



Clinical trial results:

Assessment of the Safety, Efficacy, Tolerability and Pharmacokinetics of PEG-Intron Plus REBETOL for Pediatric Patients with Chronic Hepatitis C

Summary

EudraCT number	2004-000558-22
Trial protocol	IT ES Outside EU/EEA
Global end of trial date	10 January 2013

Results information

Result version number	v2 (current)
This version publication date	21 February 2016
First version publication date	21 January 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	P02538: Part 2
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00761735
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Protocol Number: P02538: Part 2

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, New Jersey, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-000071-PIP01-07, EMA-000384-PIP01-08
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 January 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 January 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety, efficacy and tolerability of the combination of PEG-Intron plus REBETOL in pediatric subjects with chronic hepatitis C

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 February 2005
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects**Subjects enrolled per country**

Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Spain: 21
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	United States: 32
Country: Number of subjects enrolled	Puerto Rico: 2
Country: Number of subjects enrolled	Argentina: 15
Country: Number of subjects enrolled	Chile: 1
Country: Number of subjects enrolled	France: 11
Worldwide total number of subjects	107
EEA total number of subjects	57

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	67
Adolescents (12-17 years)	40
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The Treatment and Follow-up Period 1 enrolled participants 3 to 17 years old with untreated, chronic hepatitis C virus (HCV) of any genotype. Other inclusion and exclusion criteria applied. The Long-term Follow-up (LTFU) Period 2 enrolled participants who received ≥ 1 dose of study drug and completed the 24-week post-treatment follow-up

Period 1

Period 1 title	Treatment and Follow-up Period 1
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	PEG-Intron plus REBETOL (Treatment and Follow-up Period 1)
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Arm description:

Participants received PEG-Intron (peginterferon alfa-2b, SCH 54031) 60 $\mu\text{g}/\text{m}^2$ subcutaneous injection once weekly plus REBETOL (ribavirin, SCH 18908) 15 mg/kg by mouth daily in two divided doses for 48 weeks for participants with Genotypes 1,4,5,6 and for participants with Genotype 3 with a high viral load ($\geq 600,000$ IU/mL). For participants with Genotype 2, or participants with Genotype 3 with a low viral load ($< 600,000$ IU/mL), the same treatment was given for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Rebetol
Investigational medicinal product code	J05AB04
Other name	Ribavirin, SCH 18908
Pharmaceutical forms	Capsule, Oral solution
Routes of administration	Oral use

Dosage and administration details:

Participants received REBETOL 15 mg/kg by mouth daily in two divided doses for 48 weeks for participants with Genotypes 1,4,5,6 and for participants with Genotype 3 with a high viral load ($\geq 600,000$ IU/mL). For participants with Genotype 2, or participants with Genotype 3 with a low viral load ($< 600,000$ IU/mL), the same treatment was given for 24 weeks.

Investigational medicinal product name	PegIntron
Investigational medicinal product code	L03AB10
Other name	peginterferon alfa-2b, SCH 54031
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received PEG-Intron 60 $\mu\text{g}/\text{m}^2$ by subcutaneous injection once weekly for 48 weeks for participants with Genotypes 1,4,5,6 and for participants with Genotype 3 with a high viral load ($\geq 600,000$ IU/mL). For participants with Genotype 2, or participants with Genotype 3 with a low viral load ($< 600,000$ IU/mL), the same treatment was given for 24 weeks

Number of subjects in period 1	PEG-Intron plus REBETOL (Treatment and Follow-up Period 1)
Started	107
Participants who completed treatment	78 ^[1]
Completed	106
Not completed	1
Did not enter follow-up for unknown reason	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This is the number of participants who completed the treatment regimen. Completion of treatment was not a requirement to complete the Treatment and Follow-up Period 1.

Period 2

Period 2 title	Long-term Follow-up Period 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	PEG-Intron plus REBETOL (Long Term Follow-up Period 2)
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Arm description:

Participants who received ≥ 1 dose of PEG-Intron plus REBETOL and completed the 24-week follow-up in the Treatment and Follow-up Period 1 were eligible to enroll in the 5-year LTFU Period of the study. No study treatment was administered in the LTFU Period 2.

Arm type	Experimental
Investigational medicinal product name	Rebetol
Investigational medicinal product code	J05AB04
Other name	Ribavirin, SCH 18908
Pharmaceutical forms	Capsule, Oral solution
Routes of administration	Oral use

Dosage and administration details:

In the Treatment and Follow-up Period, participants received REBETOL 15 mg/kg by mouth daily in two divided doses for 48 weeks for participants with Genotypes 1,4,5,6 and for participants with Genotype 3 with a high-viral-load ($\geq 600,000$ IU/mL). For participants with Genotype 2, or participants with Genotype 3 with a low-viral-load ($< 600,000$ IU/mL), the same treatment was given for 24 weeks. No study treatment was administered during the LTFU Period.

Investigational medicinal product name	PegIntron
Investigational medicinal product code	L03AB10
Other name	peginterferon alfa-2b, SCH 54031
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

In the Treatment and Follow-up Period, participants received PEG-Intron $60 \mu\text{g}/\text{m}^2$ by subcutaneous injection once weekly for 48 weeks for participants with Genotypes 1,4,5,6 and for participants with Genotype 3 with a high-viral-load ($\geq 600,000$ IU/mL). For participants with Genotype 2, or participants with Genotype 3 with a low-viral-load ($< 600,000$ IU/mL), the same treatment was given for 24 weeks. No study treatment was administered during the LTFU Period.

Number of subjects in period 2^[2]	PEG-Intron plus REBETOL (Long Term Follow-up Period 2)
Started	94
Completed	80
Not completed	14
Consent withdrawn by subject	6
Administrative	1
Lost to follow-up	6
Protocol deviation	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: Enrollment in the LTFU Period 2 was optional. Not all eligible participants enrolled in the LTFU Period 2.

Baseline characteristics

Reporting groups

Reporting group title	PEG-Intron plus REBETOL (Treatment and Follow-up Period 1)
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Reporting group description:

Participants received PEG-Intron (peginterferon alfa-2b, SCH 54031) 60 µg/m² subcutaneous injection once weekly plus REBETOL (ribavirin, SCH 18908) 15 mg/kg by mouth daily in two divided doses for 48 weeks for participants with Genotypes 1,4,5,6 and for participants with Genotype 3 with a high viral load (≥600,000 IU/mL). For participants with Genotype 2, or participants with Genotype 3 with a low viral load (<600,000 IU/mL), the same treatment was given for 24 weeks.

Reporting group values	PEG-Intron plus REBETOL (Treatment and Follow-up Period 1)	Total	
Number of subjects	107	107	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	67	67	
Adolescents (12-17 years)	40	40	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	9.7		
standard deviation	± 4	-	
Gender categorical			
Units: Subjects			
Female	56	56	
Male	51	51	

End points

End points reporting groups

Reporting group title	PEG-Intron plus REBETOL (Treatment and Follow-up Period 1)
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Reporting group description:

Participants received PEG-Intron (peginterferon alfa-2b, SCH 54031) 60 µg/m² subcutaneous injection once weekly plus REBETOL (ribavirin, SCH 18908) 15 mg/kg by mouth daily in two divided doses for 48 weeks for participants with Genotypes 1,4,5,6 and for participants with Genotype 3 with a high viral load (≥600,000 IU/mL). For participants with Genotype 2, or participants with Genotype 3 with a low viral load (<600,000 IU/mL), the same treatment was given for 24 weeks.

Reporting group title	PEG-Intron plus REBETOL (Long Term Follow-up Period 2)
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Reporting group description:

Participants who received ≥1 dose of PEG-Intron plus REBETOL and completed the 24-week follow-up in the Treatment and Follow-up Period 1 were eligible to enroll in the 5-year LTFU Period of the study. No study treatment was administered in the LTFU Period 2.

Subject analysis set title	PEG-Intron plus REBETOL 24 Weeks
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants who received ≥1 dose of PEG-Intron plus REBETOL in the 24-week treatment group and completed the 24-week follow-up in the Treatment and Follow-up Period 1 were eligible to enroll in the 5-year LTFU Period 2 of the study. No study treatment was administered in the LTFU Period 2.

Subject analysis set title	PEG-Intron plus REBETOL 48 weeks
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants who received ≥1 dose of PEG-Intron plus REBETOL in the 48-week treatment group and completed the 24-week follow-up in the Treatment and Follow-up Period 1 were eligible to enroll in the 5-year LTFU Period 2 of the study. No study treatment was administered in the LTFU Period 2.

Subject analysis set title	PEG-Intron plus REBETOL Females
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Female participants who received ≥1 dose of PEG-Intron plus REBETOL and completed the 24-week follow-up in the Treatment and Follow-up Period 1 were eligible to enroll in the 5-year LTFU Period 2 of the study. No study treatment was administered in the LTFU Period 2.

Subject analysis set title	PEG-Intron plus REBETOL Males
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Male participants who received ≥1 dose of PEG-Intron plus REBETOL and completed the 24-week follow-up in the Treatment and Follow-up Period 1 were eligible to enroll in the 5-year LTFU Period 2 of the study. No study treatment was administered in the LTFU Period 2.

Primary: Number of Participants with a Sustained Virologic Response

End point title	Number of Participants with a Sustained Virologic Response ^[1]
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End point description:

Sustained virologic response was defined as undetectable plasma HCV RNA at 24 weeks post-treatment

End point type	Primary
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End point timeframe:

24 weeks after end of treatment (up to 72 weeks)

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: No between-group statistical analysis was conducted for Number of Participants with a Sustained Virologic Response

End point values	PEG-Intron plus REBETOL (Treatment and Follow-up Period 1)			
Subject group type	Reporting group			
Number of subjects analysed	107			
Units: Participants	70			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants Who Relapsed

End point title	Number of Participants Who Relapsed ^[2]
End point description: Relapse was defined as undetectable plasma HCV RNA at the last treatment visit and plasma HCV RNA above the lower limit of quantification at the last follow-up visit in the LTFU Period 2	
End point type	Primary
End point timeframe: End of LTFU Period 2 (5 years)	
Notes: [2] - 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: No statistical analysis was conducted for Number of Participants who Relapsed	

End point values	PEG-Intron plus REBETOL (Long Term Follow-up Period 2)			
Subject group type	Reporting group			
Number of subjects analysed	54 ^[3]			
Units: Participants	0			

Notes:
[3] - Participants with sustained virologic response at the last treatment visit and completing LTFU

Statistical analyses

No statistical analyses for this end point

Primary: Mean Height Percentile

End point title	Mean Height Percentile ^[4]
End point description: To determine long-term effects of treatment on height, changes in height during LTFU Period 2 were evaluated using height percentiles based on 2000 Centers for Disease Control growth charts for the general population	
End point type	Primary
End point timeframe: Treatment and Follow-up Period 1: pre-treatment baseline; LTFU Period 2: year 1, year 2, year 3, year 4, year 5, and last available visit up to year 5	

Notes:

[4] - 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: No statistical analysis was conducted for Mean Height Percentile

End point values	PEG-Intron plus REBETOL 24 Weeks	PEG-Intron plus REBETOL 48 weeks		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	48		
Units: Percentile of participants				
arithmetic mean (standard deviation)				
Pre-treatment baseline	48.94 (± 27.38)	52.5 (± 29.98)		
Year 1 (N=40, 44)	49.21 (± 29.03)	43.37 (± 27.87)		
Year 2 (N=39, 39)	50.56 (± 29.18)	46.24 (± 29.19)		
Year 3 (N=39, 44)	48.05 (± 28.38)	46 (± 28.24)		
Year 4 (N=40, 38)	49.62 (± 30.87)	45.27 (± 29.44)		
Year 5 (N=38, 42)	47.61 (± 29.57)	43.51 (± 27.57)		
Last available visit (N=46, 48)	45.96 (± 30.45)	43.56 (± 27.19)		

Statistical analyses

No statistical analyses for this end point

Primary: Mean Weight Percentile

End point title	Mean Weight Percentile ^[5]
End point description: To determine long-term effects of treatment on weight, changes in weight during LTFU Period 2 were evaluated using weight percentiles based on the 2000 Centers for Disease Control growth charts for the general population	
End point type	Primary
End point timeframe: Treatment and Follow-up Period 1: pre-treatment baseline; LTFU Period 2: year 1, year 2, year 3, year 4, year 5, and last available visit up to year 5	

Notes:

[5] - 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: No statistical analysis was conducted for Mean Weight Percentile

End point values	PEG-Intron plus REBETOL 24 Weeks	PEG-Intron plus REBETOL 48 weeks		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	48		
Units: Percentile of participants				
arithmetic mean (standard deviation)				
Pre-treatment baseline	52.5 (± 26.83)	58.56 (± 30.56)		

Year 1 (N=40, 44)	53.62 (± 26.75)	56.38 (± 30.55)		
Year 2 (N=39, 39)	51.73 (± 26.89)	52.03 (± 30.47)		
Year 3 (N=39, 44)	53.18 (± 29.12)	54.26 (± 30.37)		
Year 4 (N=40, 38)	51.75 (± 28.9)	49.5 (± 30.37)		
Year 5 (N=38, 42)	51.16 (± 27.16)	53.12 (± 31.38)		
Last available visit (N=46, 48)	50.15 (± 28.44)	55.53 (± 30.67)		

Statistical analyses

No statistical analyses for this end point

Primary: Mean Body Mass Index Percentile

End point title	Mean Body Mass Index Percentile ^[6]
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End point description:

To determine long-term effects of treatment on Body Mass Index (BMI), changes in BMI during LTFU Period 2 were evaluated using BMI percentiles base on 2000 Centers for Disease Control growth charts for the general population

End point type	Primary
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End point timeframe:

Treatment and Follow-up Period 1: pre-treatment baseline; LTFU Period): year 1, year 2, year 3, year 4, year 5, and last available visit up to year 5

Notes:

[6] - 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: No statistical analysis was conducted for Mean Body Mass Index Percentile

End point values	PEG-Intron plus REBETOL 24 Weeks	PEG-Intron plus REBETOL 48 weeks		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	48		
Units: Percentile of participants				
arithmetic mean (standard deviation)				
Pre-treatment baseline	50.4 (± 29.63)	59.76 (± 31.52)		
Year 1 (N=40, 44)	51.15 (± 30.27)	59.91 (± 31.55)		
Year 2 (N=39, 39)	48.11 (± 29.59)	52.89 (± 30.82)		
Year 3 (N=39, 44)	52.14 (± 31)	54.96 (± 30.89)		
Year 4 (N=40, 38)	48.44 (± 30.46)	48.69 (± 31.52)		
Year 5 (N=38, 42)	48.61 (± 29.72)	52.34 (± 31.87)		
Last available visit (N=46, 48)	48.79 (± 29.4)	55.38 (± 31.48)		

Statistical analyses

No statistical analyses for this end point

Primary: Mean Age at Attained Tanner Stage

End point title	Mean Age at Attained Tanner Stage ^[7]
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End point description:

The Tanner Stage (TS) defines physical measurements of sexual development based on external primary and secondary sex characteristics. Female participants were evaluated for breast development and pubic hair distribution and male participants were evaluated for genital development and pubic hair distribution based on a 5-stage ordinal scale ranging from TS 1 (prepubertal/preadolescent characteristics) to TS 5 (mature or adult characteristics). Mean ages for attaining each TS in the normal population have been previously established based on measuring correlating reproductive hormone levels, and are expressed in years as follows for females (F) and males (M): TS 1= 7.1 (F+M); TS 2= 10.5 (F), 12.1 (M); TS 3= 11.6 (F), 13.6 (M); TS 4=, 12.3 (F), 15.1 (M); TS 5= 14.5 (F), 18 (M). To assess sexual maturation at the end of Period 2 long-term follow-up (last observation), females and males were staged and the mean age at each TS attained was reported.

End point type	Primary
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End point timeframe:

Last observation during LTFU Period 2 (up to 5 years)

Notes:

[7] - 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: No statistical analysis was conducted for Mean Age at Attained Tanner Stage

End point values	PEG-Intron plus REBETOL Females	PEG-Intron plus REBETOL Males		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	41 ^[8]	42 ^[9]		
Units: Years				
arithmetic mean (standard deviation)				
Tanner Stage 1 (N=4, 5)	9.75 (± 1.13)	11 (± 0.8)		
Tanner Stage 2 (N=5, 3)	11.86 (± 0.78)	12.53 (± 1.27)		
Tanner Stage 3 (N=7, 1)	15.26 (± 4.64)	13.6 (± 0)		
Tanner Stage 4 (N=4, 6)	16 (± 4.31)	14.75 (± 1.47)		
Tanner Stage 5 (N=21, 27)	17.37 (± 2.71)	19.18 (± 2.48)		

Notes:

[8] - Participants with a non-missing Tanner Stage at the last observation

[9] - Participants with a non-missing Tanner Stage at the last observation

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious AEs: Beginning of Screening to the end of the LTFU Period 2 (up to 336 weeks) Non-serious AEs: Day 1 to the end of Treatment and Follow-up Period 1 (up to 72 weeks). Non-serious AEs were not collected in the LTFU Period 2.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	PEG-Intron plus REBETOL
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Reporting group description:

Participants received PEG-Intron (peginterferon alfa-2b, SCH 54031) 60 µg/m² subcutaneous injection once weekly plus REBETOL (ribavirin, SCH 18908) 15 mg/kg by mouth daily in two divided doses for 48 weeks for participants with Genotypes 1,4,5,6 and for participants with Genotype 3 with a high-viral-load (≥600,000 IU/mL). For participants with Genotype 2, or participants with Genotype 3 with a low-viral-load (<600,000 IU/mL), the same treatment was given for 24 weeks.

Serious adverse events	PEG-Intron plus REBETOL		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 107 (5.61%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Carbon monoxide poisoning			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Talipes			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 107 (0.93%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	2 / 107 (1.87%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	PEG-Intron plus REBETOL		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	107 / 107 (100.00%)		
Investigations			
Blood thyroid stimulating hormone increased			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	9		
Weight decreased			
subjects affected / exposed	20 / 107 (18.69%)		
occurrences (all)	29		
Nervous system disorders			
Headache			
subjects affected / exposed	71 / 107 (66.36%)		
occurrences (all)	410		
Dizziness			
subjects affected / exposed	15 / 107 (14.02%)		
occurrences (all)	25		

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	86 / 107 (80.37%)		
occurrences (all)	617		
Asthenia			
subjects affected / exposed	16 / 107 (14.95%)		
occurrences (all)	40		
Chills			
subjects affected / exposed	23 / 107 (21.50%)		
occurrences (all)	58		
Fatigue			
subjects affected / exposed	32 / 107 (29.91%)		
occurrences (all)	125		
Influenza like illness			
subjects affected / exposed	10 / 107 (9.35%)		
occurrences (all)	51		
Injection site erythema			
subjects affected / exposed	31 / 107 (28.97%)		
occurrences (all)	50		
Irritability			
subjects affected / exposed	16 / 107 (14.95%)		
occurrences (all)	42		
Malaise			
subjects affected / exposed	10 / 107 (9.35%)		
occurrences (all)	24		
Pain			
subjects affected / exposed	10 / 107 (9.35%)		
occurrences (all)	20		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 107 (11.21%)		
occurrences (all)	20		
Leukopenia			
subjects affected / exposed	11 / 107 (10.28%)		
occurrences (all)	15		
Lymphadenopathy			

subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	10 / 107 (9.35%) 14 35 / 107 (32.71%) 61		
Eye disorders Eye pain subjects affected / exposed occurrences (all)	6 / 107 (5.61%) 7		
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Aphthous stomatitis subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	15 / 107 (14.02%) 24 28 / 107 (26.17%) 58 6 / 107 (5.61%) 12 16 / 107 (14.95%) 20 22 / 107 (20.56%) 41 36 / 107 (33.64%) 76		
Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Oropharyngeal pain	7 / 107 (6.54%) 10 24 / 107 (22.43%) 31		

subjects affected / exposed occurrences (all)	15 / 107 (14.02%) 20		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	6		
Alopecia			
subjects affected / exposed	19 / 107 (17.76%)		
occurrences (all)	21		
Dry skin			
subjects affected / exposed	15 / 107 (14.02%)		
occurrences (all)	19		
Eczema			
subjects affected / exposed	8 / 107 (7.48%)		
occurrences (all)	9		
Erythema			
subjects affected / exposed	8 / 107 (7.48%)		
occurrences (all)	9		
Rash			
subjects affected / exposed	8 / 107 (7.48%)		
occurrences (all)	14		
Psychiatric disorders			
Nervousness			
subjects affected / exposed	9 / 107 (8.41%)		
occurrences (all)	9		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	18 / 107 (16.82%)		
occurrences (all)	70		
Back pain			
subjects affected / exposed	8 / 107 (7.48%)		
occurrences (all)	13		
Myalgia			
subjects affected / exposed	20 / 107 (18.69%)		
occurrences (all)	100		
Pain in extremity			

subjects affected / exposed occurrences (all)	11 / 107 (10.28%) 28		
Infections and infestations			
Pharyngitis			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	7		
Nasopharyngitis			
subjects affected / exposed	11 / 107 (10.28%)		
occurrences (all)	15		
Pharyngitis streptococcal			
subjects affected / exposed	6 / 107 (5.61%)		
occurrences (all)	6		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	54 / 107 (50.47%)		
occurrences (all)	75		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported