



Clinical trial results:

A Randomized, Open-Labelled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 and ABT-333 Co-administered with Ribavirin Compared to Telaprevir Co-administered with Pegylated Interferon -2a and Ribavirin in Treatment-Experienced Adults with Chronic Hepatitis C Genotype 1 Virus Infection (MALACHITE II)

Summary

EudraCT number	2012-003738-18
Trial protocol	HU FI SK PL
Global end of trial date	20 July 2015

Results information

Result version number	v1 (current)
This version publication date	29 July 2016
First version publication date	29 July 2016

Trial information

Trial identification

Sponsor protocol code	M13-862
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01854528
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	Abbott House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6 4XE
Public contact	Global Medical Information, AbbVie, 001 800-633-9110,
Scientific contact	Yan Luo, MD, PhD, AbbVie, yan.luo@abbvie.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?	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	20 July 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the efficacy (the percentage of subjects achieving 12-week sustained virologic response, SVR12, [HCV RNA < LLOQ 12 weeks post-treatment]) and safety of ABT-450/r/ABT-267 and ABT-333 co-administered with RBV for 12 weeks compared to 12 weeks of treatment with telaprevir and pegIFN/RBV followed by either 12 weeks or 36 weeks of pegIFN/RBV, per local prescribing information, in treatment-experienced HCV genotype 1-infected adults.

Protection of trial subjects:

Subject read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 34
Country: Number of subjects enrolled	Slovakia: 15
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	Hungary: 17
Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Australia: 20
Country: Number of subjects enrolled	Chile: 9
Country: Number of subjects enrolled	Romania: 57
Worldwide total number of subjects	154
EEA total number of subjects	124

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	152
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 154 subjects were randomized: 6 subjects did not receive at least 1 dose of study drug and were excluded from the analyses; 148 subjects received at least 1 dose and were included in the intent-to-treat (ITT) population.

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	3-DAA/RBV

Arm description:

3-DAA (ABT-450/r/ABT-267 [150 mg/ 100 mg/ 25 mg once daily] and ABT-333 [250 mg twice daily]) plus weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	ABT-450/r/ABT-267
Investigational medicinal product code	
Other name	ABT-267 also known as ombitasvir, ABT-450 also known as paritaprevir, Viekirax
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-450 (150 mg) coformulated with ritonavir (100 mg) and ABT-267 (25 mg) administered once daily

Investigational medicinal product name	ABT-333
Investigational medicinal product code	
Other name	dasabuvir, Exviera
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ABT-333 250 mg administered twice daily

Investigational medicinal product name	Ribivarin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

weight-based ribivarin administered twice daily

Arm title	TPV/RBV
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Arm description:

TPV (750 mg every 8 hours) coadministered with pegIFN (180 micrograms subcutaneously [SC] weekly) and weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks, followed by pegIFN (180 micrograms SC weekly) and weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for either 12 or 36 weeks, per local prescribing information.

Arm type	Active comparator
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Investigational medicinal product name	Pegylated Interferon a-2a (PegINF)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use
Dosage and administration details: PegINF 180 mcg administered weekly	
Investigational medicinal product name	Telaprevir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: telepravir 750 mg administered every 8 hours.	
Investigational medicinal product name	Ribivarin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: weight-based ribivarin administered twice daily	

Number of subjects in period 1^[1]	3-DAA/RBV	TPV/RBV
Started	101	47
Completed	101	32
Not completed	0	15
Virologic failure	-	9
Adverse event	-	4
Withdrawal by subject	-	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: A total of 154 subjects were randomized: 6 subjects did not receive at least 1 dose of study drug and were excluded from the analyses; 148 subjects received at least 1 dose and were included in the intent-to-treat (ITT) population.

Baseline characteristics

Reporting groups

Reporting group title	3-DAA/RBV
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Reporting group description:

3-DAA (ABT-450/r/ABT-267 [150 mg/ 100 mg/ 25 mg once daily] and ABT-333 [250 mg twice daily]) plus weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks.

Reporting group title	TPV/RBV
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Reporting group description:

TPV (750 mg every 8 hours) coadministered with pegIFN (180 micrograms subcutaneously [SC] weekly) and weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks, followed by pegIFN (180 micrograms SC weekly) and weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for either 12 or 36 weeks, per local prescribing information.

Reporting group values	3-DAA/RBV	TPV/RBV	Total
Number of subjects	101	47	148
Age categorical			
Units: Subjects			

Age continuous			
All randomized subjects who received at least 1 dose of study drug (ITT population) were included in baseline analysis population.			
Units: years			
arithmetic mean	46.9	45	
standard deviation	± 12.15	± 10.35	-
Gender categorical			
All randomized subjects who received at least 1 dose of study drug (ITT population) were included in baseline analysis population.			
Units: Subjects			
Female	46	19	65
Male	55	28	83

End points

End points reporting groups

Reporting group title	3-DAA/RBV
Reporting group description: 3-DAA (ABT-450/r/ABT-267 [150 mg/ 100 mg/ 25 mg once daily] and ABT-333 [250 mg twice daily]) plus weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks.	
Reporting group title	TPV/RBV
Reporting group description: TPV (750 mg every 8 hours) coadministered with pegIFN (180 micrograms subcutaneously [SC] weekly) and weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks, followed by pegIFN (180 micrograms SC weekly) and weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for either 12 or 36 weeks, per local prescribing information.	

Primary: Percentage of Subjects With Sustained Virologic Response 12 Weeks After Treatment

End point title	Percentage of Subjects With Sustained Virologic Response 12 Weeks After Treatment
End point description: The percentage of subjects with sustained virologic response (plasma Hepatitis C virus ribonucleic acid [HCV RNA] level less than the lower limit of quantitation [$< \text{LLOQ}$]) 12 weeks after the last dose of study drug. The LLOQ for the assay was 25 IU/mL.	
End point type	Primary
End point timeframe: 12 weeks after the last dose of study drug	

End point values	3-DAA/RBV	TPV/RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101 ^[1]	47 ^[2]		
Units: percentage of subjects				
number (not applicable)	100	66		

Notes:

[1] - ITT population: All randomized subjects who received at least 1 dose of study drug.

[2] - ITT population: All randomized subjects who received at least 1 dose of study drug.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: P-value for the difference in sustained virologic response rates 12 weeks after the last dose between treatment groups with HCV subgenotype (1a, non-1a) from stratum adjusted Mantel-Haenszel with previous type of response to pegIFN/RBV treatment (relapser, partial or null responder) as strata.	
Comparison groups	3-DAA/RBV v TPV/RBV

Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Stratum adjusted Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	34.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	21.09
upper limit	47.42

Secondary: Mean Change From Baseline to Final Treatment Visit in the Mental Component Summary (MCS) Score of the Short-Form 36 Health Survey - Version 2 (SF-36v2)

End point title	Mean Change From Baseline to Final Treatment Visit in the Mental Component Summary (MCS) Score of the Short-Form 36 Health Survey - Version 2 (SF-36v2)
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End point description:

The SF-36v2 is a general health-related quality of life (HRQoL) instrument with extensive use in multiple disease states. The SF-36v2 instrument comprises a total of 36 items (questions) targeting a subject's functional health and well-being in 8 domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health). Domain scores were aggregated into an MCS score (from 0 to 100; a higher score indicates better mental function and well-being).

End point type	Secondary
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End point timeframe:

Baseline and Final Treatment Visit (up to Week 12 for 3-DAA/RBV and up to Week 24 or 48 for TPV/RBV)

End point values	3-DAA/RBV	TPV/RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101 ^[3]	45 ^[4]		
Units: units on a scale				
arithmetic mean (standard deviation)	-1.3 (± 8.32)	-9.8 (± 11.05)		

Notes:

[3] - All subjects in the ITT population with evaluable data

[4] - All subjects in the ITT population with evaluable data

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

P-value from ANCOVA model including baseline score and region as covariates and treatment arm as a factor.

Comparison groups	3-DAA/RBV v TPV/RBV
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Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	8.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.43
upper limit	11.85

Secondary: Mean Change From Baseline to Final Treatment Visit in the Physical Component Summary (PCS) Score of the Short-Form 36 Health Survey - Version 2 (SF-36v2)

End point title	Mean Change From Baseline to Final Treatment Visit in the Physical Component Summary (PCS) Score of the Short-Form 36 Health Survey - Version 2 (SF-36v2)
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End point description:

The SF-36v2 is a general health-related quality of life (HRQoL) instrument with extensive use in multiple disease states. The SF-36v2 instrument comprises a total of 36 items (questions) targeting a subject's functional health and well-being in 8 domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health). Domain scores were aggregated into a PCS score (range = 0 to 100; a higher score indicates better mental function and well-being).

End point type	Secondary
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End point timeframe:

Baseline and Final Treatment Visit (up to Week 12 for 3-DAA/RBV and up to Week 24 or 48 for TPV/RBV)

End point values	3-DAA/RBV	TPV/RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101 ^[5]	45 ^[6]		
Units: units of a scale				
arithmetic mean (standard deviation)	0.4 (± 7.16)	-7.7 (± 7.72)		

Notes:

[5] - All subjects in the ITT population with evaluable data

[6] - All subjects in the ITT population with evaluable data

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

P-value from ANCOVA model including baseline score and region as covariates and treatment arm as a factor.

Comparison groups	3-DAA/RBV v TPV/RBV
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Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	7.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.11
upper limit	9.98

Secondary: Percentage of Subjects With Sustained Virologic Response 24 Weeks After Treatment

End point title	Percentage of Subjects With Sustained Virologic Response 24 Weeks After Treatment
End point description:	
The percentage of subjects with sustained virologic response (plasma Hepatitis C virus ribonucleic acid [HCV RNA] level less than the lower limit of quantitation [< LLOQ]) 24 weeks after the last dose of study drug. The LLOQ for the assay was 25 IU/mL.	
End point type	Secondary
End point timeframe:	
24 weeks after the last dose of study drug	

End point values	3-DAA/RBV	TPV/RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101 ^[7]	47 ^[8]		
Units: percentage of subjects				
number (not applicable)	99	66		

Notes:

[7] - All subjects in the ITT population with evaluable data

[8] - All subjects in the ITT population with evaluable data

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
P-value from logistic regression model including treatment arm, baseline log ₁₀ HCV RNA level, HCV subgenotype, and previous response to pegIFN/RBV treatment as predictors.	
Comparison groups	3-DAA/RBV v TPV/RBV
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	54.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	6.9
upper limit	435.1

Secondary: Percentage of Subjects With Virologic Failure During Treatment

End point title	Percentage of Subjects With Virologic Failure During Treatment
End point description: Virologic failure during treatment was defined as HCV ribonucleic acid (RNA) confirmed greater than or equal to the lower limit of quantification (\geq LLOQ) after HCV RNA < LLOQ during treatment or confirmed HCV RNA \geq LLOQ at the end of treatment.	
End point type	Secondary
End point timeframe: Baseline to end of treatment (12 weeks for 3-DAA/RBV and 24 or 48 weeks for TPV/RBV)	

End point values	3-DAA/RBV	TPV/RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101 ^[9]	47 ^[10]		
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 3.7)	19.1 (7.9 to 30.4)		

Notes:

[9] - ITT population

[10] - ITT population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Virologic Relapse After Treatment

End point title	Percentage of Subjects With Virologic Relapse After Treatment
End point description: Subjects who completed treatment with plasma HCV RNA less than the lower limit of quantification (<LLOQ) at the end of treatment were considered to have virologic relapse if they had confirmed HCV RNA \geq LLOQ during the posttreatment period.	
End point type	Secondary
End point timeframe: Between end of treatment (Week 12 for 3-DAA/RBV and Week 24 or 48 for TPV/RBV) and Post-treatment (up to Week 12 Post-treatment)	

End point values	3-DAA/RBV	TPV/RBV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101 ^[11]	47 ^[12]		
Units: percentage of subjects				
number (confidence interval 95%)	0 (0 to 3.7)	6.3 (0 to 14.6)		

Notes:

[11] - ITT population

[12] - ITT population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were collected from the time of study drug administration to 30 days after last dose of study drug (up to 52 weeks); SAEs were also collected from the time that informed consent was obtained until the end of the study (total up to 101 weeks).

Adverse event reporting additional description:

AEs were collected from first dose to 30 days after last dose (16 weeks for 12-week treatment, 28 weeks for 24-week treatment, 52 weeks for 48-week treatment); SAEs were collected from the time that informed consent was obtained to end of study (up to 65 weeks for 12-week treatment, 77 weeks for 24-week treatment, 101 weeks for 48-week treatment).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	3-DAA/RBV
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Reporting group description:

3-DAA (ABT-450/r/ABT-267 [150 mg/ 100 mg/ 25 mg once daily] and ABT-333 [250 mg twice daily]) plus weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks.

Reporting group title	TPV/RBV
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Reporting group description:

TPV (750 mg every 8 hours) coadministered with pegIFN (180 micrograms subcutaneously [SC] weekly) and weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for 12 weeks, followed by pegIFN (180 micrograms SC weekly) and weight-based RBV (dosed 1,000 or 1,200 mg daily divided twice a day) for either 12 or 36 weeks, per local prescribing information.

Serious adverse events	3-DAA/RBV	TPV/RBV	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 101 (0.99%)	5 / 47 (10.64%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Nervous system disorders			
Epilepsy			
subjects affected / exposed	1 / 101 (0.99%)	0 / 47 (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			
Anaemia			
subjects affected / exposed	0 / 101 (0.00%)	2 / 47 (4.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Injection site phlebitis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 101 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 101 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 47 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 101 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 47 (2.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	3-DAA/RBV	TPV/RBV	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	54 / 101 (53.47%)	43 / 47 (91.49%)	
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	5 / 101 (4.95%) 5	7 / 47 (14.89%) 8	
Dysgeusia subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1	4 / 47 (8.51%) 4	
Headache subjects affected / exposed occurrences (all)	29 / 101 (28.71%) 34	21 / 47 (44.68%) 23	
Lethargy subjects affected / exposed occurrences (all)	5 / 101 (4.95%) 5	3 / 47 (6.38%) 3	
Paraesthesia subjects affected / exposed occurrences (all)	0 / 101 (0.00%) 0	3 / 47 (6.38%) 3	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	3 / 101 (2.97%) 5	14 / 47 (29.79%) 20	
Leukopenia subjects affected / exposed occurrences (all)	0 / 101 (0.00%) 0	5 / 47 (10.64%) 12	
Neutropenia subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1	12 / 47 (25.53%) 24	
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 101 (0.00%) 0	4 / 47 (8.51%) 4	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	8 / 101 (7.92%) 8	16 / 47 (34.04%) 16	
Chest pain subjects affected / exposed occurrences (all)	0 / 101 (0.00%) 0	3 / 47 (6.38%) 3	
Chills			

subjects affected / exposed	3 / 101 (2.97%)	5 / 47 (10.64%)	
occurrences (all)	3	6	
Fatigue			
subjects affected / exposed	12 / 101 (11.88%)	12 / 47 (25.53%)	
occurrences (all)	14	13	
General physical health deterioration			
subjects affected / exposed	0 / 101 (0.00%)	3 / 47 (6.38%)	
occurrences (all)	0	3	
influenza like illness			
subjects affected / exposed	0 / 101 (0.00%)	4 / 47 (8.51%)	
occurrences (all)	0	5	
Injection site erythema			
subjects affected / exposed	0 / 101 (0.00%)	3 / 47 (6.38%)	
occurrences (all)	0	3	
Pyrexia			
subjects affected / exposed	2 / 101 (1.98%)	15 / 47 (31.91%)	
occurrences (all)	2	19	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 101 (2.97%)	4 / 47 (8.51%)	
occurrences (all)	3	4	
Abdominal pain upper			
subjects affected / exposed	3 / 101 (2.97%)	4 / 47 (8.51%)	
occurrences (all)	3	4	
Anal pruritus			
subjects affected / exposed	0 / 101 (0.00%)	12 / 47 (25.53%)	
occurrences (all)	0	12	
Aphthous stomatitis			
subjects affected / exposed	0 / 101 (0.00%)	3 / 47 (6.38%)	
occurrences (all)	0	4	
Haemorrhoids			
subjects affected / exposed	0 / 101 (0.00%)	3 / 47 (6.38%)	
occurrences (all)	0	4	
Nausea			
subjects affected / exposed	10 / 101 (9.90%)	20 / 47 (42.55%)	
occurrences (all)	11	22	

Vomiting subjects affected / exposed occurrences (all)	3 / 101 (2.97%) 3	7 / 47 (14.89%) 8	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	7 / 101 (6.93%) 8 1 / 101 (0.99%) 1	12 / 47 (25.53%) 16 3 / 47 (6.38%) 3	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Eczema subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Pruritus generalised subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	0 / 101 (0.00%) 0 0 / 101 (0.00%) 0 0 / 101 (0.00%) 0 13 / 101 (12.87%) 19 0 / 101 (0.00%) 0 3 / 101 (2.97%) 4	6 / 47 (12.77%) 6 7 / 47 (14.89%) 7 3 / 47 (6.38%) 3 19 / 47 (40.43%) 21 3 / 47 (6.38%) 3 12 / 47 (25.53%) 15	
Psychiatric disorders Depressed mood subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all)	0 / 101 (0.00%) 0 0 / 101 (0.00%) 0	3 / 47 (6.38%) 3 3 / 47 (6.38%) 3	

Insomnia subjects affected / exposed occurrences (all)	6 / 101 (5.94%) 6	10 / 47 (21.28%) 10	
Irritability subjects affected / exposed occurrences (all)	2 / 101 (1.98%) 2	5 / 47 (10.64%) 5	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	3 / 101 (2.97%) 3	8 / 47 (17.02%) 10	
Muscle spasms subjects affected / exposed occurrences (all)	2 / 101 (1.98%) 2	3 / 47 (6.38%) 3	
Myalgia subjects affected / exposed occurrences (all)	3 / 101 (2.97%) 3	9 / 47 (19.15%) 14	
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all)	2 / 101 (1.98%) 2	3 / 47 (6.38%) 3	
Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 101 (4.95%) 5	5 / 47 (10.64%) 9	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	3 / 101 (2.97%) 3	8 / 47 (17.02%) 8	
Hypertriglyceridaemia subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1	3 / 47 (6.38%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 December 2012	The purpose of this amendment was to clarify the definition of relapser and study activities and procedures.
10 April 2013	The purpose of this amendment was to prohibit the use of hormonal contraceptives during study drug administration.
18 June 2013	The purpose of this amendment was to adjust the stratification proportion of genotype 1a versus non-1a subjects, clarify re-screening criteria, allow enrollment of subjects with a borderline pregnancy test result under certain circumstances, and allow appropriate use of over-the-counter and prescription medication.
30 October 2013	The purpose of this amendment was to adjust the stratification proportion of genotype 1a versus non-1a subjects and include the option of conducting certain visits in the home.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported