Clinical trial results:
A prospective, randomised, open-label phase IIb clinical trial assessing the effect of pegylated Interferon alfa-2a (Pegasys®) 180 µg once weekly for 48 weeks in addition to an ongoing nucelos(t)ide based treatment on quantitative HBsAg levels in patients with chronic HBeAg-negative hepatitis B

Summary

EudraCT number	2011-002812-10
Trial protocol	DE
Global end of trial date	29 March 2018

Results information

Result version number	v1 (current)
This version publication date	25 April 2022
First version publication date	25 April 2022

Trial information

Trial identification

Sponsor protocol code	PADD-ON

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Medical Center of the Johannes Gutenberg-University Mainz
Sponsor organisation address	Langenbeckstraße 1, Mainz, Germany, 55131
Public contact	Peter Galle, University Medical Center of the Johannes Gutenberg University Mainz, 0049 06131177275, peter.galle@unimedizin-mainz.de
Scientific contact	Peter Galle, University Medical Center of the Johannes Gutenberg University Mainz, 0049 06131177275, peter.galle@unimedizin-mainz.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 March 2018
Global end of trial reached?	Yes
Global end of trial date	29 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to investigate whether the add-on of pegylated interferon alfa-2a to a continued treatment with nucleos(t)ide analogues increases the percentage of patients who have significant decrease (≥1log10) of HBs-antigen after 48 weeks.

Protection of trial subjects:

All patients were insured according to §40 AMG requirements. Assessment of safety and tolerability by documentation of adverse events and serious adverse events. The study fulfills all ethical standards according to the independent ethics committee (IEC), such as GCP, Federal Data Protection Law and the Declaration of Helsinki (DoH). To evaluate safety and tolerability of pegylated interferon alfa-2a when combined with tenofovir, entecavir, lamivudine, adefovir, or a combination of lamivudine or entecavir with adefovir or tenofovir the following data was collected: adverse events, vital signs, physical examination, laboratory test abnormalities, laboratory test value changes over time.

Background therapy:

Treatment with nucleos(t)ides.

Evidence for comparator:

Treatment with nucleos(t)ide analogues partly restores HBV directed immune responses and reduces HBsAg levels during long-term administration, with the newer drugs being more potent. Therefore the nucleos(t)ides analogues lamivudine, adefovir, entecavir, tenofovir or a combination thereof were chosen as active comparator. Due to the increased neurotoxicity of pegylated interferon alfa-2a when combined with telbivudine in a previous study, use of telbivudine was not allowed.
Recent data further support that interferon treatment is even more effective in preventing HBV associated complications than high potent nucleos(t)ide analogues. This included a better prevention of cirrhosis and hepatocellular carcinoma following interferon treatment compared to an ongoing entecavir therapy. We may speculate that interferon induces a sustaining immunological surveillance of HBV infection, which positively affects long-term prognosis. Other studies have investigated an add-on interferon approach in the setting of HBeAg positive hepatitis B and provide additional evidence for this novel approach. However, stopping stable nucleos(t)ide therapy has emerged as simple and safe alternative to promote HBsAg clearance by an endogenous inflammatory flare during therapy discontinuation.

Actual start date of recruitment	03 September 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 201
Worldwide total number of subjects	201
EEA total number of subjects	201

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	199
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment and treatment of subjects were performed in 24 trial sites in Germany. Originally it was planned to replace patients who dropped out of the study before receiving any trial treatment, but further recruitment was not possible. Therefore not all randomized 170 patients could be included in the mITT population and the primary analysis.

Pre-assignment

Screening details:

There was an individual screening period of approximately 4 weeks. After randomisation, the treatment period took 48 weeks. Follow-up continued for another 24 weeks (72 weeks in total).

Pre-assignment period milestones

Number of subjects started	201
Number of subjects completed	170

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Meeting any eclusion criterion: 15
Reason: Number of subjects	Violation of inclusion criteria: 16

Period 1

Period 1 title	Treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention Group (Pegasys®)

Arm description:

The group received addiotional treatment with Pegasys in the following treatment period. After the treatment period, both groups were treated with the standard therapeutic use of Nucleos(t)ides.

Arm type	Experimental
Investigational medicinal product name	pegylated interferon alfa-2a
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

In this trial the dosage and duration of Pegasys® is 180 micrograms once weekly for 48 weeks by subcutaneous administration in the abdomen or thigh which is consistent with the recommended dosage and duration for both HBeAg-positive and –negative chronic hepatitis B. Temporary interruptions of study drug(s) administration are discouraged; patients are to remain on treatment for the entire duration of the trial; and the dose of peg-IFN should not be changed during the trial, unless dose reduction is indicated because of laboratory abnormalities/adverse events (c.f. Section 4.1.8 for instructions for dose reduction). The patients must be counselled regarding the importance of not missing doses of peg-IFN.

Arm title	Control Group

Arm description:

Group receiving the standard nucleos(t)ide treatment without the add-on drug [pegylated Interferon alfa-2a (Pegasys®)].

Arm type	Active comparator

Investigational medicinal product name	nucleos(t)ides
Investigational medicinal product code	
Other name	amivudine, adefovir, entecavir, tenofovir or one of the following combinations: lamivudine/adefovir, lamivudine/tenofovir, entecavir/adefovir or entecavir/tenof
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dose and administration according to individual summary of product characteristics.

Number of subjects in period 1[1]	Intervention Group (Pegasys®)	Control Group
Started	112	58
Completed	89	49
Not completed	23	9
Consent withdrawn by subject	4	4
Other(unknown)	6	1
Adverse event, non-fatal	9	-
Other (Unallowed concomitant medication indicated)	1	-
Lost to follow-up	1	4
Other(significant change of medical condition))	2	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline values were collected before randomization after a screening procedure.

Period 2

Period 2 title	Follow Up
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Intervention Group (Pegasys®)

Arm description:

The group received addiotional treatment with Pegasys in the following treatment period. After the treatment period, both groups were treated with the standard therapeutic use of Nucleos(t)ides.

Arm type	Experimental
Investigational medicinal product name	pegylated interferon alfa-2a
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

In this trial the dosage and duration of Pegasys® is 180 micrograms once weekly for 48 weeks by subcutaneous administration in the abdomen or thigh which is consistent with the recommended dosage and duration for both HBeAg-positive and –negative chronic hepatitis B. Temporary interruptions of study drug(s) administration are discouraged; patients are to remain on treatment for the entire

duration of the trial; and the dose of peg-IFN should not be changed during the trial, unless dose reduction is indicated because of laboratory abnormalities/adverse events (c.f. Section 4.1.8 for instructions for dose reduction). The patients must be counselled regarding the importance of not missing doses of peg-IFN.

Number of subjects in period 2[2]	Intervention Group (Pegasys®)
Started	112
Completed	103
Not completed	9
Administrative/regulatory reasons	2
Consent withdrawn by subject	1
Adverse event, non-fatal	5
other reasons (unspecified)	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The numbers from the safety population were used for reporting.

Baseline characteristics

Reporting groups	
Reporting group title	Intervention Group (Pegasys®)
Reporting group description:	
The group received addiotional treatment with Pegasys in the following treatment period. After the treatment period, both groups were treated with the standard therapeutic use of Nucleos(t)ides.	
Reporting group title	Control Group
Reporting group description:	
Group receiving the standard nucleos(t)ide treatment without the add-on drug [pegylated Interferon alfa-2a (Pegasys®)].	

Reporting group values	Intervention Group (Pegasys®)	Control Group	Total
Number of subjects	112	58	170
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	43.8	45.1	
standard deviation	± 9.6	± 9.7	-
Gender categorical Units: Subjects			
Female	26	16	42
Male	86	42	128
Ethnicity Units: Subjects			
European	85	39	124
Asian	15	6	21
African	7	6	13
Others	3	4	7
Missing	2	3	5
HBV DNA quant. negative ? Units: Subjects			
Yes	109	54	163
No	1	1	2
Missing	2	3	5
Anti-HBs Units: Subjects			
Positive	7	2	9

Negative	103	53	156
Missings	2	3	5
HBeAg Units: Subjects			
Negative	110	55	165
Missing	2	3	5
Anti-HBe Units: Subjects			
Positive	96	45	141
Negative	11	10	21
Missing	5	3	8
Anti-HBc Units: Subjects			
Positive	94	48	142
Negative	15	7	22
Missing	3	3	6
HCV Units: Subjects			
Negative	110	55	165
Missing	2	3	5
HDV Units: Subjects			
Negative	110	55	165
Missings	2	3	5
HIV Units: Subjects			
Negative	109	55	164
Missing	3	3	6
Is the HBV Genotype known? Units: Subjects			
Yes	22	12	34
No	88	43	131
Missing	2	3	5
HBV Genotype Units: Subjects			
Genotype A	2	1	3
Genotype C	1	0	1
Genotype D	16	11	27
Genotype E	1	0	1
Wildtyp	1	0	1
Missing	91	46	137
HBs antigen concentration Units: IU/ ml			
arithmetic mean	6547.5	8434.9	
standard deviation	± 10326.2	± 12660.1	-
ALT			
(liver function)			
Units: U/ l			
arithmetic mean	32.4	34.8	
standard deviation	± 15.7	± 19.2	-
AST (GOT)			

Units: U/ l			
arithmetic mean	26.6	28.2	
standard deviation	± 8.7	± 12.3	-
Alkaline phosphatase			
Units: U/ l			
arithmetic mean	65.6	70.7	
standard deviation	± 18.3	± 20.2	-
GGT			
Units: U/l			
arithmetic mean	26.7	30.3	
standard deviation	± 20.7	± 22.1	-
Elastography			
Fibroscan			
Units: kPa			
arithmetic mean	6.5	6.9	
standard deviation	± 8.3	± 9.2	-
Total bilirubin			
Units: mg/ dl			
arithmetic mean	0.6	0.6	
standard deviation	± 0.5	± 0.3	-
Thrombocytes			
Units: /nl			
arithmetic mean	213.8	223.1	
standard deviation	± 56.2	± 51.1	-
Albumin			
Units: g/dl			
arithmetic mean	4.3	4.4	
standard deviation	± 0.6	± 0.4	-
PT (quick)			
clinical chemistry			
Units: percent			
arithmetic mean	96.5	101.2	
standard deviation	± 12.5	± 12.1	-

End points

End points reporting groups

Reporting group title	Intervention Group (Pegasys®)
Reporting group description:	
The group received addiotional treatment with Pegasys in the following treatment period. After the treatment period, both groups were treated with the standard therapeutic use of Nucleos(t)ides.	
Reporting group title	Control Group
Reporting group description:	
Group receiving the standard nucleos(t)ide treatment without the add-on drug [pegylated Interferon alfa-2a (Pegasys®)].	
Reporting group title	Intervention Group (Pegasys®)
Reporting group description:	
The group received addiotional treatment with Pegasys in the following treatment period. After the treatment period, both groups were treated with the standard therapeutic use of Nucleos(t)ides.	

Primary: Objective response after 48 weeks

End point title	Objective response after 48 weeks
End point description:	
The primary endpoint was the objective response after 48 weeks of combination therapy. The response is defined as a confirmed reduction of ≥ 1 log10 in HBsAg compared to baseline. Missing values of the primary variable were carried forward in the main Analysis and the first sensitivity analysis. In the second sensitivity analysis drop-outs before week 48 were considered as non-responders, includingpatients with missing baseline values.	
End point type	Primary
End point timeframe:	
The primary endpoint was the objective response after 48 weeks of combination therapy. Objective response is defined as confirmed reduction of ≥ 1 log10 in HBsAg compared to baseline.	

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: Yes, No, Missing				
confirmed reduction of ≥ 1 log10 in HBsAg	26	1		
no reduction	80	53		
missing	4	1		

Statistical analyses

Statistical analysis title	Response of HBs Antigen after 48 weeks
Comparison groups	Intervention Group (Pegasys®) v Control Group

Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact

Secondary: Decline of HBs antigen at week 12 (mITT)

End point title	Decline of HBs antigen at week 12 (mITT)

End point description:

Differences between screening after 12 weeks compared to baseline. Modified Intention-to-treat (mITT) population was investigated.

End point type	Secondary

End point timeframe:

12 weeks.

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110[1]	55[2]		
Units: IU/ml				
geometric mean (confidence interval 95%)	0.7058 (0.5803 to 0.8585)	0.9380 (0.7154 to 1.2297)		

Notes:

[1] - modified Intention-to-treat (mITT) population.

[2] - modified Intention-to-treat (mITT) population.

Statistical analyses

No statistical analyses for this end point

Secondary: Decline of HBs antigen at week 24 (mITT)

End point title	Decline of HBs antigen at week 24 (mITT)

End point description:

Differences between screening after 24 weeks compared to baseline. Modified Intention-to-treat (mITT) population was investigated.

End point type	Secondary

End point timeframe:

24 weeks.

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: IU/ml				
geometric mean (confidence interval 95%)	0.3694 (0.2872 to 0.4752)	0.7995 (0.5646 to 1.1322)		

Statistical analyses

No statistical analyses for this end point

Secondary: Patients with minimum 10% HBsAg loss at week 24 (compared to baseline)

End point title	Patients with minimum 10% HBsAg loss at week 24 (compared to baseline)

End point description:

Decline of HBs antigen rate at week 24 at least 10% compared to baseline.

End point type	Secondary

End point timeframe:

24 weeks.

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: Yes, No, Missing				
Yes	72	21		
No	38	32		
Missing	0	2		

Statistical analyses

Statistical analysis title	Fisher's Exact test
Comparison groups	Intervention Group (Pegasys®) v Control Group
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1799
Method	Fisher exact

Secondary: HBsAg seroconversion detected

End point title	HBsAg seroconversion detected

End point description:

HBsAg seroconversion was defined as percentage of subjects who became HBsAg negative (<10 IU/ml) and anti-HBs positive (≥10 IU/l) at least once during the observation period (baseline - EoFU).

End point type	Secondary

End point timeframe:

HBsAg seroconversion defined as percentage of subjects who became HBsAg negative and anti-HBs positive during the observation period

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: Subjects				
Yes	6	0		
No	104	55		

Statistical analyses

No statistical analyses for this end point

Secondary: Visit when HBsAg seroconversion was detected

End point title	Visit when HBsAg seroconversion was detected

End point description:

Visit when HBs antigen seroconversion was first detected

End point type	Secondary

End point timeframe:

During the whole study period.

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: Visits				
Visit 9	1	0		
Visit 11	1	0		
Visit 13	3	0		
Visit 14	1	0		
Missing	104	55		

Statistical analyses

No statistical analyses for this end point

Secondary: Seroconversion at end of follow-up

End point title	Seroconversion at end of follow-up

End point description:

End point type	Secondary

End point timeframe:

Week 48-72.

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: Subjects				
Yes	2	0		
No	4	0		
Missing	104	55		

Statistical analyses

No statistical analyses for this end point

Secondary: HBsAg levels at all measurement times

End point title	HBsAg levels at all measurement times

End point description:

End point type	Secondary

End point timeframe:

Week 12

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: IU/ml				
arithmetic mean (standard deviation)	7001.3 (± 13903.8)	9277.5 (± 17574.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Decline of HBs antigen at week 36 (mITT)

End point title	Decline of HBs antigen at week 36 (mITT)

End point description:

36 Weeks.

End point type	Secondary

End point timeframe:

Differences between screening after 36 weeks compared to baseline. Modified Intention-to-treat (mITT) population was investigated.

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: IU/ml				
geometric mean (confidence interval 95%)	0.1931 (0.1304 to 0.2858)	0.7937 (0.4749 to 1.3266)		

Statistical analyses

No statistical analyses for this end point

Secondary: Decline of HBs antigen at week 48 (mITT)

End point title	Decline of HBs antigen at week 48 (mITT)

End point description:

Differences between screening after 48 weeks compared to baseline. Modified Intention-to-treat (mITT) population was investigated.

End point type	Secondary

End point timeframe:

48 weeks.

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: IU/ml				
geometric mean (confidence interval 95%)	0.1859 (0.1279 to 0.2701)	0.7372 (0.4350 to 1.2494)		

Statistical analyses

No statistical analyses for this end point

Secondary: Decline of HBs antigen at week 72 (mITT)

End point title	Decline of HBs antigen at week 72 (mITT)

End point description:

Differences between screening after 72 weeks compared to baseline. Modified Intention-to-treat (mITT) population was investigated.

End point type	Secondary

End point timeframe:

72 weeks.

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: IU/ml				
geometric mean (confidence interval 95%)	0.2535 (0.1849 to 0.3476)	0.6581 (0.4225 to 1.0250)		

Statistical analyses

No statistical analyses for this end point

Secondary: Systolic Blood pressure week 24

End point title	Systolic Blood pressure week 24

End point description:

End point type	Secondary

End point timeframe:
24 weeks.

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: mmHg				
arithmetic mean (standard deviation)	127.34 (± 14.29)	129.85 (± 16.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Systolic Blood pressure week 36

End point title	Systolic Blood pressure week 36

End point description:

End point type	Secondary

End point timeframe:
36 weeks.

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: mmHg				
arithmetic mean (standard deviation)	126.36 (± 14.43)	131.00 (± 16.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Systolic Blood Pressure (EoT)

End point title	Systolic Blood Pressure (EoT)

End point description:

End point type	Secondary

End point timeframe:
48 weeks/ end of study.

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: mmHg				
arithmetic mean (standard deviation)	124.75 (± 14.16)	130.13 (± 15.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pulse (EoT)

End point title	Pulse (EoT)

End point description:

End point type	Secondary

End point timeframe:
End of trial. 48 weeks.

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: bpm				
arithmetic mean (standard deviation)	73.86 (± 9.48)	72.30 (± 7.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: body weight week 12

End point title	body weight week 12

End point description:

End point type	Secondary

End point timeframe:
Week 12.

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: kg				
arithmetic mean (standard deviation)	79.64 (± 12.93)	79.35 (± 15.49)		

Statistical analyses

No statistical analyses for this end point

Secondary: body weight week 24

End point title	body weight week 24

End point description:

End point type	Secondary

End point timeframe:
24 weeks.

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: kg				
arithmetic mean (standard deviation)	78.77 (± 12.40)	79.64 (± 15.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: body weight week 36

End point title	body weight week 36

End point description:

End point type	Secondary

End point timeframe:
36 weeks.

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: kg				
arithmetic mean (standard deviation)	79.02 (± 11.63)	79.13 (± 15.44)		

Statistical analyses

No statistical analyses for this end point

Secondary: body weight (EoT)

End point title	body weight (EoT)

End point description:

End point type	Secondary

End point timeframe:
End of Trial. 48 weeks.

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: kg				
arithmetic mean (standard deviation)	77.72 (± 12.33)	79.79 (± 15.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: BMI week 12

End point title	BMI week 12

End point description:

End point type	Secondary

End point timeframe:
12 weeks.

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: kg/m²				
arithmetic mean (standard deviation)	26.19 (± 3.86)	26.76 (± 4.31)		

Statistical analyses

No statistical analyses for this end point

Secondary: BMI week 24

End point title	BMI week 24

End point description:

End point type	Secondary

End point timeframe:
24 weeks.

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: kg/m²				
arithmetic mean (standard deviation)	25.91 (± 3.61)	26.85 (± 4.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: BMI week 36

End point title	BMI week 36

End point description:

End point type	Secondary

End point timeframe:
Week 36.

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: kg/m²				
arithmetic mean (standard deviation)	25.88 (± 3.56)	26.75 (± 4.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: BMI (EoT)

End point title	BMI (EoT)

End point description:

End point type	Secondary

End point timeframe:

End of Trial. 48 weeks.

End point values	Intervention Group (Pegasys®)	Control Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	110	55		
Units: kg/m²				
arithmetic mean (standard deviation)	25.56 (± 3.60)	26.88 (± 4.28)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

In this trial, the period of observation for adverse events extended from the time the subject had signed the informed consent document up to the end of follow up at week 72 (visit 15 of the treatment group or visit 7 of the control group).

Adverse event reporting additional description:

If the investigator detected a serious adverse event after the period of observation, considering the event possibly related to this trial, he should contact the sponsor to determine how the adverse event should be documented & reported. Serious adverse events had to be immediately (within 24h of the investigator's awareness) reported to IZKS Mainz

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Intervention Group (Pegasys®)

Reporting group description:

The group received addiotional treatment with Pegasys in the following treatment period. After the treatment period, both groups were treated with the standard therapeutic use of Nucleos(t)ides.

Reporting group title	Control Group

Reporting group description:

Group receiving the standard nucleos(t)ide treatment without the add-on drug [pegylated Interferon alfa-2a (Pegasys®)].

Serious adverse events	Intervention Group (Pegasys®)	Control Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 112 (11.61%)	4 / 58 (6.90%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine leiomyoma			
subjects affected / exposed	0 / 112 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	1 / 112 (0.89%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Aortic valve replacement	Additional description: recovered/resolved		

subjects affected / exposed	1 / 112 (0.89%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Internal fixation of fracture	Additional description: recovered/resolved		
subjects affected / exposed	1 / 112 (0.89%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis	Additional description: recovered/resolved		
subjects affected / exposed	1 / 112 (0.89%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pain	Additional description: recovered/resolved		
subjects affected / exposed	1 / 112 (0.89%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyarthritis	Additional description: recovered/resolved		
subjects affected / exposed	1 / 112 (0.89%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Postmenopausal haemorrhage	Additional description: recovering/resolving		
subjects affected / exposed	0 / 112 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hyperplasia			
subjects affected / exposed	0 / 112 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Nasal turbinate hypertrophy	Additional description: hypertrophy recovering/resolving		

subjects affected / exposed	0 / 112 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Facial bones fracture	Additional description: recovered/resolved		
subjects affected / exposed	1 / 112 (0.89%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture	Additional description: recovered/resolved		
subjects affected / exposed	1 / 112 (0.89%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 112 (0.89%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury	Additional description: recovering/resolving		
subjects affected / exposed	1 / 112 (0.89%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Coronary artery disease	Additional description: recovered/resolved		
subjects affected / exposed	1 / 112 (0.89%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	1 / 112 (0.89%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal haemorrhage	Additional description: recovered/resolved		

subjects affected / exposed	1 / 112 (0.89%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin hyperpigmentation	Additional description: recovered/resolved		
subjects affected / exposed	0 / 112 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 112 (0.89%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism	Additional description: recovered/resolved		
subjects affected / exposed	1 / 112 (0.89%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: recovered/resolved with sequel		
subjects affected / exposed	1 / 112 (0.89%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity	Additional description: recovered/resolved		
subjects affected / exposed	0 / 112 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyelonephritis	Additional description: recovered/resolved		
subjects affected / exposed	0 / 112 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection	Additional description: recovered/resolved		

subjects affected / exposed	0 / 112 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chlamydial infection	Additional description: recovering/resolving		
subjects affected / exposed	1 / 112 (0.89%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Intervention Group (Pegasys®)	Control Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	106 / 112 (94.64%)	20 / 58 (34.48%)	
Investigations			
Transaminases increased			
subjects affected / exposed	6 / 112 (5.36%)	0 / 58 (0.00%)	
occurrences (all)	9	0	
Weight decreased			
subjects affected / exposed	8 / 112 (7.14%)	1 / 58 (1.72%)	
occurrences (all)	8	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 112 (9.82%)	0 / 58 (0.00%)	
occurrences (all)	18	0	
Headache			
subjects affected / exposed	40 / 112 (35.71%)	0 / 58 (0.00%)	
occurrences (all)	48	0	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	11 / 112 (9.82%)	0 / 58 (0.00%)	
occurrences (all)	19	0	
Fatigue			
subjects affected / exposed	48 / 112 (42.86%)	2 / 58 (3.45%)	
occurrences (all)	52	2	
Influenza like illness			

subjects affected / exposed	13 / 112 (11.61%)	2 / 58 (3.45%)	
occurrences (all)	21	2	
Injection site erythema			
subjects affected / exposed	11 / 112 (9.82%)	0 / 58 (0.00%)	
occurrences (all)	12	0	
Pyrexia			
subjects affected / exposed	25 / 112 (22.32%)	0 / 58 (0.00%)	
occurrences (all)	28	0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	8 / 112 (7.14%)	0 / 58 (0.00%)	
occurrences (all)	11	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	11 / 112 (9.82%)	6 / 58 (10.34%)	
occurrences (all)	11	10	
Diarrhoea			
subjects affected / exposed	9 / 112 (8.04%)	1 / 58 (1.72%)	
occurrences (all)	12	1	
Nausea			
subjects affected / exposed	12 / 112 (10.71%)	1 / 58 (1.72%)	
occurrences (all)	13	1	
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	6 / 112 (5.36%)	0 / 58 (0.00%)	
occurrences (all)	6	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 112 (8.04%)	2 / 58 (3.45%)	
occurrences (all)	10	2	
Oropharyngeal pain			
subjects affected / exposed	7 / 112 (6.25%)	0 / 58 (0.00%)	
occurrences (all)	8	0	
Skin and subcutaneous tissue disorders			
Alopecia			

subjects affected / exposed	17 / 112 (15.18%)	0 / 58 (0.00%)	
occurrences (all)	17	0	
Dry skin			
subjects affected / exposed	7 / 112 (6.25%)	0 / 58 (0.00%)	
occurrences (all)	7	0	
Pruritus			
subjects affected / exposed	15 / 112 (13.39%)	0 / 58 (0.00%)	
occurrences (all)	17	0	
Rash			
subjects affected / exposed	8 / 112 (7.14%)	0 / 58 (0.00%)	
occurrences (all)	10	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	9 / 112 (8.04%)	0 / 58 (0.00%)	
occurrences (all)	10	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	31 / 112 (27.68%)	0 / 58 (0.00%)	
occurrences (all)	45	0	
Back pain			
subjects affected / exposed	15 / 112 (13.39%)	2 / 58 (3.45%)	
occurrences (all)	17	3	
Myalgia			
subjects affected / exposed	19 / 112 (16.96%)	0 / 58 (0.00%)	
occurrences (all)	21	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	28 / 112 (25.00%)	3 / 58 (5.17%)	
occurrences (all)	31	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 112 (5.36%)	0 / 58 (0.00%)	
occurrences (all)	9	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2011	Added following inclusion criteria: -Treatment with a nucleos(t)ide regimen (lamivudine, adefovir, entecavir, tenofovir or one of the following combinations: lamivudine/adefovir, lamivudine/tenofovir, entecavir/adefovir or entecavir/tenofovir) and a fully suppressed viral load for at least 12 months (below limit of detection in conventional HBV-PCR assays, i.e. <116 copies/ml). Added following exclusion criteria: -Preexisting polyneuropathy -If polyneuropathy develops and is confirmed by a neurologist, withdrawal will be discussed according to severity of the symptoms Declared the following as secondary objectives: -To evaluate safety and tolerability of pegylated interferon alfa-2a when combined with tenofovir, entecavir, lamivudine, adefovir, or a combination of lamivudine or entecavir with adefovir or tenofovir. Added the following information to the basic treatment section: The known dosing instructions, contraindications, side effects and risks for each drug must be taken into account accoring to the maufacturers' recommendations. Regular laboratory and clinical assessments throughout the course of this study are to provide adequate monitoring of potential toxicities. Added the following info on physical examination: As an increased incidence of polyneuropathy was observed during combination therapy with pegylated interferon alfa-2a and telbivudine, special attention should be paid to the development of polyneuropathy or other neurological symptoms in subjects on combination therapy. Investigators need to question patients about development of hyp- or dysesthesia, muscle weakness or any other neurological symptoms. If neurological symptoms occur, they need to be documented as adverse events, and the patients will then be referred to a neurologist for further examination.
19 April 2013	The amendment contains the change of: - the coordinating investigator - the inclusion criterion "HBsAg ≥1000 IU/ml" to "HBsAg ≥100 IU/ml" - the following exclusion criteria: - Decompensated liver disease, or history of decompensated liver disease, as evidenced by ascites, portal hypertension, jaundice or hepatic encephalopathy, coagulopathy, varices, history of varicose bleeding, or any othe clinical evidence of decompensation. (Patients with stable liver cirrhosis are eligible for this study, if a history of decompensated liver disease as outlined above has been excluded.) -Usage of any investigational drugs within 3 months before enrolment removed: Histologically proven liver cirrhosis (exclusion criteria). Earlier: Usage of any investigational drugs within 12 months before enrolment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported