IU/ml (n=1) for subjects infected with HCV GT4a, GT4d, GT4k, GT4l, and GT4o, respectively.

Table A3-2: SVR12 Rates in Study 068 (HCV GT4, MK-5172 100 mg + MK-8742 50 mg + RBV for 12 Weeks).

	All HCV GT4	HCV GT4a	HCV GT4d	HCV GT4k	HCV GT4l	HCV GT4o
SVR12	14/15 (93%)	7/7 (100%)	4/5 (80%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
Any VF	1/15 (7%)	0/7 (0%)	1/5 (20%)	0/1 (0%)	0/1 (0%)	0/1 (0%)
Breakthrough	0/15 (0%)	0/7 (0%)	0/5 (0%)	0/1 (0%)	0/1 (0%)	0/1 (0%)
Relapse	1/15 (7%)	0/7 (0%)	1/5 (20%)	0/1 (0%)	0/1 (0%)	0/1 (0%)
Others	0/15 (0%)	0/7 (0%)	0/5 (0%)	0/1 (0%)	0/1 (0%)	0/1 (0%)
IL28B CC	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
IL28B CT	11/12 (92%)	6/6 (100%)	4/5 (80%)	0/0 (0%)	1/1 (100%)	0/0 (0%)
IL28B TT	3/3 (100%)	1/1 (100%)	0/0 (0%)	1/1 (100%)	0/0 (0%)	1/1 (100%)
≤800,000 IU/mL	2/2 (100%)	1/1 (100%)	1/1 (100%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
>800,000 IU/mL	12/13 (92%)	6/6 (100%)	3/4 (75%)	1/1 (100%)	1/1 (100%)	1/1 (100%)
Cirrhotic	4/5 (80%)	3/3 (100%)	0/1 (0%)	0/0 (0%)	0/0 (0%)	1/1 (100%)
Non-Cirrhotic	10/10 (100%)	4/4 (100%)	4/4 (100%)	1/1 (100%)	1/1 (100%)	0/0 (0%)
HCV monoinfected	13/14 (93%)	6/6 (100%)	4/5 (80%)	1/1 (100%)	1/1 (100%)	1/1 (100%)

	All HCV GT4	HCV GT4a	HCV GT4d	HCV GT4k	HCV GT4l	HCV GT4o
HIV coinfected	1/1 (100%)	1/1 (100%)	0/0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
P/R RELAPSER	4/4 (100%)	2/2 (100%)	1/1 (100%)	0/0 (0%)	0/0 (0%)	1/1 (100%)
P/R PARTIAL RESPONDER	3/3 (100%)	1/1 (100%)	1/1 (100%)	0/0 (0%)	1/1 (100%)	0/0 (0%)
P/R NULL RESPONDER	7/8 (88%)	4/4 (100%)	2/3 (67%)	1/1 (100%)	0/0 (0%)	0/0 (0%)

MK-5172 100 mg + MK-8742 50 mg for 16 Weeks

The overall ITT SVR12 rates were 1/3 (33%) and 2/2 (100%) for subjects infected with HCV GT4a and GT4d, respectively (Table A3-3, FDA Analysis). Both of the virologic failures infected with HCV GT4a experienced breakthroughs and had baseline HCV RNA >800,000 IU/mL. There were no clear differences between IL28B CC vs. IL28B non-CC subjects or between cirrhotic and non-cirrhotic subjects. The median baseline HCV RNA levels were 1.9 x 10^6 IU/ml (n=3) and 2.1 x 10^6 IU/ml (n=2) for subjects infected with HCV GT4a and GT4d, respectively.

Table A3-3: SVR12 Rates in Study 068 (HCV GT4, MK-5172 100 mg + MK-8742 50 mg for 16 Weeks).

	All HCV GT4	HCV GT4a	HCV GT4d
SVR12	3/5 (60%)	1/3 (33%)	2/2 (100%)
Any VF	2/5 (40%)	2/3 (67%)	0/2 (0%)
Breakthrough	2/5 (40%)	2/3 (67%)	0/2 (0%)
Relapse	0/5 (0%)	0/3 (0%)	0/2 (0%)
Others	0/5 (0%)	0/3 (0%)	0/2 (0%)
IL28B CC	1/1 (100%)	0/0 (0%)	1/1 (100%)
IL28B CT	1/2 (50%)	1/2 (50%)	0/0 (0%)
IL28B TT	1/2 (50%)	0/1 (0%)	1/1 (100%)
≤800,000 IU/mL	1/1 (100%)	1/1 (100%)	0/0 (0%)
>800,000 IU/mL	2/4 (50%)	0/2 (0%)	2/2 (100%)
Cirrhotic	1/2 (50%)	1/2 (50%)	0/0 (0%)
Non-Cirrhotic	2/3 (67%)	0/1 (0%)	2/2 (100%)
HCV monoinfected	2/4 (50%)	1/3 (33%)	1/1 (100%)
HIV coinfected	1/1 (100%)	0/0 (0%)	1/1 (100%)
P/R RELAPSER	0/0 (0%)	0/0 (0%)	0/0 (0%)
P/R PARTIAL RESPONDER	2/2 (100%)	1/1 (100%)	1/1 (100%)
P/R NULL RESPONDER	1/3 (33%)	0/2 (0%)	1/1 (100%)

(b) (4)

[redacted]

(b) (4)

[redacted]

MK-5172 100 mg + MK-8742 50 mg + RBV for 16 Weeks

The overall ITT SVR12 rates were 4/4 (100%) and 4/4 (100%) for subjects infected with HCV GT4a and GT4d, respectively (Table A3-5, FDA Analysis). There were no clear differences between IL28B CC vs. IL28B non-CC subjects or between cirrhotic and non-cirrhotic subjects. The median baseline HCV RNA levels were 1.3 x 10^6 IU/ml (n=4) and 8.8 x 10^5 IU/ml (n=4) for subjects infected with HCV GT4a and GT4d, respectively.

Table A3-5: SVR12 Rates in Study 068 (HCV GT4, MK-5172 100 mg + MK-8742 50 mg + RBV for 16 Weeks).

	All HCV GT4	HCV GT4a	HCV GT4d
SVR12	8/8 (100%)	4/4 (100%)	4/4 (100%)
Any VF	0/8 (0%)	0/4 (0%)	0/4 (0%)
Breakthrough	0/8 (0%)	0/4 (0%)	0/4 (0%)
Relapse	0/8 (0%)	0/4 (0%)	0/4 (0%)
Others	0/8 (0%)	0/4 (0%)	0/4 (0%)
IL28B CC	2/2 (100%)	1/1 (100%)	1/1 (100%)
IL28B CT	5/5 (100%)	2/2 (100%)	3/3 (100%)
IL28B TT	1/1 (100%)	1/1 (100%)	0/0 (0%)
≤800,000 IU/mL	3/3 (100%)	1/1 (100%)	2/2 (100%)
>800,000 IU/mL	5/5 (100%)	3/3 (100%)	2/2 (100%)
Cirrhotic	4/4 (100%)	3/3 (100%)	1/1 (100%)
Non-Cirrhotic	4/4 (100%)	1/1 (100%)	3/3 (100%)
HCV monoinfected	7/7 (100%)	3/3 (100%)	4/4 (100%)
HIV coinfected	1/1 (100%)	1/1 (100%)	0/0 (0%)
P/R RELAPSER	3/3 (100%)	1/1 (100%)	2/2 (100%)
P/R PARTIAL RESPONDER	1/1 (100%)	1/1 (100%)	0/0 (0%)
P/R NULL RESPONDER	4/4 (100%)	2/2 (100%)	2/2 (100%)

(b) (4)

[redacted] (b) (4). There were no clear differences between IL28B CC vs. IL28B non-CC subjects or between cirrhotic and non-cirrhotic subjects. The median baseline HCV RNA level was 1.3 x 10^7 IU/ml (n=2).

(b) (4)

[redacted]

Appendix A4: Study 047 (C-SCAPE)

This study evaluated the safety, tolerability, and efficacy of regimens containing MK-5172, MK-8742 and/or RBV for a duration of 12 weeks among TN, non-cirrhotic subjects infected with HCV GT2, GT4, GT5, or GT6. The results of this study were then used to define the scope of genotypes to be included in Phase 3 studies. The protocol was conducted in 2 parts:

Part A: 30 TN, non-cirrhotic GT2-infected subjects were given MK-5172 100 mg QD + MK-8742 50 QD mg + RBV (twice daily) for 12 weeks (Arm A1).

Part B:

- Arm B1: 30 TN, non-cirrhotic GT2-infected subjects were given MK-5172 100 mg QD + RBV (twice daily) for 12 weeks
- Arm B2: 19 TN, non-cirrhotic, GT4-, GT5-, or GT6-infected subjects were given MK-5172 100 mg QD + MK-8742 50 mg QD + RBV (twice daily) for 12 weeks
- Arm B3: 19 TN, non-cirrhotic, GT4-, GT5-, or GT6-infected subjects were given MK-5172 100 mg QD + MK-8742 50 mg QD for 12 weeks

The primary efficacy endpoint was the proportion of subjects achieving SVR12, which is defined as HCV RNA <25 IU/mL either target detected but unquantifiable (TD[u]) or target not detected (TND) 12 weeks after the end of all study therapy.

(b) (4)

[redacted]

(b) (4) (b) (4)

Table A4-3: SVR12 and Virologic Failure Results in Study 047 (GT 4, 5, 6, MK-5172 100 mg QD + MK-8742 50 mg QD + RBV). (b) (4)

	HCV GT4-All	HCV GT4a	HCV GT4d	HCV GT4-Other
SVR12	10/10 (100%)	6/6 (100%)	3/3 (100%)	1/1 (100%)
Any VF	0/10 (0%)	0/6 (0%)	0/3 (0%)	0/1 (0%)
Breakthrough	0/10 (0%)	0/6 (0%)	0/3 (0%)	0/1 (0%)
Relapse	0/10 (0%)	0/6 (0%)	0/3 (0%)	0/1 (0%)
Non-responder	0/10 (0%)	0/6 (0%)	0/3 (0%)	0/1 (0%)
Others	0/10 (0%)	0/6 (0%)	0/3 (0%)	0/1 (0%)

Part B3 (HCV GT4, 5, 6, MK-5172 100 mg QD + MK-8742 50 mg QD)

The overall ITT SVR12 rates were 4/5 (80%), 4/4 (100%), and 1/1 (100%) for subjects infected with HCV GT4a, GT4d, and GT4k, respectively (Table A4-4, FDA Analysis). The overall ITT SVR12 rate was (b) (4) for subjects infected with HCV GT5. (b) (4)

Table A4-4: SVR12 and Virologic Failure Results in Study 047 (GT 4, 5, 6, MK-5172 100 mg QD + MK-8742 50 mg QD). (b) (4)

	HCV GT4-All	HCV GT4a	HCV GT4d	HCV GT4k
SVR12	9/10 (90%)	4/5 (80%)	4/4 (100%)	1/1 (100%)
Any VF	1/10 (10%)	1/5 (7%)	0/4 (0%)	0/1 (0%)
Breakthrough	0/10 (0%)	0/5 (0%)	0/4 (0%)	0/1 (0%)
Relapse	0/10 (0%)	0/5 (0%)	0/4 (0%)	0/1 (0%)
Non-responder	0/10 (0%)	0/5 (0%)	0/4 (0%)	0/1 (0%)
Others	1/10 (10%)	1/5 (7%)	0/4 (0%)	0/1 (0%)

Appendix A5: Study 074 (C-SWIFT)

Study 074 was an open-label, single-center, multiple-arm trial of a fixed dose combination of MK-5172/MK-8742 (100mg/50mg), and 400 mg of sofosbuvir (SOF) in GT1- or GT3-infected treatment-naïve subjects with or without cirrhosis. This was an open-label trial, but at the time of enrollment, the investigator and the subject were blinded to treatment duration. The study included four cohorts of subjects defined by HCV genotype (GT1 or GT3) and disease characteristic (cirrhotic or non-cirrhotic). Within each of the first three cohorts, a separate randomization assigned subjects into one of two groups defined by duration of therapy (4 or 6 weeks, 6 or 8 weeks, and 8 or 12 weeks) according to a computer generated allocation schedule. Within the fourth cohort, patients were assigned to the 12 week duration group (no randomization). Randomization of subjects within the GT1 cohorts (treatment arms 1-4) was stratified based on Genotype Sub-type (1a vs. non-1a). Non-cirrhotics were enrolled in the Treatment Arms 1, 2, 5, and 6, whereas cirrhotics were enrolled in Arms 3, 4, and 7. A total of 143 subjects were to be enrolled.

The primary efficacy endpoint was the proportion of subjects achieving SVR12, defined as HCV RNA <15 IU/mL (either TD[u] or TND) 12 weeks after the end of study therapy.

A regimen of MK-5172+MK-8742+sofosbuvir, administered for 4 weeks, is insufficient to clear HCV GT1 infection in most subjects (Table A5-1, FDA Analysis). A regimen of MK-5172+MK-8742+sofosbuvir, administered for 6 weeks, resulted in sharp increase in SVR12 rates among non-cirrhotic, treatment-naïve, GT1-infected subjects (Table A5-2, FDA Analysis). A regimen of MK-5172+MK-8742+sofosbuvir, administered for 6 or 8 weeks, resulted in SVR12 rates of <90% among cirrhotic, treatment-naïve, GT1-infected subjects (Table A5-3 & Table A5-4, FDA Analysis). Collectively, these results indicate that this combination regimen is not sufficient for treatment duration ≤8 weeks in GT1-infected subjects.

Table A5-1: MK-5172 100 mg + MK-8742 50 mg + Sofosbuvir 400 mg for 4 Weeks (GT1 Non-cirrhotic).

	HCV GT1a (n=26)	HCV GT1b (n=5)
SVR12	7/26 (26%)	3/5 (60%)
Any VF	18/26 (69%)	2/5 (40%)
Breakthrough	0/26 (0%)	0/5 (0%)
Relapse	18/26 (69%)	2/5 (40%)
Others	1/26 (4%)	0/5 (0%)
IL28B CC	4/10 (40%)	0/1 (0%)
IL28B CT	2/9 (22%)	3/3 (100%)
IL28B TT	1/7 (14%)	0/1 (0%)
Cirrhotic	0/0 (0%)	0/0 (0%)
Non-Cirrhotic	7/26 (27%)	3/5 (60%)
≤800,000 IU/mL	2/6 (33%)	1/2 (50%)
>800,000 IU/mL	5/20 (25%)	2/3 (67%)

Table A5-2: MK-5172 100 mg + MK-8742 50 mg + Sofosbuvir 400 mg for 6 Weeks (GT1 Non-cirrhotic).

	HCV GT1a (n=26)	HCV GT1b (n=4)
SVR12	22/26 (84%)	4/4 (100%)
Any VF	4/26 (15%)	0/4 (0%)
Breakthrough	0/26 (0%)	0/4 (0%)
Relapse	4/26 (15%)	0/4 (0%)
Others	0/26 (0%)	0/4 (0%)
IL28B CC	7/7 (100%)	1/1 (100%)
IL28B CT	12/15 (80%)	2/2 (100%)
IL28B TT	3/4 (75%)	1/1 (100%)
Cirrhotic	0/0 (0%)	0/0 (0%)

	HCV GT1a (n=26)	HCV GT1b (n=4)
Non-Cirrhotic	22/26 (85%)	4/4 (100%)
≤800,000 IU/mL	8/8 (100%)	1/1 (100%)
>800,000 IU/mL	14/18 (78%)	3/3 (100%)

Table A5-3: MK-5172 100 mg + MK-8742 50 mg + Sofosbuvir 400 mg for 6 Weeks (GT1 Cirrhotic).

	HCV GT1a (n=16)	HCV GT1b (n=4)
SVR12	13/16 (81%)	3/4 (75%)
Any VF	3/16 (19%)	1/4 (25%)
Breakthrough	0/16 (0%)	0/4 (0%)
Relapse	3/16 (19%)	1/4 (25%)
Others	0/16 (0%)	0/4 (0%)
IL28B CC	5/5 (100%)	1/1 (100%)
IL28B CT	7/9 (78%)	2/2 (100%)
IL28B TT	1/2 (50%)	0/1 (0%)
Cirrhotic	13/16 (81%)	3/4 (75%)
Non-Cirrhotic	0/0 (0%)	0/0 (0%)
≤800,000 IU/mL	6/7 (86%)	0/0 (0%)
>800,000 IU/mL	7/9 (78%)	3/4 (75%)

Table A5-4: MK-5172 100 mg + MK-8742 50 mg + Sofosbuvir 400 mg for 8 Weeks (GT1 Cirrhotic).

	HCV GT1a (n=16)	HCV GT1b (n=5)
SVR12	14/16 (88%)	3/5 (60%)
Any VF	1/16 (6%)	1/5 (20%)
Breakthrough	0/16 (0%)	0/5 (0%)
Relapse	1/16 (6%)	1/5 (20%)
Others	1/16 (6%)	1/5 (20%)
IL28B CC	5/5 (100%)	0/0 (0%)
IL28B CT	6/8 (75%)	2/3 (67%)
IL28B TT	3/3 (100%)	1/2 (50%)
Cirrhotic	14/16 (88%)	3/5 (60%)
Non-Cirrhotic	0/0 (0%)	0/0 (0%)
≤800,000 IU/mL	3/3 (100%)	2/2 (100%)
>800,000 IU/mL	11/13 (85%)	1/3 (33%)

A regimen of MK-5172+MK-8742+sofosbuvir, administered for 8 to 12 weeks, achieved SVR12 rates >90% among non-cirrhotic, treatment-naïve, GT3-infected subjects (Table A5-5, FDA Analysis). A regimen of MK-5172+MK-8742+sofosbuvir, administered for 12 weeks, resulted in SVR12 rate of (b) (4) among cirrhotic, treatment-naïve, GT3-infected subjects. Relapse is the primary mechanism of failure to clear HCV GT1 or GT3 infection following administration of MK-5172+MK-8742+sofosbuvir.

(b) (4)

Appendix A6: Site-directed Mutant Phenotype Data (MK-5172; study report 044zpl)

Table A6-1: Activity of MK-5172 against HCV Replicon with NS3 Substitutions Observed in the Clinical Studies.

Genotype	NS3 Substitutions	Protocol	EC_{50} +/- SD (nM)	Fold-Shift vs. WT
1a	V36L	PN035, PN048, PN068	0.5 ± 0.3	1.5
1a	V36M	PN035, PN060, PN061, PN074	0.3 ± 0.2	1
1a	V55A	PN060, PN061	0.5 ± 0.3	1.4
1a	Y56H	PN004, PN035, PN060, PN068	5.7 ± 4.3	16.1
1a	Q80K	PN035, PN048, PN060, PN061, PN068, PN074	0.3 ± 0.3	0.9
1a	Q80S	PN068	n/a	n/a
1a	V107I	PN035, PN068	0.2 ± 0.1	0.7
1a	S122G[a]	PN035, PN060, PN074	0.3 ± 0.1	1
1a	S122T[a]	PN035	0.6 ± 0.2	2
1a	I132V[a]	PN035	0.4 ± 0.2	1.5
1a	R155I	PN068	n/a	n/a
1a	R155K	PN004, PN048, PN068	1.3 ± 0.7	3.7
1a	R155T	PN048	3.4 ± 1.7	9.7
1a	A156G	PN004, PN035	1.7 ± 0.1	4.8
1a	A156T	PN004, PN035, PN048, PN068	unfit	n/a
1a	A156V	PN035	unfit	n/a
1a	V158A	PN048, PN068	n/a	n/a
1a	D168A	PN004, PN035, PN060, PN061, PN068	28.6 ± 13.0	80.7
1a	D168G	PN060	9.6 ± 6.9	27.2
1a	D168E	PN004, PN035, PN074	4.9 ± 4.2	13.9
1a	D168N	PN035, PN048	0.9 ± 0.4	2.5
1a	D168V	PN035, PN060, PN068	10.5 ± 5.0	29.7
1a	D168Y	PN035	6.9 ± 5.2	21
1a	I170V[a]	PN035, PN068, PN074	0.7 ± 0.3	2.3
1b	T54S	PN048, PN060	0.6 ± 0.3	1.2
1b	Y56F	PN048, PN061, PN068	0.7 ± 0.4	1.5
1b	Y56H	PN004, PN047	6.3 ± 2.8	12.6
1b	Q80L	PN048, PN068	1.1 ± 0.8	2.1
1b	V107I	PN052, PN061	0.5 ± 0.2	1
1b	S122N	PN035, PN047	n/a	n/a
1b	S122R	PN074	0.3 ± 0.1	0.5
1b	S122T[a]	PN047, PN068	0.6 ± 0.2	2
1b	V132I	PN047	n/a	n/a
1b	V132L	PN074	n/a	n/a
1b	R155Q	PN047	1.2 ± 0.6	2.4
1b	R155W	PN004	13.4 ± 2.2	26.7

Genotype	NS3 Substitutions	Protocol	EC_{50} +/- SD (nM)	Fold-Shift vs. WT
1b	A156T	PN004, PN047, PN048	140.1 ± 59.1	279.5
1b	D168A	PN047	6.8 ± 3.2	13.6
1b	D168E	PN004	1.6 ± 0.7	3.2
1b	D168N	PN047	0.4 ± 0.2	0.7
1b	V170I	PN047, PN048, PN052, PN060	0.4 ± 0.3	0.9
4a	A156M	PN068	n/a	n/a
4a	A156T	PN068	n/a	n/a
4a	A156V	PN068	n/a	n/a
4a	D168A[b]	PN068	96 ± 12	320
4a	D168G	PN068	n/a	n/a
4a	V170I	PN068	n/a	n/a
6	V36I	PN047, PN060	n/a	n/a
6a	V36L	PN047	n/a	n/a
6a	Y56H[c]	PN047, PN060	(b) (4)	
6a	L80K	PN060	n/a	n/a
6e, 6n, 6q	L80Q	PN047, PN060	n/a	n/a
6a, e, 6q	I132L	PN047, PN060	n/a	n/a
6	A156M	PN047	n/a	n/a
6	A156T	PN047	n/a	n/a
6	A156V	PN047	n/a	n/a
6q	D168C	PN047	(b) (4)	
6a	D168E[d]	PN060		
6q	D168Y	PN047, PN060	n/a	n/a
6a, 6e, 6n, 6q	I170V	PN047, PN060	n/a	n/a

a. Activity was estimated using GT1a transient virus transfection assay.
b. The GT4a replicon contained tissue culture adaptive substitution G162R in NS3.
c. The chimeric replicon has the GT6a (JN180455.1) NS3 sequence in GT1b_N strain background in Huh7.
d. The chimeric replicon has the GT6a (JN180455.1) NS3 sequence in GT1b_N strain background in Huh7 and contained tissue culture adaptive substitution E176G in NS3.

Appendix A7: Site-directed Mutant Phenotype Data (MK-8742; study report 044zpl)

Table A7-1: Activity of MK-8742 against HCV Replicon with NS5A Substitutions Observed in the Clinical Studies.

Genotype	NS5A Substitutions	Protocol	EC_{50} +/- SD (nM)	Fold-Shift vs. WT
1a	M28A[a]	PN035, PN060, PN074	0.427 ± 0.22	61
1a	M28G[a]	PN035, PN060	500 ± 54	71429
1a	M28T[a]	PN002, PN035, PN048, PN068, PN074	0.108 ± 0.03	15
1a	M28V	PN035, PN052, PN060, PN074	0.008 ± 0.002	2
1a	Q30H	PN002, PN035, PN048, PN060, PN068, PN074	0.03 ± 0.002	7.5
1a	Q30K	PN061, PN074	0.006 ± 0.003	1.5
1a	Q30L[a]	PN035, PN060, PN074	0.006 ± 0.002	1
1a	Q30N	PN074	n/a	n/a
1a	Q30R	PN002, PN035, PN048, PN052, PN060, PN061, PN068, PN074	0.5 ± 0.5	125
1a	Q30Y	PN035	n/a	n/a
1a	L31I	PN068	n/a	n/a
1a	L31M	PN002, PN035, PN052, PN060, PN061, PN068, PN074	0.002± 0.001	0.5
1a	L31V	PN002, PN035, PN060	0.5 + 0.3	125
1a	H58D[a]	PN035, PN048, PN060, PN068	0.041 ± 0.02	6
1a	Y93C	PN074	0.2 ± 0.07	50
1a	Y93H	PN002, PN035, PN048, PN060, PN068, PN074	2.4 ± 1.3	600
1a	Y93N[a]	PN002, PN035, PN060, PN068, PN074	6.5 ± 1.25	929
1a	Y93S	PN061, PN068	n/a	n/a
1b	L28M	PN068	0.006 + 0.003	2
1b	R30Q	PN047	0.009 ± 0.003	3
1b	L31F	PN060	0.05 ± 0.02	16.7
1b	L31I	PN068	0.001 ± 0.0004	0.3
1b	L31M	PN035, PN047, PN048, PN052, PN068	0.003 ± 0.001	1
1b	L31V	PN035	0.01 ± 0.01	3.3
1b	P58S	PN047	n/a	n/a
1b	Y93H	PN002, PN035, PN048, PN052, PM060, PN068	0.05 ± 0.03	16.7
4a	L28M	PN068	n/a	n/a
4d	L28S	PN061, PN068	n/a	n/a
4a	L28T	PN068	n/a	n/a

Genotype	NS5A Substitutions	Protocol	EC_{50} +/- SD (nM)	Fold-Shift vs. WT
4d	L30R	PN035	n/a	n/a
4d	M31I	PN068	n/a	n/a
4d	M31V	PN068	0.0005 ± 0.0004	2.5
4a	P58D	PN068	n/a	n/a
4d	P58T	PN068	n/a	n/a
4a	P58Y	PN068	n/a	n/a
4d	Y93H	PN068	0.0015 ± 0.002	7.5
6a	F28L	PN060	n/a	n/a
6q	V28M	PN047	n/a	n/a
6a	L31M	PN060	n/a	n/a

a. Activity was estimated using GT1a transient virus transfection assay.

Appendix A8: Study 035 (C-WORTHy)

Study 035 was a multicenter, randomized, parallel-group trial that evaluated MK-5172 with MK-8742 ± RBV for treatment of hepatitis C. The protocol was conducted in 4 parts (Parts A-C were in GT1, described in Section 3.6):

Part D

An additional 41 treatment-naïve, non-cirrhotic subjects with HCV GT3 were randomized to 2 treatment arms in a ratio of 1:1 (Arms D1 and D2) to receive 12 or 18 weeks of open label MK-5172 100 mg + MK-8742 50 mg + RBV.

(b) (4)

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