

Baltic Post-marketing Study of Pegylated Interferon α -2a 40 KD Efficacy and Safety in Patients with HBeAg – Positive and HBeAg – Negative Chronic Hepatitis B

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Abstract

Introduction: Pegylated interferon alpha-2a 40KD (Pegasys[®]) is registered in European Union, and is indicated for the treatment of HBeAg positive or HBeAg negative chronic hepatitis B in adult patients with compensated liver disease, evidence of viral replication and increased ALT. The aim of this study was to evaluate efficacy and safety of Pegasys[®] for Pegasys[®] treatment naive patients with HBeAg positive and HBeAg negative chronic hepatitis B.

Materials and methods: Multicenter trial design (8 centers in the Baltic States), prospective, non-randomized, open label study. In total, 39 patients with chronic active hepatitis B were enrolled in the study. Study drug – Pegasys[®] 180 mcg, once per week. After completion of the treatment, patients were followed up for additional 24 weeks. Neutrophils, platelets, ALT, HBV DNA, HBeAg, HBsAg, HBeAb, and HBsAb were controlled.

Results: For efficacy assessment, 36 patients were analyzed. Safety analysis was performed for 39 patients. No serious adverse events and laboratory abnormalities were observed for 37 patients. Adverse events were self limited without drug ordination after stopping the study medication.

Conclusions: Peg-interferon α -2a 40 KD–Pegasys[®] therapy for chronic hepatitis B patients is efficient and demonstrates good tolerability, minimal number of self limited side effects—only neutropenia, thrombocytopenia.

Keywords: Chronic hepatitis B; Pegylated interferon; Treatment efficacy and safety

Introduction

Approximately one third of the world's population has serological evidence of past or present infection with HBV. 350 million people worldwide are chronically infected with HBV.

The spectrum of disease and natural history of chronic HBV infection are diverse and variable, ranging from a low viremic carrier state to progressive chronic hepatitis, which may evolve to cirrhosis and hepatocellular carcinoma (HCC). HB –related end-stage liver disease or HCC is responsible for over 1 million deaths per year, and currently represents 5-10% of cases of liver transplantation. Host and viral factors, as well as co-infection with other viruses, in particular hepatitis C, hepatitis D virus, HIV together with other co-morbidities, including alcohol abuse and overweight, can affect the natural course of HBV infection, as well as the efficacy of antiviral strategies [1,2].

The worldwide incidence of HCC has increased, mostly due to HBV and HCV infections; at present, it constitutes the fifth most common cancer, representing about 5% of all cancers [3].

Since the early and mid-1990s, a growing number of intravenous drug users have resulted in very high incidence rates of hepatitis B in Northwest Russia and the Baltic countries. Incidence of acute hepatitis B in 2001 per 100 000 in Estonia was 32.8, in Latvia 35.5, and in Lithuania 10.9 [4]. The number of acute hepatitis B cases per 100 000 population registered in 2003 in Estonia was 12.7, in Latvia 14.4, and in Lithuania 5.0. The incidence of HBV infection is the highest among persons aged 15-29 years, and in general, is higher among men [5-7].

Peg IFN-alpha 2a is the only pegylated interferon approved for the treatment of chronic hepatitis B in USA. The recommended dose is 180 mcg weekly for 48 weeks [8,9].

Pegasys[®] was registered in European Union on February 23, 2005, and since then has been indicated for the treatment of HBeAg

positive or HBeAg negative chronic hepatitis B in adult patients with compensated liver disease and evidence of viral replication, increased ALT, and/or histologically verified inflammation, and/or fibrosis [9].

The objective of the study was to evaluate the efficacy and safety of Pegasys[®] given for 48 weeks to patients with HBeAg positive or HBeAg negative chronic hepatitis B in Lithuania, Latvia and Estonia.

Materials and Methods

Overall the study design is described as multicenter, open-label, single arm, non-comparative, clinical study including 8 centers (1 center in Latvia, 3 centers in Estonia, 4–in Lithuania), without placebo and without randomization. 39 treatment naive patients with chronic active hepatitis B, HBeAg positive or HBeAg negative were enrolled in the study.

Study drug–Pegasys[®] 180 mcg once per week.

Inclusion criteria

To be eligible for this study, patients had to have the following criteria documented:

- Age range from 18 and to 70 years.

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- HBeAg-positive patients: HBV DNA >100 000 copies/ml.
- HBeAg-negative patients: HBV DNA >10 000 copies/ml.
- HBsAg positive for at least 6 months, anti HBs negative.
- Elevated serum ALT >2x U/L but \leq 10x U/L, as determined by two abnormal values taken >14 days apart during the six months before the dose of study drug, with at least one of the determinations obtained <35 days prior to the first dose.
- No previous antiviral treatment with interferon (standard or pegylated).
- Negative urine or serum pregnancy test (for women of childbearing potential) documented within the 24-hour period, prior to the first dose of study drug. They must be willing to use reliable contraception during the study, and for 4 months after treatment completion.
- Serum bilirubin level >2 times the upper limit of normal value at screening.
- Serum creatinine level >1.5 times the upper limit of normal value at screening.
- Severe psychiatric disease including:
 - Current uncontrolled psychiatric disease, especially depression;
 - Previous documented suicide attempts;
 - Any patient with history of hospitalization for psychiatric disease, or current antidepressant medication or major tranquilizer should be reviewed by consultant psychiatrist regarding suitability for interferon therapy.
- History of a severe seizure disorder or current anticonvulsant use.

Exclusion criteria

Patients with any of the following criteria were not being eligible for participation:

- Patients who have received interferon based therapy for their chronic hepatitis B before enrolment.
- Treatment with a nucleoside analogue within 3 month prior to baseline.
- Pregnant or breast feeding women.
- Evidence of decompensated liver disease, including anyone of the following:
 - Serum albumin <3.5 g/dL;
 - Prothrombine time \geq 4 seconds prolonged;
 - Serum bilirubin >34 μ mol/L;
 - History of encephalopathy;
 - History of variceal bleeding;
 - Ascites.
- Co-infection with hepatitis A, hepatitis C, hepatitis D, and/or Human Immunodeficiency Virus (HIV).
- History or other evidence of a medical condition associated with chronic liver disease, other than viral hepatitis (e.g. hemochromatosis, autoimmune hepatitis, metabolic liver disease, alcoholic liver disease, toxin exposures, and thalassemia).
- Previous or current hepatocellular carcinoma.
- History of or other evidence of bleeding from esophageal varices, or other conditions consistent with decompensated liver disease.
- Alpha-fetoprotein levels of >100 ng/ml. Patients with values of >20 ng/ml and \leq 100 ng/ml may be enrolled, if hepatic neoplasia has been excluded by liver imaging.
- Neutrophil count <1500 cells/mm³ or platelet count <90000 cells/mm³ at screening.
- Haemoglobin <11.5 g/dl for females and <12.5 g/dl for men at screening.
- History of immunologically mediated disease, chronic pulmonary disease associated with functional limitation, severe cardiac disease, major organ transplantation or other evidence of severe illness, malignancy, or any other conditions which would make the patient, in the opinion of the investigator, unsuitable for the study.
- Thyroid disease uncontrolled by prescribed medications.
- Evidence of severe retinopathy (e.g. CMV retinitis, macular degeneration).
- Evidence of drug abuse within one year prior to study entry.
- Alcohol intake of more than 3 standard drinks per day for men and 2 standard drinks for women (1 standard drink contains 10 g alcohol).
- Patients included in another trial or having been given investigational drugs within 12 weeks prior to screening.
- Inability or unwillingness to provide informed consent or abide by the requirements of the study, including scheduled blood tests and clinic appointments.

Reassessments: If a patient fails to meet the above inclusion/exclusion criteria for a reason thought to be reversible, this patient may be reassessed for entry on two additional occasions at most. If the parameter out of range for inclusion is ALT >10x U/L, the patient should be reassessed \geq 3 months after the date, corresponding to the value that is >10x U/L. For other parameters and ALT \leq 2x U/L, the reassessment may be done \geq 4 weeks following the original assessment.

Criteria for dose modification or withdrawal from treatment

The patient has the right to withdraw his/her consent at any time. The investigator also has the right to withdraw subjects from the study in the event of intercurrent illness, adverse events, and treatment failure after a prescribed procedure, protocol violations, and cure, administrative or other reasons (Table 1).

Assessment

(Table 1)

Assessments schedule

(Table 2)

List of screening assessments

(Table 3)

ASSESSMENTS OF:	
- EFFICACY	Primary Treatment Endpoints at the end of follow-up: <ul style="list-style-type: none"> • HBV DNA reduction 10-fold Secondary Treatment Endpoints at the end of treatment and follow-up: <ul style="list-style-type: none"> • (1) HBV DNA <400 copies/ml • (2) HBsAg seroconversion (HBsAg neg, anti-HBs+) • (3) Normalisation of ALT • Sustained HBe seroconversion defined as: Loss of HBeAg and presence of anti-HBe for HBeAg-positive patients
- SAFETY	All patients receiving at least one dose of PEGASYS® have to be included in a descriptive safety analysis (adverse events, vital signs and clinical laboratory parameters)

Table 1: Criteria for dose modification or withdrawal from treatment.

Assessment/Procedure	Screening (Days)	Treatment Period (Weeks)												Follow-up (Weeks)		
	-35 to -1	BL	1	2	4	8	12	18	24	32	40	48	52	60	72	
Informed Consent	X															
Complete Medical History, including family history of HBV	X															
HBV histological confirmation	X															
Physical examination	X															
Ophthalmologic examination	X	Repeat in patients with preexisting findings or those developing symptoms														
Vital Signs&Symptom-Directed Physical	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine or serum HCG Pregnancy	X															
Chest x-ray (selected patients)	X															
Ultrasound, CT or MRI (selected patients)	X															
Electrocardiogram (selected patients)	X															
Alfa-fetoprotein	X															
Anti-HAV IgM, anti-HCV, anti-HIV, anti-HDV	X															
alfa 1, AT, AMA, ANA, ASMA	X															
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ALT only				X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry	X	X			X		X		X	X		X	X	X	X	X
HBeAg, anti-HBe	X	X					opt		opt	opt		X	opt			X
HBV DNA	X	X*					opt		opt	opt		X				X
HBsAg, anti-HBs	X											X				X
Adverse Events (h)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug accountability/ compliance		X	X	X	X	X	X	X	X	X	X	X				
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

*opt - optional

Table 2: Assessments schedule.

List of laboratory tests and equipment

1. Clinical laboratory parameters–neutrophils, platelets – Operators manual automated hematology analyzer KX-21. Code No.461-2261-1, SYSMEX CORPORATION Kobe, Japan, blood film examination.
2. Biochemical blood tests in serum–AST, ALT – GPT, GOT IFCC mod.ligui. UV tests, Human, Germany.
3. Immunochemical blood tests–HBeAg (ELISA HBeAg detection/AxSYM system HBe 2.0. ABBOTT, USA), HBsAg (ELISA/Enzygnost HBsAg 5.0, Siemens, USA), anti HBe (ELISA/ETI-AB-EBK, Dia Sorin s.r.l. USA-Italy), anti HBs (ELISA/ AxSYM anti-HBs, ABBOTT, USA).
4. Virological blood tests–VHB Viral load (polymerase chain reaction HBV-DNA detection/Cobas AmpliPrep/Cobas TagMan HBV Tests-Roche).

Statistics: Descriptive statistics was calculated for all studied variables (parameters)– frequencies were calculated for categorical data and mean, median, standard error of mean and standard deviation–

for linear data. Kolmogorov-Smirnov test was used to define the data distribution of all linear variables. Paired t-test was used to compare means, and to test the statistical significance of observed differences or linear variables with normal distribution. Nonparametric Wilcoxon test was used to test the statistical significance for linear variables without normal distribution. Values of $p < 0,05$ were considered statistically significant. The data were analyzed using the statistical package SPSS version 15.0 statistical software.

Results and Discussion

39 treatment naive patients were enrolled in the study: 23–from Lithuania, 13–from Latvia, 3–from Estonia.

36 patients completed all study visits.

The study drug efficacy was analyzed in 36 patients, two patients were excluded due to loss of follow-up and one–due to missing data.

Safety analysis was performed for 39 patients.

Patients average age was 36 years.

Distribution by gender–32 male and 7 female.

Medical History and Physical Examination	Includes body weight, vital signs
Clinical Chemistry	ALT, AST, total bilirubin, alkaline phosphatase, total protein, albumin, BUN, creatinine, uric acid, cholesterol, triglycerides, glucose. Calcium, phosphorus, sodium, chloride and potassium are analyzed at BL. Electrolytes should be monitored on the other visits whenever clinically indicated
Hematology	Complete blood count (hematocrit, WBC, platelets), including, differential, prothrombin time
Immunology and Special Chemistry	α_1 -antitrypsin*, HAV IgM Ab*, HBsAg*, HBsAb*, HCV Ab*, HDV Ab*, AMA*, ANA*, ASA*, HIV Ab*, HBeAg, alpha-fetoprotein*
Virology	Quantitative HBV-DNA measured by PCR
Thyroid Function Tests*	TSH, T3 or T4
Urinalysis	Dipstick with subsequent microscopic evaluation if positive for hemoglobin
Chest X-Ray*	Only for patients with pre-existing pulmonary disease. [Not necessary if (1) a chest X-ray available to the investigator has been obtained within the past 12 months and (2) the patient's pulmonary disease has been clinically stable]
Electrocardiogram*	Only for men \geq 40 years of age, women \geq 50 years of age, and anyone else with a history of preexisting cardiac disease
Liver Imaging (Ultrasound, CT or MRI)	Only for patients with cirrhosis or marked fibrosis on prior liver biopsy or raised AFP to exclude hepatic neoplasia
HCG Pregnancy Test	For women of childbearing potential, a negative urine (or serum) HCG test needs to be documented within 24 hours prior to the first dose
Ocular examination	All patients at screening should have a baseline eye examination conducted by the investigator or another physician/ ophthalmologist (including fundoscopic examination). In patients identified as having mild to moderate retinopathy at screening, a thorough eye examination (including fundoscopic examination) by an ophthalmologist should be performed as part of the screening process to establish a baseline prior to randomization and treatment

Note: Tests marked above with an asterisk (*) do not need to be repeated if patients do not receive study drug any more.

Table 3: List of screening assessments.

All included patients met inclusion criteria.

Coexisting diseases were registered for two patients—arterial hypertension and eczema—without specific treatment.

22 patients were HBeAg-positive, 17 patients—HBeAg-negative.

Overview of efficacy

Primary efficacy endpoint: Primary treatment endpoints at the end of follow-up (week 72)—HBV DNA <100,000 copies/ml (HBeAg positive patients) were achieved in the 6 out of 22 cases, HBV DNA <10 000 copies/ml (HBeAg negative patients)—achieved in the 6 out of 17 cases.

Secondary efficacy endpoint: After treatment course, a stable HBs seroconversion was detected in 1 patient (3%). Although during the treatment period HBs seroconversion to anti HBs was detected in 3 patients, at week 72 it remained only in one case.

After the treatment course, HBe seroconversion was detected in 5 patients (25%), this laboratory finding increased to 6 patients (29%) at week 72.

Statistically significant ALT reduction was detected at weeks 12 and 48, but at the end of treatment and follow-up, ALT increased again (at week 60 and continued for all period of observation).

Only 4 patients achieved HBV DNA <400 copies/ml at week 72, two of them were HBeAg positive and two—HBeAg negative.

Primary efficacy endpoint: Primary treatment endpoints at the end of follow-up (week 72)—HBV DNA <100 000 copies/ml (HBeAg positive patients) were achieved in 6 cases (Tables 4-6 and Figures 1-3).

Only 4 patients achieved HBV DNA <400 copies/ml at week 72.

Primary treatment endpoints at the end of follow-up—HBV DNA <10 000 copies/ml (HBeAg negative patients) were achieved in 6 cases.

Analysis of HBV DNA dynamic changes during treatment period and follow-up as well showed fluctuating HBV DNA levels. At present, there is no explanation of this phenomenon, although the other researchers have also described this finding [10], associating it with elevated ALT and HBV precore and core promoter mutants.

Secondary efficacy endpoint: After the full course of therapy, HBsAg seroconversion was detected in 1 patient (3%), this laboratory finding was stable during the observation period until week 72 (Tables 7-10 and Figures 4-6).

During the treatment period, HBs seroconversion to anti HBs was detected for 3 patients, but in the follow-up period seroconversion continued only in 1 patient.

After the full course of therapy, HBeAg seroconversion was detected in 5 patients (25%), this laboratory data increased to 6 patients (29%) in week 72 of the observation period.

HBe seroconversion to anti HBe was detected in 7 patients during the treatment period, but in the follow-up period seroconversion continued only in 6 patients.

According to Chen and Yang [11], data from study for over 19 years in Taiwan, the annual seroclearance rate for HBeAg was 1.97% for HBV DNA, and 2.26% for HBsAg with more than 10 000 copies/ml. After HBeAg clearance, the annual rate of HBV DNA clearance was 3.2% and annual rate of HBsAg clearance was 6%. Data obtained in our study correspond with the finding of the above mentioned study.

The impact of viral and host factors on rates of HBV DNA clearance, HBeAg and HBsAg seroconversion have been elucidated [10], and should be elucidated further.

Moreover, current ability to predict patient's response to treatment is limited [10]. But, like in case of hepatitis C, 205 HBeAg positive CHB patients treated with pegylated interferon were analyzed for IL28B gene polymorphisms, and as a result the favourable AA or CC IL28B genotypes strongly predicted HBeAg seroconversion, with 50% compared with 29% responding to interferon [12].

Mean ALT were 141.32 U/L at the screening visit (min.70.7–max 330.20), ALT activity was similar, and did not differ statistically in patients of all three countries. Statistically significant ALT reduction was detected at week 12 and week 48, but at the end of treatment and follow-up, ALT increased again (at week 60 and continued for whole period of observation).

ALT activity was elevated in one patient from week 6 to week 10–537 U/L, 959 U/L, 180 U/L, respectively, after a dose reduction (90

		Baseline visit	48 th week	72 nd week
N	Valid	22	21	21
	Missing	0	1	1
Mean		2.2×10^7	6.2×10^5	1.7×10^6
Std. Error of Mean		9.6×10^6	5.0×10^5	8.4×10^5
Std. Deviation		4.5×10^7	2.2×10^6	3.8×10^6

Table 4: Descriptive statistics of HBV DNA (IU/ml) for HBeAg positive patients.

		Baseline visit	48 th week	72 nd week
N	Valid	17	16	16
	Missing	0	1	1
Mean		1.7×10^6	2.1×10^6	7.4×10^5
Std. Error of Mean		1.4×10^6	1.9×10^6	5.0×10^5
Std. Deviation		5.2×10^6	7.4×10^6	2.1×10^6

Table 5: Descriptive statistics of HBV DNA (IU/ml) for HBeAg negative patients.

		Baseline visit	48 th week	72 nd week
N	Valid	39	37	37
	Missing	0	2	2
Mean		1.3×10^7	1.2×10^6	1.3×10^6
Std. Error of Mean		5.7×10^6	8.5×10^5	5.2×10^5
Std. Deviation		3.6×10^7	5.1×10^6	3.2×10^6

Table 6: Descriptive statistics of HBV DNA (IU/ml) during the period from baseline visit to week 72 visit.

mcg) ALT normalized. Other reasons for increased ALT activities were excluded.

Neutropenia in 6 cases was the reason for dose reduction. Minimal neutrophils count was $500/\text{mm}^3$.

Neutropenia was self-limited without specific drug ordination for all patients after treatment completion.

Thrombocytopenia was not a reason of therapy reduction for the study patients.

Overview of safety

During the treatment period, 7 patients experienced adverse events and due to this, the dose of interferon has been reduced. Treatment was associated with good tolerability, and adverse events disappeared after treatment discontinuation. One medically significant adverse event was reported. Due to this adverse event, patients discontinued treatment earlier.

The reason of therapy dose reduction was neutropenia, for one patient, the reason of dose reduction was increasing ALT.

One patient in Estonia used a reduced dose of interferon from week 8 to 48, dose 135 mcg weekly.

Three patients in Latvia—one patient used reduced dose of interferon from week 4 to week 48—dose 135 mcg, other patient from

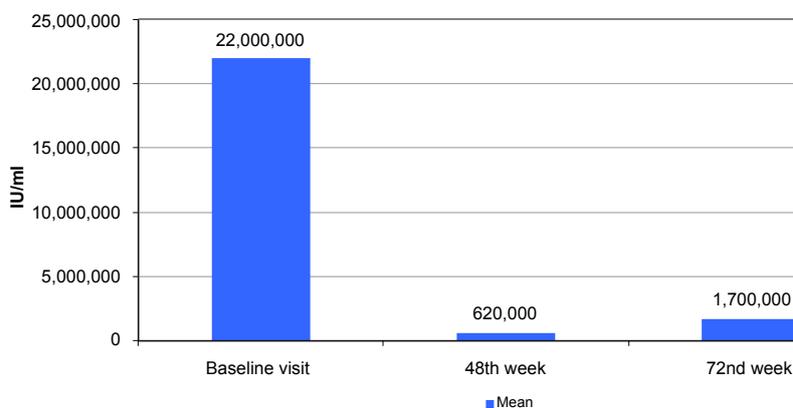


Figure 1: Mean values of HBV DNA (IU/ml) for HBeAg positive patients.

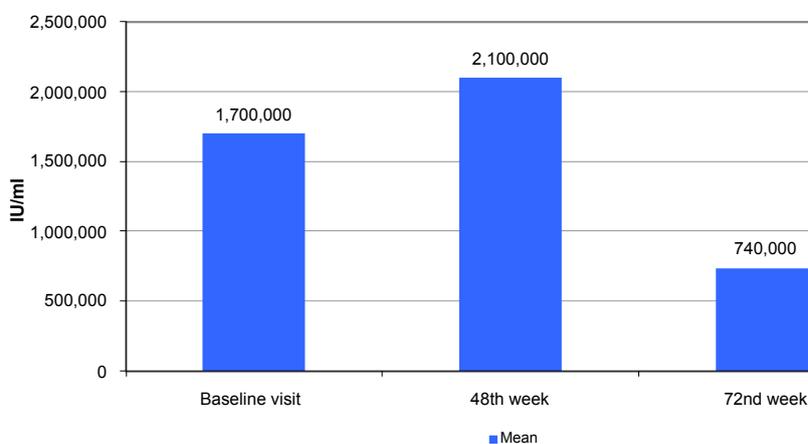


Figure 2: Mean values of HBV DNA (IU/ml) for HBeAg negative patients.

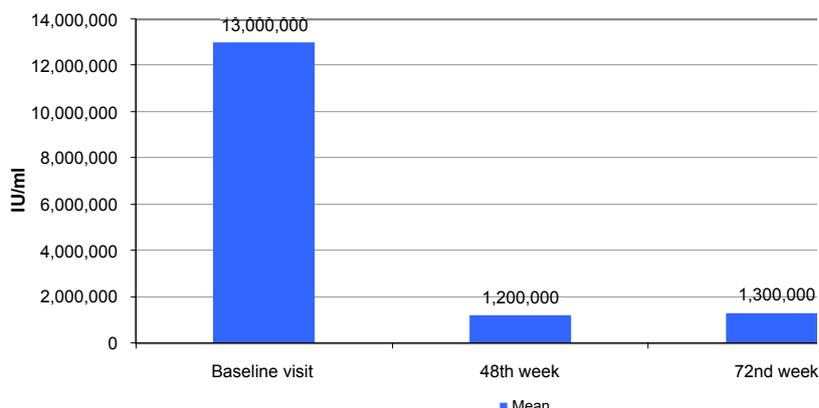


Figure 3: Mean values of HBV DNA (IU/ml) during the period from baseline visit to week 72 visit.

	Baseline visit	48 th week	72 th week
Positive	39 100%	35 97%	35 97%
Negative	0 0%	1 3%	1 3%

Table 7: HBsAg positive patients' analysis during the period between baseline visit and week 72 visit.

	Baseline visit	48 th week	72 th week
Positive	0 0%	3 8%	1 3%
Negative	39 100%	33 92%	34 97%

Table 8: Anti HBs negative patients' analysis during the period between baseline visit and week 72 visit.

	Baseline visit	48 th week	72 th week
Positive	22 100%	15 75%	15 75%
Negative	0 0%	5 25%	6 29%

Table 9: HBeAg positive patients' analysis during the period from baseline visit to week 72 visit.

	Baseline visit	48 th week	72 th week
Positive	0 0%	7 41%	6 33%
Negative	20 100%	10 59%	12 67%

Table 10: Anti HBe negative patients' analysis during the period between baseline visit and week 72 visit.

week 40 to week 48–dose 135 mcg, the third patient from week 6 to week 10–90 mcg.

Three patients in Lithuania–first patient–from week 4 to week 12–dose 90 mcg, second patient–from week 1 to week 32–dose 90 mcg, and from week 32 to week 48–dose of interferon was increased to 135 mcg, third patient–from week 2 to week 4–dose 90 mcg, and from week 4 to week 12–dose was increased to 135 mcg.

In the group of patients which used a low dose of IFN, the seroconversion was detected in one patient, ALT reduction, and decreasing of HBV DNA in serum was detected in all patients of this group. Neutropenia was self-limited, without specific drug ordination for all patients after treatment completion.

List of adverse events

One medically significant adverse event–rash, which led to

treatment discontinuation has been reported during study. No deaths were reported (Table 11).

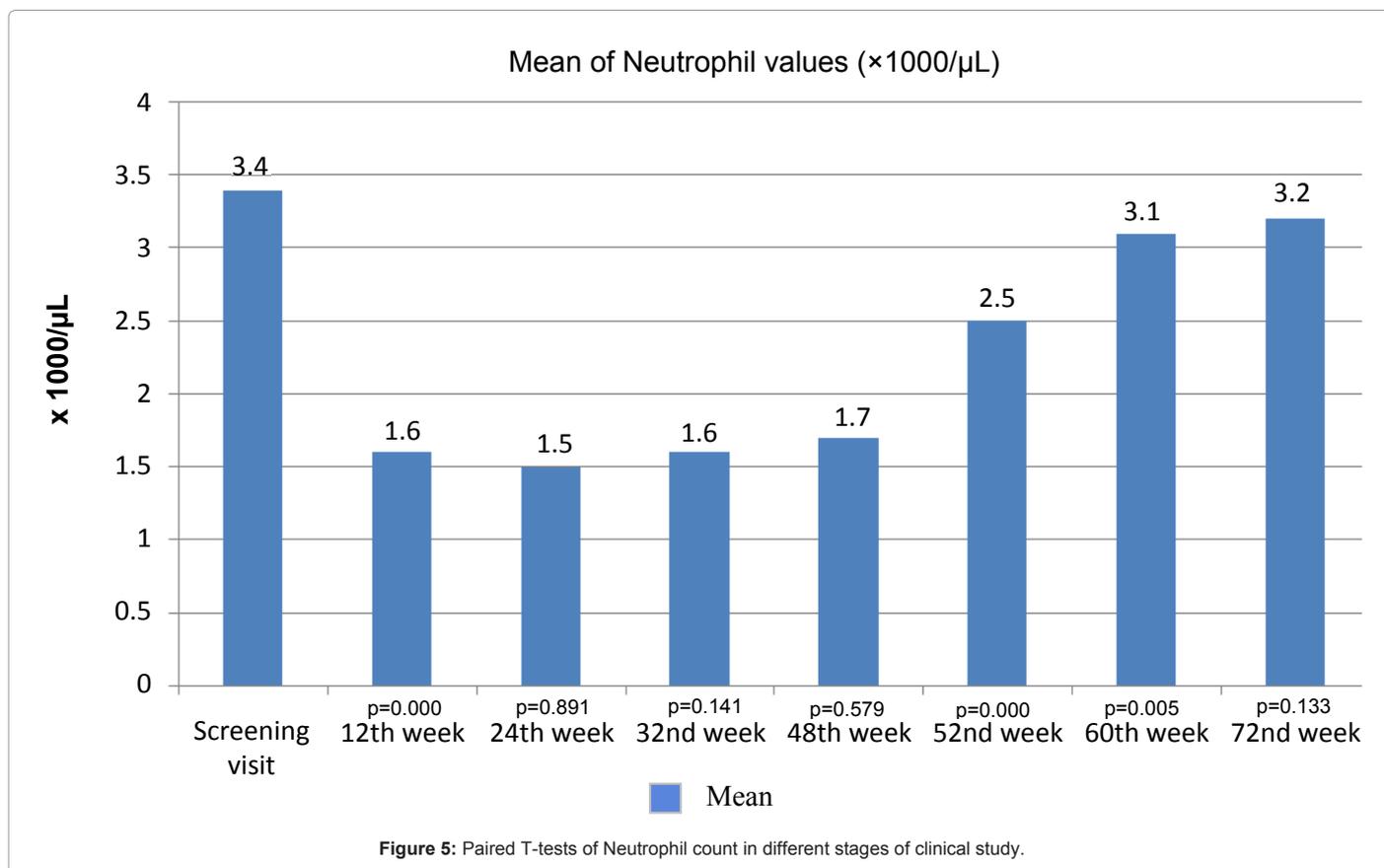
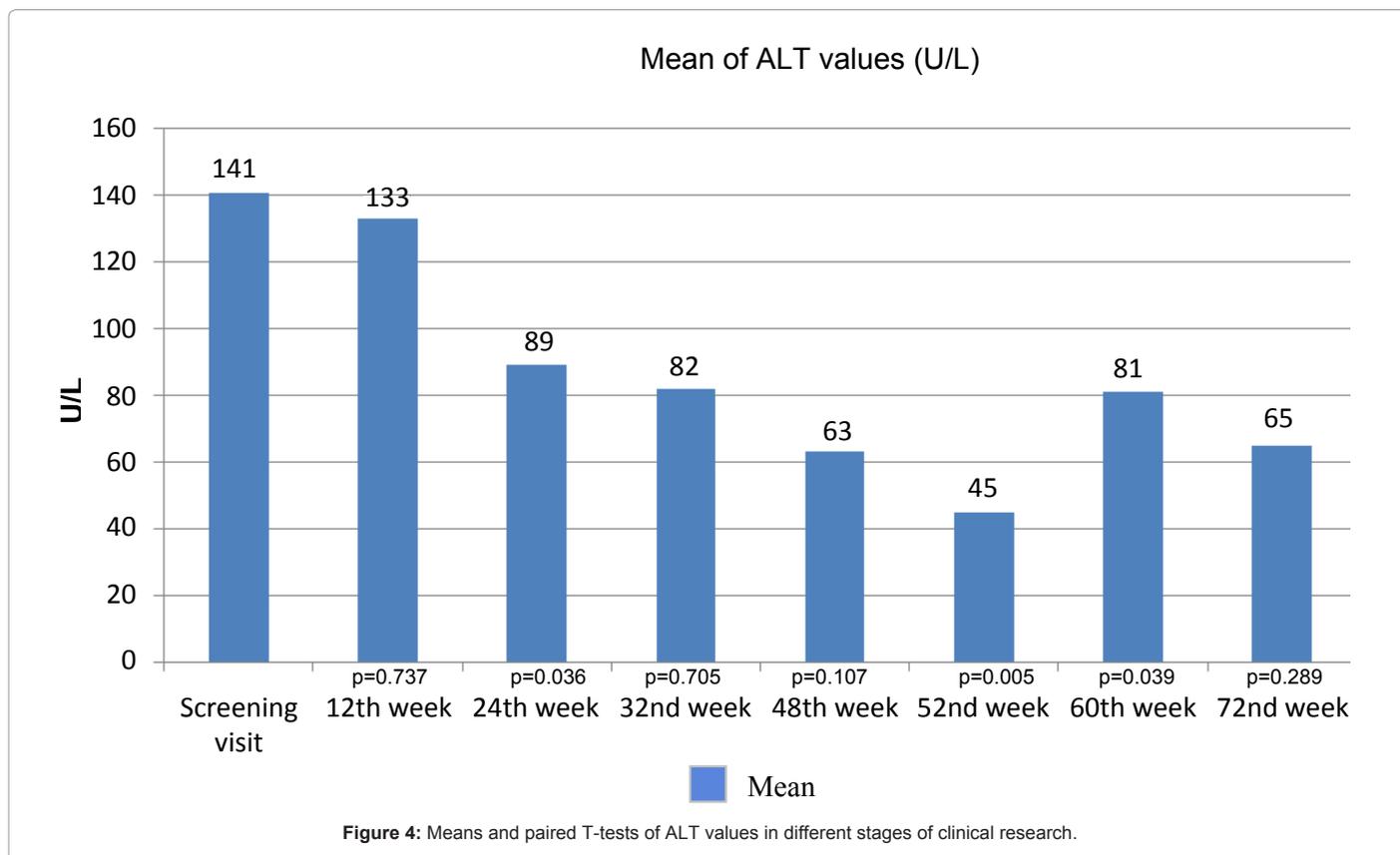
If the patients used monotherapy with Pegasys[®] for a longer period, the resistance did not develop.

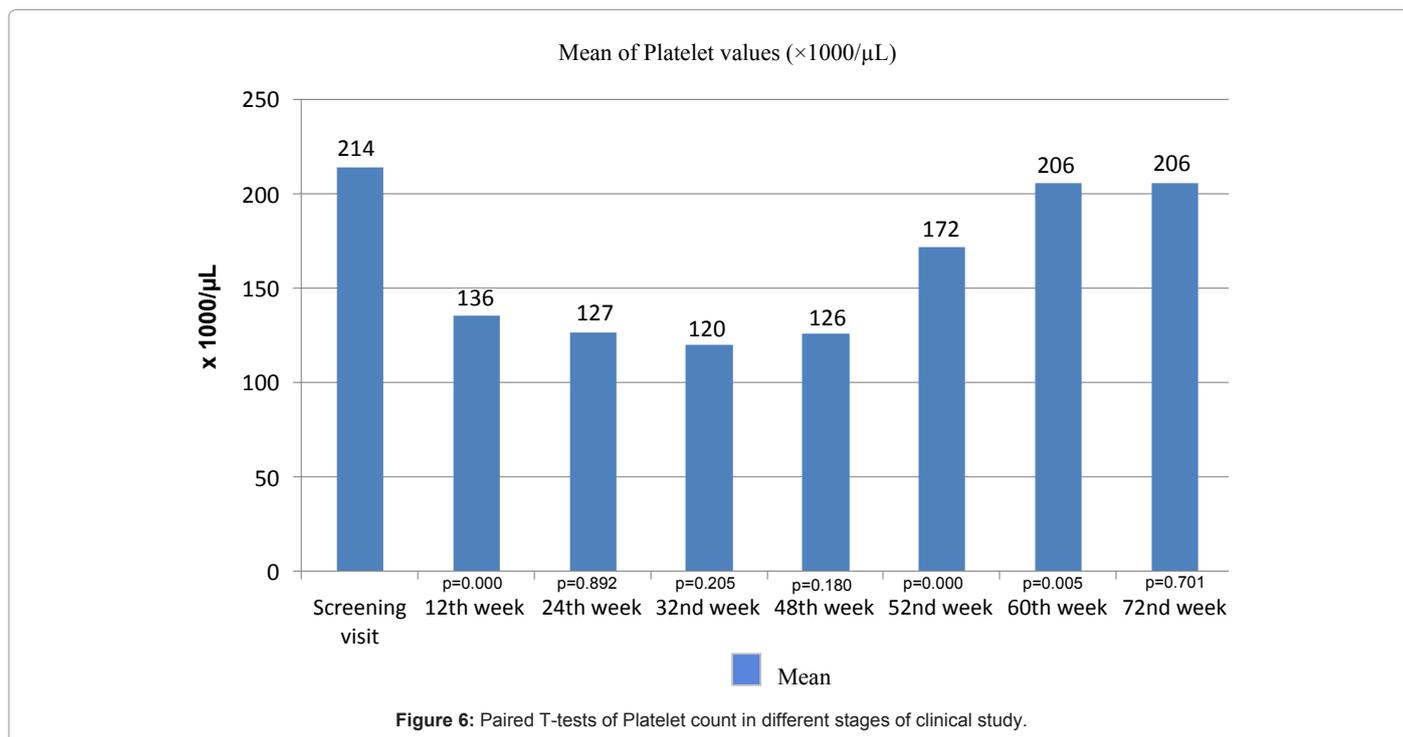
Conclusion

Pegylated interferon alpha-2a -PEGASYS[®] therapy for treatment of chronic active hepatitis B patients is characterized by good tolerability, minimal number of self-limited adverse events, such as neutropenia and thrombocytopenia and unpretentious therapy effectiveness, adequate for the level of understanding about the role of virus-host interaction existing worldwide at the time when the use of PEGASYS[®] therapy was started.

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The authors thank the study collaborators from Lithuania- A Ambrozaitis,





Symptoms	No of patients	Grade	SAE	Start and end time (study week)	Outcome	Relation	Unex-pected AE	AE leading to withdrawal
Subfebrile temperature	1	Mild	No	1-52	Resolved	Yes	No	No
Weakness	1	Moderate	No	8-60	Improved	Yes	No	No
Headache	1	Moderate	No	8-60	Improved	Yes	No	No
Anxiety	1	Moderate	No	8-52	Resolved	Yes	No	No
Hair loss	1	Mild	No	14-52	Resolved	Yes	No	No
Rash	1	Mild	No	19-20	Resolved	Yes	No	No
Eczema	1	Mild	No	Pre study- 72	Persistent	Yes	No	No
Chr. headache	1	Mild	No	36-72	Improved	Yes	No	No
Heartburn	1	Mild	No	8-72	Improved	Yes	No	No
Barrett esophagus	1	Moderate	No	12-12	Resolved, but residual effects persist	Yes	No	No
Arterial hypertension	1	Moderate	No	No data	Persistent	Yes	No	No
Blood in stool	1	Mild	No	32-32	Resolved	Yes	No	No
Prostate hyperplasia	1	Mild	No	40-72	Persistent	Yes	No	No
Rash	1	Mild	No	1-6	Resolved	Yes	No	No
Dryness of mouth	1	Mild	No	6-20	Resolved	Yes	No	No
Stomach ache	1	Mild	No	Baseline-2	Resolved	Yes	Yes	No
Urine tract infection	1	Mild	No	24-24	Resolved	No	Yes	No

Table 11: List of reported adverse events.

E Audickiene, L Balciuniene, A Buivydiene, J Jakutiene, J Kondrackiene, L Kupcinkas, A Laiskonis, V Petrenkiene, J Valantinas, A Voinic and Estonia- M Aua, N Fomicheva, K Ott, H Rimmel, T Rimmel, R.Salupere.

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Conflict of Interest

The authors state no conflict of interest.

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