1. TITLE PAGE

SYNOPTIC CLINICAL STUDY REPORT
MK-5172

A Randomized, Partially Double-Blind, Active-Controlled, Dose-Ranging Estimation Study to Evaluate the Safety, Tolerability, and Efficacy of Different Regimens of MK-5172 When Administered Concomitantly with Pegylated-Interferon and Ribavirin in Treatment-Naive Patients with Chronic Genotype 2 or 3 Hepatitis C Virus Infection

Generic Name:	Not Applicable
Protocol	012-01
EudraCT Number	2011-003299-36
Dosage Form:	Tablets
Phase	IIb
Indication:	Hepatitis C Virus Infection
Study Design:	Partially double-blind, multicenter, randomized, active-controlled, dose-ranging, estimation study
Sponsor Name:	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Clinical Monitor:	[redacted]
Study Initiation Date (FPE):	30-Nov-2011
Study Early Termination Date (if applicable):	27-Feb-2012
Study Completion Date (LPLV):	1-May-2012
Investigator Name/Affiliation:	3 sites in the United States had treated patients at the time of cancellation of the study.
GCP Compliance:	This study was conducted in conformance with Good Clinical Practice (GCP)
Interim CSRs for this protocol	Not Applicable
Questions about the clinical study report should be directed to the individual listed on the accompanying correspondence.	

2. SYNOPSIS

MERCK SHARP & DOHME CORP., A SUBSIDIARY OF MERCK & CO., INC. MK-5172 Tablets, hivinfection	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Randomized, Partially Double-Blind, Active-Controlled, Dose-Ranging Estimation Study to Evaluate the Safety, Tolerability, and Efficacy of Different Regimens of MK-5172 When Administered Concomitantly with Pegylated-Interferon and Ribavirin in Treatment-Naïve Patients with Chronic Genotype 2 or 3 Hepatitis C Virus Infection #012

PROTECTION OF HUMAN SUBJECTS: This study was conducted in conformance with Good Clinical Practice (GCP) standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

INVESTIGATORS/STUDY CENTERS: This study was discontinued early and canceled, 3 sites in the United States had treated patients at the time of cancellation of the study.

PUBLICATIONS:
N/A

PRIMARY THERAPY PERIOD: 30-Nov-2011 to 1-May-2012 (last patient last visit). **CLINICAL PHASE:** IIb

DURATION OF TREATMENT: MK-5172 in combination with Peg-IFN alfa-2b and RBV (Arms 1, 2, 3) relative to the control regimen (Arm 4) was intended to be given for at least 12 weeks. The study was discontinued early. Patients who were enrolled and treated were all discontinued from study therapy and were given up to 8 weeks of Peg-IFN/ RBV therapy with the recommendation for the subjects to be followed to the end of treatment per the standard of care for GT2/3 patients. Three patients received study medication prior to the trial being terminated. Two patients received 400mg of MK-5172, one for 22 days and one for 36 days. One patient received placebo for 37 days.

OBJECTIVES:

Primary

In TN patients with chronic HCV GT 2 or GT 3 infection with pre-treatment HCV RNA of at least 10,000 IU/mL:

(1)To evaluate the antiviral activity in each of the three arms of MK-5172 (Arms 1, 2, 3) administered in combination with Peg-IFN alfa-2b and RBV as assessed by the proportion of patients achieving undetectable HCV RNA at Week 12 (End-of-Treatment Response, EOTR). (2) **Objective:** To evaluate the safety and tolerability in each of the three arms of MK- 5172 in combination with Peg-IFN alfa-2b and RBV (Arms 1, 2, 3) relative to the control regimen (Arm 4).

STUDY STATUS: The study was suspended from enrolling patients on 22-Feb-2012 and formally discontinued on 27-Feb-2012 The decision to discontinue PN012 was based on the preliminary results from the planned interim analysis on data from the vanguard cohort of PN003 (MK-5172 with Peginterferon alfa-2b and Ribavirin in Treatment-Naive Genotype 1 Hepatitis C Patients). The planned interim analysis in PN003 was conducted when 136 patients reached Week 16 of the study. The results suggested a dose relationship with respect to elevated transaminase levels observed during the MK-5172/placebo dosing period. Specifically, transaminase levels to >5x ULN were observed only in the 400 and 800 mg PO QD dose groups. The elevations tended to occur between days 28 and 84 of the study. As a result of these finding in PN 003, the 3 patients that were actively on study drug, MK-5172/placebo, were discontinued from MK-5172/placebo, and advised to continue on 24 weeks of therapy of Peg-IFN/ RBV. The patients were given 8 weeks of Peg-IFN/RBV and followed during that period. They were then referred to the Investigator/ Primary physician for any additional follow up or treatment in order to complete the balance of the recommended 24 weeks of therapy.

STUDY DESIGN:

This was a partially double-blind, multicenter, randomized, active-controlled, dose-ranging, estimation study with a planned sample size of 120 treatment-naïve GT 2 or GT 3 HCV-infected patients, 18 years of age or above, with an HCV RNA level of at least 1x105 IU/mL. Patients were to be randomly assigned to 1 of 4 treatment arms in a 1:1:1:1 ratio, using a central randomization system. Patients were stratified according to HCV genotype (GT 2 vs. GT 3) and screening HCV RNA level for GT 3 patients (low, < 400,000 IU/mL vs. high, ≥ 400,000 IU/mL) into three strata levels. One-third (~40 patients) would be GT 2, one-third (~40 patients) would be GT 3 with a viral load < 400,000 IU/mL, and one-third (~40 patients) would be GT 3 with a viral load ≥ 400,000 IU/mL. The study plan was to have approximately 30 patients enrolled in each of the treatment arms for a total of 120 patients in the primary analysis population.

Patients in the study were to receive MK-5172 (200 mg, 400 mg, or 800 mg QD) in combination with Peg-IFN alfa-2b and RBV. HCV RNA data were to be collected to evaluate efficacy for the duration of study therapy and at the post-treatment follow-up visits

PATIENT DISPOSITION:

Patient disposition is summarized for the 5 patients that were enrolled in the trial, of whom only 3 were treated in the study. All patients discontinued study drug due to the sponsor terminating the trial, 1 patient was lost to follow up during the termination and closing of study sites. Of the 3 patients treated, 2 were in the MK-5172 400 mg treatment group and 1 was in the placebo group.

Disposition of Subjects
With Respect to Study

	MK-5172 200 mg + Peg-IFN + RBV		MK-5172 400 mg + Peg-IFN + RBV		Placebo + Peg-IFN + RBV		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Not Randomized							23	
Subjects in population	1		3		1		5	
Study Disposition								
Discontinued	1	(100.0)	3	(100.0)	1	(100.0)	5	(100.0)
Lost To Follow-Up	0	(0.0)	1	(33.3)	0	(0.0)	1	(20.0)
Study Terminated By Sponsor	1	(100.0)	2	(66.7)	1	(100.0)	4	(80.0)

Each subject is counted once for Study Disposition based on the latest corresponding disposition record.
This table includes two subjects who were randomized but did not receive study therapy.

Baseline Characteristics are summarized for the 3 patients treated in the trial.

Subject Characteristics

	MK-5172 400 mg + Peg-IFN + RBV		Placebo + Peg-IFN + RBV		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	2		1		3	
Gender						
Male	1	(50.0)	0	(0.0)	1	(33.3)
Female	1	(50.0)	1	(100.0)	2	(66.7)
Age (Years)						
18 to 35	1	(50.0)	0	(0.0)	1	(33.3)
36 to 50	1	(50.0)	0	(0.0)	1	(33.3)
Over 50	0	(0.0)	1	(100.0)	1	(33.3)
Mean	40.5		51.0		44.0	
SD	7.8				8.2	
Median	40.5		51.0		46.0	
Range	35 to 46		51 to 51		35 to 51	
Race						
White	2	(100.0)	1	(100.0)	3	(100.0)
Ethnicity						
Not Hispanic Or Latino	2	(100.0)	1	(100.0)	3	(100.0)
HCV Genotype						
3	0	(0.0)	1	(100.0)	1	(33.3)
3a	2	(100.0)	0	(0.0)	2	(66.7)
Screening HCV RNA						
<400,000 IU/mL	1	(50.0)	0	(0.0)	1	(33.3)
≥400,000 IU/mL	1	(50.0)	1	(100.0)	2	(66.7)

STUDY DOSAGE:

Patients were to receive either MK-5172 at 200, 400, 800 mg, or placebo to MK-5172 QD each in combination with Peg-IFN plus RBV. In Arms 1-3, MK-5172 QD was administered orally without regard to food in combination with Peg-IFN (1.5 µg/kg/wk) and weight-based RBV BID in a blinded fashion. Total treatment duration was planned for 12 wks. In Arm 4, for the first 12 weeks (Day 1 to Week 12), Peg-IFN (1.5 µg/kg/wk) and weight-based RBV BID was administered with Placebo to MK-5172 QD in a blinded fashion. For the remaining 12 weeks (TW12 through TW24), Peg-IFN (1.5 µg/kg/wk) and weight-based RBV BID were planned to be administered in an open-label fashion. Total treatment duration would have been 24 wks.

Peg-IFN alfa-2b (PegIntron), was administered as weekly subcutaneous injections at a dose of 1.5 µg/kg/wk. RBV (Rebetol), was administered at a total daily dose of 600 mg to 1400 mg based on the patients weight on Day1, as twice-daily oral doses.

Clinical Drug Supplies

Bulk Product Description	Manufacturing Lot Numbers
MK-5172 100mg Tablet	[redacted]
MK-5172 100mg Placebo	
Ribavirin (REBETOL) Capsules 200mg Capsule	
Peginterferon Alfa-2b (PEGINTRON) 50 µg/0.5 mL vial	
Peginterferon Alfa-2b (PEGINTRON) Redipen 80 µg / 0.5 mL Redipen	
Peginterferon Alfa-2b (PEGINTRON) Redipen 120 µg / 0.5 mL Redipen	
Peginterferon Alfa-2b (PEGINTRON) Redipen 150 µg / 0.5 mL Redipen	
Peginterferon Alfa-2b (PEGINTRON) vial 50 µg / 0.5 mL vial	
Peginterferon Alfa-2b (PEGINTRON) vial 150 µg / 0.5 mL vial	

DIAGNOSIS/INCLUSION CRITERIA: Patients with documented CHC GT2 or GT3 infection who were ≥18 years of age with a screening HCV RNA ≥ 10,000 IU/mL at screening. All patients must have met a number of laboratory criteria and must have been declared clinically stable by the Investigator to participate in this trial. Patients could not be enrolled if they had cirrhosis, hepatocellular carcinoma (HCC) or were under evaluation for HCC. Both Female and Male patients of reproductive potential agreed to use two acceptable methods of birth control throughout the study, and for all women of childbearing potential, a negative urine pregnancy test was required prior to randomization for female patients.

EVALUATION CRITERIA:

Efficacy Measurements: Blood was drawn from patients to assess plasma HCV RNA levels using the Roche COBAS® Taqman® HCV Test, v2.0 at all study visits. Results from the sample collected at the screening visit were used to determine eligibility. Samples collected at other time points were used for primary or supportive efficacy analyses. They were also used for determining the course of treatment and identifying virologic failures.

Pharmacokinetics: PK samples were collected from all patients who participated in the study. PK samples were collected prior to the morning dose of MK-5172/placebo, RBV, and Peg-IFN alfa-2b on Days 1, 3, and 7; and at Weeks 4, and 12. At Weeks 4 and 12, one additional MK-5172 PK sample was also collected approximately 2 hours post dose. At Weeks 2 and 8, MK-5172 PK samples were collected irrespective of the time of MK-5172/placebo dosing.

Safety Measurements: The safety and tolerability of MK-5172 was monitored from the first study dose through the last dose of study medications (including peg-IFN and RBV) by clinical assessment of adverse experiences reported to the study staff and repeated measurements of vital signs, 12-lead ECGs, physical examinations, and standard laboratory safety tests (hematology, chemistry including liver function tests and urinalysis) were monitored at every study visit. Additionally, all adverse experiences, regardless of relationship to the study medications (including Peg-IFN alfa-2b and RBV) were collected throughout the course of study therapy and through completion of the post-treatment evaluation periods. Medical history and lab evaluations were performed at screening to determine eligibility.

STATISTICAL PLANNING AND ANALYSIS: Due to early termination of the study and only 3 patients being enrolled and treated with study drug, no official statistical analysis was performed

RESULTS:

EFFICACY: There were no formal efficacy analyses conducted for this study due to early termination. At early discontinuation all patients were not detectable for HCV virus, however these patients were not followed for sustained viral response.

PHARMACOKINETICS: There were no formal pharmacokinetic analyses conducted for this study due to early termination.

SAFETY: Of the three patients that were enrolled and treated in the study, none experienced a serious adverse experience or discontinued study drug due to an adverse experience. All three patients experienced adverse experiences and drug related adverse experiences in both the MK-5172 treatment period and the Peg-IFN + RBV follow up period after the study was terminated. For the AEs reported, in the MK-5172, 400 mg treatment group and the placebo group that were considered drug related, all events were considered related to peg-IFN or RBV with and without MK-5172. Based on a review of patient lab values for liver function tests (AST, ALT, ALP), there were no significant increases or abnormalities from baseline throughout the period that patients were treated.

Adverse Event Summary
Treatment and Follow-Up Phases

	MK-5172 400 mg + Peg-IFN + RBV		Placebo + Peg-IFN + RBV	
	n	(%)	n	(%)
Subjects in population	2		1	
with one or more adverse events	2	(100.0)	1	(100.0)
with no adverse event	0	(0.0)	0	(0.0)
with drug-related[†] adverse events	2	(100.0)	1	(100.0)
with serious adverse events	0	(0.0)	0	(0.0)
with serious drug-related adverse events	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse event	0	(0.0)	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the drug.

[‡] Study medication withdrawn.

The mean drug exposure to MK-5172 was 29 days (22 to 36 days) for the two patients who were randomized to the MK-5172, 400 mg +Peg-IFN/RBV treatment group.

Extent of Exposure to MK-5172 by Dose

MK-5172	<3 weeks	3 weeks to 4 weeks	5 weeks to 6 weeks	Total Subjects	Duration Range	Mean Duration
Any Dose	0	1	1	2	22 to 36 days	29.0 days
400 mg	0	1	1	2	22 to 36 days	29.0 days
Each subject is counted once on each applicable dosage category row.						

Data Source: [16.2]

Exposure to either Peg-IFN or RBV occurred for patients for between 23 and 105 days, since patients were offered an additional 8 weeks of Peg-IFN/RBV therapy after the trial was terminated and patients discontinued MK-5172 therapy.

Extent of Exposure to Peg-IFN by Dose

Peg-IFN	1 week to 2 weeks	3 weeks to 4 weeks	5 weeks to 10 weeks	11 weeks to 12 weeks	13 weeks to 14 weeks	15 weeks to 16 weeks	Total Subjects	Duration Range	Mean Duration
Any Dose	0	1	0	0	1	1	3	28 to 105 days	77.0 days
80 mcg	0	0	0	0	0	1	1	105 to 105 days	105.0 days
96 mcg	0	1	0	0	0	0	1	28 to 28 days	28.0 days
120 mcg	0	0	0	0	1	0	1	98 to 98 days	98.0 days
Each subject is counted once on each applicable dosage category row.									
Duration of exposure is calculated assuming one day of dosing = 7 days of exposure.									

Data Source: [16.2]

Extent of Exposure to Ribavirin by Dose

Ribavirin	<1 week	1 week to 2 weeks	3 weeks to 4 weeks	5 weeks to 10 weeks	11 weeks to 12 weeks	13 weeks to 14 weeks	15 weeks to 16 weeks	Total Subjects	Duration Range	Mean Duration
Any Dose	0	0	1	0	0	2	0	3	24 to 99 days	73.7 days
<600 mg	3	0	0	0	0	0	0	3	1 to 1 days	1.0 days
600 mg	1	0	0	0	0	0	0	1	1 to 1 days	1.0 days
800 mg	0	0	1	0	0	1	0	2	23 to 98 days	60.5 days
1000 mg	0	1	0	0	0	0	0	1	11 to 11 days	11.0 days
1200 mg	0	0	0	0	1	0	0	1	85 to 85 days	85.0 days
Each subject is counted once on each applicable dosage category row.										

Data Source: [16.2]

CONCLUSIONS:
No formal conclusions could be drawn from this study due to its early termination.

AUTHORS: [redacted]

2. APPENDIX

Appendix 16.2.7.1

Subjects With Serious Adverse Events, to be Reported to www.clinicaltrials.gov (Incidence > 0% in One or More Treatment Groups)
Treatment and Follow-Up Phases

	MK-5172 400 mg + Peg-IFN + RBV			Placebo + Peg-IFN + RBV		
	n	(%)	Number of Events	n	(%)	Number of Events
Subjects in population	2			1		
with one or more serious adverse events	0	(0.0)	0	0	(0.0)	0
with no serious adverse events	2	(100.0)		1	(100.0)	

Every subject is counted a single time for each applicable serious adverse event.

A system organ class appears on this report only if one or more specific serious adverse events in that system organ class appear on this report.

Appendix 16.2.7.2

Subjects With Non-serious Adverse Events, to be Reported to www.clinicaltrials.gov (Incidence > 0% in One or More Treatment Groups)
Treatment and Follow-Up Phases

	MK-5172 400 mg + Peg-IFN + RBV			Placebo + Peg-IFN + RBV		
	n	(%)	Number of Events	n	(%)	Number of Events
Subjects in population	2			1		
with one or more non-serious adverse events that met the incidence cutoff	2	(100.0)	15	1	(100.0)	15
with no non-serious adverse events that met the incidence cutoff	0	(0.0)		0	(0.0)	
Blood and lymphatic system disorders						
Anaemia	1	(50.0)	1	0	(0.0)	0
Gastrointestinal disorders						
Dry mouth	1	(50.0)	1	0	(0.0)	0
Nausea	2	(100.0)	2	0	(0.0)	0
General disorders and administration site conditions						
Chills	1	(50.0)	1	1	(100.0)	1
Fatigue	0	(0.0)	0	1	(100.0)	1

Subjects With Non-serious Adverse Events, to be Reported to www.clinicaltrials.gov (Incidence > 0% in One or More Treatment Groups)
Treatment and Follow-Up Phases

	MK-5172 400 mg + Peg-IFN + RBV			Placebo + Peg-IFN + RBV		
	n	(%)	Number of Events	n	(%)	Number of Events
General disorders and administration site conditions						
Injection site reaction	0	(0.0)	0	1	(100.0)	1
Irritability	0	(0.0)	0	1	(100.0)	1
Pyrexia	1	(50.0)	1	0	(0.0)	0
Infections and infestations						
Fungal infection	0	(0.0)	0	1	(100.0)	1
Localised infection	0	(0.0)	0	1	(100.0)	1
Injury, poisoning and procedural complications						
Skeletal injury	0	(0.0)	0	1	(100.0)	1
Metabolism and nutrition disorders						
Decreased appetite	1	(50.0)	1	0	(0.0)	0
Musculoskeletal and connective tissue disorders						

Subjects With Non-serious Adverse Events, to be Reported to www.clinicaltrials.gov (Incidence > 0% in One or More Treatment Groups)
Treatment and Follow-Up Phases

	MK-5172 400 mg + Peg-IFN + RBV			Placebo + Peg-IFN + RBV		
	n	(%)	Number of Events	n	(%)	Number of Events
Musculoskeletal and connective tissue disorders						
Bone pain	1	(50.0)	1	0	(0.0)	0
Myalgia	1	(50.0)	1	1	(100.0)	1
Pain in extremity	0	(0.0)	0	1	(100.0)	1
Nervous system disorders						
Headache	2	(100.0)	2	1	(100.0)	1
Restless legs syndrome	0	(0.0)	0	1	(100.0)	1
Psychiatric disorders						
Depression	1	(50.0)	1	0	(0.0)	0
Insomnia	1	(50.0)	1	0	(0.0)	0
Skin and subcutaneous tissue disorders						
Alopecia	0	(0.0)	0	1	(100.0)	1
Eczema	1	(50.0)	1	0	(0.0)	0

Subjects With Non-serious Adverse Events, to be Reported to www.clinicaltrials.gov (Incidence > 0% in One or More Treatment Groups)
Treatment and Follow-Up Phases

	MK-5172 400 mg + Peg-IFN + RBV			Placebo + Peg-IFN + RBV		
	n	(%)	Number of Events	n	(%)	Number of Events
Skin and subcutaneous tissue disorders						
Night sweats	1	(50.0)	1	0	(0.0)	0
Pruritus	0	(0.0)	0	1	(100.0)	1
Rash	0	(0.0)	0	1	(100.0)	1
Skin lesion	0	(0.0)	0	1	(100.0)	1

Every subject is counted a single time for each applicable non-serious adverse event. Serious adverse events are not counted in this report.

A specific non-serious adverse event appears on this report only if its incidence in one or more of the columns is greater than the percent incidence specified in the report title, prior to rounding. A system organ class appears on this report only if one or more specific non-serious adverse events in that system organ class appear on this report.