Clinical trial results:
Phase IIIb, Randomized, Open-Label Study of Pegylated Interferon Alfa-2a in Combination with Lamivudine or Entecavir Compared with Untreated Control Patients in Children with HBeAg-Positive Chronic Hepatitis B in the Immune-Tolerant Phase

Summary

EudraCT number	2006-000977-31
Trial protocol	GB DE BE IT
Global end of trial date	29 January 2020

Results information

Result version number	v2 (current)
This version publication date	06 September 2020
First version publication date	01 August 2020
Version creation reason	• Correction of full data set Some clarifying changes are added to be in alignment with CTg Results summary

Trial information

Trial identification

Sponsor protocol code	NV25361

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02263079
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124., Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com

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?	Yes
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 January 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 January 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to evaluate the efficacy of Pegasys® + lamivudine or entecavir compared with an untreated control in children with CHB, as measured by loss of HBsAg 24 weeks post-end of treatment/end of untreated observation.

Protection of trial subjects:

All study subjects, parent or legal guardian were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 June 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Turkey: 15
Country: Number of subjects enrolled	Ukraine: 1
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	United States: 7
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Malaysia: 1
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Russian Federation: 4
Worldwide total number of subjects	59
EEA total number of subjects	28

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)	25
Adolescents (12-17 years)	34
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study began as a single-site, three arm IST and was adapted as a multi-center, two arm study, conducted at 22 sites. Enrollment was stopped prematurely, at which time 62 subjects had been enrolled. Due to the low subject number (n=3) in the Pegasys montherapy arm, data was not analysed and not presented to avoid subject re-identification.

Pre-assignment

Screening details:

The screening period was up to 6 weeks.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Peg-IFN-Alfa-2A + Lamivudine or Entecavir

Arm description:

Subjects received lamivudine or entecavir alone for 8 weeks followed by peg-IFN-alfa-2A in combination with lamivudine or entecavir for 48 weeks.

Arm type	Experimental
Investigational medicinal product name	Peginterferon Alfa 2A
Investigational medicinal product code	RO025-8310
Other name	Pegasys
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received Peginterferon Alfa 2A subcutaneously once weekly with dosing based on body surface area (BSA) categories for 48 weeks.

Investigational medicinal product name	Lamivudine
Investigational medicinal product code	
Other name	Epivir
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Subjects received 100 mg lamivudine as a film-coated tablet or oral solution once daily at a dose of 3 mg/kg (maximum daily dose 100 mg) or 0.5 mg entecavir as a film-coated tablet or oral solution at a dose of 0.015 mg/kg once daily (maximum dose of 0.5 mg), given alone for 8 weeks then in combination with Pegasys® for 48 weeks.

Investigational medicinal product name	Entecavir
Investigational medicinal product code	
Other name	Baraclude
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Subjects received 100 mg lamivudine as a film-coated tablet or oral solution once daily at a dose of 3 mg/kg (maximum daily dose 100 mg) or 0.5 mg entecavir as a film-coated tablet or oral solution at a dose of 0.015 mg/kg once daily (maximum dose of 0.5 mg), given alone for 8 weeks then in combination with Pegasys® for 48 weeks.

Investigational medicinal product name	Entecavir
Investigational medicinal product code	
Other name	Baraclude
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 100 mg lamivudine as a film-coated tablet or oral solution once daily at a dose of 3 mg/kg (maximum daily dose 100 mg) or 0.5 mg entecavir as a film-coated tablet or oral solution at a dose of 0.015 mg/kg once daily (maximum dose of 0.5 mg), given alone for 8 weeks then in combination with Pegasys® for 48 weeks.

Investigational medicinal product name	Lamivudine
Investigational medicinal product code	
Other name	Epivir
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received 100 mg lamivudine as a film-coated tablet or oral solution once daily at a dose of 3 mg/kg (maximum daily dose 100 mg) or 0.5 mg entecavir as a film-coated tablet or oral solution at a dose of 0.015 mg/kg once daily (maximum dose of 0.5 mg), given alone for 8 weeks then in combination with Pegasys® for 48 weeks.

Arm title	Untreated Control Subjects

Arm description:

Untreated control subjects were observed up to 80 weeks.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Peg-IFN-Alfa-2A + Lamivudine or Entecavir	Untreated Control Subjects
Started	26	33
Completed	23	25
Not completed	3	8
Physician decision	1	-
Consent withdrawn by subject	2	8

Baseline characteristics

Reporting groups	
Reporting group title	Peg-IFN-Alfa-2A + Lamivudine or Entecavir
Reporting group description:	
Subjects received lamivudine or entecavir alone for 8 weeks followed by peg-IFN-alfa-2A in combination with lamivudine or entecavir for 48 weeks.	
Reporting group title	Untreated Control Subjects
Reporting group description:	
Untreated control subjects were observed up to 80 weeks.	

Reporting group values	Peg-IFN-Alfa-2A + Lamivudine or Entecavir	Untreated Control Subjects	Total
Number of subjects	26	33	59
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	8	17	25
Adolescents (12-17 years)	18	16	34
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	11.9	10.9	
standard deviation	± 3.2	± 3.7	-
Sex: Female, Male Units:			
Female	16	14	30
Male	10	19	29
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	25	33	58
Race/Ethnicity, Customized Units: Subjects			
Asian	11	11	22
Black or African American	4	2	6
Multiple	2	0	2
Other	0	3	3
White	9	17	26

End points

End points reporting groups

Reporting group title	Peg-IFN-Alfa-2A + Lamivudine or Entecavir
Reporting group description:	
Subjects received lamivudine or entecavir alone for 8 weeks followed by peg-IFN-alfa-2A in combination with lamivudine or entecavir for 48 weeks.	
Reporting group title	Untreated Control Subjects
Reporting group description:	
Untreated control subjects were observed up to 80 weeks.	
Subject analysis set title	Intent-to-Treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intent to treat (ITT) population was defined as all subjects who received at least one dose of study medication of treated group. For untreated group, the ITT population included all randomized subjects.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population was defined as all subjects who received at least one dose of study medication and had at least one post-baseline safety assessment. For untreated group, the safety population included all randomized subjects who had at least one post-baseline safety assessment.	

Primary: Proportion of Subjects With Loss of Hepatitis B Surface Antigen (HBsAg) at 24 Weeks Post-End of Treatment/End of Untreated Observation

End point title	Proportion of Subjects With Loss of Hepatitis B Surface Antigen (HBsAg) at 24 Weeks Post-End of Treatment/End of Untreated Observation[1]
End point description:	
This endpoint is defined as loss of HBsAg at 24 weeks post-treatment (follow-up Week 24)/end of untreated observation (Week 80). The percentage of responders (response rate) and 95% CI (using the Clopper-Pearson method) for the response rate are presented for each group. The analysis population was the Intent-to-Treat (ITT) population, that included all randomized subjects, who received at least one dose of study medication of treated group. For untreated group, the ITT population included all randomized subjects.	
End point type	Primary
End point timeframe:	
24 weeks post-treatment/at the end of untreated observation (Week 80)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Peg-IFN-Alfa-2A + Lamivudine or Entecavir	Untreated Control Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	33		
Units: Percentage of Subjects				
number (confidence interval 95%)	3.8 (0.10 to 19.64)	0.0 (0.00 to 10.58)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Loss of HBsAg

End point title	Proportion of Subjects With Loss of HBsAg[2]

End point description:

This endpoint is defined as loss of HBsAg at 1 year post-treatment in the treated group. The 95% Confidence Interval of response rate is calculated by Clopper-Pearson method. The analysis population included subjects from the Peg-INF-Alfa-2A arm, who received at least one dose of study medication of treated group. None of the subjects from the untreated group were assessed for this end point at 1 year post-end of treatment as they were only observed up to 80 weeks (=24 weeks post-treatment for treated subjects).

End point type	Secondary

End point timeframe:

1 year post-end of treatment (End of treatment = Week 56)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Peg-IFN-Alfa-2A + Lamivudine or Entecavir			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Percentage of Subjects				
number (confidence interval 95%)	3.8 (0.10 to 19.64)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Loss of Hepatitis B Virus Envelope Antigen (HBeAg)

End point title	Proportion of Subjects With Loss of Hepatitis B Virus Envelope Antigen (HBeAg)

End point description:

This endpoint is defined as loss of HBeAg at 24 weeks post-treatment (follow-up Week 24)/end of untreated observation (Week 80) and at 1 year post-end of treatment in the treated group. The 95% Confidence Interval of response rate is calculated by Clopper-Pearson method. The analysis population was the Intent-to-Treat (ITT) population, that included all randomized subjects, who received at least one dose of study medication of treated group. For untreated group, the ITT population included all randomized subjects. None of the subjects from the untreated group were assessed at 1 year post-end of treatment as they were only observed up to 80 weeks (=24 weeks post-treatment for treated subjects). 9999=not observed

End point type	Secondary

End point timeframe:

24 weeks post-treatment /end of untreated observation (Week 80), and 1 year post-end of treatment (End of treatment = Week 56)

End point values	Peg-IFN-Alfa-2A + Lamivudine or Entecavir	Untreated Control Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	33		
Units: Percentage of Subjects				
number (confidence interval 95%)				
24 Weeks post-treatment/Week 80	3.8 (0.10 to 19.64)	12.1 (3.40 to 28.20)		
1 year post-end of treatment	11.5 (2.45 to 30.15)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Seroconversion to Hepatitis B Surface Antibody (Anti-HBs), Defined as Loss of HBsAg and Presence of anti-HBs

End point title	Proportion of Subjects With Seroconversion to Hepatitis B Surface Antibody (Anti-HBs), Defined as Loss of HBsAg and Presence of anti-HBs

End point description:

This endpoint measures the seroconversion to anti-HBs defined as loss of HBsAg and presence of anti-HBs at 24 weeks post-treatment (follow-up Week 24)/end of untreated observation (Week 80) and at 1 year post-end of treatment in the treated group. The 95% Confidence Interval of response rate is calculated by Clopper-Pearson method. The analysis population was the Intent-to-Treat (ITT) population, that included all randomized subjects, who received at least one dose of study medication of treated group. For untreated group, the ITT population included all randomized subjects. None of the subjects from the untreated group were assessed at 1 year post-end of treatment as they were only observed up to 80 weeks (=24 weeks post-treatment for treated subjects). 9999=not observed

End point type	Secondary

End point timeframe:

24 weeks post-treatment /end of untreated observation (Week 80), and 1 year post-end of treatment (End of treatment = Week 56)

End point values	Peg-IFN-Alfa-2A + Lamivudine or Entecavir	Untreated Control Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	33		
Units: Percentage of Subjects				
number (confidence interval 95%)				
24 Weeks post-treatment/Week 80	3.8 (0.10 to 19.64)	0.0 (0.00 to 10.58)		
1 year post-end of treatment	3.8 (0.10 to 19.64)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Seroconversion to Hepatitis B Envelope Antibody (Anti-HBe), Defined as Loss of HBeAg and Presence of anti-HBe

End point title	Proportion of Subjects With Seroconversion to Hepatitis B Envelope Antibody (Anti-HBe), Defined as Loss of HBeAg and Presence of anti-HBe

End point description:

This endpoint measures the seroconversion to anti-HBe defined as loss of HBeAg and presence of anti-HBe at 24 weeks post-treatment (follow-up Week 24)/end of untreated observation (Week 80) and at 1 year post-end of treatment in the treated group. The 95% Confidence Interval of response rate is calculated by Clopper-Pearson method. The analysis population was the Intent-to-Treat (ITT) population, that included all randomized subjects, who received at least one dose of study medication of treated group. For untreated group, the ITT population included all randomized subjects. None of the subjects from the untreated group were assessed at 1 year post-end of treatment as they were only observed up to 80 weeks (=24 weeks post-treatment for treated subjects). 9999=not observed

End point type	Secondary

End point timeframe:

24 weeks post-treatment /end of untreated observation (Week 80), and 1 year post-end of treatment (End of treatment = Week 56)

End point values	Peg-IFN-Alfa-2A + Lamivudine or Entecavir	Untreated Control Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	33		
Units: Percentage of Subjects				
number (confidence interval 95%)				
24 Weeks post-treatment/Week 80	0.0 (0.00 to 13.23)	9.1 (1.92 to 24.33)		
1 year post-end of treatment	7.7 (0.95 to 25.13)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Different Hepatitis B Virus (HBV) Deoxyribonucleic Acid (DNA) Levels (Less Than [<] 20,000 International Units per Milliliter [IU/mL], < 2000 IU/mL, or Undetectable HBV DNA)

End point title	Proportion of Subjects With Different Hepatitis B Virus (HBV) Deoxyribonucleic Acid (DNA) Levels (Less Than [<] 20,000

	International Units per Milliliter [IU/mL], < 2000 IU/mL, or Undetectable HBV DNA)

End point description:

This endpoint measures different HBV DNA levels (<20000 IU/mL, <2000 IU/mL and undetectable) measured by PCR or hybridization at 24 weeks post-treatment (follow-up Week 24)/end of untreated observation (Week 80) and at 1 year post-end of treatment in the treated group. HBV-DNA undetectable is defined as <29 IU/mL. The 95% Confidence Interval of response rate is calculated by Clopper-Pearson method. The analysis population was the Intent-to-Treat (ITT) population, that included all randomized subjects, who received at least one dose of study medication of treated group. For untreated group, the ITT population included all randomized subjects. None of the subjects from the untreated group were assessed at 1 year post-end of treatment as they were only observed up to 80 weeks (=24 weeks post-treatment for treated subjects). 9999=not observed

End point type	Secondary

End point timeframe:

24 weeks post-treatment /end of untreated observation (Week 80), and 1 year post-end of treatment (End of treatment = Week 56)

End point values	Peg-IFN-Alfa-2A + Lamivudine or Entecavir	Untreated Control Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	33		
Units: Percentage of Subjects				
number (confidence interval 95%)				
HBV-DNA <20000 IU/mL at follow up Week 24/Week 80	7.7 (0.95 to 25.13)	12.1 (3.40 to 28.20)		
HBV-DNA <2000 IU/mL at follow up Week 24/Week 80	7.7 (0.95 to 25.13)	12.1 (3.40 to 28.20)		
HBV-DNA Undetectable at follow up Week 24/Week 80	0.0 (0.00 to 13.23)	6.1 (0.74 to 20.23)		
HBV-DNA <20000 IU/mL 1 year post-end of treatment	15.4 (4.36 to 34.87)	9999 (9999 to 9999)		
HBV-DNA <2000 IU/mL 1 year post-end of treatment	7.7 (0.95 to 25.13)	9999 (9999 to 9999)		
HBV-DNA Undetectable 1 year post-end of treatment	0.0 (0.00 to 13.23)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HBV DNA Levels in the Peg-INF-Alfa-2A (Treated) Arm

End point title	Change From Baseline in HBV DNA Levels in the Peg-INF-Alfa-2A (Treated) Arm[3]

End point description:

This end point presents HBV DNA levels measured at defined time points from Baseline in the Treated arm. The analysis population included subjects from the Peg-INF-Alfa-2A arm, who received at least one dose of study medication of treated group. Only subjects for whom data were collected are included in the analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 8, 20, 32, 44, 56, Follow up Week 4 and 24

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Peg-IFN-Alfa-2A + Lamivudine or Entecavir			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: log10 IU/mL				
arithmetic mean (standard deviation)				
Baseline	8.02 (± 0.93)			
Week 8	4.74 (± 1.01)			
Week 20	3.54 (± 0.81)			
Week 32	2.56 (± 0.84)			
Week 44	2.15 (± 0.70)			
Week 56	2.21 (± 0.90)			
Fu Week 4	4.34 (± 2.65)			
Fu Week 24	7.31 (± 1.99)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HBV DNA Levels in the Untreated Control Subjects

End point title	Change From Baseline in HBV DNA Levels in the Untreated Control Subjects[4]

End point description:

This end point presents HBV DNA levels measured at defined time points from Baseline in the Untreated Control arm. The analysis population included subjects from the Untreated Control arm. Only subjects for whom data were collected are included in the analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 32, 56 and End of Untreated Observation (Week 80)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Untreated Control Subjects			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: log10 IU/mL				
arithmetic mean (standard deviation)				
Baseline	8.22 (± 1.07)			

Week 32	8.29 (± 0.97)			
Week 56	7.57 (± 1.96)			
Week 80	7.24 (± 2.58)			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Combined Response for HBeAg Seroconversion (Defined as Loss of HBeAg and Presence of anti-HBe) and HBV DNA Levels <20,000 IU/mL

End point title	Proportion of Subjects With Combined Response for HBeAg Seroconversion (Defined as Loss of HBeAg and Presence of anti-HBe) and HBV DNA Levels <20,000 IU/mL

End point description:

This endpoint measures the combined response for HBeAg Seroconversion and HBV DNA Levels <20,000 IU/mL at 24 weeks post-treatment (follow-up Week 24)/end of untreated observation (Week 80) and at 1 year post-end of treatment in the treated group. The HBeAg is defined as loss of HBeAg and presence of anti-HBe. The 95% Confidence Interval of response rate is calculated by Clopper-Pearson method. The analysis population was the Intent-to-Treat (ITT) population, that included all randomized subjects, who received at least one dose of study medication of treated group. For untreated group, the ITT population included all randomized subjects. None of the subjects from the untreated group were assessed at 1 year post-end of treatment as they were only observed up to 80 weeks (=24 weeks post-treatment for treated subjects). 9999=not observed

End point type	Secondary

End point timeframe:

24 weeks post-treatment /end of untreated observation (Week 80), and 1 year post-end of treatment (End of treatment = Week 56)

End point values	Peg-IFN-Alfa-2A + Lamivudine or Entecavir	Untreated Control Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	33		
Units: Percentage of Subjects				
number (confidence interval 95%)				
24 Weeks post-treatment/Week 80	0.0 (0.00 to 13.23)	9.1 (1.92 to 24.33)		
1 year post-end of treatment	7.7 (0.95 to 25.13)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Combined Response for HBeAg Seroconversion (Defined as Loss of HBeAg and Presence of anti-HBe) and HBV DNA Levels <2000 IU/mL

End point title	Proportion of Subjects With Combined Response for HBeAg Seroconversion (Defined as Loss of HBeAg and Presence of anti-HBe) and HBV DNA Levels <2000 IU/mL

End point description:

This endpoint measures the combined response for HBeAg Seroconversion and HBV DNA Levels <2000 IU/mL at 24 weeks post-treatment (follow-up Week 24)/end of untreated observation (Week 80) and at 1 year post-end of treatment in the treated group. The HBeAg is defined as loss of HBeAg and presence of anti-HBe. The 95% Confidence Interval of response rate is calculated by Clopper-Pearson method. The analysis population was the Intent-to-Treat (ITT) population, that included all randomized subjects, who received at least one dose of study medication of treated group. For untreated group, the ITT population included all randomized subjects. None of the subjects from the untreated group were assessed at 1 year post-end of treatment as they were only observed up to 80 weeks (=24 weeks post-treatment for treated subjects). 9999=not observed

End point type	Secondary

End point timeframe:

24 weeks post-treatment /end of untreated observation (Week 80), and 1 year post-end of treatment (End of treatment = Week 56)

End point values	Peg-IFN-Alfa-2A + Lamivudine or Entecavir	Untreated Control Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	33		
Units: Percentage of Subjects				
number (confidence interval 95%)				
24 Weeks post-treatment/Week 80	0.0 (0.00 to 13.23)	9.1 (1.92 to 24.33)		
1 year post-end of treatment	7.7 (0.95 to 25.13)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Adverse Events

End point title	Proportion of Subjects With Adverse Events

End point description:

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. The safety population included all subjects who received at least one dose of study medication and had at least one post-baseline safety assessment. For untreated group, the safety population included all randomized subjects who had at least one post-baseline safety assessment.

End point type	Secondary

End point timeframe:

Baseline up to 24 weeks post-treatment/end of untreated observation (Week 80)

End point values	Peg-IFN-Alfa-2A + Lamivudine or Entecavir	Untreated Control Subjects		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	33		
Units: Percentage of Subjects				
number (not applicable)				
With at least one Non-Serious AE	92.3	45.5		
With at least one Serious Adverse Event (SAE)	0.0	3.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects with AEs Leading to Dose Modification or Interruption

End point title	Proportion of Subjects with AEs Leading to Dose Modification or Interruption[5]

End point description:

This endpoint measures AEs and lab abnormalities leading to dose interruption or dose modification. Does modification included dose reduced, dose increased or drug interrupted. Adverse events included laboratory abnormalities reported as adverse events. The safety population included all subjects who received at least one dose of study medication and had at least one post-baseline safety assessment in the Peg-INF-Alfa-2A treated arm. This end point only applies to the treated group.

End point type	Secondary

End point timeframe:

Baseline up to 24 weeks post-end of treatment

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Peg-IFN-Alfa-2A + Lamivudine or Entecavir			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Percentage of Subjects				
number (not applicable)	23.0			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Peg-INF-Alfa-2A

End point title	Serum Concentration of Peg-INF-Alfa-2A[6]

End point description:

The serum concentration of Peg-INF-Alfa-2A was measured in picogram/milliliter. The analysis population was the Peg-IFN-Alfa-2A + Lamivudine or Entecavir arm. The untreated arm did not receive any study medication.

End point type	Secondary

End point timeframe:

At Weeks 12, 16, 20, 32, 44, 56

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only descriptive statistics was planned to be reported in the endpoint.

End point values	Peg-IFN-Alfa-2A + Lamivudine or Entecavir			
Subject group type	Reporting group			
Number of subjects analysed	14[7]			
Units: pg/mL				
arithmetic mean (standard deviation)				
Week 12 Predose	8430 (± 6090)			
Week 16 Predose	16300 (± 10100)			
Week 20 Predose	13800 (± 8740)			
Week 32 Predose	14900 (± 7710)			
Week 32 24-48h Post-dose	22700 (± 6070)			
Week 32 72-96h Post-dose	23000 (± 4900)			
Week 32 168h Post-dose	19300 (± 5880)			
Week 44 Predose	21900 (± 14200)			
Week 56 Predose	25400 (± 13100)			

Notes:

[7] - Only subjects for whom data were collected are included in the analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to 1 year post-end of treatment in the treated arm; From Baseline to end of untreated observation (Week 80) in the untreated group [up to clinical cut-off date 29 Jan 2020]

Adverse event reporting additional description:

The Adverse Event reporting was carried out in the Safety Analysis Population. The Pegasys monotherapy arm (n=3) had no deaths or SAEs, and AEs are not reported in consideration of subject re-identification.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Untreated Control Subjects

Reporting group description:

Untreated control subjects were observed up to 80 weeks.

Reporting group title	Peg-IFN-Alfa-2A + Lamivudine or Entecavir

Reporting group description:

Subjects received lamivudine or entecavir alone for 8 weeks followed by peg-IFN-alfa-2A in combination with lamivudine or entecavir for 48 weeks.

Serious adverse events	Untreated Control Subjects	Peg-IFN-Alfa-2A + Lamivudine or Entecavir	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 33 (3.03%)	0 / 26 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Infections and infestations			
PHARYNGITIS			
subjects affected / exposed	1 / 33 (3.03%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	1 / 33 (3.03%)	0 / 26 (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	Untreated Control Subjects	Peg-IFN-Alfa-2A + Lamivudine or Entecavir	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 33 (30.30%)	21 / 26 (80.77%)	
Injury, poisoning and procedural complications			
CONTUSION			
subjects affected / exposed	0 / 33 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	7	
LIMB INJURY			
subjects affected / exposed	0 / 33 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	0 / 33 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	5	
HEADACHE			
subjects affected / exposed	0 / 33 (0.00%)	14 / 26 (53.85%)	
occurrences (all)	0	91	
MIGRAINE			
subjects affected / exposed	0 / 33 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 33 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
FATIGUE			
subjects affected / exposed	0 / 33 (0.00%)	5 / 26 (19.23%)	
occurrences (all)	0	11	
HYPERTHERMIA			
subjects affected / exposed	0 / 33 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	3	
INJECTION SITE BRUISING			
subjects affected / exposed	0 / 33 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
PAIN			

subjects affected / exposed	0 / 33 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	5	
PYREXIA			
subjects affected / exposed	0 / 33 (0.00%)	11 / 26 (42.31%)	
occurrences (all)	0	21	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	2 / 33 (6.06%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	3 / 33 (9.09%)	3 / 26 (11.54%)	
occurrences (all)	3	3	
NAUSEA			
subjects affected / exposed	1 / 33 (3.03%)	4 / 26 (15.38%)	
occurrences (all)	1	5	
VOMITING			
subjects affected / exposed	1 / 33 (3.03%)	3 / 26 (11.54%)	
occurrences (all)	1	4	
Respiratory, thoracic and mediastinal disorders			
EPISTAXIS			
subjects affected / exposed	1 / 33 (3.03%)	3 / 26 (11.54%)	
occurrences (all)	1	8	
Skin and subcutaneous tissue disorders			
ACNE			
subjects affected / exposed	1 / 33 (3.03%)	2 / 26 (7.69%)	
occurrences (all)	1	2	
ALOPECIA			
subjects affected / exposed	0 / 33 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
ECZEMA			
subjects affected / exposed	0 / 33 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 33 (3.03%)	2 / 26 (7.69%)	
occurrences (all)	1	4	

MYALGIA			
subjects affected / exposed	0 / 33 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	5	
Infections and infestations			
GASTROENTERITIS			
subjects affected / exposed	0 / 33 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
INFLUENZA			
subjects affected / exposed	2 / 33 (6.06%)	1 / 26 (3.85%)	
occurrences (all)	2	1	
NASOPHARYNGITIS			
subjects affected / exposed	1 / 33 (3.03%)	3 / 26 (11.54%)	
occurrences (all)	1	3	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 33 (3.03%)	2 / 26 (7.69%)	
occurrences (all)	1	3	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	0 / 33 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 May 2013	Modification of Pegasys dosing categories for alignment across pediatric studies and to conform to the recently approved pediatric dosing regimen for hepatitis C; The hepatitis B virus DNA (HBV-DNA) level required for study inclusion has been corrected; To enhance recruitment and avoid unnecessary exclusion of patient with true chronic hepatitis B (CHB) (positive hepatitis B envelope antibody [HBeAg], positive hepatitis B surface antigen [HBsAg], detectable HBV-DNA), the requirement for negative hepatitis B surface antibody (anti-HBs) and hepatitis B envelope antibody (anti-HBe) has been removed from the inclusion criteria. The diagnostic criteria of CHB does not require measurement of antibodies; The seroconversion stopping rule has been updated to reflect the full seroconversion definition of both HBsAg loss and presence of anti-HBs.
11 July 2013	The Schedule of Assessments have been updated with respect to lactate and tyrosine-methionine-aspartate-aspartate (YMDD). These were originally only included for the Schedule of Assessments for the Pegasys + Lamivudine treatment arm, but it may be difficult to ensure drawing of baseline bloods only after randomization at site. Therefore, these parameters are identical for all patients (regardless of treatment arm), and the YMDD parameter has been moved to screening instead of baseline; Text has been added to reflect the fact that exploratory analyses may be conducted not only to ascertain the presence of YMDD mutations but others as required.
22 August 2013	The NV25361 protocol version numbers and EUDRACT number have been amended. This study was originally an investigator-lead single-center study sponsored by King's College Hospital/King's College London (KCH/KCL) and, as such, already had a EUDRACT number assigned (2006-000977-31). The KCH/KCL protocol underwent four amendments, with the final amendment being Version 5 dated 29 April 2010. Plans were then agreed with KCH/KCL for Roche to become the study sponsor and continue the study as a multi-center study. Roche prepared a protocol amendment, which was numbered Version 1 (2 January 2013) and a new (different) EUDRACT number (2012-005356-42) was assigned. Roche then prepared a subsequent amendment, Version 2 (8 May 2013). However, the original EUDRACT number should have been maintained and the protocol version should have followed on from the latest KCH/KCL protocol version number such that the subsequent versions amended by Roche should have been Versions 6 and 7, respectively, rather than Versions 1 and 2. In the future, the protocol version numbers will continue to follow on sequentially from the KCH/KCL protocol version numbering under the original EUDRACT number assigned at the start of the study (2006-000977-31).

03 February 2014	The Pegasys monotherapy arm has been removed. Concerns regarding the probable low response rates to treatment with Pegasys monotherapy were raised by the study Data Safety Monitoring Board (DSMB) members and potential study investigators during feasibility; Some subjects were recruited into the study under the previous single-site investigator led three-arm study, which included the Pegasys monotherapy arm, and have all now completed their treatment. Text has been included to say that these subjects will roll over into the Roche-sponsor protocol and all data will be reported when the study has been completed. The Pegasys monotherapy schedule of assessments has been updated to include the long-term follow-up period for these subjects; The primary endpoint has been changed from seroconversion to anti-HBs at 1-year post-end of treatment/end of untreated observation to loss of HBsAg at 24 weeks post-end of treatment/end of untreated observation; The secondary endpoints and schedule of assessments have been updated accordingly, and the length of the untreated observation period has been reduced from 100 weeks to 80 weeks to coincide with the earlier primary endpoint; The safety objectives of the study have been updated to clarify that assessment of AEs will include neurological and psychiatric events; For clarity, the efficacy and safety outcome measures have been updated to include the timepoints at which they will be measured; For consistency, AEs of concern have been amended to non-serious AEs of special interest; The diagnosis of CHB is defined as presence of HBsAg for 6 or more months. Hence, the inclusion criterion for positive HBsAg and HBeAg has been changed from more than 1 year to more than 6 months prior to baseline to ensure that eligible subjects diagnosed with CHB within 6-12 months are not unnecessarily excluded. The seroconversion stopping rule has been removed.
26 June 2014	Analysis of anti-drug antibodies (ADAs) has been added as an exploratory objective in order to follow regulatory guidelines for increased level of immunogenicity testing for new indications (EMA 2008 – Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins); The Ministry of Healthcare of the Russian Federation requires completion of efficacy and safety clinical studies with Pegasys in combination with lamivudine in children with Hepatitis B aged 12 to 17 years of age prior to enrollment of children below 12 years of age. Therefore, the age inclusion criterion has been updated, specifically for Russia, to specify that only patients >/= 12 years old can be enrolled in this study; The inclusion criterion regarding informed consent has been updated to clarify that those subjects <18 years of age at baseline who are legally considered to be adults according to national legislation must consent in their own right if required by national legislation. In addition, the informed consent section has been updated to clarify that minors who attain legal adulthood during the course of the study must consent in their own right at that time, if required by national legislation.
31 July 2015	Randomization stratification factor (HBV genotype) has been amended from 'genotype A vs non-A' (2 levels) to 'genotype A vs. B/C vs. D/others' (3 levels) to prevent any potential imbalance of HBV genotype allocation between the 2 randomized arms, since it is expected that reasonable proportions of B,C and D HBV genotypes will be recruited. Sub-analyses from the Pegasys adult immune-active CHB study) have shown different efficacy response according to HBV genotype, with response rates being similar in genotypes B and C; Pegasys dose modification guidance has been updated with recommendations for dosage modification for management of psychiatric disorders as outlined in Table 3 of the Pegasys United States Prescribing Information (USPI) dated March 2015; Assessments on sexual maturation (Tanner staging, date of menarche onset) have been added following an FDA request, and relevant section and the schedule of assessments have been updated accordingly; Pharmacokinetic (PK) sampling has been revised.

15 February 2016	Study treatment has been modified to include entecavir as a nucleoside analogue option for the combination treatment with Pegasys. Prior to randomization investigators will choose between lamivudine or entecavir. Subjects are treated for the 8-week lead-in phase and the subsequent 48-week Pegasys-combination phase with the same nucleoside analogue throughout the study (if applicable); The Ministry of Healthcare of India required the exclusion of younger subjects from this study. Therefore, the age inclusion criterion has been updated, specifically for India, to specify that only subjects >/= 12 years old can be enrolled in this study; The inclusion criterion regarding HBV DNA level has been updated to > 20,000 IU/mL following review of published data and guidelines on the management of hepatitis B of patients with CHB in the immune-tolerant phase as well as following recommendation of Health Authorities that have evaluated this protocol; The primary analysis of the study has been updated to include the new study treatment option, Pegasys + entecavir. Furthermore testing of the primary endpoint has been updated to clarify that it is a superiority test.
26 October 2018	Results from two multicenter clinical trials (sponsored by the National Institutes of Health [NIH]) evaluating the entecavir plus Pegasys treatment regimen in subjects with immune-tolerant chronic hepatitis B (CHB) were made available in October 2017 at the American Association for the Study of Liver Diseases Congress in Washington, USA. These two NIH studies demonstrated minimal to no efficacy of the intervention in both adult and pediatric subject populations with immune-tolerant CHB. Moreover, both studies had a similar design to Study NV25361. The conclusion was that the combination of entecavir with Pegasys, administered for up to 48 weeks, rarely led to loss of hepatitis B envelope antigen with sustained suppression of hepatitis B virus (HBV) DNA levels and was associated with frequent but not serious adverse events. The authors also concluded that more potent and more broadly targeted regimens against HBV are needed to treat children in the immune-tolerant phase of chronic HBV infection. Because of the similar study design, treatment regimen and efficacy assessments compared with these two NIH-sponsored studies, Study NV25361 was not expected to demonstrate efficacy in the target subject population. Based on the results of the NIH pediatric study and following a Pediatric Investigational Plan (PIP) modification procedure, the PDCO agreed in March 2018 to modify the PIP for Pegasys and remove Study NV25361 from the PIP commitments.
26 October 2018	After this decision, the Sponsor terminated recruitment in the study on 28 March 2018 after enrollment of 62 patients (26 patients had been randomized to the active combination treatment, and 3 subjects had been randomized to Pegasys monotherapy before Roche became the study sponsor). This decision to terminate recruitment was also in accordance with the recommendation from the Data Safety Monitoring Board on 22 March 2018 based on the NIH results demonstrating minimal efficacy and a changed benefit-risk assessment. No specific safety concerns were identified in their scheduled review of the study. The protocol for Study NV25361 has been amended because of the expected lack of efficacy of the treatment regimen and the premature termination of recruitment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

In accordance with the recommendation from the DSMB, enrollment was stopped due to low efficacy and a changed benefit risk assessment. Enrolled participants were allowed to complete treatment and were followed up for 1 year after the end of treatment

Notes: