This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2 Synopsis

Name of finished product: IDX320

Study Description

Title of study: A Phase I/IIa Study Assessing Single and Multiple Doses of HCV Protease Inhibitor IDX320 in Healthy and Genotype 1 HCV-Infected Subjects

Investigator(s):

Parts A and B: [redacted] (Principal Investigator), [redacted] The Netherlands.

Parts C and D: [redacted] (Coordinating Investigator), [redacted] Poland.

Study center(s): 2 in The Netherlands; 4 in Poland; 3 in Hungary

Publication (reference): [Reesink HW, de Bruijne J, van Vliet AA, et al (2010)] Antiviral activity, safety and pharmacokinetics of IDX320, a novel macrocyclic HCV protease inhibitor, in a 3-day proof-of-concept study in patients with chronic hepatitis C. 61st Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), Oct 30-Nov 2, 2010, Boston (MA); Poster #LB16.

[van de Wetering de Rooij J, Zhou XJ, Temam MF et al (2010)] IDX320, a novel macrocyclic HCV protease inhibitor: safety, tolerability and pharmacokinetics (PK) in a phase I clinical study. The 5th International Workshop on Clinical Pharmacology of Hepatitis Therapy, Jun 23-24, 2010, Boston (MA).

Study Methods

Study period:

First patient enrolled: 25-Jan-2010 (first subject consented into Part A)

Last patient completed: 30-Aug-2010 (last Day 28 Follow-up Visit of Part D)

Objectives, development phase, study status: This was a phase I/IIa study.

The primary objectives were:

- To evaluate safety and tolerability.
- To evaluate antiviral activity.

The secondary objectives were:

- To evaluate plasma and urine PK of IDX320.
- To evaluate the effect of food on the PK of IDX320

The study was completed as planned.

Methodology and treatment duration: This was a multi-part study conducted in sequential steps.

Part A –This part was a randomized, double-blind, placebo-controlled, sequential dose escalation study in healthy male subjects. Eight subjects per cohort were randomized 6:2 (IDX320:placebo) to receive active drug or placebo once a day (QD) as shown in Table 2-1. Safety reviews occurred between ascending dose cohorts.

Table 2-1 Part A design

	Treatment	Fed/Fasted	Drug administration
A	50 mg	Fed	50 mg IDX320 or placebo QD x 1 day
B	100 mg	Fed	100 mg IDX320 or placebo QD x 1 day
C	200 mg	Fed	200 mg IDX320 or placebo QD x 1 day
D	400 mg	Fed	400 mg IDX320 or placebo QD x 1 day
E	400 mg	Fasted	400 mg IDX320 or placebo QD x 1 day
F	400 mg	Fed	400 mg IDX320 or placebo QD x 3 days

Part B – This part was an open-label study in two treatment-naïve or treatment-experienced, genotype 1, hepatitis C virus (HCV)-infected subjects (Table 2-2).

Table 2-2 Part B design

Treatment	Fed/Fasted	Drug administration
200 mg	Fed	200 mg IDX320 QD x 1 day

Part C – This part was a randomized, double-blind, placebo-controlled, parallel group study in treatment-naïve, genotype 1, HCV-infected subjects. Thirty (30) subjects were randomized equally across the five treatment arms to receive active drug or placebo once a day (QD) for 3 days (Table 2-3).

Table 2-3 Part C design

Treatment	Fed/Fasted	Drug administration
50 mg	Fed	50 mg IDX320 QD x 3 days
100 mg	Fed	100 mg IDX320 QD x 3 days
200 mg	Fed	200 mg IDX320 QD x 3 days
400 mg	Fed	400 mg IDX320 QD x 3 days
Placebo	Fed	Placebo QD x 3 days

Pegylated-interferon alfa/ribavirin (Peg-IFN/RBV), reimbursed by the Sponsor, could have been initiated following completion of the Day 4 assessments.

Part D – This part was a randomized, double-blind, placebo-controlled study in treatment-naïve, genotype 1, HCV-infected subjects. Eight subjects were randomized 6:2 (IDX320:placebo) to receive active drug or placebo twice a day (BID) for 3 days (Table 2-4).

Table 2-4 Part D design

Treatment	Fed/Fasted	Drug administration
200 mg BID	Fed	200 mg IDX320 BID or placebo BID x 3 days

Peg-IFN/RBV (reimbursed by the Sponsor) could have been initiated following completion of the Day 4 assessments.

The schedule of assessments for each part of the study, including blood sampling timepoints for safety laboratory parameters, pharmacokinetic (PK) analyses and HCV ribonucleic acid (RNA) quantitation are described in the protocol [Appendix 16.1.1].

Number of subjects (planned and analyzed):

Part A – 48 planned, 48 analyzed

Part B – 2 planned, 2 analyzed

Part C – 30 planned, 30 analyzed

Part D – 8 planned, 8 analyzed

Diagnosis and main criteria for inclusion:

Part A subjects were healthy male volunteers.

Part B subjects were treatment-experienced or treatment-naïve subjects with genotype 1 chronic hepatitis C infection, plasma HCV RNA ≥ 5 $\log_{10}$ IU/mL and compensated liver disease.

Parts C and D subjects were treatment-naïve subjects with genotype 1 chronic hepatitis C infection, plasma HCV RNA ≥ 5 $\log_{10}$ IU/mL and compensated liver disease.

Full inclusion/exclusion criteria are listed in [protocol Section 5, Appendix 16.1.1.].

Test product and reference therapy – dose, dosage form, administration mode, batch numbers:

IDX320 was supplied as a tablet for oral administration, which consisted of 50 mg drug substance formulated with mannitol, microcrystalline cellulose, povidone K30 and croscarmellose sodium, magnesium stearate, sodium starch glycolate, and sodium lauryl sulfate. Matching placebo tablets were also supplied.

Dose and mode of administration are described in the Methodology and Treatment Duration Section, above. Lot numbers are provided in [Section 9.4.2].

Criteria for evaluation

Safety and tolerability: Safety and tolerability measurements included clinical laboratory evaluations, physical examination, vital signs, 12-lead electrocardiograms (ECGs), concomitant medication, adverse event (AE) and dose-limiting toxicity (DLT) assessments as described in [Protocol IDX-07A-001, Appendix 16.1.1].

Cohort stopping rules are described in [Section 4.1 of Protocol IDX-07A-001, Appendix 16.1.1].

Efficacy evaluations: HCV RNA was quantified at a central laboratory using a validated real-time polymerase chain reaction (PCR) assay (COBAS® TaqMan®) with a quantification range of 43-69*10^6 IU/mL and a lower limit of detection (LLOD) of 15 IU/mL. The efficacy endpoints were the change in plasma HCV RNA from baseline, and the emergence of resistance mutations (to be described in a separate report).

Pharmacokinetic and pharmacodynamic (PD) evaluations: Plasma and urine concentrations of IDX320 were quantitated using validated liquid chromatographic methods with mass-spectrometric detection (LC/MS/MS). The lower limit of quantitation for IDX320 was 2.0 ng/mL.

[redacted]

Statistical methods: Data were summarized using descriptive statistics. Placebo subjects were pooled in Part A (single and multiple-dose data) and in Parts C and D (QD and BID data). PK parameters were determined in plasma and urine using noncompartmental methods (see [Section 9.5.4]). A full description of the statistical methods is provided in the statistical analysis plan (SAP) in [Appendix 16.1.9].

Summary - Conclusions

Efficacy

Part B

The two, genotype 1a, HCV-infected subjects had maximal HCV RNA reductions of 1.9 and 2.8 $\log_{10}$ IU/mL with a single 200 mg dose. Viral load in both subjects returned toward baseline once plasma IDX320 levels fell below approximately 100 ng/mL.

Parts C and D

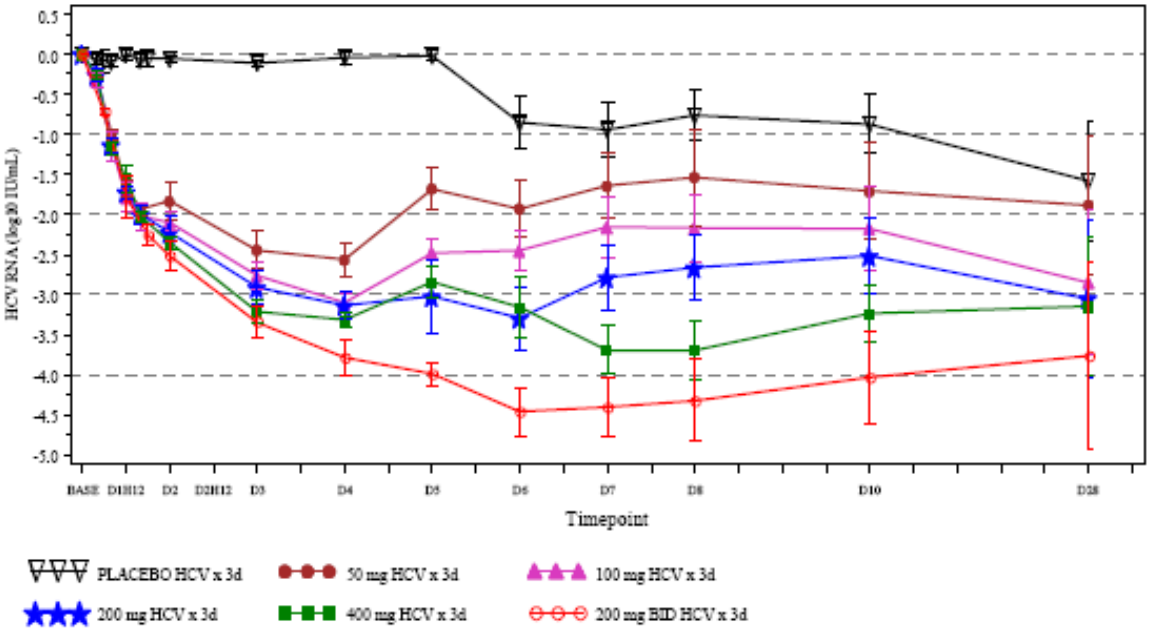
Mean HCV RNA reductions on Day 4 were greater in the groups receiving IDX320 compared to the group receiving placebo and increased with increasing IDX320 dose (Table 2-5 and Figure 2-1). Mean HCV RNA reductions were 0.04, 2.6, 3.1, 3.1, 3.3, and 3.8 $\log_{10}$ IU/mL at Day 4 in the placebo, 50 mg IDX320 QD, 100 mg IDX320 QD, 200 mg IDX320 QD, 400 mg IDX320 QD, and 200 mg IDX320 BID treatment groups, respectively. Viral loads tended to increase after Day 4 in most subjects then varied, depending on whether Peg-IFN/RBV was initiated. By Day 28, mean HCV RNA reductions were greater in the IDX320 groups as opposed to the placebo group, although not as great as the reductions observed during the IDX320/placebo monotherapy portion of the study.

Table 2-5 HCV RNA change from baseline ($\log_{10}$ IU/mL, Parts C and D efficacy evaluable population)

Visit	Statistic	Placebo x 3 days N=8	50 mg QD x 3 days N=5	100 mg QD x 3 days N=6	200 mg QD x 3 days N=6	400 mg QD x 3 days N=7	200 mg BID x 3 days N=6
Change from baseline							
Day 1 H12	Mean (SE)	-0.01 (0.057)	-1.68 (0.106)	-1.79 (0.187)	-1.72 (0.082)	-1.55 (0.159)	-1.78 (0.256)
	Median	0.03	-1.61	-1.86	-1.80	-1.56	-1.58
	SD	0.160	0.238	0.458	0.200	0.421	0.627
	25%, 75%	-0.17, 0.12	-1.84, -1.53	-2.12, -1.62	-1.82, -1.76	-1.90, -1.43	-1.87, -1.41
	Min, Max	-0.2, 0.2	-2.0, -1.4	-2.3, -1.0	-1.8, -1.3	-2.0, -0.7	-3.0, -1.3
Day 2	Mean (SE)	-0.06 (0.041)	-1.83 (0.244)	-2.09 (0.118)	-2.23 (0.212)	-2.34 (0.084)	-2.51 (0.175)
	Median	-0.08	-1.46	-2.09	-2.42	-2.44	-2.52
	SD	0.116	0.545	0.290	0.519	0.222	0.428
	25%, 75%	-0.15, 0.03	-2.21, -1.45	-2.32, -1.82	-2.44, -2.35	-2.47, -2.09	-2.89, -2.22
	Min, Max	-0.2, 0.1	-2.6, -1.4	-2.5, -1.7	-2.6, -1.2	-2.7, -2.1	-3.0, -1.9
Day 3	Mean (SE)	-0.11 (0.044)	-2.44 (0.238)	-2.76 (0.174)	-2.91 (0.200)	-3.21 (0.141)	-3.34 (0.191)
	Median	-0.14	-2.50	-2.90	-3.07	-3.36	-3.44
	SD	0.125	0.532	0.426	0.491	0.372	0.467
	25%, 75%	-0.16, -0.01	-2.73, -1.93	-3.08, -2.41	-3.14, -2.72	-3.47, -2.80	-3.68, -3.14
	Min, Max	-0.3, 0.1	-3.1, -1.9	-3.2, -2.1	-3.4, -2.0	-3.6, -2.6	-3.8, -2.5
Day 4	Mean (SE)	-0.04 (0.075)	-2.56 (0.220)	-3.10 (0.120)	-3.13 (0.166)	-3.31 (0.105)	-3.78 (0.212)
	Median	-0.06	-2.50	-3.13	-3.23	-3.38	-3.92
	SD	0.212	0.492	0.293	0.406	0.277	0.520
	25%, 75%	-0.23, 0.08	-2.86, -2.39	-3.32, -2.84	-3.32, -2.87	-3.48, -3.27	-4.10, -3.22
	Min, Max	-0.3, 0.4	-3.2, -1.9	-3.5, -2.7	-3.6, -2.5	-3.6, -2.7	-4.4, -3.1
Day 28	Mean (SE)	-1.58 (0.738)	-1.88 (0.872)	-2.85 (0.907)	-3.05 (0.982)	-3.15 (0.871)	-3.76 (1.158)
	Median	-0.74	-2.67	-3.88	-3.17	-3.27	-5.48
	SD	2.087	1.951	2.222	2.406	2.304	2.836
	25%, 75%	-3.53, 0.22	-2.81, 0.10	-4.62, -0.09	-4.84, -0.69	-5.59, -0.78	-5.60, -0.49
	Min, Max	-4.9, 0.3	-4.2, 0.2	-4.7, 0.1	-6.0, -0.4	-5.7, -0.4	-5.8, 0.2

H = hour
Source: Table 14.2-1.2.2

Figure 2-1 Mean (+/- SE) HCV RNA change from baseline (log_{10} IU/mL, Parts C and D efficacy evaluable population)



Source: [Figure 14.2-1.1.2]

None of the subjects achieved undetectable levels of HCV RNA by Day 4. The only subjects to achieve undetectable levels of HCV RNA by Day 28 were those randomized to one of the IDX320 treatment groups.

None of the subjects experienced virologic breakthrough during the IDX320/placebo dosing period.

Pharmacokinetics

Parts A and B

After administration of a single rising dose in healthy subjects under fed conditions, peak and total plasma exposures of IDX320 were less than dose-proportional with approximately 3-fold to 4-fold increase in mean C_{max} and AUC when doses escalated from 50 to 400 mg, an 8-fold change. By contrast, C_{trough} appeared dose proportional with a 10-fold increase in the studied dose range (Table 2-6). Mean C_{max} was reached at a median T_{max} of 3h regardless of dose amount. Mean $T_{1/2}$ was 24-26h for doses ≥ 100 mg.

Two HCV-infected subjects received a single 200 mg dose and their plasma exposures of IDX320 did not appear to be substantively high compared to healthy subjects considering the variability associated with a small sample size (N=2).

Compared to fasting state, IDX320 exposure was 2-fold to 3-fold higher with food.

Table 2-6 IDX320 pharmacokinetic parameters for single-dose cohorts (Part A, cohorts A to E, and Part B; PK population)

Dose (mg)	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0-\infty}$ (ng*h/mL)	$T_{1/2}$ (h)	C_{trough} (ng/mL)
50	346±86.9	3.0 (3.0-3.0)	2433±403.2	15.5±5.95	8.40±4.78 (2.00-15.9)
100	467±72.1	3.0 (2.0-4.1)	3544±1011	24.0±7.14	19.0±8.68 (9.70-35.1)
200	982±463	3.0 (2.0-3.0)	7239±2927	26.0±7.08	53.1±26.3 (23.6-77.9)
400	1124±505	3.1 (2.0-4.0)	9440±2319	24.7±6.52	89.0±16.4 (71.9-116)
400 fasted	368±89.1	3.0 (2.0-4.0)	4195±1593	15.4±7.47	53.7±27.6 (27.3-99.3)
200 HCV[1]	1060 (819, 1300)	3.6 (3.0-4.1)	13874 (8926, 18821)	31.5 (30.5, 32.4)	131.7 (74.4, 189)

Values are reported as mean±SD, except for T_{max} where medians (min-max) are reported. For C_{trough}, (min-max) is also shown.
[1] N=2 for HCV-infected subjects, therefore SD is not applicable. Instead, mean and individual data are presented.
Source: Table 14.2-2.2.1 and Table 14.2-2.2.2

After QD dosing for 3 days, mean plasma C_{max} and AUCτ of IDX320 400 mg on Day 3 remained comparable to the values on Day 1. By contrast, there was an approximately 70% increase in mean C_{trough} on Day 3 over Day 1 (Table 2-7).

Table 2-7 IDX320 pharmacokinetic parameters for multiple-dose cohort in healthy subjects (Part A, cohort F; PK population)

Dose (mg)	PK Day	C_{max} (ng/mL)	T_{max} (h)	AUC_{τ} (ng*h/mL)	$T_{1/2}$ (h)	C_{trough} (ng/mL)
400	1	1154±381.0	3.0 (2.0-4.0)	8145±2957		117±52.7 (62.5-216)
	3	1307±344.7	3.5 (3.0-6.0)	10028±4395	31.2±7.62	197±112 (119-420)

Values are reported as mean±SD, except for T_{max} where medians (min-max) are reported. For C_{24h}, (min-max) is also shown.
Source: Table 14.2-2.2.1

Parts C and D

Similar to the observations in healthy subjects, plasma exposure of IDX320 in HCV-infected subjects was also less than dose proportional (Table 2-8). Following repeat QD and BID dosing for 3 days, IDX320 did not appear to appreciably accumulate in terms of C_{max} and AUC considering the associated interindividual variability. However, there appeared to be a steady increase in C_{trough} over time. For the same total daily dose, while maintaining comparable peak exposure, trough concentrations were about 2-fold to 3-fold higher with the 200 mg BID dose than with the 400 mg QD dose.

Overall, peak and total plasma exposures of IDX320 in HCV-infected subjects and healthy subjects were comparable; however, trough concentration appeared to be consistently higher in HCV-infected subjects (approximately 2-fold at doses ≥ 200 mg QD) than healthy subjects.

Table 2-8 Summary pharmacokinetics of IDX320 after QD and BID dosing for 3 days in HCV-infected subjects (Parts C and D; PK population)

Dose (mg)	PK Day	C_{max} (ng/mL)	T_{max} (h)	AUC_{τ}[1] (ng*h/mL)	$T_{1/2}$ (h)	C_{trough} (ng/mL)
50 QD	1	471±179	4.0 (3.0-4.0)	3930±1787		46.0±36.5 (24.8-110)
	3	547±127	2.0 (2.0-4.0)	4543±1886	25.2±5.68	65.0±39.6 (22.6-126)
100 QD	1	679±164	3.0 (2.0-6.0)	5602±2079		81.0±57.0 (34.9-171)
	3	749±229	3.5 (2.0-4.0)	6603±2796	26.0±2.54	119±71.1 (54.2-210)
200 QD	1	1100±374	4.0 (3.0-4.0)	8765±3564		129±73.2 (28.2-225)
	3	972±400	4.0 (3.0-4.0)	9304±3649	25.2±6.85	174±90.2 (57.7-275)
400 QD	1	1344±724	3.0 (2.0-4.0)	10377±6179		188±142 (46.0-443)
	3	1713±1159	3.0 (2.0-6.0)	13520±9150	28.9±13.7	274±231 (71.1-694)
200 BID	1 AM	1421±742	3.0 (3.0-6.0)	9927±4427		478±211 (228-759)
	1 PM	1678±858	4.0 (2.0-6.0)	12753±6612		727±361 (368-1370)
	3 AM	2040±1059	3.0 (3.0-4.0)	13863±6630		686±323 (327-1250)
	3 PM	1620±696	3.5 (3.0-6.0)	13236±5528	52.6±26.2	781±358 (311-1340)

Values are reported as mean±SD, except for T_{max} where medians (min-max) are reported. For C_{trough}, (min-max) is also shown; C_{trough} is C_{24h} for QD and C_{12h} for BID.
[1] AUC_{τ} is AUC_{0-24h} for QD and AUC_{0-12h} for BID; For BID, daily AUC_{0-24h} (not shown) can be calculated as the sum of the AM and PM AUC_{τ}.
Source: Table 14.2-2.2.3

There were only 4 subjects who had a urine fraction with measurable levels of IDX320. The amounts of IDX320 in these fractions, ranging from 0.4 to 2.7µg or <0.01 % of administered doses (200-400 mg), were negligible.

[redacted]

Safety

No deaths or serious adverse events were reported in this study. DLTs were rare (two HCV-infected subjects), did not result in discontinuation of study drug and had no apparent relationship to IDX320 dose. Headache was the most common AE, although there was no clear relationship to IDX320 dose. There were no discernable patterns in AEs across treatment groups in healthy or HCV-infected subjects. The majority of AEs in the study were mild or moderate in intensity.

[redacted]

There were no other discernable patterns in laboratory parameters (including ALT/AST), vital signs, physical examination or ECG parameters between the IDX320 groups and placebo.

In the HCV-infected subjects who received Peg-IFN/RBV after three days of dosing with IDX320, the most common AEs observed were consistent with Peg-IFN/RBV and included headache, pyrexia, myalgia, arthralgia. There were no obvious patterns or trends in the occurrence of AEs

during the 6-day follow-up period in the 12 subjects who elected not to initiate Peg-IFN/RBV after IDX320 dosing.

Conclusions

- IDX320 exhibited dose-related but less than dose-proportional plasma exposure of IDX320 in healthy and HCV-infected subjects.
- Compared to fasting state, food enhanced overall plasma exposure by 2 to 3-fold.
- After repeat daily dosing for 3 days, there was no appreciable accumulation with respect to peak and overall plasma exposure in healthy and HCV-infected subjects; however, there was a steady increase in trough concentration.
- Peak and total exposures of IDX320 between healthy and HCV-infected subjects were similar. However, trough concentration appeared to be consistently higher in HCV-infected subjects (approximately 2-fold at doses ≥ 200 mg QD) than healthy subjects.
- For the same total daily dose of 400 mg, 200 mg BID dosing achieved 2 to 3-fold higher trough concentrations than QD dosing while maintaining comparable peak exposure.
- Urine excretion of IDX320 was negligible.
- Antiviral activity of IDX320 was initially demonstrated in two, genotype 1a, HCV-infected subjects with a single 200 mg dose. Maximal HCV RNA reductions were 1.9 and 2.8 $\log_{10}$ IU/mL and viral load in both subjects returned toward baseline once plasma IDX320 levels fell below approximately 100 ng/mL.
- IDX320 demonstrated potent, dose and exposure-related antiviral activity in genotype 1 HCV-infected subjects after three days of dosing. Mean HCV RNA reductions were 0.04, 2.6, 3.1, 3.1, 3.3, and 3.8 $\log_{10}$ IU/mL at Day 4 in the placebo, 50 mg IDX320 QD, 100 mg IDX320 QD, 200 mg IDX320 QD, 400 mg IDX320 QD, and 200 mg IDX320 BID treatment groups, respectively.
- [redacted]
- There were no deaths, serious adverse events or premature discontinuations of study drug.
- DLTs were rare (two HCV-infected subjects), did not result in discontinuation of study drug and had no apparent relationship to IDX320 dose.
- Headache was the most common AE, although there was no clear relationship to IDX320 dose. There were no discernable patterns in AEs across treatment groups in healthy or HCV-infected subjects. The majority of AEs in the study were mild or moderate in intensity.
- [redacted]
- There were no other discernable patterns in laboratory parameters (including ALT/AST), vital signs, physical examination or ECG parameters between the IDX320 groups and placebo.
- AEs and laboratory abnormalities during the follow-up period in HCV-infected subjects (in Parts C and D) were consistent with Peg-IFN/RBV dosing, which began after Day 4 in the majority of the subjects.

Date of the report: 07-December-2010