



Clinical trial results:

A Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Vemurafenib (RO5185426) Adjuvant Therapy in Patients with Surgically Resected, Cutaneous BRAF-Mutant Melanoma at High Risk for Recurrence

Summary

EudraCT number	2011-004011-24
Trial protocol	GB AT SE CZ DE FR BE IT ES NL EE PT IE PL
Global end of trial date	13 July 2018

Results information

Result version number	v2 (current)
This version publication date	27 July 2019
First version publication date	21 June 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	GO27826
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01667419
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?	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	13 July 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	13 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of vemurafenib adjuvant treatment administered over a 52-week period in subjects with completely resected BRAF V600 mutation–positive, cutaneous melanoma, as measured by disease-free survival (DFS).

Protection of trial subjects:

Subjects (or legally authorized representative) were required to read and sign an informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 September 2012
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?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 42
Country: Number of subjects enrolled	Brazil: 9
Country: Number of subjects enrolled	South Africa: 9
Country: Number of subjects enrolled	Argentina: 2
Country: Number of subjects enrolled	United States: 51
Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	Italy: 93
Country: Number of subjects enrolled	United Kingdom: 41
Country: Number of subjects enrolled	Russian Federation: 39
Country: Number of subjects enrolled	France: 26
Country: Number of subjects enrolled	Poland: 20
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	Ukraine: 18
Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	Czech Republic: 16
Country: Number of subjects enrolled	Israel: 15
Country: Number of subjects enrolled	Serbia: 15
Country: Number of subjects enrolled	Germany: 12

Country: Number of subjects enrolled	Ireland: 9
Country: Number of subjects enrolled	Croatia: 7
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Estonia: 2
Country: Number of subjects enrolled	Switzerland: 1
Worldwide total number of subjects	498
EEA total number of subjects	277

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	424
From 65 to 84 years	74
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Adult subjects with completely resected, BRAF V600 mutation-positive melanoma were included in this study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 Vemurafenib

Arm description:

Subjects with completely resected Stage IIC, IIIA, or IIIB cutaneous melanoma) received vemurafenib, 960 milligrams (mg) twice daily, in 28-day cycles, for up to 52 weeks

Arm type	Experimental
Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects with completely resected Stage IIC, IIIA, or IIIB cutaneous melanoma) received vemurafenib, 960 mg twice daily, in 28-day cycles, for up to 52 weeks.

Arm title	Cohort 1 Placebo
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Arm description:

Subjects with completely resected Stage IIC, IIIA, or IIIB cutaneous melanoma) received vemurafenib-matching placebo twice daily, in 28-day cycles, for up to 52 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects with completely resected Stage IIC, IIIA, or IIIB cutaneous melanoma) received vemurafenib-matching placebo twice daily, in 28-day cycles, for up to 52 weeks.

Arm title	Cohort 2 Vemurafenib
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Arm description:

Subjects with Stage IIIC cutaneous melanoma received vemurafenib, 960 mg twice daily, in 28-day cycles, for up to 52 weeks

Arm type	Experimental
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Investigational medicinal product name	Vemurafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects with Stage IIIC cutaneous melanoma received vemurafenib, 960 mg twice daily, in 28-day cycles, for up to 52 weeks.

Arm title	Cohort 2 Placebo
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Arm description:

Subjects with Stage IIIC cutaneous melanoma received vemurafenib-matching placebo twice daily, in 28-day cycles, for up to 52 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects with Stage IIIC cutaneous melanoma received vemurafenib-matching placebo twice daily, in 28-day cycles, for up to 52 weeks.

Number of subjects in period 1	Cohort 1 Vemurafenib	Cohort 1 Placebo	Cohort 2 Vemurafenib
Started	157	157	93
Completed	114	110	57
Not completed	43	47	36
Adverse event, serious fatal	18	33	25
Consent withdrawn by subject	16	8	9
Reason Not Specified	1	-	-
Non-compliance	-	-	-
Lost to follow-up	7	6	2
Protocol deviation	1	-	-

Number of subjects in period 1	Cohort 2 Placebo
Started	91
Completed	52
Not completed	39
Adverse event, serious fatal	26
Consent withdrawn by subject	8
Reason Not Specified	-
Non-compliance	1
Lost to follow-up	4
Protocol deviation	-

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1 Vemurafenib
Reporting group description: Subjects with completely resected Stage IIC, IIIA, or IIIB cutaneous melanoma) received vemurafenib, 960 milligrams (mg) twice daily, in 28-day cycles, for up to 52 weeks	
Reporting group title	Cohort 1 Placebo
Reporting group description: Subjects with completely resected Stage IIC, IIIA, or IIIB cutaneous melanoma) received vemurafenib-matching placebo twice daily, in 28-day cycles, for up to 52 weeks	
Reporting group title	Cohort 2 Vemurafenib
Reporting group description: Subjects with Stage IIIC cutaneous melanoma received vemurafenib, 960 mg twice daily, in 28-day cycles, for up to 52 weeks	
Reporting group title	Cohort 2 Placebo
Reporting group description: Subjects with Stage IIIC cutaneous melanoma received vemurafenib-matching placebo twice daily, in 28-day cycles, for up to 52 weeks	

Reporting group values	Cohort 1 Vemurafenib	Cohort 1 Placebo	Cohort 2 Vemurafenib
Number of subjects	157	157	93
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean	50.7	49.6	51.6
standard deviation	± 12.4	± 12.7	± 14.1
Sex: Female, Male			
Units: Subjects			
Female	73	69	41
Male	84	88	52
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	12	2	8
Not Hispanic or Latino	138	148	79
Unknown or Not Reported	7	7	6
Race/Ethnicity, Customized			
Units: Subjects			
White	150	150	84
Other	1	2	1
Multiple	0	0	1
Unknown	6	5	7

Reporting group values	Cohort 2 Placebo	Total	
Number of subjects	91	498	

Age categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	49.1 ± 12.9	-	
Sex: Female, Male Units: Subjects			
Female	32	215	
Male	59	283	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	3	25	
Not Hispanic or Latino	80	445	
Unknown or Not Reported	8	28	
Race/Ethnicity, Customized Units: Subjects			
White	81	465	
Other	2	6	
Multiple	0	1	
Unknown	8	26	

End points

End points reporting groups

Reporting group title	Cohort 1 Vemurafenib
Reporting group description: Subjects with completely resected Stage IIC, IIIA, or IIIB cutaneous melanoma) received vemurafenib, 960 milligrams (mg) twice daily, in 28-day cycles, for up to 52 weeks	
Reporting group title	Cohort 1 Placebo
Reporting group description: Subjects with completely resected Stage IIC, IIIA, or IIIB cutaneous melanoma) received vemurafenib-matching placebo twice daily, in 28-day cycles, for up to 52 weeks	
Reporting group title	Cohort 2 Vemurafenib
Reporting group description: Subjects with Stage IIIC cutaneous melanoma received vemurafenib, 960 mg twice daily, in 28-day cycles, for up to 52 weeks	
Reporting group title	Cohort 2 Placebo
Reporting group description: Subjects with Stage IIIC cutaneous melanoma received vemurafenib-matching placebo twice daily, in 28-day cycles, for up to 52 weeks	

Primary: Disease-Free Survival (DFS) as Assessed Using Contrast-Enhanced Magnetic Resonance Imaging (MRI) or Contrast Enhanced Computed Tomography (CT)

End point title	Disease-Free Survival (DFS) as Assessed Using Contrast-Enhanced Magnetic Resonance Imaging (MRI) or Contrast Enhanced Computed Tomography (CT)
End point description: DFS was defined as the time from randomization until the date of the first local, regional, or distant melanoma recurrence, occurrence of new primary melanoma, or death from any cause. The ITT population included all subjects enrolled in the study, whether or not they had received study medication. Here, 99999 = not estimable due to low number of events.	
End point type	Primary
End point timeframe: From randomization until the date of the first local, regional, or distant melanoma recurrence, occurrence of new primary melanoma, or death from any cause (up to the April 17, 2017 data cut-off, approximately 4.5 years)	

End point values	Cohort 1 Vemurafenib	Cohort 1 Placebo	Cohort 2 Vemurafenib	Cohort 2 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	72	52	53
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	36.9 (21.4 to 99999)	23.1 (18.6 to 26.5)	15.4 (11.1 to 35.9)

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Cohort 1 Vemurafenib v Cohort 1 Placebo
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.78

Statistical analysis title	Statistical Analysis 2
Comparison groups	Cohort 2 Vemurafenib v Cohort 2 Placebo
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2598
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.18

Secondary: Distant Metastasis-Free Survival (DMFS) as Assessed Using Contrast-Enhanced MRI or Contrast Enhanced CT

End point title	Distant Metastasis-Free Survival (DMFS) as Assessed Using Contrast-Enhanced MRI or Contrast Enhanced CT
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End point description:

DMFS was defined as the time from randomization until the date of diagnosis of distant (i.e. non-locoregional) metastases or death from any cause. The ITT population included all subjects enrolled in the study, whether or not they had received study medication. Here, 99999 = not estimable due to low number of events.

End point type	Secondary
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End point timeframe:

From randomization until the date of diagnosis of distant (i.e., non-locoregional) metastases or death from any cause (up to the April 17, 2017 data cut-off, approximately 4.5 years)

End point values	Cohort 1 Vemurafenib	Cohort 1 Placebo	Cohort 2 Vemurafenib	Cohort 2 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	34	52	38	37
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (36.9 to 99999)	37.2 (22.1 to 99999)	30.7 (24.5 to 99999)

Statistical analyses

Statistical analysis title	Statistical Analysis 3
Comparison groups	Cohort 1 Vemurafenib v Cohort 1 Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0133
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.9

Statistical analysis title	Statistical Analysis 4
Comparison groups	Cohort 2 Vemurafenib v Cohort 2 Placebo
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6815
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.44

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

OS is defined as the time from randomization until the date of death from any cause. The ITT population included all subjects enrolled in the study, whether or not they had received study medication. Here,

99999 = not estimable due to low number of events.

End point type	Secondary
End point timeframe:	
From randomization until the date of death from any cause (up to the July 13, 2018 data cut-off, approximately 6 years)	

End point values	Cohort 1 Vemurafenib	Cohort 1 Placebo	Cohort 2 Vemurafenib	Cohort 2 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	33	25	25
Units: months				
median (confidence interval 95%)	99999 (60.0 to 99999)	99999 (99999 to 99999)	59.9 (54.6 to 59.9)	99999 (52.6 to 99999)

Statistical analyses

Statistical analysis title	Statistical Analysis 5
Comparison groups	Cohort 1 Vemurafenib v Cohort 1 Placebo
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0274
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.94

Statistical analysis title	Statistical Analysis 6
Comparison groups	Cohort 2 Vemurafenib v Cohort 2 Placebo
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8597
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.66

Secondary: Percentage of Subjects With Adverse Events

End point title	Percentage of Subjects With Adverse Events
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End point description:

An adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. The safety population included all subjects who received at least one dose of study medication.

End point type	Secondary
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End point timeframe:

From randomization up to data cut-off (up to 3-July-2018, approximately 6 years)

End point values	Cohort 1 Vemurafenib	Cohort 1 Placebo	Cohort 2 Vemurafenib	Cohort 2 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	154	156	93	91
Units: percentage of subjects				
number (not applicable)	99.4	88.5	100.0	89.0

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in European Organisation for Research and Treatment of Cancer (EORTC) 30-Item Quality of Life Questionnaire (QLQ-C30) Score

End point title	Change from Baseline in European Organisation for Research and Treatment of Cancer (EORTC) 30-Item Quality of Life Questionnaire (QLQ-C30) Score
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End point description:

EORTC QLQ-C30 assessments: appetite loss, constipation, diarrhea, dyspnea, fatigue, nausea/vomiting, pain, insomnia, function (cognitive, emotional, physical, role, and social), financial difficulties, and a global health status (GHS)/health-related quality of life (HRQoL). Either a 4-point scale (1 'Not at all' to 4 'Very much' or 7-point scale (1 'very poor' to 7 'Excellent') were used. Scores were averaged and transformed to a 0 - 100 scale. HRQoL subscales: higher scores=higher levels of functioning. Symptom subscales: higher scores=higher levels of symptoms/problems. Changes of 5 - 10 points=considered minimally important difference to subjects. Patient-reported outcome (PRO)-evaluable population: subjects with at least one dose of vemurafenib and with a baseline and at least one post-baseline QLQ-C30 with a score. PT=post-treatment; EOT=End of Treatment; Wks=weeks; C=Cycle; D=Day. 999=1 subject analyzed, therefore, standard deviation not applicable. 99999=0 subjects analyzed.

End point type	Secondary
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End point timeframe:

Days 1 and 15 of Cycles 1 and 2; Day 1 of Cycles 3-13; at end of treatment (up to 13 months); every 13 weeks thereafter until recurrence or occurrence of a new primary melanoma (up to the April 17, 2017 data cut-off, approximately 4.5 years)

End point values	Cohort 1 Vemurafenib	Cohort 1 Placebo	Cohort 2 Vemurafenib	Cohort 2 Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	138	147	87	89
Units: score on a scale				
arithmetic mean (standard deviation)				
App. Loss: C1 D1 (Baseline, n=138,147,86,89)	3.6 (± 11.2)	3.9 (± 14.9)	3.5 (± 10.3)	3.4 (± 11.3)
App. Loss: Change at C1 D8 (n=24,22,16,19)	2.8 (± 9.4)	1.5 (± 7.1)	10.4 (± 16.0)	0.0 (± 11.1)
App. Loss: Change at C1 D15 (n=132,139,79,84)	16.7 (± 26.5)	1.4 (± 12.0)	12.2 (± 22.8)	1.2 (± 17.5)
App. Loss: Change at C1 D22 (n=22,21,15,17)	7.6 (± 14.3)	3.2 (± 10.0)	11.1 (± 20.6)	3.9 (± 20.0)
App. Loss: Change at C2 D1 (n=126,142,82,84)	9.5 (± 21.0)	1.2 (± 10.1)	12.2 (± 23.7)	1.6 (± 15.4)
App. Loss: Change at C2 D15 (n=119,134,79,81)	9.5 (± 22.2)	1.0 (± 12.2)	6.8 (± 16.3)	0.8 (± 14.9)
App. Loss: Change at C3 D1 (n=119,129,80,77)	10.4 (± 20.7)	1.6 (± 10.1)	8.3 (± 18.0)	0.4 (± 14.8)
App. Loss: Change at C4 D1 (n=119,129,78,76)	9.5 (± 20.9)	1.3 (± 12.1)	10.3 (± 20.3)	2.6 (± 15.2)
App. Loss: Change at C5 D1 (n=110,117,72,64)	13.3 (± 23.5)	1.4 (± 12.7)	7.4 (± 15.0)	-0.5 (± 12.6)
App. Loss: Change at C6 D1 (n=106,112,69,63)	9.7 (± 21.1)	2.4 (± 12.4)	13.0 (± 21.6)	1.1 (± 17.9)
App. Loss: Change at C7 D1 (n=106,108,68,59)	10.7 (± 22.8)	1.5 (± 14.0)	7.4 (± 16.1)	4.0 (± 18.7)
App. Loss: Change at C8 D1 (n=105,105,65,53)	10.2 (± 22.7)	1.9 (± 13.7)	10.8 (± 18.7)	-0.6 (± 12.2)
App. Loss: Change at C9 D1 (n=100,101,63,52)	9.7 (± 25.2)	2.3 (± 13.5)	7.9 (± 17.7)	3.8 (± 15.7)
App. Loss: Change at C10 D1 (n=96,97,63,47)	7.3 (± 18.9)	1.7 (± 15.5)	4.8 (± 15.7)	0.0 (± 12.0)
App. Loss: Change at C11 D1 (n=93,93,57,48)	5.4 (± 19.2)	1.8 (± 14.2)	4.7 (± 13.3)	0.7 (± 12.8)
App. Loss: Change at C12 D1 (n=90,91,55,48)	8.5 (± 20.9)	1.5 (± 14.0)	7.3 (± 15.3)	0.0 (± 11.9)
App. Loss: Change at C13 D1 (n=82,89,54,45)	5.7 (± 17.2)	1.9 (± 13.6)	6.2 (± 14.6)	0.7 (± 11.2)
App. Loss: Change at EOT (n=123,125,66,75)	2.7 (± 16.3)	0.8 (± 20.1)	5.1 (± 18.7)	2.7 (± 18.8)
App. Loss: Change at PT 13 Weeks (n=90,74,55,38)	0.0 (± 13.2)	1.8 (± 16.5)	-1.2 (± 6.3)	1.8 (± 10.8)
App. Loss: Change at PT 26 Weeks (n=90,72,47,35)	0.7 (± 16.6)	-1.4 (± 15.3)	3.5 (± 17.4)	1.0 (± 12.7)
App. Loss: Change at PT 39 Weeks (n=79,68,42,33)	-0.4 (± 12.5)	-0.5 (± 7.0)	-0.8 (± 9.0)	2.0 (± 14.3)
App. Loss: Change at PT 52 Weeks (n=76,62,26,25)	0.4 (± 17.6)	0.0 (± 12.1)	-1.3 (± 6.5)	2.7 (± 9.2)
App. Loss: Change at PT 65 Weeks (n=53,38,17,18)	-1.9 (± 12.1)	0.9 (± 14.5)	0.0 (± 0.0)	5.6 (± 17.1)
App. Loss: Change at PT 78 Weeks (n=46,33,15,9)	-0.7 (± 11.1)	2.0 (± 14.3)	0.0 (± 0.0)	3.7 (± 11.1)
App. Loss: Change at PT 91 Weeks (n=32,29,15,12)	2.1 (± 16.8)	2.3 (± 12.4)	0.0 (± 0.0)	2.8 (± 9.6)
App. Loss: Change at PT 104 Weeks (n=27,25,10,9)	-1.2 (± 11.3)	-1.3 (± 6.7)	0.0 (± 0.0)	-3.7 (± 11.1)
App. Loss: Change at PT 117 Weeks (n=22,17,9,5)	-1.5 (± 12.5)	2.0 (± 14.3)	0.0 (± 0.0)	0.0 (± 0.0)

App. Loss: Change at PT 130 Weeks (n=17,12,5,5)	0.0 (± 0.0)	2.8 (± 17.2)	0.0 (± 0.0)	0.0 (± 0.0)
App. Loss: Change at PT 143 Weeks (n=7,2,3,2)	-4.8 (± 12.6)	0.0 (± 0.0)	0.0 (± 0.0)	0.0 (± 0.0)
App. Loss: Change at PT 156 Weeks (n=3,1,0,2)	0.0 (± 0.0)	0.0 (± 999)	99999 (± 99999)	16.7 (± 23.6)
App. Loss: Change at PT 169 Weeks (n=2,1,0,0)	0.0 (± 0.0)	0.0 (± 999)	99999 (± 99999)	99999 (± 99999)
App. Loss: Change at PT 182 Weeks (n=3,0,0,0)	0.0 (± 0.0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
App. Loss: Change at PT/Discont. (n=8,1,6,1)	0.0 (± 0.0)	0.0 (± 999)	0.0 (± 0.0)	0.0 (± 999)
Cog. Func. C1 D1 (Baseline, n=138,147,87,89)	93.0 (± 14.1)	92.0 (± 16.2)	91.4 (± 17.2)	94.9 (± 11.6)
Cog. Func.: Change at C1 D8 (n=24,22,16,19)	-2.1 (± 12.3)	1.5 (± 14.5)	0.0 (± 10.5)	2.6 (± 6.2)
Cog. Func.: Change at C1 D15 (n=132,139,78,84)	-4.3 (± 13.1)	0.8 (± 12.6)	-3.8 (± 13.4)	-0.8 (± 11.5)
Cog. Func.: Change at C1 D22 (n=22,21,15,17)	-0.8 (± 17.4)	1.6 (± 11.7)	-3.3 (± 9.3)	-4.9 (± 14.1)
Cog. Func.: Change at C2 D1 (n=127,142,82,84)	-2.4 (± 14.2)	-2.5 (± 14.3)	-2.2 (± 12.2)	0.0 (± 13.9)
Cog. Func.: Change at C2 D15 (n=119,134,80,80)	-3.8 (± 15.1)	-1.1 (± 14.6)	-3.1 (± 11.9)	-0.4 (± 15.2)
Cog. Func.: Change at C3 D1 (n=119,129,81,78)	-3.6 (± 13.4)	-0.6 (± 12.0)	-2.5 (± 12.4)	-2.1 (± 13.3)
Cog. Func.: Change at C4 D1 (n=119,129,78,76)	-3.8 (± 14.6)	-1.3 (± 15.1)	-4.9 (± 13.5)	-2.9 (± 13.7)
Cog. Func.: Change at C5 D1 (n=110,116,72,64)	-6.2 (± 17.3)	-2.0 (± 14.9)	-3.9 (± 12.7)	-3.6 (± 15.3)
Cog. Func.: Change at C6 D1 (n=106,112,69,63)	-5.7 (± 15.8)	-2.1 (± 12.5)	-4.1 (± 16.0)	-3.4 (± 18.2)
Cog. Func.: Change at C7 D1 (n=106,108,68,59)	-6.3 (± 17.3)	-3.1 (± 13.3)	-3.9 (± 15.5)	-5.6 (± 15.0)
Cog. Func.: Change at C8 D1 (n=104,106,65,53)	-7.4 (± 16.1)	-3.6 (± 16.9)	-5.1 (± 16.6)	-4.7 (± 13.2)
Cog. Func.: Change at C9 D1 (n=100,101,63,52)	-8.2 (± 18.1)	-4.6 (± 17.3)	-5.8 (± 17.7)	-5.4 (± 12.2)
Cog. Func.: Change at C10 D1 (n=96,97,63,47)	-9.0 (± 20.1)	-3.6 (± 17.4)	-4.5 (± 17.5)	-8.2 (± 19.3)
Cog. Func.: Change at C11 D1 (n=93,93,57,48)	-10.6 (± 20.1)	-2.9 (± 15.9)	-5.0 (± 15.1)	-3.8 (± 12.5)
Cog. Func.: Change at C12 D1 (n=90,91,55,48)	-8.7 (± 21.5)	-4.0 (± 14.6)	-3.9 (± 13.6)	-4.5 (± 14.5)
Cog. Func.: Change at C13 D1 (n=82,89,54,45)	-7.7 (± 20.7)	-3.9 (± 16.1)	-6.5 (± 15.7)	-5.2 (± 12.7)
Cog. Func.: Change at EOT (n=123,125,67,75)	-4.9 (± 17.3)	-3.5 (± 19.5)	-4.0 (± 17.2)	-6.9 (± 14.3)
Cog. Func.: Change at PT 13 Weeks (n=90,74,56,38)	-4.4 (± 14.9)	-1.6 (± 14.1)	-1.5 (± 14.0)	-3.5 (± 14.1)
Cog. Func.: Change at PT 26 Weeks (n=90,72,47,35)	-2.8 (± 16.2)	-2.5 (± 14.2)	-2.1 (± 15.4)	-3.8 (± 13.5)
Cog. Func.: Change at PT 39 Weeks (n=79,68,41,33)	-2.1 (± 13.2)	-1.0 (± 14.6)	-2.0 (± 11.9)	-3.0 (± 11.4)
Cog. Func.: Change at PT 52 Weeks (n=76,62,27,25)	-3.5 (± 17.3)	-1.9 (± 9.1)	1.2 (± 13.0)	-7.3 (± 12.8)
Cog. Func.: Change at PT 65 Weeks (n=53,38,17,18)	-4.4 (± 17.3)	-3.9 (± 15.2)	-1.0 (± 12.5)	-4.6 (± 11.2)
Cog. Func.: Change at PT 78 Weeks (n=46,33,15,9)	-2.5 (± 17.2)	-3.5 (± 19.4)	-1.1 (± 14.7)	-7.4 (± 12.1)
Cog. Func.: Change at PT 91 Weeks (n=33,29,15,12)	-2.5 (± 16.2)	-2.3 (± 15.9)	3.3 (± 11.3)	-5.6 (± 13.0)

Cog. Func.: Change at PT 104 Weeks (n=27,25,10,9)	1.2 (± 14.6)	-4.0 (± 16.9)	3.3 (± 13.1)	-5.6 (± 11.8)
Cog. Func.: Change at PT 117 Weeks (n=22,17,8,5)	1.5 (± 12.5)	0.0 (± 10.2)	-2.1 (± 5.9)	-6.7 (± 14.9)
Cog. Func.: Change at PT 130 Weeks (n=17,12,5,5)	-3.9 (± 15.1)	-1.4 (± 15.0)	0.0 (± 0.0)	-6.7 (± 14.9)
Cog. Func.: Change at PT 143 Weeks (n=7,2,3,2)	4.8 (± 18.5)	0.0 (± 0.0)	0.0 (± 0.0)	-8.3 (± 11.8)
Cog. Func.: Change at PT 156 Weeks (n=3,1,0,2)	11.1 (± 19.2)	0.0 (± 999)	99999 (± 99999)	-16.7 (± 23.6)
Cog. Func.: Change at PT 169 Weeks (n=2,1,0,0)	16.7 (± 23.6)	0.0 (± 999)	99999 (± 99999)	99999 (± 99999)
Cog. Func.: Change at PT 182 Weeks (n=3,0,0,0)	11.1 (± 19.2)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Cog. Func.: Change at PT/Discont. (n=8,1,6,1)	-2.1 (± 16.5)	0.0 (± 999)	-5.6 (± 8.6)	0.0 (± 999)
Constip.: C1 D1 (Baseline, n=138,146,87,88)	3.1 (± 10.6)	5.7 (± 16.3)	4.6 (± 12.6)	5.7 (± 15.3)
Constip.: Change at C1 D8 (n=23,22,16,19)	-2.9 (± 13.9)	0.0 (± 0.0)	-2.1 (± 8.3)	-5.3 (± 12.5)
Constip.: Change at C1 D15 (n=130,138,80,83)	2.1 (± 17.0)	0.7 (± 13.0)	1.7 (± 13.9)	-0.4 (± 16.9)
Constip.: Change at C1 D22 (n=21,21,15,17)	-1.6 (± 19.7)	1.6 (± 7.3)	0.0 (± 12.6)	-3.9 (± 16.2)
Constip.: Change at C2 D1 (n=124,141,82,83)	1.1 (± 12.7)	1.4 (± 10.4)	1.6 (± 13.8)	-0.4 (± 16.9)
Constip.: Change at C2 D15 (n=117,133,79,79)	1.4 (± 14.8)	0.0 (± 13.0)	0.0 (± 11.9)	-1.3 (± 15.5)
Constip.: Change at C3 D1 (n=115,127,79,77)	-1.2 (± 12.4)	1.0 (± 13.9)	0.4 (± 12.5)	-1.7 (± 18.7)
Constip.: Change at C4 D1 (n=118,127,78,75)	0.6 (± 11.5)	0.5 (± 16.8)	0.0 (± 10.7)	-2.2 (± 14.8)
Constip.: Change at C5 D1 (n=107,116,71,64)	-0.6 (± 9.1)	0.3 (± 16.7)	3.8 (± 14.4)	-3.1 (± 17.5)
Constip.: Change at C6 D1 (n=104,112,68,63)	0.6 (± 13.1)	1.8 (± 16.6)	5.4 (± 16.9)	-3.7 (± 20.0)
Constip.: Change at C7 D1 (n=106,108,67,59)	3.1 (± 18.1)	1.5 (± 19.0)	3.0 (± 12.6)	-4.0 (± 15.3)
Constip.: Change at C8 D1 (n=103,106,64,53)	1.9 (± 14.6)	1.6 (± 16.2)	4.2 (± 15.1)	-1.9 (± 17.8)
Constip.: Change at C9 D1 (n=97,101,62,52)	1.4 (± 11.7)	-2.3 (± 13.5)	3.2 (± 14.4)	-0.6 (± 20.3)
Constip.: Change at C10 D1 (n=96,97,62,47)	1.4 (± 10.7)	-1.4 (± 12.7)	1.6 (± 11.2)	-4.3 (± 17.9)
Constip.: Change at C11 D1 (n=92,93,56,48)	2.2 (± 14.7)	0.0 (± 16.3)	2.4 (± 14.0)	-4.9 (± 15.4)
Constip.: Change at C12 D1 (n=90,91,54,48)	4.8 (± 19.1)	-1.8 (± 14.4)	3.1 (± 13.4)	-3.5 (± 14.2)
Constip.: Change at C13 D1 (n=81,89,54,45)	4.1 (± 18.5)	0.0 (± 18.8)	0.0 (± 11.2)	-3.7 (± 19.1)
Constip.: Change at EOT (n=122,124,67,74)	3.3 (± 15.1)	2.4 (± 19.1)	4.5 (± 17.3)	-1.4 (± 17.8)
Constip.: Change at PT 13 Weeks (n=88,74,56,38)	0.4 (± 17.1)	-0.5 (± 17.0)	6.0 (± 16.9)	0.9 (± 21.2)
Constip.: Change at PT 26 Weeks (n=89,71,47,35)	-0.4 (± 13.8)	-0.9 (± 13.8)	2.8 (± 9.4)	-1.0 (± 18.9)
Constip.: Change at PT 39 Weeks (n=77,67,41,33)	0.4 (± 14.8)	-0.5 (± 13.6)	2.4 (± 13.7)	-4.0 (± 16.2)
Constip.: Change at PT 52 Weeks (n=75,62,27,25)	0.0 (± 13.4)	0.0 (± 14.8)	0.0 (± 9.2)	0.0 (± 13.6)
Constip.: Change at PT 65 Weeks (n=53,37,17,18)	3.8 (± 14.1)	3.6 (± 21.9)	2.0 (± 14.3)	0.0 (± 11.4)

Constip.: Change at PT 78 Weeks (n=46,33,15,9)	-1.4 (± 9.8)	6.1 (± 25.6)	0.0 (± 0.0)	0.0 (± 0.0)
Constip.: Change at PT 91 Weeks (n=31,28,15,12)	-4.3 (± 11.4)	6.0 (± 18.3)	2.2 (± 8.6)	0.0 (± 14.2)
Constip.: Change at PT 104 Weeks (n=26,25,10,9)	1.3 (± 14.8)	4.0 (± 14.7)	-3.3 (± 10.5)	0.0 (± 16.7)
Constip.: Change at PT 117 Weeks (n=20,17,9,5)	-6.7 (± 13.7)	9.8 (± 19.6)	0.0 (± 0.0)	-6.7 (± 14.9)
Constip.: Change at PT 130 Weeks (n=16,12,5,5)	-8.3 (± 14.9)	5.6 (± 13.0)	0.0 (± 23.6)	-6.7 (± 14.9)
Constip.: Change at PT 143 Weeks (n=7,2,3,2)	-9.5 (± 16.3)	0.0 (± 0.0)	0.0 (± 0.0)	0.0 (± 0.0)
Constip.: Change at PT 156 Weeks (n=3,1,0,2)	0.0 (± 0.0)	0.0 (± 999)	99999 (± 99999)	-16.7 (± 23.6)
Constip.: Change at PT 169 Weeks (n=2,1,0,0)	0.0 (± 0.0)	0.0 (± 999)	99999 (± 99999)	99999 (± 99999)
Constip.: Change at PT 182 Weeks (n=3,0,0,0)	-11.1 (± 19.2)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Constip.: Change at PT/Discont.(n=8,1,6,1)	0.0 (± 0.0)	0.0 (± 999)	0.0 (± 0.0)	0.0 (± 999)
Diarrhoea: C1 D1 (Baseline, n=138,147,87,89)	4.1 (± 13.0)	5.4 (± 17.5)	3.8 (± 13.9)	4.1 (± 16.5)
Diarrhoea: Change at C1 D8 (n=24,22,16,19)	4.2 (± 11.3)	0.0 (± 10.3)	-4.2 (± 20.6)	-8.8 (± 24.4)
Diarrhoea: Change at C1 D15 (n=132,139,77,84)	2.5 (± 21.3)	-0.7 (± 14.7)	1.7 (± 19.4)	-1.6 (± 17.1)
Diarrhoea: Change at C1 D22 (n=22,21,15,17)	3.0 (± 9.8)	-1.6 (± 16.6)	-2.2 (± 23.5)	-9.8 (± 25.7)
Diarrhoea: Change at C2 D1 (n=127,142,82,84)	1.3 (± 19.9)	-0.9 (± 16.3)	4.9 (± 21.7)	0.0 (± 20.0)
Diarrhoea: Change at C2 D15 (n=119,134,80,80)	1.7 (± 21.2)	-1.5 (± 19.1)	0.4 (± 17.2)	0.0 (± 16.8)
Diarrhoea: Change at C3 D1 (n=119,129,81,78)	3.4 (± 21.9)	-0.3 (± 18.4)	3.3 (± 19.4)	-0.9 (± 15.2)
Diarrhoea: Change at C4 D1 (n=119,129,78,76)	3.9 (± 23.0)	0.3 (± 19.8)	5.6 (± 18.2)	-2.6 (± 18.7)
Diarrhoea: Change at C5 D1 (n=110,116,72,64)	7.6 (± 23.7)	-1.4 (± 20.3)	2.8 (± 20.0)	-3.6 (± 18.9)
Diarrhoea: Change at C6 D1 (n=106,112,69,63)	7.2 (± 25.2)	-0.6 (± 20.0)	7.2 (± 24.8)	-2.6 (± 19.2)
Diarrhoea: Change at C7 D1 (n=106,108,68,59)	9.4 (± 24.2)	-1.5 (± 21.6)	4.9 (± 22.5)	-4.5 (± 18.0)
Diarrhoea: Change at C8 D1 (n=104,106,65,52)	5.1 (± 19.6)	-0.9 (± 21.3)	5.6 (± 20.9)	-3.2 (± 16.5)
Diarrhoea: Change at C9 D1 (n=100,101,62,52)	7.7 (± 25.0)	0.7 (± 24.5)	4.3 (± 19.5)	-1.9 (± 23.3)
Diarrhoea: Change at C10 D1 (n=96,97,62,47)	6.9 (± 21.6)	-0.3 (± 22.3)	5.9 (± 23.8)	-2.1 (± 18.9)
Diarrhoea: Change at C11 D1 (n=93,93,57,48)	6.1 (± 19.6)	1.1 (± 23.3)	4.7 (± 23.1)	-0.7 (± 20.0)
Diarrhoea: Change at C12 D1 (n=90,91,55,47)	7.4 (± 25.4)	-0.7 (± 23.3)	7.9 (± 24.8)	-0.7 (± 19.0)
Diarrhoea: Change at C13 D1 (n=82, 89,54,45)	8.5 (± 24.5)	0.4 (± 25.4)	8.0 (± 28.9)	-1.5 (± 20.0)
Diarrhoea: Change at EOT (n=123,125,67,75)	0.8 (± 21.5)	0.0 (± 20.7)	-1.0 (± 16.4)	-1.8 (± 18.9)
Diarrhoea: Change at PT 13 Weeks (n=90,74,56,38)	-0.4 (± 15.4)	-1.8 (± 24.0)	0.0 (± 18.0)	0.0 (± 15.5)
Diarrhoea: Change at PT 26 Weeks (n=89,72,47,35)	-2.2 (± 16.5)	-3.2 (± 24.5)	0.7 (± 8.5)	-1.9 (± 19.7)
Diarrhoea: Change at PT 39 Weeks (n=79,68,41,33)	-1.7 (± 15.9)	-4.9 (± 23.2)	1.6 (± 14.8)	0.0 (± 18.6)

Diarrhoea: Change at PT 52 Weeks (n=75,62,27,25)	-1.8 (± 17.2)	-3.8 (± 23.5)	-1.2 (± 21.6)	0.0 (± 19.2)
Diarrhoea: Change at PT 65 Weeks (n=53,38,17,18)	0.0 (± 19.6)	-6.1 (± 29.9)	2.0 (± 8.1)	-7.4 (± 24.4)
Diarrhoea: Change at PT 78 Weeks (n=46,33,15,9)	-0.7 (± 20.5)	-7.1 (± 29.8)	0.0 (± 0.0)	-3.7 (± 11.1)
Diarrhoea: Change at PT 91 Weeks (n=33,29,15,12)	4.0 (± 16.2)	-9.2 (± 25.0)	0.0 (± 0.0)	-8.3 (± 28.9)
Diarrhoea: Change at PT 104 Weeks (n=27,25,10,9)	0.0 (± 9.2)	-5.3 (± 28.3)	3.3 (± 10.5)	-11.1 (± 33.3)
Diarrhoea: Change at PT 117 Weeks (n=22,17,8,5)	0.0 (± 10.3)	-11.8 (± 31.0)	0.0 (± 0.0)	0.0 (± 0.0)
Diarrhoea: Change at PT 130 Weeks (n=17,12,5,5)	-2.0 (± 8.1)	-2.8 (± 43.7)	6.7 (± 14.9)	13.3 (± 18.3)
Diarrhoea: Change at PT 143 Weeks (n=7,2,3,2)	0.0 (± 0.0)	0.0 (± 0.0)	0.0 (± 0.0)	0.0 (± 0.0)
Diarrhoea: Change at PT 156 Weeks (n=3,1,0,2)	0.0 (± 0.0)	0.0 (± 999)	99999 (± 99999)	0.0 (± 0.0)
Diarrhoea: Change at PT 169 Weeks (n=2,1,0,0)	0.0 (± 0.0)	0.0 (± 999)	99999 (± 99999)	99999 (± 99999)
Diarrhoea: Change at PT 182 Weeks (n=3,0,0,0)	0.0 (± 0.0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Diarrhoea: Change at PT/Discont. (n=8,1,6,1)	0.0 (± 17.8)	-33.3 (± 999)	0.0 (± 0.0)	0.0 (± 999)
Dyspnoea: C1 D1 (Baseline, (n=138,147,87,89)	3.6 (± 10.4)	4.8 (± 12.9)	5.0 (± 12.0)	3.0 (± 10.8)
Dyspnoea: Change at C1 D8 (n=24,22,16,19)	4.2 (± 11.3)	-1.5 (± 7.1)	4.2 (± 16.7)	-1.8 (± 7.6)
Dyspnoea: Change at C1 D15 (n=132,139,80,84)	6.3 (± 18.9)	0.2 (± 8.5)	2.9 (± 15.2)	1.2 (± 12.1)
Dyspnoea: Change at C1 D22 (n=21,21,15,17)	4.8 (± 12.0)	-1.6 (± 7.3)	0.0 (± 17.8)	0.0 (± 0.0)
Dyspnoea: Change at C2 D1 (n=126,142,83,84)	1.9 (± 13.5)	0.2 (± 11.6)	4.8 (± 20.9)	3.2 (± 14.3)
Dyspnoea: Change at C2 D15 (n=119,134,80,81)	2.8 (± 16.0)	1.0 (± 13.5)	4.6 (± 18.9)	4.1 (± 17.0)
Dyspnoea: Change at C3 D1 (n=119,129,81,78)	3.4 (± 17.0)	1.8 (± 13.4)	3.7 (± 18.3)	3.8 (± 12.0)
Dyspnoea: Change at C4 D1 (n=119,129,78,76)	3.1 (± 15.6)	3.1 (± 14.7)	3.0 (± 18.8)	1.8 (± 14.3)
Dyspnoea: Change at C5 D1 (n=110,116,72,64)	5.2 (± 14.4)	4.0 (± 14.7)	3.7 (± 19.0)	3.1 (± 15.4)
Dyspnoea: Change at C6 D1 (n=106,112,69,63)	3.8 (± 16.8)	2.4 (± 13.9)	3.9 (± 19.4)	2.1 (± 15.7)
Dyspnoea: Change at C7 D1 (n=106,108,68,59)	5.3 (± 16.7)	3.7 (± 17.3)	3.9 (± 17.8)	2.8 (± 12.8)
Dyspnoea: Change at C8 D1 (n=104,106,65,53)	4.2 (± 16.5)	4.1 (± 17.6)	2.6 (± 14.8)	3.1 (± 13.5)
Dyspnoea: Change at C9 D1 (n=100,101,63,52)	5.7 (± 17.1)	5.3 (± 16.8)	2.1 (± 16.8)	4.5 (± 18.7)
Dyspnoea: Change at C10 D1 (n=96,97,63,47)	5.2 (± 20.1)	4.5 (± 16.4)	6.3 (± 18.8)	3.5 (± 12.5)
Dyspnoea: Change at C11 D1 (n=93,93,57,48)	5.7 (± 19.4)	5.0 (± 19.0)	7.0 (± 20.6)	3.5 (± 14.2)
Dyspnoea: Change at C12 D1 (n=90,91,55,48)	6.7 (± 24.1)	5.5 (± 18.1)	3.6 (± 18.9)	5.6 (± 15.9)
Dyspnoea: Change at C13 D1 (n=82,89,54,45)	6.5 (± 19.2)	4.9 (± 15.5)	4.9 (± 19.9)	5.9 (± 14.7)
Dyspnoea: Change at EOT (n=123,125,67,75)	4.1 (± 14.5)	2.4 (± 19.9)	3.0 (± 18.1)	6.2 (± 16.2)
Dyspnoea: Change at PT 13 Weeks (n=90,74,55,38)	3.0 (± 17.1)	3.2 (± 16.7)	3.0 (± 16.1)	2.6 (± 12.0)

Dyspnoea: Change at PT 26 Weeks (n=90,72,47,35)	4.8 (± 16.2)	1.4 (± 16.3)	3.5 (± 19.9)	-1.0 (± 5.6)
Dyspnoea: Change at PT 39 Weeks (n=79,68,42,33)	1.7 (± 14.0)	2.5 (± 13.3)	4.8 (± 18.9)	3.0 (± 12.8)
Dyspnoea: Change at PT 52 Weeks (n=76,62,27,25)	1.8 (± 15.3)	3.8 (± 16.1)	2.5 (± 15.8)	5.3 (± 15.8)
Dyspnoea: Change at PT 65 Weeks (n=53,38,17,18)	3.8 (± 14.1)	6.1 (± 15.2)	-3.9 (± 11.1)	1.9 (± 7.9)
Dyspnoea: Change at PT 78 Weeks (n=46,33,15,9)	4.3 (± 13.3)	7.1 (± 18.2)	0.0 (± 21.8)	0.0 (± 16.7)
Dyspnoea: Change at PT 91 Weeks (n=33,29,15,12)	3.0 (± 9.7)	5.7 (± 12.8)	-2.2 (± 15.3)	0.0 (± 14.2)
Dyspnoea: Change at PT 104 Weeks (n=27,25,10,8)	0.0 (± 16.0)	6.7 (± 16.7)	0.0 (± 22.2)	8.3 (± 15.4)
Dyspnoea: Change at PT 117 Weeks (n=22,17,9,5)	0.0 (± 14.5)	5.9 (± 13.1)	-3.7 (± 20.0)	6.7 (± 14.9)
Dyspnoea: Change at PT 130 Weeks (n=17,12,5,5)	-2.0 (± 8.1)	0.0 (± 0.0)	0.0 (± 23.6)	13.3 (± 18.3)
Dyspnoea: Change at PT 143 Weeks (n=7,2,3,2)	9.5 (± 25.2)	0.0 (± 0.0)	-11.1 (± 19.2)	0.0 (± 0.0)
Dyspnoea: Change at PT 156 Weeks (n=3,1,0,2)	0.0 (± 0.0)	0.0 (± 999)	99999 (± 99999)	16.7 (± 23.6)
Dyspnoea: Change at PT 169 Weeks (n=2,1,0,0)	0.0 (± 0.0)	0.0 (± 999)	99999 (± 99999)	99999 (± 99999)
Dyspnoea: Change at PT 182 Weeks (n=3,0,0,0)	0.0 (± 0.0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Dyspnoea: Change at PT/Discont. (n=8,1,6,1)	0.0 (± 0.0)	0.0 (± 999)	0.0 (± 0.0)	0.0 (± 999)
Emot. func.: C1 D1 (Baseline, n=138,147,87,89)	83.8 (± 15.1)	86.1 (± 16.4)	81.6 (± 21.5)	84.5 (± 17.4)
Emot. func.: Change at C1 D8 (n=24,22,16,19)	-4.5 (± 15.5)	1.9 (± 12.0)	3.6 (± 11.4)	1.8 (± 14.0)
Emot. func.: Change at C1 D15 (n=132,139,78,84)	-5.2 (± 18.0)	1.9 (± 12.3)	-1.0 (± 16.6)	3.8 (± 12.0)
Emot. func.: Change at C1 D22 (n=22,21,15,17)	-6.4 (± 20.6)	2.4 (± 9.9)	-0.6 (± 12.8)	-0.5 (± 17.3)
Emot. func.: Change at C2 D1 (n=127,142,82,84)	-1.2 (± 16.0)	2.5 (± 13.2)	-1.0 (± 17.5)	4.0 (± 12.7)
Emot. func.: Change at C2 D15 (n=119,134,80,80)	0.2 (± 18.7)	2.0 (± 15.4)	-0.5 (± 11.7)	3.8 (± 13.6)
Emot. func.: Change at C3 D1 (n=119,129,81,78)	-0.1 (± 17.3)	2.3 (± 13.2)	-0.8 (± 16.8)	3.5 (± 13.9)
Emot. func.: Change at C4 D1 (n=119,129,78,76)	-2.7 (± 18.9)	1.8 (± 15.1)	-1.2 (± 15.9)	2.4 (± 14.9)
Emot. func.: Change at C5 D1 (n=110,116,72,64)	-3.5 (± 19.8)	-0.2 (± 18.4)	-0.8 (± 15.4)	3.0 (± 14.4)
Emot. func.: Change at C6 D1 (n=106,112,69,63)	-2.8 (± 17.5)	-0.7 (± 16.7)	-2.6 (± 16.0)	1.4 (± 18.7)
Emot. func.: Change at C7 D1 (n=106,108,68,59)	-3.0 (± 18.5)	0.5 (± 16.4)	-2.3 (± 16.1)	-0.5 (± 14.4)
Emot. func.: Change at C8 D1 (n=104,106,65,53)	-3.5 (± 20.0)	-0.9 (± 15.5)	-1.9 (± 15.9)	0.2 (± 13.1)
Emot. func.: Change at C9 D1 (n=100,101,63,52)	-1.6 (± 22.1)	-0.9 (± 17.0)	0.1 (± 15.8)	-0.2 (± 16.1)
Emot. func.: Change at C10 D1 (n=96,97,63,47)	-1.0 (± 20.5)	-1.1 (± 14.3)	-0.1 (± 16.5)	0.0 (± 14.6)
Emot. func.: Change at C11 D1 (n=93,93,57,48)	0.0 (± 19.6)	0.5 (± 14.1)	1.2 (± 15.7)	0.7 (± 14.3)
Emot. func.: Change at C12 D1 (n=90,91,55,48)	-2.3 (± 20.0)	-2.2 (± 16.4)	1.1 (± 14.6)	-1.6 (± 14.1)
Emot. func.: Change at C13 D1 (n=82,89,54,45)	-2.0 (± 20.4)	-2.5 (± 18.6)	0.2 (± 16.5)	0.2 (± 13.5)

Emot. func.: Change at EOT (n=123,125,67,75)	1.5 (± 18.8)	-2.0 (± 19.6)	2.2 (± 22.2)	-4.4 (± 19.9)
Emot. func.: Change at PT 13 Weeks (n=90,74,56,38)	3.2 (± 17.4)	-1.0 (± 19.5)	6.4 (± 16.7)	3.5 (± 13.8)
Emot. func.: Change at PT 26 Weeks (n=90,72,47,35)	4.9 (± 18.3)	-1.4 (± 14.1)	3.0 (± 18.2)	1.2 (± 16.2)
Emot. func.: Change at PT 39 Weeks (n=79,68,41,33)	2.5 (± 15.5)	-0.2 (± 14.9)	4.1 (± 19.0)	2.3 (± 12.9)
Emot. func.: Change at PT 52 Weeks (n=76,62,27,25)	2.4 (± 17.8)	-0.7 (± 16.3)	9.0 (± 16.8)	1.7 (± 14.2)
Emot. func.: Change at PT 65 Weeks (n=53,38,17,18)	1.1 (± 17.9)	-2.0 (± 17.5)	10.3 (± 17.1)	3.7 (± 16.0)
Emot. func.: Change at PT 78 Weeks (n=46,33,15,9)	2.9 (± 14.6)	-1.8 (± 22.1)	8.9 (± 16.2)	1.9 (± 10.8)
Emot. func.: Change at PT 91 Weeks (n=33,29,15,12)	1.8 (± 16.8)	0.0 (± 17.3)	13.3 (± 16.6)	-0.7 (± 20.6)
Emot. func.: Change at PT 104 Weeks (n=27,25,10,9)	6.5 (± 14.3)	-7.0 (± 21.9)	4.2 (± 13.2)	1.9 (± 20.7)
Emot. func.: Change at PT 117 Weeks (n=22,17,8,5)	7.2 (± 12.7)	-2.9 (± 14.7)	0.0 (± 16.7)	3.3 (± 29.8)
Emot. func.: Change at PT 130 Weeks (n=17,12,5,5)	8.7 (± 12.8)	-4.9 (± 15.3)	3.3 (± 20.1)	1.7 (± 32.5)
Emot. func.: Change at PT 143 Weeks (n=7,2,3,2)	0.0 (± 18.0)	-4.2 (± 5.9)	0.0 (± 25.0)	-16.7 (± 23.6)
Emot. func.: Change at PT 156 Weeks (n=3,1,0,2)	22.2 (± 9.6)	0.0 (± 999)	99999 (± 99999)	4.2 (± 53.0)
Emot. func.: Change at PT 169 Weeks (n=2,1,0,0)	25.0 (± 11.8)	0.0 (± 999)	99999 (± 99999)	99999 (± 99999)
Emot. func.: Change at PT 182 Weeks (n=3,0,0,0)	16.7 (± 16.7)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Emot. func.: Change at PT/Discont. (n=8,1,6,1)	-5.2 (± 28.1)	0.0 (± 999)	1.4 (± 11.1)	8.3 (± 999)
Fatigue: C1 D1 (Baseline, n=138,147,87,89)	13.2 (± 14.7)	16.1 (± 19.4)	15.5 (± 18.2)	14.7 (± 18.6)
Fatigue: Change at C1 D8 (n=24,22,16,19)	7.9 (± 19.0)	-0.3 (± 9.8)	7.6 (± 13.3)	5.3 (± 10.1)
Fatigue: Change at C1 D15 (n=132,139,80,84)	22.6 (± 26.1)	2.3 (± 14.2)	18.2 (± 27.0)	3.4 (± 13.1)
Fatigue: Change at C1 D22 (n=22,21,15,17)	15.2 (± 21.3)	-1.9 (± 14.4)	17.0 (± 21.4)	9.2 (± 15.8)
Fatigue: Change at C2 D1 (n=127,142,83,84)	13.2 (± 22.0)	2.5 (± 15.2)	13.7 (± 24.2)	2.5 (± 14.5)
Fatigue: Change at C2 D15 (n=119,134,80,81)	15.2 (± 23.5)	1.5 (± 18.2)	10.7 (± 19.9)	2.1 (± 16.5)
Fatigue: Change at C3 D1 (n=119,129,81,78)	14.1 (± 22.5)	1.5 (± 16.4)	12.6 (± 23.1)	4.7 (± 15.9)
Fatigue: Change at C4 D1 (n=119,129,78,76)	12.6 (± 21.7)	2.0 (± 18.4)	13.3 (± 23.1)	3.2 (± 18.1)
Fatigue: Change at C5 D1 (n=110,117,72,64)	14.2 (± 23.7)	1.9 (± 16.1)	13.6 (± 18.9)	4.7 (± 17.2)
Fatigue: Change at C6 D1 (n=106,112,69,63)	11.9 (± 21.6)	1.5 (± 17.4)	13.8 (± 22.2)	3.0 (± 18.7)
Fatigue: Change at C7 D1 (n=106,108,68,59)	13.1 (± 21.0)	0.2 (± 18.3)	13.2 (± 23.2)	6.0 (± 17.7)
Fatigue: Change at C8 D1 (n=105,106,65,53)	14.1 (± 23.9)	3.9 (± 21.9)	12.7 (± 22.7)	5.0 (± 15.5)
Fatigue: Change at C9 D1 (n=100,101,63,52)	16.3 (± 25.3)	2.7 (± 20.5)	13.7 (± 24.1)	6.0 (± 21.3)
Fatigue: Change at C10 D1 (n=96,97,63,47)	11.3 (± 22.6)	3.4 (± 18.7)	11.3 (± 25.0)	3.3 (± 16.2)
Fatigue: Change at C11 D1 (n=93,93,57,48)	11.5 (± 22.7)	2.7 (± 18.2)	10.7 (± 20.9)	7.6 (± 18.4)

Fatigue: Change at C12 D1 (n=90,91,55,48)	10.3 (± 23.8)	2.1 (± 16.2)	10.7 (± 22.5)	3.2 (± 17.0)
Fatigue: Change at C13 D1 (n=82,89,54,45)	11.1 (± 23.1)	4.0 (± 19.0)	13.4 (± 26.6)	4.7 (± 15.6)
Fatigue: Change at EOT (n=123,125,67,75)	6.5 (± 21.3)	2.2 (± 24.2)	3.3 (± 21.9)	6.4 (± 20.9)
Fatigue: Change at PT 13 Weeks (n=90,74,56,38)	1.6 (± 18.4)	0.7 (± 19.8)	-1.2 (± 19.0)	1.5 (± 14.9)
Fatigue: Change at PT 26 Weeks (n=90,72,47,35)	2.5 (± 18.4)	1.0 (± 15.5)	0.5 (± 21.6)	-1.3 (± 18.8)
Fatigue: Change at PT 39 Weeks (n=79,68,42,33)	-1.0 (± 16.9)	0.7 (± 17.2)	-0.5 (± 18.2)	-0.3 (± 12.6)
Fatigue: Change at PT 52 Weeks (n=76,62,27,25)	1.6 (± 16.7)	1.7 (± 17.6)	-1.2 (± 14.6)	1.3 (± 20.6)
Fatigue: Change at PT 65 Weeks (n=53,38,17,18)	1.3 (± 16.5)	4.4 (± 18.5)	-4.6 (± 11.8)	-1.2 (± 17.8)
Fatigue: Change at PT 78 Weeks (n=46,33,15,9)	2.4 (± 16.2)	4.7 (± 20.8)	-4.4 (± 10.1)	-4.9 (± 18.5)
Fatigue: Change at PT 91 Weeks (n=33,29,15,12)	-0.8 (± 16.3)	3.8 (± 18.8)	-3.7 (± 15.5)	-2.8 (± 26.0)
Fatigue: Change at PT 104 Weeks (n=27,25,10,9)	-1.2 (± 14.6)	8.9 (± 18.7)	-1.1 (± 17.7)	-1.2 (± 29.1)
Fatigue: Change at PT 117 Weeks (n=22,17,9,5)	-3.0 (± 13.4)	4.2 (± 19.2)	-7.4 (± 15.7)	0.0 (± 28.3)
Fatigue: Change at PT 130 Weeks (n=17,12,5,5)	-0.7 (± 15.5)	6.5 (± 19.2)	-4.4 (± 16.9)	0.0 (± 33.3)
Fatigue: Change at PT 143 Weeks (n=7,2,3,2)	-1.6 (± 14.9)	5.6 (± 7.9)	-3.7 (± 17.0)	16.7 (± 23.6)
Fatigue: Change at PT 156 Weeks (n=3,1,0,2)	-11.1 (± 11.1)	0.0 (± 999)	99999 (± 99999)	33.3 (± 15.7)
Fatigue: Change at PT 169 Weeks (n=2,1,0,0)	-16.7 (± 7.9)	0.0 (± 999)	99999 (± 99999)	99999 (± 99999)
Fatigue: Change at PT 182 Weeks (n=3,0,0,0)	-14.8 (± 6.4)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Fatigue: Change at PT/Discont. (n=8,1,6,1)	6.9 (± 16.7)	-22.2 (± 999)	-11.1 (± 25.3)	0.0 (± 999)
Fin. diff.: C1 D1 (Baseline, n=137,147,87,88)	12.4 (± 25.2)	20.9 (± 30.0)	16.5 (± 30.4)	15.9 (± 26.3)
Fin. diff.: Change at C1 D8 (n=24,22,16,19)	-9.7 (± 25.0)	-3.0 (± 14.2)	2.1 (± 8.3)	-7.0 (± 17.8)
Fin. diff.: Change at C1 D15 (n=131,139,78,84)	1.5 (± 17.5)	-1.9 (± 20.0)	0.0 (± 15.2)	-4.4 (± 21.2)
Fin. diff.: Change at C1 D22 (n=22,21,15,17)	-1.5 (± 26.2)	-3.2 (± 14.5)	0.0 (± 0.0)	0.0 (± 20.4)
Fin. diff.: Change at C2 D1 (n=126,141,82,83)	0.0 (± 17.9)	-3.1 (± 21.0)	0.8 (± 16.5)	-4.4 (± 19.3)
Fin. diff.: Change at C2 D15 (n=119,134,80,79)	1.1 (± 20.8)	-2.2 (± 20.1)	-0.4 (± 17.2)	-7.2 (± 20.4)
Fin. diff.: Change at C3 D1 (n=119,129,80,77)	0.3 (± 21.5)	-5.2 (± 24.1)	1.3 (± 20.2)	-5.6 (± 19.8)
Fin. diff.: Change at C4 D1 (n=119,129,78,75)	-0.8 (± 23.6)	-2.8 (± 24.3)	-0.4 (± 19.7)	-5.8 (± 18.5)
Fin. diff.: Change at C5 D1 (n=110,116,72,64)	1.2 (± 23.0)	-5.5 (± 26.7)	2.3 (± 18.0)	-7.8 (± 23.6)
Fin. diff.: Change at C6 D1 (n=106,112,69,63)	-0.6 (± 22.5)	-7.4 (± 26.4)	2.9 (± 20.4)	-5.8 (± 22.0)
Fin. diff.: Change at C7 D1 (n=106,107,68,59)	1.9 (± 26.8)	-5.6 (± 26.1)	4.9 (± 27.2)	-5.6 (± 21.6)
Fin. diff.: Change at C8 D1 (n=104,106,65,53)	-0.6 (± 23.2)	-4.7 (± 27.0)	4.1 (± 26.7)	-3.1 (± 20.9)
Fin. diff.: Change at C9 D1 (n=100,101,63,52)	2.0 (± 24.1)	-8.9 (± 23.0)	4.2 (± 23.6)	-5.8 (± 20.6)

Fin. diff.: Change at C10 D1 (n=96,97,63,47)	1.0 (± 23.4)	-8.6 (± 25.1)	2.6 (± 22.6)	-6.4 (± 20.4)
Fin. diff.: Change at C11 D1 (n=93,93,57,48)	1.4 (± 21.4)	-7.5 (± 21.5)	0.6 (± 20.4)	-8.3 (± 22.3)
Fin. diff.: Change at C12 D1 (n=89,90,55,48)	-0.4 (± 24.4)	-6.3 (± 23.9)	0.0 (± 26.4)	-6.3 (± 23.5)
Fin. diff.: Change at C13 D1 (n=82,89,54,45)	1.2 (± 23.7)	-6.0 (± 22.2)	-1.9 (± 27.8)	-8.1 (± 24.8)
Fin. diff.: Change at EOT (n=122,125,67,75)	2.5 (± 23.1)	-3.7 (± 26.5)	-2.5 (± 23.4)	-0.9 (± 23.9)
Fin. diff.: Change at PT 13 Weeks (n=90,74,56,38)	0.4 (± 26.2)	-5.9 (± 24.3)	-10.1 (± 27.6)	-8.8 (± 25.3)
Fin. diff.: Change at PT 26 Weeks (n=89,72,47,35)	-3.0 (± 22.3)	-6.0 (± 18.8)	-5.7 (± 26.3)	-7.6 (± 25.7)
Fin. diff.: Change at PT 39 Weeks (n=78,68,41,33)	-1.7 (± 22.1)	-7.8 (± 25.8)	-2.4 (± 28.3)	-8.1 (± 26.4)
Fin. diff.: Change at PT 52 Weeks (n=75,62,27,25)	-2.2 (± 21.5)	-5.4 (± 21.1)	-11.1 (± 24.5)	-1.3 (± 32.6)
Fin. diff.: Change at PT 65 Weeks (n=52,38,17,18)	2.6 (± 26.3)	-6.1 (± 30.9)	-9.8 (± 19.6)	-7.4 (± 31.4)
Fin. diff.: Change at PT 78 Weeks (n=45,33,15,9)	2.2 (± 27.9)	-8.1 (± 31.2)	-11.1 (± 20.6)	0.0 (± 16.7)
Fin. diff.: Change at PT 91 Weeks (n=31,29,15,12)	0.0 (± 27.2)	-10.3 (± 29.7)	-11.1 (± 20.6)	-11.1 (± 32.8)
Fin. diff.: Change at PT 104 Weeks (n=26,25,10,9)	-2.6 (± 18.7)	-8.0 (± 30.9)	-13.3 (± 23.3)	-18.5 (± 37.7)
Fin. diff.: Change at PT 117 Weeks (n=22,17,8,5)	-6.1 (± 22.1)	-5.9 (± 24.3)	-4.2 (± 11.8)	-13.3 (± 18.3)
Fin. diff.: Change at PT 130 Weeks (n=17,12,5,5)	-7.8 (± 27.7)	-5.6 (± 31.2)	0.0 (± 0.0)	-20.0 (± 29.8)
Fin. diff.: Change at PT 143 Weeks (n=7,2,3,2)	4.8 (± 40.5)	16.7 (± 23.6)	0.0 (± 0.0)	0.0 (± 0.0)
Fin. diff.: Change at PT 156 Weeks (n=3,1,0,2)	-22.2 (± 38.5)	0.0 (± 999)	99999 (± 99999)	-16.7 (± 23.6)
Fin. diff.: Change at PT 169 Weeks (n=2,1,0,0)	0.0 (± 0.0)	0.0 (± 999)	99999 (± 99999)	99999 (± 99999)
Fin. diff.: Change at PT 182 Weeks (n=3,0,0,0)	-22.2 (± 38.5)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Fin. diff.: Change at PT/Discont. (n=8,1,6,1)	0.0 (± 17.8)	0.0 (± 999)	0.0 (± 0.0)	0.0 (± 999)
Naus./vom.: C1 D1 (Baseline, n=138,147,87,89)	1.4 (± 5.1)	1.8 (± 9.6)	1.9 (± 7.4)	1.3 (± 5.2)
Naus./vom.: Change at C1 D8 (n=24,22,16,19)	4.2 (± 8.9)	0.8 (± 6.3)	5.2 (± 8.0)	3.5 (± 8.9)
Naus./vom.: Change at C1 D15 (n=132,139,80,84)	9.8 (± 16.9)	1.8 (± 6.9)	8.8 (± 17.0)	1.2 (± 7.7)
Naus./vom.: Change at C1 D22 (n=22,21,15,17)	6.1 (± 12.1)	0.8 (± 6.4)	5.6 (± 10.3)	2.9 (± 8.8)
Naus./vom.: Change at C2 D1 (n=127,142,83,84)	5.2 (± 12.9)	0.9 (± 5.9)	4.6 (± 11.1)	1.4 (± 7.9)
Naus./vom.: Change at C2 D15 (n=119,134,80,81)	6.3 (± 14.1)	1.1 (± 8.5)	2.9 (± 9.1)	1.6 (± 10.4)
Naus./vom.: Change at C3 D1 (n=119,129,81,78)	5.7 (± 13.1)	1.6 (± 7.3)	4.5 (± 9.9)	1.3 (± 8.4)
Naus./vom.: Change at C4 D1 (n=119,129,78,76)	5.6 (± 13.6)	1.9 (± 11.7)	6.6 (± 14.3)	1.3 (± 10.8)
Naus./vom.: Change at C5 D1 (n=110,117,72,64)	7.3 (± 16.4)	2.6 (± 9.2)	5.1 (± 10.7)	-0.5 (± 7.8)
Naus./vom.: Change at C6 D1 (n=106,112,69,63)	5.3 (± 13.1)	2.4 (± 9.7)	6.3 (± 12.2)	-0.5 (± 7.9)
Naus./vom.: Change at C7 D1 (n=106,108,68,59)	4.7 (± 11.7)	2.0 (± 7.8)	4.2 (± 11.3)	0.6 (± 6.9)

Naus./vom.: Change at C8 D1 (n=105,106,65,53)	4.6 (± 11.9)	1.1 (± 9.0)	5.9 (± 15.7)	2.5 (± 12.4)
Naus./vom.: Change at C9 D1 (n=100,101,63,52)	5.5 (± 15.7)	2.5 (± 10.4)	4.0 (± 10.2)	0.3 (± 7.0)
Naus./vom.: Change at C10 D1 (n=96,97,63,47)	5.2 (± 13.1)	0.9 (± 10.3)	4.8 (± 10.6)	0.4 (± 6.5)
Naus./vom.: Change at C11 D1 (n=93,93,57,48)	3.4 (± 10.9)	2.0 (± 8.5)	3.2 (± 8.6)	-0.3 (± 5.4)
Naus./vom.: Change at C12 D1 (n=90,91,55,48)	4.3 (± 12.6)	1.3 (± 7.9)	4.8 (± 10.5)	3.5 (± 13.7)
Naus./vom.: Change at C13 D1 (n=82,89,54,45)	2.8 (± 11.7)	1.7 (± 7.1)	3.4 (± 9.9)	2.2 (± 9.8)
Naus./vom.: Change at EOT (n=123,125,67,75)	0.9 (± 6.5)	0.3 (± 12.5)	1.5 (± 11.9)	3.8 (± 13.9)
Naus./vom.: Change at PT 13 Weeks (n=90,74,56,38)	0.2 (± 6.4)	1.8 (± 8.5)	0.6 (± 6.3)	0.9 (± 6.7)
Naus./vom.: Change at PT 26 Weeks (n=90,72,47,35)	2.2 (± 8.7)	0.7 (± 15.7)	0.7 (± 10.4)	-1.0 (± 3.9)
Naus./vom.: Change at PT 39 Weeks (n=79,68,42,33)	0.2 (± 5.7)	0.2 (± 6.1)	1.6 (± 8.1)	1.5 (± 6.4)
Naus./vom.: Change at PT 52 Weeks (n=76,62,27,25)	0.9 (± 6.0)	0.3 (± 4.8)	0.0 (± 4.6)	0.7 (± 3.3)
Naus./vom.: Change at PT 65 Weeks (n=53,38,17,18)	0.0 (± 5.7)	3.5 (± 12.9)	-1.0 (± 4.0)	2.8 (± 8.6)
Naus./vom.: Change at PT 78 Weeks (n=46,33,15,9)	0.4 (± 5.5)	2.0 (± 11.6)	-1.1 (± 4.3)	1.9 (± 5.6)
Naus./vom.: Change at PT 91 Weeks (n=32,29,15,12)	1.6 (± 6.5)	2.3 (± 8.6)	-1.1 (± 4.3)	1.4 (± 4.8)
Naus./vom.:Change at PT 104 Weeks (n=27,25,10,9)	1.9 (± 10.7)	0.0 (± 4.8)	0.0 (± 0.0)	0.0 (± 0.0)
Naus./vom.:Change at PT 117 Weeks (n=22,17,9,5)	-1.5 (± 4.9)	4.9 (± 9.8)	-1.9 (± 5.6)	0.0 (± 0.0)
Naus./vom.:Change at PT 130 Weeks (n=17,12,5,5)	0.0 (± 5.9)	4.2 (± 10.4)	-3.3 (± 7.5)	0.0 (± 0.0)
Naus./vom.:Change at PT 143 Weeks (n=7,2,3,2)	-2.4 (± 6.3)	0.0 (± 0.0)	0.0 (± 0.0)	0.0 (± 0.0)
Naus./vom.:Change at PT 156 Weeks (n=3,1,0,2)	0.0 (± 0.0)	0.0 (± 999)	99999 (± 99999)	8.3 (± 11.8)
Naus./vom.:Change at PT 169 Weeks (n=2,1,0,0)	0.0 (± 0.0)	0.0 (± 999)	99999 (± 99999)	99999 (± 99999)
Naus./vom.:Change at PT 182 Weeks (n=3,0,0,0)	0.0 (± 0.0)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Naus./vom.: Change at PT/Discont. (n=8,1,6,1)	4.2 (± 11.8)	0.0 (± 999)	8.3 (± 13.9)	0.0 (± 999)
Pain: C1 D1 (Baseline, n=138,147,87,89)	11.6 (± 17.5)	12.8 (± 21.6)	10.9 (± 19.0)	14.6 (± 23.9)
Pain: Change at C1 D8 (n=24,22,16,19)	9.7 (± 22.5)	-1.5 (± 15.4)	10.4 (± 14.8)	-3.5 (± 8.9)
Pain: Change at C1 D15 (n=132,139,80,84)	20.8 (± 28.5)	0.5 (± 12.4)	16.3 (± 28.1)	-1.4 (± 14.7)
Pain: Change at C1 D22 (n=22,21,15,17)	15.9 (± 28.9)	-3.2 (± 13.6)	22.2 (± 18.5)	9.8 (± 21.3)
Pain: Change at C2 D1 (n=127,142,83,84)	12.9 (± 26.5)	0.5 (± 15.1)	15.1 (± 28.9)	-3.8 (± 18.0)
Pain: Change at C2 D15 (n=119,134,80,81)	14.3 (± 27.5)	2.4 (± 17.2)	12.7 (± 23.3)	-3.5 (± 18.0)
Pain: Change at C3 D1 (n=119,129,81,78)	11.8 (± 20.2)	1.2 (± 16.3)	13.2 (± 25.6)	-0.6 (± 17.1)
Pain: Change at C4 D1 (n=119,129,78,76)	9.0 (± 22.1)	4.0 (± 19.7)	12.0 (± 25.9)	-2.4 (± 19.6)
Pain: Change at C5 D1 (n=110,117,72,64)	12.7 (± 24.3)	1.9 (± 17.6)	14.6 (± 21.1)	-4.9 (± 20.5)

Pain: Change at C6 D1 (n=106,112,69,63)	8.8 (± 22.7)	2.2 (± 18.9)	14.5 (± 22.9)	-3.7 (± 20.0)
Pain: Change at C7 D1 (n=106,108,68,59)	8.2 (± 21.4)	0.9 (± 16.6)	8.3 (± 20.5)	-2.0 (± 19.1)
Pain: Change at C8 D1 (n=105,106,65,53)	11.0 (± 24.9)	3.6 (± 20.1)	12.1 (± 23.7)	-1.6 (± 18.3)
Pain: Change at C9 D1 (n=100,101,63,52)	12.8 (± 27.5)	3.6 (± 21.2)	10.3 (± 23.5)	-0.3 (± 23.9)
Pain: Change at C10 D1 (n=96,97,63,47)	8.9 (± 22.0)	1.9 (± 17.5)	11.6 (± 24.6)	-3.2 (± 16.9)
Pain: Change at C11 D1 (n=93,93,57,48)	10.0 (± 25.0)	2.7 (± 21.3)	13.5 (± 26.1)	-0.7 (± 24.3)
Pain: Change at C12 D1 (n=90,91,55,48)	12.2 (± 24.6)	1.3 (± 19.8)	12.7 (± 19.5)	-2.1 (± 20.2)
Pain: Change at C13 D1 (n=82,89,54,45)	11.6 (± 23.5)	3.4 (± 21.2)	16.4 (± 27.4)	-1.9 (± 22.0)
Pain: Change at EOT (n=123,125,67,75)	4.9 (± 23.4)	4.1 (± 23.3)	6.7 (± 21.1)	1.6 (± 21.4)
Pain: Change at PT 13 Weeks (n=90,74,56,38)	-0.6 (± 17.6)	-0.2 (± 18.2)	4.2 (± 19.7)	-4.8 (± 23.5)
Pain: Change at PT 26 Weeks (n=90,72,47,35)	1.1 (± 21.8)	-1.2 (± 16.6)	7.1 (± 24.0)	-4.3 (± 19.5)
Pain: Change at PT 39 Weeks (n=79,68,42,33)	0.6 (± 19.9)	2.2 (± 22.1)	7.5 (± 23.0)	-7.6 (± 23.2)
Pain: Change at PT 52 Weeks (n=76,62,27,25)	2.0 (± 18.0)	0.0 (± 16.3)	9.3 (± 21.8)	-1.3 (± 20.4)
Pain: Change at PT 65 Weeks (n=53,38,17,18)	-0.3 (± 19.7)	0.9 (± 21.2)	6.9 (± 15.7)	-4.6 (± 12.5)
Pain: Change at PT 78 Weeks (n=46,33,15,9)	0.7 (± 20.2)	2.5 (± 19.6)	1.1 (± 14.7)	-5.6 (± 8.3)
Pain: Change at PT 91 Weeks (n=33,29,15,12)	-2.5 (± 18.7)	4.6 (± 25.9)	4.4 (± 14.7)	-9.7 (± 21.9)
Pain: Change at PT 104 Weeks (n=27,25,10,9)	-1.2 (± 17.9)	11.3 (± 22.4)	3.3 (± 13.1)	-13.0 (± 21.7)
Pain: Change at PT 117 Weeks (n=22,17,9,5)	-4.5 (± 18.0)	8.8 (± 22.9)	1.9 (± 13.0)	-10.0 (± 25.3)
Pain: Change at PT 130 Weeks (n=17,12,5,5)	2.9 (± 19.8)	6.9 (± 31.3)	6.7 (± 27.9)	-13.3 (± 32.1)
Pain: Change at PT 143 Weeks (n=7,2,3,2)	-2.4 (± 20.2)	8.3 (± 11.8)	5.6 (± 25.5)	0.0 (± 0.0)
Pain: Change at PT 156 Weeks (n=3,1,0,2)	-22.2 (± 19.2)	0.0 (± 999)	99999 (± 99999)	8.3 (± 11.8)
Pain: Change at PT 169 Weeks (n=2,1,0,0)	-8.3 (± 11.8)	0.0 (± 999)	99999 (± 99999)	99999 (± 99999)
Pain: Change at PT 182 Weeks (n=3,0,0,0)	-22.2 (± 19.2)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Pain: Change at PT/Discont. (n=8,1,6,1)	12.5 (± 14.8)	-33.3 (± 999)	-2.8 (± 19.5)	0.0 (± 999)
Phys. func.: C1 D1 (Baseline, n=138,147,87,89)	92.7 (± 11.0)	92.3 (± 11.6)	91.3 (± 13.6)	92.7 (± 13.1)
Phys. func.: Change at C1 D8 (n=24,22,16,19)	-4.4 (± 8.7)	0.3 (± 4.4)	-5.0 (± 6.7)	-2.5 (± 11.6)
Phys. func.: Change at C1 D15 (n=132,139,80,84)	-9.7 (± 17.4)	-0.2 (± 8.2)	-7.4 (± 15.0)	-1.5 (± 6.5)
Phys. func.: Change at C1 D22 (n=22,21,15,17)	-10.3 (± 16.6)	-0.6 (± 7.0)	-10.2 (± 15.3)	-2.7 (± 9.7)
Phys. func.: Change at C2 D1 (n=127,142,83,84)	-6.2 (± 14.4)	-0.3 (± 9.1)	-9.2 (± 16.9)	-1.8 (± 8.2)
Phys. func.: Change at C2 D15 (n=119,134,80,81)	-7.1 (± 16.4)	-0.7 (± 10.8)	-7.6 (± 13.9)	-1.4 (± 9.4)
Phys. func.: Change at C3 D1 (n=119,129,81,78)	-6.6 (± 14.8)	-0.7 (± 11.0)	-7.3 (± 15.0)	-2.7 (± 10.4)

Phys. func.: Change at C4 D1 (n=119,129,81,78)	-4.9 (± 13.1)	-0.2 (± 10.8)	-7.4 (± 13.8)	-1.0 (± 10.3)
Phys. func.: Change at C5 D1 (n=110,117,72,64)	-6.1 (± 14.7)	-1.0 (± 11.3)	-5.6 (± 13.3)	-1.8 (± 12.7)
Phys. func.: Change at C6 D1 (n=106,112,69,63)	-4.7 (± 14.5)	-0.8 (± 12.1)	-7.5 (± 15.2)	-0.6 (± 10.0)
Phys. func.: Change at C7 D1 (n=106,108,68,59)	-4.7 (± 13.6)	0.4 (± 11.2)	-8.0 (± 12.7)	0.2 (± 9.5)
Phys. func.: Change at C8 D1 (n=105,106,65,53)	-5.2 (± 13.6)	-0.8 (± 13.1)	-6.7 (± 12.6)	-0.3 (± 11.0)
Phys. func.: Change at C9 D1 (n=100,101,63,52)	-6.7 (± 18.2)	-0.5 (± 12.2)	-5.5 (± 10.6)	-1.5 (± 14.7)
Phys. func.: Change at C10 D1 (n=96,97,63,47)	-4.9 (± 14.0)	-1.6 (± 11.8)	-6.5 (± 13.2)	-1.7 (± 9.9)
Phys. func.: Change at C11 D1 (n=93,93,57,48)	-4.2 (± 14.4)	-1.3 (± 10.8)	-6.0 (± 12.8)	-3.3 (± 13.5)
Phys. func.: Change at C12 D1 (n=90,91,55,48)	-5.4 (± 15.7)	-1.6 (± 11.5)	-4.8 (± 11.9)	-0.6 (± 10.8)
Phys. func.: Change at C13 D1 (n=82,89,54,45)	-4.5 (± 15.0)	-3.0 (± 14.7)	-5.6 (± 12.4)	-1.9 (± 12.3)
Phys. func.: Change at EOT (n=123,125,67,75)	-2.8 (± 13.3)	-2.9 (± 16.0)	-5.8 (± 13.8)	-5.1 (± 14.7)
Phys. func.: Change at PT 13 Weeks (n=90,74,56,38)	0.5 (± 11.3)	0.1 (± 9.8)	-0.8 (± 10.9)	-0.5 (± 12.6)
Phys. func.: Change at PT 26 Weeks (n=90,72,47,35)	-1.9 (± 12.5)	0.0 (± 8.5)	-4.1 (± 10.5)	0.6 (± 12.6)
Phys. func.: Change at PT 39 Weeks (n=79,68,42,33)	0.4 (± 10.7)	-1.7 (± 13.5)	-3.3 (± 13.4)	0.6 (± 8.1)
Phys. func.: Change at PT 52 Weeks (n=76,62,27,25)	-1.4 (± 10.0)	-0.5 (± 11.7)	-1.4 (± 9.6)	-1.1 (± 14.2)
Phys. func.: Change at PT 65 Weeks (n=53,38,17,18)	-0.9 (± 8.6)	-2.6 (± 13.6)	2.7 (± 9.7)	-0.4 (± 10.3)
Phys. func.: Change at PT 78 Weeks (n=46,33,15,9)	-0.5 (± 8.6)	-1.0 (± 10.8)	2.7 (± 10.0)	-3.7 (± 11.6)
Phys. func.: Change at PT 91 Weeks (n=33,29,15,12)	0.2 (± 7.2)	-3.4 (± 12.9)	-0.9 (± 10.3)	0.0 (± 17.5)
Phys. func.: Change at PT 104 Weeks (n=27,25,10,9)	2.5 (± 8.3)	-4.9 (± 10.3)	1.3 (± 11.2)	1.5 (± 18.2)
Phys. func.: Change at PT 117 Weeks (n=22,17,9,5)	1.2 (± 8.1)	-7.1 (± 14.2)	0.7 (± 13.1)	2.7 (± 19.2)
Phys. func.: Change at PT 130 Weeks (n=17,12,5,5)	-1.2 (± 4.2)	-5.0 (± 11.4)	-2.7 (± 10.1)	5.3 (± 20.2)
Phys. func.: Change at PT 143 Weeks (n=7,2,3,2)	0.0 (± 8.6)	0.0 (± 0.0)	-4.4 (± 20.4)	-3.3 (± 4.7)
Phys. func.: Change at PT 156 Weeks (n=3,1,0,2)	2.2 (± 3.8)	0.0 (± 999)	99999 (± 99999)	-6.7 (± 9.4)
Phys. func.: Change at PT 169 Weeks (n=2,1,0,0)	3.3 (± 4.7)	0.0 (± 999)	99999 (± 99999)	99999 (± 99999)
Phys. func.: Change at PT 182 Weeks (n=3,0,0,0)	2.2 (± 3.8)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Phys. func.: Change at PT/Discont. (n=8,1,6,1)	-0.8 (± 8.3)	0.0 (± 999)	10.0 (± 15.6)	0.0 (± 999)
GHS/QoL: C1 D1 (Baseline, n=138,147,87,89)	79.0 (± 16.7)	77.9 (± 18.4)	76.5 (± 20.6)	78.8 (± 17.6)
GHS/QoL: Change at C1 D8 (n=24,22,16,19)	-9.4 (± 20.5)	0.4 (± 7.5)	-9.9 (± 15.9)	1.3 (± 6.4)
GHS/QoL: Change at C1 D15 (n=132,139,78,83)	-19.1 (± 24.2)	-0.4 (± 11.4)	-14.5 (± 20.4)	-0.3 (± 11.7)
GHS/QoL: Change at C1 D22 (n=22,21,15,17)	-17.8 (± 27.0)	1.2 (± 10.3)	-16.7 (± 19.9)	0.5 (± 11.2)
GHS/QoL: Change at C2 D1 (n=127,142,82,84)	-9.8 (± 19.7)	-1.2 (± 14.5)	-10.9 (± 17.6)	1.0 (± 10.8)

GHS/QoL: Change at C2 D15 (n=118,134,80,80)	-11.5 (± 21.0)	0.2 (± 13.5)	-9.5 (± 18.0)	-1.4 (± 14.4)
GHS/QoL: Change at C3 D1 (n=119,129,81,78)	-10.6 (± 19.0)	-1.0 (± 14.6)	-9.4 (± 17.0)	-0.9 (± 14.6)
GHS/QoL: Change at C4 D1 (n=119,129,78,76)	-10.2 (± 19.6)	-1.0 (± 14.9)	-8.4 (± 18.9)	-1.8 (± 15.4)
GHS/QoL: Change at C5 D1 (n=110,116,72,64)	-12.0 (± 20.4)	-0.1 (± 15.1)	-8.9 (± 17.3)	0.4 (± 16.6)
GHS/QoL: Change at C6 D1 (n=106,112,69,63)	-8.9 (± 18.9)	-2.2 (± 16.1)	-12.4 (± 19.3)	-0.5 (± 16.5)
GHS/QoL: Change at C7 D1 (n=106,108,68,59)	-10.7 (± 19.4)	-1.6 (± 16.8)	-11.8 (± 17.9)	-2.3 (± 15.8)
GHS/QoL: Change at C8 D1 (n=104,106,65,53)	-10.3 (± 18.3)	-1.6 (± 17.6)	-11.2 (± 20.5)	-3.3 (± 17.0)
GHS/QoL: Change at C9 D1 (n=100,101,63,52)	-11.3 (± 21.9)	-0.5 (± 16.9)	-8.3 (± 19.7)	-1.6 (± 16.6)
GHS/QoL: Change at C10 D1 (n=96,97,63,47)	-7.6 (± 19.1)	-0.7 (± 15.9)	-9.8 (± 18.7)	0.2 (± 15.0)
GHS/QoL: Change at C11 D1 (n=93,93,57,48)	-7.8 (± 19.5)	-0.8 (± 15.3)	-8.8 (± 18.9)	-3.1 (± 18.2)
GHS/QoL: Change at C12 D1 (n=90,91,55,48)	-9.3 (± 20.2)	-0.8 (± 16.0)	-10.5 (± 17.4)	-3.6 (± 18.0)
GHS/QoL: Change at C13 D1 (n=82,89,54,45)	-7.5 (± 17.5)	-3.4 (± 19.4)	-9.4 (± 18.9)	-3.9 (± 15.8)
GHS/QoL: Change at EOT (n=123,125,67,75)	-5.2 (± 19.0)	-3.6 (± 19.0)	-3.0 (± 18.4)	-7.4 (± 21.7)
GHS/QoL: Change at PT 13 Weeks (n=90,74,56,38)	0.1 (± 16.0)	-0.1 (± 15.7)	-1.0 (± 18.1)	0.2 (± 20.0)
GHS/QoL: Change at PT 26 Weeks (n=90,72,47,35)	-2.2 (± 16.2)	0.5 (± 14.8)	0.4 (± 19.5)	0.0 (± 19.7)
GHS/QoL: Change at PT 39 Weeks (n=79,68,41,33)	-4.1 (± 21.6)	-0.9 (± 15.2)	-0.4 (± 16.9)	-1.3 (± 19.9)
GHS/QoL: Change at PT 52 Weeks (n=76,62,27,25)	-2.3 (± 15.6)	-0.7 (± 15.3)	2.2 (± 13.2)	-2.0 (± 23.6)
GHS/QoL: Change at PT 65 Weeks (n=53,38,17,18)	-0.9 (± 17.7)	-2.0 (± 15.1)	1.5 (± 15.1)	-0.5 (± 17.7)
GHS/QoL: Change at PT 78 Weeks (n=46,33,15,9)	-0.9 (± 15.6)	-1.5 (± 15.8)	1.7 (± 14.8)	-0.9 (± 13.5)
GHS/QoL: Change at PT 91 Weeks (n=33,29,15,12)	0.3 (± 17.4)	-2.6 (± 17.6)	6.1 (± 15.3)	-2.1 (± 24.7)
GHS/QoL: Change at PT 104 Weeks (n=27,25,10,9)	1.2 (± 14.9)	-4.7 (± 19.4)	-3.3 (± 19.3)	0.0 (± 29.2)
GHS/QoL: Change at PT 117 Weeks (n=22,17,8,5)	0.4 (± 20.5)	2.5 (± 15.0)	-1.0 (± 13.7)	6.7 (± 21.6)
GHS/QoL: Change at PT 130 Weeks (n=16,12,5,5)	2.1 (± 7.1)	-3.5 (± 16.8)	-3.3 (± 12.6)	5.0 (± 24.0)
GHS/QoL: Change at PT 143 Weeks (n=7,2,3,2)	-1.2 (± 18.9)	-4.2 (± 5.9)	-11.1 (± 9.6)	-8.3 (± 11.8)
GHS/QoL: Change at PT 156 Weeks (n=3,1,0,2)	11.1 (± 4.8)	0.0 (± 999)	99999 (± 99999)	12.5 (± 5.9)
GHS/QoL: Change at PT 169 Weeks (n=2,1,0,0)	8.3 (± 0.0)	0.0 (± 999)	99999 (± 99999)	99999 (± 99999)
GHS/QoL: Change at PT 182 Weeks (n=3,0,0,0)	19.4 (± 12.7)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
GHS/QoL: Change at PT/Discont. (n=8,1,6,1)	-4.2 (± 19.9)	0.0 (± 999)	0.0 (± 31.2)	0.0 (± 999)
Role func.: C1 D1 (Baseline, n=138,147,87,89)	86.7 (± 21.9)	87.2 (± 22.5)	86.6 (± 22.0)	88.6 (± 23.2)
Role func.: Change at C1 D8 (n=24,22,16,19)	-2.8 (± 15.3)	-0.8 (± 10.9)	-1.0 (± 16.6)	4.4 (± 18.3)
Role func.: Change at C1 D15 (n=132,139,80,84)	-19.4 (± 29.1)	0.2 (± 16.3)	-15.2 (± 27.6)	-2.4 (± 19.6)

Role func.: Change at C1 D22 (n=22,21,15,17)	-10.6 (± 28.4)	1.6 (± 9.0)	-16.7 (± 20.9)	-1.0 (± 25.3)
Role func.: Change at C2 D1 (n=127,142,83,84)	-13.0 (± 26.6)	0.2 (± 16.6)	-13.3 (± 27.5)	0.4 (± 17.5)
Role func.: Change at C2 D15 (n=119,134,80,81)	-11.1 (± 25.7)	-0.6 (± 18.4)	-9.6 (± 21.5)	-0.4 (± 17.5)
Role func.: Change at C3 D1 (n=119,129,81,78)	-9.7 (± 25.4)	0.4 (± 19.0)	-8.2 (± 21.3)	-2.1 (± 21.2)
Role func.: Change at C4 D1 (n=119,129,78,76)	-8.4 (± 23.8)	0.3 (± 21.3)	-9.0 (± 19.7)	-1.3 (± 19.0)
Role func.: Change at C5 D1 (n=110,117,72,64)	-11.1 (± 26.0)	0.6 (± 20.5)	-10.4 (± 22.3)	0.8 (± 22.7)
Role func.: Change at C6 D1 (n=106,111,69,63)	-5.8 (± 24.2)	-0.5 (± 18.3)	-11.6 (± 22.9)	0.5 (± 20.1)
Role func.: Change at C7 D1 (n=106,108,68,59)	-9.9 (± 27.6)	0.9 (± 21.5)	-8.8 (± 24.0)	0.3 (± 21.3)
Role func.: Change at C8 D1 (n=105,105,65,53)	-9.2 (± 26.5)	-1.9 (± 23.0)	-9.5 (± 24.5)	-0.3 (± 21.3)
Role func.: Change at C9 D1 (n=100,100,63,52)	-11.2 (± 28.4)	0.0 (± 20.7)	-7.9 (± 23.5)	-1.9 (± 25.7)
Role func.: Change at C10 D1 (n=96,97,63,47)	-8.5 (± 25.5)	-1.7 (± 19.3)	-7.7 (± 23.2)	3.9 (± 22.3)
Role func.: Change at C11 D1 (n=93,93,57,48)	-6.6 (± 24.5)	-1.3 (± 19.7)	-10.2 (± 25.0)	-3.5 (± 24.8)
Role func.: Change at C12 D1 (n=90,91,55,48)	-8.7 (± 26.2)	-0.4 (± 17.2)	-8.2 (± 25.2)	0.3 (± 26.3)
Role func.: Change at C13 D1 (n=82,89,54,45)	-8.1 (± 24.6)	-4.5 (± 22.2)	-8.3 (± 25.9)	-2.2 (± 24.3)
Role func.: Change at EOT (n=123,125,67,75)	-4.7 (± 25.0)	-1.3 (± 23.2)	-4.2 (± 25.0)	-6.0 (± 27.6)
Role func.: Change at PT 13 Weeks (n=90,74,56,38)	2.0 (± 21.8)	1.8 (± 17.6)	1.2 (± 19.0)	5.3 (± 26.9)
Role func.: Change at PT 26 Weeks (n=90,72,47,35)	0.9 (± 24.7)	3.0 (± 17.3)	0.4 (± 20.1)	5.2 (± 24.5)
Role func.: Change at PT 39 Weeks (n=79,68,42,33)	2.7 (± 24.2)	0.2 (± 21.1)	0.4 (± 21.3)	7.1 (± 28.0)
Role func.: Change at PT 52 Weeks (n=76,62,27,25)	2.4 (± 23.8)	0.8 (± 20.3)	0.6 (± 18.2)	4.0 (± 29.0)
Role func.: Change at PT 65 Weeks (n=53,38,17,18)	5.3 (± 19.3)	-1.3 (± 16.6)	3.9 (± 11.1)	7.4 (± 29.3)
Role func.: Change at PT 78 Weeks (n=46,33,15,9)	-1.4 (± 25.5)	-4.0 (± 20.0)	4.4 (± 11.7)	-3.7 (± 13.9)
Role func.: Change at PT 91 Weeks (n=33,29,15, 12)	3.5 (± 27.2)	-1.7 (± 17.4)	1.1 (± 14.7)	16.7 (± 35.5)
Role func.: Change at PT 104 Weeks (n=27,25,10,9)	6.2 (± 22.2)	-7.3 (± 20.5)	6.7 (± 14.1)	14.8 (± 38.6)
Role func.: Change at PT 117 Weeks (n=22,17,9,5)	7.6 (± 26.6)	-2.0 (± 10.0)	5.6 (± 11.8)	26.7 (± 41.8)
Role func.: Change at PT 130 Weeks (n=17,12,5,5)	6.9 (± 21.3)	-5.6 (± 14.8)	3.3 (± 18.3)	23.3 (± 43.5)
Role func.: Change at PT 143 Weeks (n=7,2,3,2)	7.1 (± 18.9)	0.0 (± 0.0)	11.1 (± 19.2)	8.3 (± 11.8)
Role func.: Change at PT 156 Weeks (n=3,1,0,2)	27.8 (± 25.5)	0.0 (± 999)	99999 (± 99999)	16.7 (± 23.6)
Role func.: Change at PT 169 Weeks (n=2,1,0,0)	16.7 (± 23.6)	0.0 (± 999)	99999 (± 99999)	99999 (± 99999)
Role func.: Change at PT 182 Weeks (n=3,0,0,0)	27.8 (± 25.5)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Role func.: Change at PT/Discont. (n=8,1,6,1)	-8.3 (± 23.6)	0.0 (± 999)	11.1 (± 17.2)	0.0 (± 999)
Soc. func.: C1 D1 (Baseline, (n=138,147,87,89)	89.6 (± 16.6)	88.2 (± 20.8)	87.7 (± 21.2)	90.4 (± 19.9)

Soc. func.: Change at C1 D8 (n=24,22,16,19)	1.4 (± 18.3)	0.8 (± 12.0)	2.1 (± 14.8)	0.9 (± 8.7)
Soc. func.: Change at C1 D15 (n=132,139,78,84)	-15.0 (± 26.9)	0.8 (± 13.8)	-7.5 (± 18.9)	0.4 (± 13.4)
Soc. func.: Change at C1 D22 (n=22,21,15,17)	-9.1 (± 28.0)	5.6 (± 13.3)	-5.6 (± 17.4)	-2.0 (± 20.3)
Soc. func.: Change at C2 D1 (n=127,142,82,84)	-8.0 (± 22.9)	2.2 (± 16.6)	-10.2 (± 23.8)	3.0 (± 13.7)
Soc. func.: Change at C2 D15 (n=118,134,80,80)	-8.3 (± 21.5)	2.7 (± 16.9)	-7.7 (± 18.2)	4.0 (± 17.0)
Soc. func.: Change at C3 D1 (n=119,129,81,78)	-8.1 (± 21.5)	2.3 (± 17.8)	-7.4 (± 21.1)	1.5 (± 17.9)
Soc. func.: Change at C4 D1 (n=119,129,78,76)	-7.1 (± 21.5)	1.7 (± 18.1)	-7.5 (± 20.6)	1.3 (± 13.5)
Soc. func.: Change at C5 D1 (n=110,116,72,64)	-9.4 (± 21.7)	3.3 (± 17.6)	-9.5 (± 18.5)	2.6 (± 18.6)
Soc. func.: Change at C6 D1 (n=106,112,69,63)	-7.2 (± 22.2)	1.9 (± 17.6)	-11.4 (± 22.4)	0.0 (± 17.2)
Soc. func.: Change at C7 D1 (n=106,108,68,59)	-8.0 (± 22.7)	4.5 (± 17.0)	-9.6 (± 22.9)	0.0 (± 17.2)
Soc. func.: Change at C8 D1 (n=104,106,65,53)	-8.3 (± 23.6)	2.2 (± 17.7)	-7.9 (± 23.0)	0.6 (± 16.0)
Soc. func.: Change at C9 D1 (n=100,101,63,52)	-11.0 (± 26.2)	1.7 (± 19.7)	-8.2 (± 22.8)	-3.8 (± 21.5)
Soc. func.: Change at C10 D1 (n=96,97,63,47)	-8.7 (± 24.9)	0.0 (± 16.1)	-8.7 (± 23.4)	-0.7 (± 16.3)
Soc. func.: Change at C11 D1 (n=93,93,57,48)	-8.6 (± 24.4)	1.4 (± 15.1)	-9.9 (± 23.1)	-2.1 (± 21.6)
Soc. func.: Change at C12 D1 (n=90,91,55,48)	-10.6 (± 24.2)	-0.4 (± 15.7)	-9.1 (± 22.2)	0.0 (± 16.5)
Soc. func.: Change at C13 D1 (n=82,89,54,45)	-8.3 (± 24.2)	-1.9 (± 21.1)	-10.2 (± 25.2)	1.5 (± 17.7)
Soc. func.: Change at EOT (n=123,125,67,75)	-6.1 (± 21.8)	1.2 (± 25.8)	-5.5 (± 23.3)	-3.3 (± 21.2)
Soc. func.: Change at PT 13 Weeks (n=90,74,56,38)	-1.7 (± 18.9)	2.7 (± 15.4)	1.2 (± 16.2)	1.3 (± 19.5)
Soc. func.: Change at PT 26 Weeks (n=90,72,47,35)	-2.6 (± 20.3)	4.2 (± 15.0)	0.0 (± 13.9)	2.4 (± 14.1)
Soc. func.: Change at PT 39 Weeks (n=79,68,41,33)	3.4 (± 16.5)	2.7 (± 15.4)	0.0 (± 18.3)	5.1 (± 17.4)
Soc. func.: Change at PT 52 Weeks (n=76,62,27,25)	-0.7 (± 18.9)	1.6 (± 14.7)	2.5 (± 13.6)	-1.3 (± 18.0)
Soc. func.: Change at PT 65 Weeks (n=53,38,17,18)	2.8 (± 18.7)	0.9 (± 16.0)	4.9 (± 11.4)	0.9 (± 10.7)
Soc. func.: Change at PT 78 Weeks (n=46,33,15,9)	0.7 (± 20.8)	6.1 (± 14.3)	4.4 (± 13.3)	-1.9 (± 13.0)
Soc. func.: Change at PT 91 Weeks (n=32,29,15,12)	2.6 (± 21.6)	1.7 (± 20.1)	2.2 (± 13.9)	2.8 (± 12.0)
Soc. func.: Change at PT 104 Weeks (n=27,25,10,9)	2.5 (± 18.3)	0.0 (± 19.2)	3.3 (± 10.5)	1.9 (± 13.0)
Soc. func.: Change at PT 117 Weeks (n=22,17,8,5)	9.1 (± 15.2)	2.0 (± 21.1)	-2.1 (± 5.9)	3.3 (± 18.3)
Soc. func.: Change at PT 130 Weeks (n=17,12,5,5)	9.8 (± 15.7)	6.9 (± 16.6)	0.0 (± 0.0)	10.0 (± 32.5)
Soc. func.: Change at PT 143 Weeks (n=7,2,3,2)	7.1 (± 18.9)	0.0 (± 0.0)	0.0 (± 0.0)	-8.3 (± 11.8)
Soc. func.: Change at PT 156 Weeks (n=3,1,0,2)	27.8 (± 9.6)	0.0 (± 999)	99999 (± 99999)	0.0 (± 0.0)
Soc. func.: Change at PT 169 Weeks (n=2,1,0,0)	25.0 (± 11.8)	0.0 (± 999)	99999 (± 99999)	99999 (± 99999)
Soc. func.: Change at PT 182 Weeks (n=3,0,0,0)	27.8 (± 9.6)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

Soc. func.: Change at PT/Discont. (n=8,1,6,1)	-4.2 (± 21.4)	0.0 (± 999)	0.0 (± 10.5)	0.0 (± 999)
Insomnia: C1 D1 (Baseline, n=138,147,87,89)	18.4 (± 23.2)	17.0 (± 25.4)	17.2 (± 23.2)	18.7 (± 24.6)
Insomnia: Change at C1 D8 (n=24,22,16,19)	11.1 (± 18.8)	-3.0 (± 14.2)	2.1 (± 22.7)	1.8 (± 20.7)
Insomnia: Change at C1 D15 (n=132,139,80,84)	6.8 (± 29.6)	1.0 (± 19.6)	9.6 (± 26.1)	-4.4 (± 21.2)
Insomnia: Change at C1 D22 (n=22,21,15,17)	9.1 (± 27.6)	-3.2 (± 23.3)	6.7 (± 18.7)	-7.8 (± 22.1)
Insomnia: Change at C2 D1 (n=127,142,83,84)	0.8 (± 23.9)	-1.2 (± 22.6)	2.4 (± 24.8)	-5.6 (± 19.9)
Insomnia: Change at C2 D15 (n=119,134,80,81)	5.9 (± 27.7)	0.5 (± 25.2)	2.1 (± 28.7)	-3.7 (± 23.0)
Insomnia: Change at C3 D1 (n=119,129,81,78)	0.6 (± 25.7)	-1.3 (± 23.0)	-0.4 (± 28.1)	-2.6 (± 22.0)
Insomnia: Change at C4 D1 (n=119,129,78,75)	2.2 (± 25.6)	-1.0 (± 25.0)	3.4 (± 26.1)	-4.9 (± 23.1)
Insomnia: Change at C5 D1 (n=110,117,72,64)	2.4 (± 27.4)	0.3 (± 23.8)	3.2 (± 26.9)	-5.7 (± 22.7)
Insomnia: Change at C6 D1 (n=106,112,68,63)	3.1 (± 28.6)	1.8 (± 25.6)	3.4 (± 26.5)	-4.2 (± 24.3)
Insomnia: Change at C7 D1 (n=106,108,68,59)	4.7 (± 26.6)	-0.3 (± 25.6)	3.4 (± 23.8)	-2.3 (± 17.4)
Insomnia: Change at C8 D1 (n=104,106,65,53)	4.2 (± 28.5)	0.6 (± 29.1)	7.7 (± 29.9)	-6.3 (± 18.6)
Insomnia: Change at C9 D1 (n=100,101,63,52)	3.3 (± 27.8)	0.7 (± 27.1)	6.3 (± 28.6)	0.0 (± 21.9)
Insomnia: Change at C10 D1 (n=96,97,63,47)	1.7 (± 22.9)	0.7 (± 22.0)	4.2 (± 27.1)	-1.4 (± 19.6)
Insomnia: Change at C11 D1 (n=93,93,57,48)	0.7 (± 25.0)	-0.7 (± 25.5)	5.3 (± 32.0)	1.4 (± 18.1)
Insomnia: Change at C12 D1 (n=89,91,55,48)	0.7 (± 24.6)	0.0 (± 27.7)	3.6 (± 29.2)	0.0 (± 23.8)
Insomnia: Change at C13 D1 (n=82,88,54,45)	4.1 (± 26.4)	3.8 (± 31.7)	6.2 (± 29.0)	-1.5 (± 22.4)
Insomnia: Change at EOT (n=123,125,67,75)	-3.0 (± 25.3)	1.3 (± 28.8)	3.5 (± 32.4)	0.4 (± 26.6)
Insomnia: Change at PT 13 Weeks (n=90,74,56,38)	-4.4 (± 21.9)	-1.8 (± 25.2)	-2.4 (± 24.5)	-0.9 (± 22.6)
Insomnia: Change at PT 26 Weeks (n=90,72,47,35)	-2.6 (± 21.9)	0.5 (± 28.2)	-1.4 (± 23.0)	-3.8 (± 22.5)
Insomnia: Change at PT 39 Weeks (n=79,68,42,33)	-5.9 (± 23.7)	-0.5 (± 29.6)	-2.4 (± 27.9)	-5.1 (± 23.7)
Insomnia: Change at PT 52 Weeks (n=76,62,27,25)	-3.9 (± 24.3)	0.5 (± 26.6)	-2.5 (± 26.0)	-8.0 (± 26.0)
Insomnia: Change at PT 65 Weeks (n=53,38,17,18)	-6.3 (± 23.6)	1.8 (± 21.8)	-3.9 (± 33.1)	-3.7 (± 22.5)
Insomnia: Change at PT 78 Weeks (n=46,33,15,9)	-2.2 (± 28.5)	1.0 (± 30.6)	-4.4 (± 27.8)	-3.7 (± 26.1)
Insomnia: Change at PT 91 Weeks (n=33,29,15,12)	-4.0 (± 16.2)	-1.1 (± 25.9)	-4.4 (± 21.3)	-2.8 (± 26.4)
Insomnia: Change at PT 104 Weeks (n=27,25,10,9)	-4.9 (± 17.8)	4.0 (± 27.8)	0.0 (± 22.2)	-3.7 (± 11.1)
Insomnia: Change at PT 117 Weeks (n=22,17,9,5)	-9.1 (± 18.3)	-7.8 (± 30.1)	0.0 (± 16.7)	-13.3 (± 29.8)
Insomnia: Change at PT 130 Weeks (n=17,12,5,5)	-7.8 (± 22.1)	-8.3 (± 20.7)	6.7 (± 27.9)	-6.7 (± 14.9)
Insomnia: Change at PT 143 Weeks (n=7,2,3,2)	-14.3 (± 17.8)	-16.7 (± 23.6)	0.0 (± 33.3)	0.0 (± 0.0)
Insomnia: Change at PT 156 Weeks (n=3,1,0,2)	-11.1 (± 19.2)	0.0 (± 999)	99999 (± 99999)	0.0 (± 0.0)

Insomnia: Change at PT 169 Weeks (n=2,1,0,0)	0.0 (± 0.0)	0.0 (± 999)	99999 (± 99999)	99999 (± 99999)
Insomnia: Change at PT 182 Weeks (n=3,0,0,0)	-11.1 (± 19.2)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
Insomnia: Change at PT/Discont. (n=8,1,6,1)	0.0 (± 17.8)	0.0 (± 999)	5.6 (± 25.1)	0.0 (± 999)

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Vemurafenib

End point title	Plasma Concentration of Vemurafenib ^[1]
End point description: The pharmacokinetic (PK)-evaluable population included all subjects who received at least one dose of vemurafenib and had provided valid PK assessments.	
End point type	Secondary
End point timeframe: Pre-morning dose (0 hour [hr]) and 1 to 4 hrs post-dose on Days 1, 8, 15, and 22 of Cycle 1; pre-morning dose (0 hr) on Days 1 and 15 of Cycle 2; pre-morning dose (0 hr) on Day 1 of Cycles 3-13; at end of treatment (up to 13 months)	

Notes:

[1] - 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: This endpoint is only applicable to treatment groups receiving vemurafenib.

End point values	Cohort 1 Vemurafenib	Cohort 2 Vemurafenib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	92		
Units: nanograms per milliliter (ng/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (nominal Day 1, n=122,77)	2880 (± 2770)	3050 (± 3010)		
Cycle 1 Day 8 (n=79,52)	49900 (± 19800)	43400 (± 13600)		
Cycle 1 Day 15 (n=55,43)	45300 (± 23000)	50200 (± 20500)		
Cycle 1 Day 22 (n=49,45)	44000 (± 22400)	48800 (± 23700)		
Cycle 2 Day 1 (n=107,69)	40200 (± 24100)	43800 (± 19400)		
Cycle 2 Day 15 (n=102,68)	42400 (± 21700)	44200 (± 21200)		
Cycle 3 Day 1 (n=100,69)	46700 (± 21500)	43700 (± 22000)		
Cycle 4 Day 1 (n=98,68)	44800 (± 19300)	47400 (± 20100)		
Cycle 5 Day 1 (n=92,61)	43100 (± 18800)	43700 (± 19400)		
Cycle 6 Day 1 (n=82,62)	46000 (± 18900)	42000 (± 22000)		
Cycle 7 Day 1 (n=86,57)	42800 (± 20500)	45200 (± 20500)		
Cycle 8 Day 1 (n=81,55)	43600 (± 19900)	42600 (± 18900)		

Cycle 9 Day 1 (n=77,51)	42900 (± 18400)	43000 (± 17700)		
Cycle 10 Day 1 (n=38,29)	41000 (± 19000)	43900 (± 18500)		
Cycle 11 Day 1 (n=35,35)	45900 (± 15300)	39700 (± 17600)		
Cycle 12 Day 1 (n=34,26)	43700 (± 15200)	46600 (± 19800)		
Cycle 13 Day 1 (n=36,26)	44000 (± 17200)	42600 (± 19900)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to the data cutoff of July 13, 2018 (approximately 6 years).

Adverse event reporting additional description:

The safety population included all subjects who received at least one dose of study medication.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	Cohort 1 Vemurafenib
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Reporting group description:

Subjects with completely resected Stage IIC, IIIA, or IIIB cutaneous melanoma) received vemurafenib, 960 mg twice daily, in 28-day cycles, for up to 52 weeks

Reporting group title	Cohort 1 Placebo
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Reporting group description:

Subjects with completely resected Stage IIC, IIIA, or IIIB cutaneous melanoma) received vemurafenib-matching placebo twice daily, in 28-day cycles, for up to 52 weeks

Reporting group title	Cohort 2 Vemurafenib
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Reporting group description:

Subjects with Stage IIIC cutaneous melanoma received vemurafenib, 960 mg twice daily, in 28-day cycles, for up to 52 weeks

Reporting group title	Cohort 2 Placebo
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Reporting group description:

Subjects with Stage IIIC cutaneous melanoma received vemurafenib-matching placebo twice daily, in 28-day cycles, for up to 52 weeks

Serious adverse events	Cohort 1 Vemurafenib	Cohort 1 Placebo	Cohort 2 Vemurafenib
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 154 (16.88%)	16 / 156 (10.26%)	15 / 93 (16.13%)
number of deaths (all causes)	17	33	25
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute promyelocytic leukaemia			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical fibroxanthoma			

subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	6 / 154 (3.90%)	7 / 156 (4.49%)	3 / 93 (3.23%)
occurrences causally related to treatment / all	2 / 7	3 / 11	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid cancer			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal stromal tumour			
subjects affected / exposed	0 / 154 (0.00%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine carcinoma			
subjects affected / exposed	0 / 154 (0.00%)	0 / 156 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			

subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic venous thrombosis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 154 (0.00%)	0 / 156 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleuritic pain			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 154 (0.00%)	0 / 156 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 154 (0.00%)	0 / 156 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Electrocardiogram QT prolonged			

subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Pericarditis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 154 (0.00%)	0 / 156 (0.00%)	2 / 93 (2.15%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			
subjects affected / exposed	0 / 154 (0.00%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 154 (0.00%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paralysis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

Lymphangiopathies			
subjects affected / exposed	0 / 154 (0.00%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Iridocyclitis			
subjects affected / exposed	0 / 154 (0.00%)	0 / 156 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Leukoplakia oral			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 154 (0.00%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			

subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic function abnormal			
subjects affected / exposed	0 / 154 (0.00%)	0 / 156 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis exfoliative			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash papular			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 154 (1.30%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Dupuytren's contracture			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 154 (0.00%)	2 / 156 (1.28%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin infection			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			

subjects affected / exposed	0 / 154 (0.00%)	0 / 156 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	0 / 154 (0.00%)	0 / 156 (0.00%)	1 / 93 (1.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperlipasaemia			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	0 / 93 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 2 Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 91 (10.99%)		
number of deaths (all causes)	26		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute promyelocytic leukaemia			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atypical fibroxanthoma			

subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Prostate cancer			
subjects affected / exposed	2 / 91 (2.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thyroid cancer			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal stromal tumour			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neuroendocrine carcinoma			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			

subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pelvic venous thrombosis			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleuritic pain			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Electrocardiogram QT prolonged			

subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lipase increased			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Pericarditis			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Coronary artery occlusion			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Facial paralysis			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

Lymphangiopathies			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Iridocyclitis			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Leukoplakia oral			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Inguinal hernia			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Bile duct stone			

subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic function abnormal			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dermatitis exfoliative			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rash papular			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Dupuytren's contracture			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Groin infection			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatitis B			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Soft tissue infection			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Erysipelas			

subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infected skin ulcer			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyperlipasaemia			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypophosphataemia			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cohort 1 Vemurafenib	Cohort 1 Placebo	Cohort 2 Vemurafenib
Total subjects affected by non-serious adverse events			
subjects affected / exposed	150 / 154 (97.40%)	117 / 156 (75.00%)	92 / 93 (98.92%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	21 / 154 (13.64%)	2 / 156 (1.28%)	19 / 93 (20.43%)
occurrences (all)	32	2	27
Seborrhoeic keratosis			
subjects affected / exposed	13 / 154 (8.44%)	7 / 156 (4.49%)	10 / 93 (10.75%)
occurrences (all)	22	7	17
Keratoacanthoma			

subjects affected / exposed occurrences (all)	14 / 154 (9.09%) 20	0 / 156 (0.00%) 0	10 / 93 (10.75%) 16
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	28 / 154 (18.18%) 31	5 / 156 (3.21%) 8	14 / 93 (15.05%) 22
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	18 / 154 (11.69%) 21	5 / 156 (3.21%) 6	11 / 93 (11.83%) 14
Injury, poisoning and procedural complications			
Sunburn subjects affected / exposed occurrences (all)	25 / 154 (16.23%) 33	2 / 156 (1.28%) 2	19 / 93 (20.43%) 35
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	29 / 154 (18.83%) 44	32 / 156 (20.51%) 41	20 / 93 (21.51%) 24
Dysgeusia subjects affected / exposed occurrences (all)	17 / 154 (11.04%) 18	4 / 156 (2.56%) 4	8 / 93 (8.60%) 8
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	52 / 154 (33.77%) 72	52 / 156 (33.33%) 56	26 / 93 (27.96%) 37
Asthenia subjects affected / exposed occurrences (all)	24 / 154 (15.58%) 38	13 / 156 (8.33%) 17	17 / 93 (18.28%) 22
Pyrexia subjects affected / exposed occurrences (all)	28 / 154 (18.18%) 32	11 / 156 (7.05%) 11	16 / 93 (17.20%) 17
Oedema peripheral subjects affected / exposed occurrences (all)	9 / 154 (5.84%) 9	8 / 156 (5.13%) 8	7 / 93 (7.53%) 7
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	59 / 154 (38.31%)	36 / 156 (23.08%)	27 / 93 (29.03%)
occurrences (all)	74	45	36
Diarrhoea			
subjects affected / exposed	38 / 154 (24.68%)	32 / 156 (20.51%)	27 / 93 (29.03%)
occurrences (all)	61	43	33
Vomiting			
subjects affected / exposed	19 / 154 (12.34%)	9 / 156 (5.77%)	14 / 93 (15.05%)
occurrences (all)	25	9	20
Constipation			
subjects affected / exposed	8 / 154 (5.19%)	11 / 156 (7.05%)	9 / 93 (9.68%)
occurrences (all)	9	14	11
Abdominal pain			
subjects affected / exposed	10 / 154 (6.49%)	7 / 156 (4.49%)	6 / 93 (6.45%)
occurrences (all)	11	7	6
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 154 (9.09%)	8 / 156 (5.13%)	6 / 93 (6.45%)
occurrences (all)	17	9	7
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	57 / 154 (37.01%)	20 / 156 (12.82%)	34 / 93 (36.56%)
occurrences (all)	88	26	52
Alopecia			
subjects affected / exposed	57 / 154 (37.01%)	10 / 156 (6.41%)	37 / 93 (39.78%)
occurrences (all)	57	10	39
Pruritus			
subjects affected / exposed	44 / 154 (28.57%)	27 / 156 (17.31%)	28 / 93 (30.11%)
occurrences (all)	52	29	32
Hyperkeratosis			
subjects affected / exposed	52 / 154 (33.77%)	6 / 156 (3.85%)	35 / 93 (37.63%)
occurrences (all)	80	8	51
Photosensitivity reaction			
subjects affected / exposed	58 / 154 (37.66%)	5 / 156 (3.21%)	26 / 93 (27.96%)
occurrences (all)	84	6	31
Dry skin			

subjects affected / exposed occurrences (all)	32 / 154 (20.78%) 37	13 / 156 (8.33%) 13	16 / 93 (17.20%) 23
Erythema subjects affected / exposed occurrences (all)	20 / 154 (12.99%) 32	8 / 156 (5.13%) 9	17 / 93 (18.28%) 36
Actinic keratosis subjects affected / exposed occurrences (all)	15 / 154 (9.74%) 29	8 / 156 (5.13%) 16	4 / 93 (4.30%) 4
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	9 / 154 (5.84%) 9	7 / 156 (4.49%) 7	12 / 93 (12.90%) 13
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	101 / 154 (65.58%) 173	37 / 156 (23.72%) 52	49 / 93 (52.69%) 92
Pain in extremity subjects affected / exposed occurrences (all)	31 / 154 (20.13%) 37	15 / 156 (9.62%) 16	17 / 93 (18.28%) 19
Myalgia subjects affected / exposed occurrences (all)	23 / 154 (14.94%) 25	9 / 156 (5.77%) 11	9 / 93 (9.68%) 9
Musculoskeletal pain subjects affected / exposed occurrences (all)	9 / 154 (5.84%) 13	8 / 156 (5.13%) 8	8 / 93 (8.60%) 11
Back pain subjects affected / exposed occurrences (all)	5 / 154 (3.25%) 6	14 / 156 (8.97%) 16	7 / 93 (7.53%) 7
Infections and infestations Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	9 / 154 (5.84%) 15	10 / 156 (6.41%) 12	4 / 93 (4.30%) 5
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	17 / 154 (11.04%) 19	11 / 156 (7.05%) 13	16 / 93 (17.20%) 18

Non-serious adverse events	Cohort 2 Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 91 (73.63%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	2 / 91 (2.20%)		
occurrences (all)	2		
Seborrhoeic keratosis			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences (all)	1		
Keratoacanthoma			
subjects affected / exposed	2 / 91 (2.20%)		
occurrences (all)	4		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 91 (4.40%)		
occurrences (all)	4		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 91 (3.30%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
Sunburn			
subjects affected / exposed	2 / 91 (2.20%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 91 (12.09%)		
occurrences (all)	14		
Dysgeusia			
subjects affected / exposed	3 / 91 (3.30%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	18 / 91 (19.78%)		
occurrences (all)	20		

Asthenia subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all)	10 / 91 (10.99%)		
	11		
	7 / 91 (7.69%)		
	8		
	4 / 91 (4.40%)		
	4		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all)	9 / 91 (9.89%)		
	13		
	9 / 91 (9.89%)		
	11		
	4 / 91 (4.40%)		
	7		
	3 / 91 (3.30%)		
	3		
	2 / 91 (2.20%)		
	2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	3 / 91 (3.30%)		
	3		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) Alopecia subjects affected / exposed occurrences (all)	10 / 91 (10.99%)		
	13		
	4 / 91 (4.40%)		
	4		

Pruritus			
subjects affected / exposed	3 / 91 (3.30%)		
occurrences (all)	4		
Hyperkeratosis			
subjects affected / exposed	0 / 91 (0.00%)		
occurrences (all)	0		
Photosensitivity reaction			
subjects affected / exposed	4 / 91 (4.40%)		
occurrences (all)	5		
Dry skin			
subjects affected / exposed	5 / 91 (5.49%)		
occurrences (all)	5		
Erythema			
subjects affected / exposed	6 / 91 (6.59%)		
occurrences (all)	12		
Actinic keratosis			
subjects affected / exposed	2 / 91 (2.20%)		
occurrences (all)	2		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	4 / 91 (4.40%)		
occurrences (all)	4		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	17 / 91 (18.68%)		
occurrences (all)	18		
Pain in extremity			
subjects affected / exposed	4 / 91 (4.40%)		
occurrences (all)	4		
Myalgia			
subjects affected / exposed	3 / 91 (3.30%)		
occurrences (all)	4		
Musculoskeletal pain			
subjects affected / exposed	4 / 91 (4.40%)		
occurrences (all)	5		
Back pain			

subjects affected / exposed occurrences (all)	2 / 91 (2.20%) 2		
Infections and infestations Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	7 / 91 (7.69%) 7		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	2 / 91 (2.20%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 April 2012	<ul style="list-style-type: none">- The reporting requirement for serious adverse events (SAEs) and non-SAEs of special interest to the investigators and the sponsors was changed from within 1 working day to within 24 hours of learning of the event.- The inclusion eligibility criteria were revised to reflect the change in randomization date for subjects participating in the trial. Two new criteria were added, specifying a negative blood stool occult test and adequate resection of all visualized polyps found at colonoscopy to the cecum at screening unless a subject had a previous colonoscopy, with or without polyp resection, within 1 year of randomization.- The liver function requirement for assessment of gamma glutamyl transferease (GGT) ≥ 2.5 the upper limit of normal was deleted, and GGT was deleted from the list of laboratory assessments.- Colonoscopy to the cecum was added to the list of study assessments. Flexible fiberoptic laryngoscopy was included as part of the head and neck evaluation.- An additional two AEs of special interest were added: gastrointestinal polyps and suspected transmission of infectious agent by study drug.
27 June 2012	<ul style="list-style-type: none">- The primary efficacy endpoint, disease-free survival (DFS), was updated to include occurrence of new primary melanoma.- The inclusion criteria were clarified to specify use of the cobas® BRAF V600 Mutation Test as a condition of eligibility.
25 March 2013	<ul style="list-style-type: none">- Language was added to clarify that a computed tomography scan of the head could be performed when a magnetic resonance imaging scan was contraindicated.- For female subjects of childbearing potential and male subjects with partners of childbearing potential, the contraception language was updated to include the need for two effective forms of contraception and also to describe the possible effect of vemurafenib decreasing the plasma exposure of hormonal contraceptives.- The time period within which a subject could be excluded from the study due to a history of a prior invasive malignancy was increased from 3 years to 5 years.- The definition of not having an invasive malignancy at the time of enrollment was clarified to include the pathology results of the screening colonoscopy and the screening Papanicolaou (Pap) smear.- The following exclusion criterion was added: personal history of more than three (>3) adenomatous colorectal polyps or a personal history of adenomatous colorectal polyp(s) >2 centimeters (cm) in size. This also applied to the screening colonoscopy.- The clarification that a current uncorrectable electrolyte disorder that affects serum levels of potassium, calcium, or magnesium was an exclusion criterion was added.- Lipase and amylase were added to the serum chemistry panel.- The prohibited therapy list was expanded to include rifampicin/rifampin, rifabutin, rifapentine, carbamazepine, phenytoin, and phenobarbital.- Collection of information on Fitzpatrick skin type and prior human papilloma virus (HPV) vaccination was added to the dermatology history and monitoring and management sections.- More specific language and closer monitoring of subjects with QTc intervals >500 milliseconds (ms) were added to the guidelines for the assessment and management of QTc abnormalities.
05 September 2013	<ul style="list-style-type: none">- Exclusion criteria were modified as follows: history of or current clinical, radiographic, or pathologic evidence of in-transit metastases satellite or microsatellite lesions.

20 December 2013	<ul style="list-style-type: none"> - The requirement for a computed tomography scan of the primary site was removed. - The requirement for immunohistochemical confirmation of melanoma diagnosis was removed from inclusion criteria. Melanoma must have been histologically confirmed. - An exclusion criterion was added to clarify that subjects who had a history of local and/or regional and/or distant melanoma recurrence (excluding first metachronous nodal recurrence) should have been excluded. Note: this did not include subjects who had a new primary melanoma. - The following safety information was added: drug-induced liver injury and neutropenia.
18 April 2014	<ul style="list-style-type: none"> - Requirement for mandatory colonoscopy at screening was discontinued, except in select subjects with personal and/or family history or signs/symptoms of colorectal cancer or adenomatous polyps. - Requirement for flexible fiberoptic laryngoscopy was removed. - The requirements for mandatory serum amylase and lipase laboratory testing were removed.
14 April 2015	<ul style="list-style-type: none"> - Safety information for the event of hepatic failure was updated. - Potentiation of radiation treatment toxicity was identified as an adverse drug reaction; accordingly, safety information for this event was added. - Pancreatitis was identified as an adverse drug reaction; accordingly, safety information for this event was added. In addition, serum amylase and lipase testing were conducted as part of the workup of any suspected case of pancreatitis, in addition to other appropriate testing (e.g., computed tomography [CT] of the abdomen). - Study design: changed the α level (two sided) from 0.025 for DFS in each independent cohort to 0.05 (two-sided) of the family-wise Type I error rate for two tests of two cohorts; decreased the power for Cohort 1 DFS analysis from 90% to 80%; Cohort 1: approx. 300 subjects (reduced from 500); Cohort 2: approx. 175 subjects (reduced from 225); the number of DFS events required at final DFS analysis was decreased from 190 to 120 in Cohort 1 and from 146 to 120 in Cohort 2; changed the median DFS for the control arm from 26.5 to 24 months in Cohort 1; two OS analyses were proposed for each cohort, one interim analysis and a final analysis; OS landmark rates were clarified to include 1-year, 2-year, and 3-year rates. - End-of-study follow-up was updated from 7 to 6 years after Cycle 1 Day 1 of study treatment. Data cutoff projections were updated to occur approximately 72 months after the first subject enrolled (initiation of enrollment, Q3 2012; final OS analysis cutoff Q4 2018). - Subject-reported outcome language was clarified with regards to outcome measures and the manner in which the results were scored. - The follow-up of subjects with new primary cancers was updated to include all nonmelanoma, new primary cancers including cutaneous squamous cell carcinoma/keratoacanthoma, which was reported to U.S. Food and Drug Administration in accordance with a post-marketing requirement for vemurafenib in the United States.
14 March 2017	<ul style="list-style-type: none"> - Protocol G027826 was amended to change the primary DFS analysis of Cohort 2. - The planned primary DFS analysis of Cohort 2 was revised to be performed at approximately 105 events (reduced from 120 events) to account for a slower than anticipated DFS event rate. The Sponsor made modifications to the study design to minimize the impact of this delay. - A total of 105 DFS events provided approximately 80% power to detect a hazard ratio of 0.58 for the vemurafenib arm versus the placebo arm at an overall two-sided 0.05 significance level. - This change corresponded to an improvement in median DFS from 7.7 months in the placebo arm to 13.3 months in the vemurafenib arm; No changes were made for Cohort 1.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported