SYNOPSIS OF THE CLINICAL STUDY REPORT

Protocol Title	An open, Phase IV, multicentric study, evaluating safety and efficacy of ribavirin (Copegus®) and peginterferon α-2a (Pegasys®) combination in specific groups		
Protocol ID	[redacted] amendment No. 1: 29.3.2006, [redacted] amendment No. 2: 19.9.2006 Roche ID: ML19387		
Coordinating Investigator	[redacted] of [redacted]		
Study sites	Czech Republic: 33 study sites Slovak Republic: 9 study sites		
Published Papers and Other References	Not available		
Study Duration First Patient In: 1. 2. 2006 Last Patient Out: 9.1.2009		Phase: Phase IV	
Primary Aim of the Study	Relative frequency and severity of adverse events in defined subgroups of subjects with chronic viral hepatitis Type C		
Secondary aims of the Study	Relative frequency of sustained virological response in specific groups of subjects suffering from (sustained response). Relative frequency of virological response in specific groups of subjects suffering from chronic viral hepatitis type C, as observed in Week 12 (early response).. Relative frequency of virological response in specific groups of subjects suffering from chronic viral hepatitis type C, as observed at the completion of treatment (end-of-treatment response).		
Design	An open study involving the following groups of subjects suffering from chronic viral hepatitis type C: Group A – subjects with elevation of ALT without simultaneous HIV infection Group B - subjects without elevation of ALT without simultaneous HIV infection Group C – subjects with HIV infection, regardless the ALT level Dosing of the study medication stratified according to the genotype of the virus.		
Study size	Planned: 300	Assigned to treatment: 372	Dosed: 371
Statisticky vyhodnoceno	Efficacy: 370	Safety: 371	
Eligibility	Inclusion Criteria 1. Chronic viral hepatitis Type C with detectable HCV RNA in serum. The quantitative assessment of viremia may precede the inclusion to the study by 56 days. · Group A will include subjects with elevation of ALT (abnormally high ALT level at the time of inclusion) and without simultaneous HIV infection · Group B will include subjects without elevation of ALT (ALT level in normal range at the time of inclusion) and without simultaneous HIV infection · Group C will include subjects with HIV infection, regardless the ALT level 2. Female and male subjects above the 18 years of age 3. Subjects with compensated liver disase, including compensated liver cirrhosis (Child-Pugh skóre A) 4. In subjects with liver cirrhosis or at the transition to liver cirrhosis, an absence of hepatocellulat carcinoma must be confirmed by: · Imagining examination (CT, MRI, ultrasound examination) · Assessment of AFP level, which must not exceed 100 µg/l. The above examinations must be performed within 2 months prior to inclusion to the study 5. Women in fertile age must be informed about obligation of using adequate contraception during and 6 month post treatment with ribavirin (Copegus®). 6. Men with a sexual partner in fertile age must be informed about obligatory contraception preventing pregnancy during the course of treatment with ribavirin (Copegus®)as well as 6 months after		

	treatment cessation. 7. Female participants in the study must have a negative pregnancy test performed not sooner than within 2 weeks preceding the planned inclusion to the study. 8. Men with a sexual partner in fertile age must produce a negative result of the partner's pregnancy test performed not sooner than within 2 weeks preceding the planned partner's inclusion to the study. 9. A reasonable chance of subject's compliance to the study procedures. 10. Signed informed consent.
	Exclusion Criteria 1. The potential study subject is under legal age 2. Pregnancy, lactation, or planned pregnancy during the prospective study participation 3. Taking another study medication within 6 weeks prior to inclusion 4. Presence of another illness with liver pathology (e.g. hemochromatosis, autoimmune hepatitis, liver damage due to alcohol, toxic liver damage, metabolic liver damage). 5. Current presence of hepatitis A or B 6. Serum kreatinin level above 176 µmol/l or kreatinin clearance below 50 ml/min 7. Presence or history of bleeding from oesophageal varicous veins or other symptoms of liver disease decompensation 8. Current systemic antiviral therapy (except anti-retrovirus treatment suffering from HIV infection), and/or cytostatic or immunomodulating therapy 9. Hemoglobin < 120 g/l in female subjects or < 130 g/l in male subjects (the result must not be older than 2 weeks prior to inclusion to the study) 10. The platelet count < 90 x 109 /l (the result must not be older than 2 weeks prior to inclusion to the study) 11. Neutrofils count < 1,5 x 109 /l (the result must not be older than 2 weeks prior to inclusion to the study) 12. Subjects with increased risk of anaemia, or subjects, at risk of serious health problems resulting from anaemia or decrease of hemoglobin (eg., subjects with serious cardiovascular or cerebrovascular disease) 13. History or presence of a serious mental disease, especially depression, which, according to investigator's opinion, does not allow administration of peginterferon α-2a (Pegasys®) 14. History or presence of a disease consequent to immunodeficiency (eg., inflammatory diseases of intestine, idiopathic thrombocytopenic purpura, systemic lupus erythematodes, rheumatoid arthritis) 15. History or presence of serious cardiovascular disease 16. History or presence of a functioning transplant, except liver transplant 17. History or presence of malignancy at any localization 18. Thyroid disorder without full compensation 19. Severe retinopathy (CMV retinitis, macular degeneration, hiabetic or hypertension retinopathy
	Criteria for treatment discontinuation The protocol of the study defined the following criteria for treatment discontinuation: In case of occurrence of at least one of the below mentioned criteria treatment would be discontinued, but the subject would continue his/her participation in the clinical study. Criteria for premature treatment discontinuation were: · Life-threatening adverse side effects of study medication (Copegus®) or peginterferon α-2a (Pegasys®) · The subject refused to continue with study treatment · Pregnancy or breastfeeding · Other serious reasons for which it would be beneficial for the subject to discontinue treatment with study medication as per investigator´s judgement
	Criteria for termination of a subject´s participation in the study Protocol of the study defined the following criteria for premature termination of a subject´s participation in the study: In case of occurrence of at least one of the below mentioned criteria a subject´s participation in the study would be terminated: · The subject refused to continue with his/her participation in the study · Non-cooperation of the subject resulting in significant protocol deviation (protocol deviation considered as significant would be determined by an agreement between the treating

	physician, sponsor and biostatistician) · Death of the subject · Other reasons for which it would be beneficial for the subject to prematurely terminate his/her participation in the study as per investigator´s judgement
Investigational products	
Initial dose and planned duration of treatment	Genotype HCV 1,4,5,6: Copegus® 1000 mg p.o. daily for subjects weighing <75 kg for 48 weeks in two doses per day *or* Copegus® 1200 mg p.o. daily for subjects weighing ≥75 kg for 48 weeks in two doses per day Pegasys® 180 µg s.c. once per week for 48 weeks (concomitant treatment required by the protocol of the study) Genotype HCV 2,3: Copegus® 800 mg p.o. daily for 24 weeks Pegasys® 180 µg s.c. once per week for 24 weeks (concomitant treatment required by the protocol of the study) Concomitant infection with HIV regardless of HCV genotype [note: planned dose, no subject infected with HIV was enrolled into the study]: Copegus® 800 mg p.o daily for 48 weeks Pegasys® 180 µg s.c. once per week for 48 weeks (concomitant treatment required by the protocol of the study)
Dose adjustments	As per investigator´s judgement and guiding criteria defined by the protocol of the study it was possible to adjust dosage of study treatment in case of: · Delayed dose administration · Adverse effects · Hematologic toxicity
Batch numbers	IMP ML19387 (COPEGUS ® tbl. 200 mg each, 168 tbl./box) Batch — Number of boxes [redacted] — 50 [redacted] — 300 [redacted] — 300 [redacted] — 380 [redacted] — 250 [redacted] — 250 [redacted] — 300 [redacted] — 500 [redacted] — 300 [redacted] — 500
Duration of treatment: see above	Duration of observation: duration of treatment + 24 weeks
Reference therapy:	Not used (open-label study)
Criteria for evaluation of efficacy	Primary endpoint was treatment efficacy, defined as relative frequency of subjects who reached sustained virological response, i.e. no HCV virus detectable in the blood 24 weeks after the end of treatment. Secondary endpoints were: · Treatment response at the end of treatment, defined as relative frequency of subjects who reached virological response at the end of treatment, i.e. no HCV virus detectable in the blood immediately after completion of dosingt. · Early treatment response, defined as relative frequency of subjects who had no HCV virus detectable in the blood or 2-log (100-fold) decrease of the HCV virus concentration in the blood after 12 weeks of study treatment.
Criteria for evaluation of safety	During the treatment period of the study, all adverse events were recorded into source documents and CRFs, provided they fulfilled at least one of the following criteria:

	· Adverse event resulted in dose adjustment or study treatment discontinuation · Anemia with hemoglobin levels < 100 g/L · ALT elevation that resulted in adjustment of study treatment dose · Thrombocyte levels < 50 x 10^9 /L · Neutrophil levels < 0.75 x 10^9 /L Adverse events present at the last visit of the treatment period (Week 24 or 48) were followed-up by investigators until resolution.
Pharmacokinetic and pharmacodynamic evaluation	Not done.
Statistical methods	Statistically evaluated subject populations *Total Population*: all subjects for whom any efficacy and/or safety data were available (intention to treat analysis) *Per Protocol Population:* all subjects of Total Population without significant protocol deviation *Safety Population:* all subjects who used at least one dose of the study medication Sample size calculation Approximately 10% of adverse drug reactions (ADR) in this group of subjects could be expected to result in discontinuation of study treatment. For the purpose of descriptive analysis of identified ADRs, it is recommended to capture at least 5 ADRs in a clinical study. To ensure 90% probability of capture of at least 5 ADRs occurring with the frequency of 10% it is necessary to enroll 80 subjects. As it could be expected that 20% of subjects do not complete the study per protocol („drop out rate"), it is recommended to enroll the total number of 100 subjects into each of the three subject subgroups. As there are 3 subject subgroups (A-C) to be analysed independently, a total of 300 subjects should be enrolled. With total sample size of 300 subjects, it is also possible to estimate the accuracy of treatment efficacy. Considering the expected treatment efficacy of 75% (sustained virological response) in subjects infected with HCV genotypes 2 and 3, CI of 95% of the subgroup of 80 evaluable subjects would be 64.1-84.0%. Considering the expected treatment efficacy of 55% (sustained virological response) in subjects infected with HCV genotype 1, CI of 95% in the subgroup of 80 evaluable subjects would be 43.5-66.2%. General methods Results were processed by Statistica StatSoft, Inc. (2010). STATISTICA (data analysis software system), version 9.1. www.statsoft.com Descriptive statistics (mean, SD, median, min, max, 95% CI) was determined for continuous parameters. Absolute and relative frequencies were determined for categorical variables. The non-parametric Kruskal-Wallis test was used to determine the significance of the change of hematology and biochemistry variables in the A and B subgroups. All tests of statistical hypotheses were performed at 5% level of significance. Evaluation of efficacy Primary endpoint was the treatment eficacy, defined as relative frequency of subjects who reached *sustained virological response*, i.e. no HCV virus detectable in the blood 24 weeks following the end of treatment. *Secondary evaluated variables were:* · *End of treatment response*, defined as relative frequency (%) of subjects with undetectable HCV viral load at the end of 24 weeks of treatment. · *Early treatment response*, defined as relative frequency (%) of subjects who had no HCV virus detectable in the blood or 2-log (100-fold) decrease of the HCV virus concentration in the blood after 12 weeks of treatment. Evaluation of safety *Adverse events* The Sponsor provided all information about suspected unexpected serious adverse drug reactions generated by the study centres and other studies with the same investigational product to the State Institute for Drug Control and via the contract research organisation to the ethic committees and investigators involved, as required by applicable law. The number and frequency of subjects that experienced an adverse event (AE) were evaluated descriptively overall, as well as split by type, seriousness and relationship to investigational products. These evaluations were performed for the subgroups separately. As the frequency of AEs could have been influenced by the dose of ribavirin (Copegus®), safety evaluations were split also by the dose of ribavirin, i.e. 800, 1000, and 1200 mg. Formal statistical comparison of clinical examination results in the subject subgroups was not the subject of this study.

Laboratory results

Hematology and biochemistry test results were summarized and evaluated by descriptive statistical methods. Each variable was evaluated for clinical significance by the investigator and categorized as follows:

- *normal value*
- *value abnormal but of no clinical significance*
- *value abnormal and of clinical significance*

A summary of laboratory results was prepared for each subgroup that followed the above mentioned categorization.

All data recorded by investigators on the CRF were used for statistical evaluations in this study. After detection of missing, illegible or nonsense data, standard queries were generated that were discussed with the study monitor. Missing values that could not have been found retrospectively were analysed as such and every parameter was evaluated for the number of missing values and their frequency. No statistical method was used to estimate missing values.

Results

Study subjects

The first subject first visit in the Czech Republic took place on February 1, 2006 and the study ended by the the last subject last visit on January 9, 2009.

The first subject first visit in Slovakia took place on May 10, 2007 and the study ended by the last subject

A total of 372 subjects were enrolled into the study. 337 subjects were enrolled in the Czech Republic and 35 subjects in Slovakia. 253 (68%) subjects completed the study per protocol, 224 (66%) in the Czech Republic and 29 (83%) in Slovakia. 119 subjects terminated his/her participation in the study prematurely.

The clinical study proceeded in the following way:

After screening period that lasted up to 56 days, subjects who fulfilled all inclusion and none exclusion criteria were enrolled into the active phase of the study. Subjects were divided into 3 treatment subgroups based on levels of ALT and co-infection with HIV. 335 (90.5%) subjects were in the subgroup A (elevated ALT without co-infection with HIV), 35 (9.5%) subjects were in the subgroup B (normal ALT without co-infection with HIV). No subject was enrolled to the subgroup C (co- infection with HIV regardless of ALT levels). Then, the subjects in the treatment groups A and B were divided, in an unblinded fashion, into 2 arms based on the genotype of HCV. The 2 arms differed in the length of study treatment (24 and 48 weeks, respectively) and ribavirin administration scheme (see above – the paragraph Investigational Products). After the study treatment cessation, the subjects were followed-up for 24 weeks. A subject who completed the study per protocol appeared for 9 or 15 study visits.

As apparent from the following table, most subjects were infected with HCV genotype 1 (80.9%). Of the other HCV genotypes, the only one with a notable frequency was the genotype 3 (17.8%), while none of the other exceeded 1%.

HCV genotype	N	%
1	299	80.9
1,3	1	0.3
2	2	0.5
3	66	17.8
Unknown	2	0.5

Efficacy

Primary endpoint was the *treatment efficacy* based on *sustained virological response*, defined as relative frequency of subjects with no HCV virus detectable in the blood 24 weeks following the end of dosing. The following table shows, that 202 (54,6%) subjects met this criterion, i.e., the efficacy at this timepoint was 54,6%. On the other hand, 76 (20,5%) subjects did not reach this target, and for 92 (24,9%) subjects, the data were not available. Splitting by group revealed the efficacy 54,3% and 57,1% in the Group A and B respectively.

Sustained response	Treatment group		
	A	B	Total
Yes	182 (54,3%)	20 (57,1%)	202 (54,6%)
No	69 (20,6%)	7 (20,0%)	76 (20,5%)
No data	84 (25,1%)	8 (22,9%)	92 (24,9%)
Total	335 (100,0%)	35 (100,0%)_	370 (100,0%)

Secondary endpoints

Early treatment response has been defined as no HCV virus detectable in the blood or 2-log (100-fold) decrease of the HCV virus concentration in the blood after 12 weeks of treatment. The following table shows, that 306 (82,7%) subjects met this criterion, i.e., the efficacy at this timepoint was 82,7%. On the other hand, 40 (10,8%) subjects did not reach this target, and for 24 (6,5%) subjects, the data were not available. Splitting by group revealed the efficacy 82,4% and 85,7% in the Group A and B respectively.

Early treatment response	Treatment group		
	A	B	Total
Yes	276 (82,4%)	30 (85,7%)	306 (82,7%)
No	37 (11,0%)	3 (8,6%)	40 (10,8%)
No data	22 (6,6%)	2 (5,7%)	24 (6,5%)
Total	335 (100,0%)	35 (100,0%)_	370 (100,0%)

End of treatment response has been defined as undetectable HCV viral load at the end of 24 weeks of treatment. The following table shows, that 265 (71,6%)subjects met this criterion, i.e., the efficacy at this timepoint was 71,6%. On the other hand, 28 (7,6%) subjects did not reach this target, and for 77 (20,8%) subjects, the data were not available. Splitting by group revealed the efficacy 71,9% and 68,6% in the Group A and B respectively.

End of treatment response	Treatment group		
	A	B	Total
Yes	241 (71,9%)	24 (68,6%)	265 (71,6%)
No	24 (7,2%)	4 (11,4%)	28 (7,6%)
No data	70 (20,9%)	7 (20,0%)	77 (20,8%)
Total	335 (100,0%)	35 (100,0%)_	370 (100,0%)

Safety (primary aim of the study)

In total, 433 AEs emerging in 205 (55,4%) subjects were reported, with a slightly lower frequency in the Group A (54,0% vs.68,6%); in 165 (44,6%) subjects, no AE has been reported.

AE	Treatment group		
	A	B	Total
Yes	181 (54,0%)	24 (68,6%)	205 (55,4%)
No	154 (46,0%)	11 (31,4%)	165 (44,6%)
Total	335 (100,0%)	35 (100,0%)	370 (100,0%)

Adjustment of dosing

In 52 participating subjects, a total of 98 changes of peginterferon α-2a dosage had to be done (some subjects had multiple changes); 94,3% of subjects with change of the dose belonged to Group A and 5,7% to Group B.

peginterferon α-2a	Treatment group		
Number of changes	A	B	Total
1	22 (42,4%)	2 (3,8%)	24 (46,2%)
2	18 (34,6%)	0 (0,0%)	18 (34,6%)
3	7 (13,5%)	0 (0,0%)	7 (13,5%)
4	0 (0,0%)	0 (0,0%)	0 (0,0%)
5	1 (1,9%)	0 (0,0%)	1 (1,9%)
6	1 (1,9%)	1 (1,9%)	2 (3,8%)
Total subjects	49 (94,3%)	3 (5,7%)	52 (100,0%)

Time spent in the study

The following table shows that in 53 participating subjects, a total of 78 changes of ribavirin dosage had to be done (some subjects had multiple changes); 86,8% subjects with change of the dose belonged to Group A and 13,2% to Group B.

Ribavirin	Treatment group		
Number of changes	A	B	Total
1	29 (54,8%)	5 (9,4%)	34 (64,2%)
2	13 (24,5%)	0 (0,0%)	13 (24,5%)
3	4 (7,5%)	2 (3,8%)	6 (11,3%)
Total subjects	46 (86,8%)	7 (13,2%)	53 (100,0%)

The treatment was prematurely terminated in 80 (21,6%) subjects. Most of them – 25 (31,6%) - due to incooperativeness, 16 (19,3%) due to refusal of treatment, 15 (18,0%) for lack of efficacy and 14 (16,9%) for adverse events.

Adverse events

Reason of premature termination	Count
Incooperativeness	25 (30,1%)
Refusal to continue	16 (19,3%)
Lack of efficacy	15 (18,0%)
AE	14 (16,9%)
Other	4 (4,8%)
No data	3 (3,6%)
Pregnancy	3 (3,6%)
Total	83 (100,0%)

The highest frequency of adverse events was reported in subjects with the daily ribavirin dose of 1000 mg (in 62,5% of subjects treated with this dose), the lowest one in the dosage group of 800 mg per day (38,3% of treated subjects).

	Daily dose of ribavirin (mg)			
AE	**800**	**1000**	**1200**	**Total**
Yes	23 (38,3%)	105 (62,5%)	77 (53,1%)	205 (55,7%)
No	37 (61,7%)	63 (37,5%)	68 (45,9%)	163 (44,3%)
Total	60 (100,0%)	168 (100,0%)	145 (100,0%)	368 (100.0%)

The most frequent adverse event was anemia (appeared in 23,2% of subjects) and neutropenia (in 19,4% subjects). The most frequent adverse events (appearance with frequency >5%) are displayed in the following table.

AE	N	%
Anemia	101	23,2
Neutropenia	88	20,4
Flu-like syndrom	20	4,5
Leucopenia	15	3,4
Thrombocytopenia	10	2,3
Weight loss	9	2,0
Fatigue	9	2,0
Exanthema	8	1,8
Mental problems	8	1,8
Hypothyreosis	7	1,6
Increased TSH	7	1,6
Common cold, fever	7	1,6
Acute pyelonephritis	5	1,2
Breathlessness	5	1,2
Decreased TSH	5	1,2

	In total, there were 7 AEs (1,7%) which were rated as severe. In case of ribavirin, the relation to treatment was non-evaluable in 80% of cases, in 61 (14,1%) cases unrelated. In case of peginterferonu α-2a, the relation to treatment was rated as probable in 198 (45,7%) of cases, and in unrelated in 79 (18,2%) of cases. In total, 45 SAEs (including 3 pregnances) was reported, 6 of them in Slovak part of the study. Since 3 subjects experienced multiple SAEs, the number of subjects with at least one SAE was 39, including 3 pregnant subjects. The sponsor reported altogether 6 SUSARs to SUKL and ECs in course of the study. Out of 3 pregnances reported during the study, 2 pregnances lead to a delivery of a healthy baby, with one of the 3 pregnant subjects contact has been lost.
SUSARs	The reported SUSARs, classified using the MedDRA preferred terms, are listed in the following table:

Subject	Report	MedDRA Preferred Term	Outcome
[redacted]	Initial	[1] Facial paresis (S)	improved
		[2] Fatigue (S)	
[redacted]	Follow-up	[1] Facial paresis (S)	improved
		[2] Fatigue (S)	
[redacted]	Follow-up 2	[1] Facial paresis (S)	improved
		[2] Fatigue (S)	
[redacted]	Initial	[1] Affective disorder (S)	resolved
[redacted]	Initial	[1] Biliary colic (S)	resolved
[redacted]	Initial	[1] Anal abscess (S)	improved
[redacted]	*Initial*	*pregnancy*	*NA*
[redacted]	*Follow-up*		*delivery w/o complications*
[redacted]	*Initial*	*pregnancy*	*unknown (lost to F-U)*
[redacted]	*Initial*	*pregnancy*	*delivery w/o complications*

During the participation in the study, 3 subjects suffered a SAE leading to death. In all 3 cases, the death occured due to malignancy, without relationship to treatment.

Subject No. [redacted] During the treatment phase of the study, a carcinoma of liver with liver metastases has been diagnosed. The subject died following premature termination of treatment and withdrawal from the study.

Subject No [redacted] A metastatic carcinoma of breast was diagnoswed during the treatment phase of the study. The immediate cause of the death was a hydrocephalus due to the brain metastases. The subject died after withdrawal from the study.

Subject No [redacted] during the treatment phase of the study, a carcinoma of liver with liver metastases has been diagnosed. The subject died following premature termination of treatment and withdrawal from the study.

Discussion and general conclusions	The relative frequency of 54,0% reported AEs reported in the Group A, showing abnormally high ALT, was lower than in Group B (68,6%), consisting of subjects with ALT within normal range. This apparently paradoxical result, however, was evaluated by descriptive statistics only and may be within statistical error. Anyway, it shows that the impaired function of liver parenchyma at the inclusion to the study is not a negative predictor of the treatment safety. On the other hand, the necessity of more frequent changes of dosage of both ribavirin and peginterferon α-2a in the Group A may indicate lower tolerance of treatment in this treatment group. The effect of ribavirin dosage on the incidence of AEs cannot be excluded, since the lowest frequency of AEs occures in the lowest dosage group. On one hand, there is a therapeutic gain, consisting in the normalization of markers of the liver damage (ALT, AST, GMT), and improvement of the metabolic function of liver; this improvement occurs in the Group A only, since abnormal baseline values yield anogh space for improvement. On the other hand, there is a decrease of albumin, probably due to the inhibition of its synthesis by ribavirin. A decrease of blood cells (erythrocytes, leucocytes, neutrophils, monocytes) is a well described AE of the combination of the drugs used, which is a standard approach due to their synergic effect and lower efficacy of monotherapy. The listing of SAEs indicates rather high frequency of inflammatory disorders, which are described in the SPC for both ribavirin and peginterferon α-2a as frequent, but regardless of that, they are evaluated as unrelated to treatment in this study. Similarly, 3 cases of neoplasms (with a fatal end) in the study subjects are not surprising taking into consideration the data in SPC, on the other hand, in case of liver cancer the effect of HCV itself may be suspected, which mitigates the possibility of relation to treatment. Furthermore, the observed disorders of the thyroid function have been also previously reported (Benelhadj S. et al, 1997). The study results are in agreement with the current knowledge of safety of a standard combination of ribavirin and peginterferon alfa-2 in type C hepatitis as to their structure, incidence and severity. Sustained virological response obtained in 54,3% subjects is in agreement with results of preceding studies with combination interferon / ribavirin, yielding the efficacy in range of 54-61% (http://www.hcvadvocate.org/hcsp/articles/Keeffe-3.html). The efficacy is highest after 12 weeks of treatment (82,7%), then decreases regardless continuation of treatment (71,6% at the end of dosing). Further decrease of of efficacy occurs 24 weeks after regular cessation of treatment, when the eficacy drops to 54,6%. The groups A and B, different as to level of liver function damage at pretreatment, do not show a marked difference concerning the treatment efficacy. The cumulative number of subjects prematurely withdrawn gradually increased during the course of the study (24 after 12 weeks, 77 at the end of treatment and 92 subjects 24 weeks after last dosing). Therefore, the decrease of efficacy in time can be, due to decrease of evaluable subject, to some extent artificial, because the prematurely withdrawn subjects merge with the category of nonresponders, while in at least some of them, the virological response could have been successful. Thus, the relative frequencies indicating the proportion of therapeutic success represent a conservative estimate and therefore the worst possible result. On the other hand, the loss of virological response due to resistence of hepatitis C virus to ribavirin has to be taken into account (Kung-Chia Young et.al, 2003). There is an additional potential of the study data in the possibility of analyzing the relationship of the efficacy and HCV genotype (1 vs. 3, the other types are practically not represented).
Completed on:	27 JUN 2010