Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase II Study Evaluating the Efficacy and Safety of Onartuzumab in Combination with Bevacizumab or Onartuzumab Monotherapy in Patients with Recurrent Glioblastoma

Summary

EudraCT number	2011-005912-27
Trial protocol	DE ES GB IT
Global end of trial date	21 January 2016

Results information

Result version number	v1 (current)
This version publication date	04 February 2017
First version publication date	04 February 2017

Trial information

Trial identification

Sponsor protocol code	GO27819

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01632228
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	21 January 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of onartuzumab + bevacizumab relative to placebo + bevacizumab as measured by investigator-assessed progression-free survival (PFS) in all subjects as well as in the subgroup of subjects with Met-positive (Met+) glioblastoma.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 June 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	United States: 41
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Switzerland: 2
Worldwide total number of subjects	129
EEA total number of subjects	76

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)	96
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Originally the study had three treatment arms, but shortly after enrollment had commenced, recruitment into the onartuzumab + placebo arm was suspended due to 4 of the 5 subjects in this treatment arm requiring hospitalisation because of cerebral oedema. None of these events were considered related to study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo + Bevacizumab

Arm description:

Bevacizumab and matching placebo to onartuzumab were administered once every 3 weeks (q3w) up till primary analysis of the progression-free survival endpoint (up to approximately 18 months).

Arm type	Active comparator
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was administered by intravenous (IV) infusion at 15 milligrams/kilogram (mg/kg) q3w up till primary analysis of the progression-free survival endpoint (up to approximately 18 months). Bevacizumab treatment can continue until there is evidence of progressive disease, treatment-limiting toxicity develops, the treating physician considers the subject to no longer be achieving benefit, or the subject decides to withdraw, whichever occurs first.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Matching placebo to onartuzumab was administered by IV infusion q3w up till primary analysis of the progression-free survival endpoint (up to approximately 18 months).

Arm title	Onartuzumab + Bevacizumab

Arm description:

Onartuzumab and bevacizumab were administered q3w up till primary analysis of the progression-free survival endpoint (up to approximately 18 months).

Arm type	Experimental

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab was administered by intravenous (IV) infusion at 15 milligrams/kilogram (mg/kg) q3w up till primary analysis of the progression-free survival endpoint (up to approximately 18 months). Bevacizumab treatment can continue until there is evidence of progressive disease, treatment-limiting toxicity develops, the treating physician considers the subject to no longer be achieving benefit, or the subject decides to withdraw, whichever occurs first.

Investigational medicinal product name	Onartuzumab
Investigational medicinal product code	
Other name	MetMAb, RO5490258
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Onartuzumab or placebo was administered by IV infusion at 15 mg/kg q3w up till primary analysis of the progression-free survival endpoint (up to approximately 18 months). After the primary efficacy analysis the decision to continue or discontinue treatment with onartuzumab is at the discretion of the investigator in consultation with the subject.

Number of subjects in period 1	Placebo + Bevacizumab	Onartuzumab + Bevacizumab
Started	65	64
Completed	0	0
Not completed	65	64
Death	45	43
Other	3	10
Study terminated by sponsor	11	2
Lost to follow-up	3	4
Progression of disease	3	-
Withdrawal by subject	-	5

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + Bevacizumab
Reporting group description:	
Bevacizumab and matching placebo to onartuzumab were administered once every 3 weeks (q3w) up till primary analysis of the progression-free survival endpoint (up to approximately 18 months).	
Reporting group title	Onartuzumab + Bevacizumab
Reporting group description:	
Onartuzumab and bevacizumab were administered q3w up till primary analysis of the progression-free survival endpoint (up to approximately 18 months).	

Reporting group values	Placebo + Bevacizumab	Onartuzumab + Bevacizumab	Total
Number of subjects	65	64	129
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	55.5	56.2	
standard deviation	± 12.6	± 12.3	-
Gender categorical			
Units: Subjects			
Female	26	20	46
Male	39	44	83

End points

End points reporting groups

Reporting group title	Placebo + Bevacizumab
Reporting group description:	
Bevacizumab and matching placebo to onartuzumab were administered once every 3 weeks (q3w) up till primary analysis of the progression-free survival endpoint (up to approximately 18 months).	
Reporting group title	Onartuzumab + Bevacizumab
Reporting group description:	
Onartuzumab and bevacizumab were administered q3w up till primary analysis of the progression-free survival endpoint (up to approximately 18 months).	
Subject analysis set title	Placebo + Bevacizumab Met+
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with Met+ glioblastoma score within the arm of Placebo + Bevacizumab. Met+ score was based on immunohistochemistry (IHC) score by 50% cutoff.	
Subject analysis set title	Onartuzumab + Bevacizumab Met+
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with Met+ glioblastoma score within the arm of Onartuzumab + Bevacizumab. Met+ score was based on immunohistochemistry (IHC) score by 50% cutoff.	

Primary: Duration of Progression-Free Survival (PFS) in Intent-to-Treat (ITT) Population

End point title	Duration of Progression-Free Survival (PFS) in Intent-to-Treat (ITT) Population
End point description:	
PFS was defined as the time from date of randomisation to the date of first documented disease progression or death, whichever occurs first. Disease progression was determined on the basis of investigator assessment using the Response Assessment in Neuro-Oncology (RANO) criteria. RANO criteria define disease progression as >/= 25% increase in enhancing lesions or significant increase in non-enhancing T2-weighted-Fluid-Attenuated Inversion Recovery (T2-FLAIR) lesions, not attributable to other non-tumour causes or any new lesions as assessed by magnetic resonance imaging (MRI). ITT population included all randomised subjects with subjects allocated to the treatment arm to which they were randomised.	
End point type	Primary
End point timeframe:	
Up to approximately 18 months	

End point values	Placebo + Bevacizumab	Onartuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	64		
Units: months				
median (confidence interval 95%)	2.9 (2.8 to 4.4)	3.9 (2.8 to 4.5)		

Statistical analyses

Statistical analysis title	Stratified Analysis
Comparison groups	Placebo + Bevacizumab v Onartuzumab + Bevacizumab
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7444 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.56

Notes:

[1] - P−value was estimated by log−rank test with Karnofsky Performance Status (70% − 80% vs 90% − 100%) and Age (< 50 yrs vs >= 50 yrs) as stratification factors.

Primary: Duration of PFS in Subjects with Met Positive (Met+) Glioblastoma Tumours

End point title	Duration of PFS in Subjects with Met Positive (Met+) Glioblastoma Tumours[2]

End point description:

PFS was defined as the time from date of randomisation to the date of first documented disease progression or death, whichever occurs first. Disease progression was determined on the basis of investigator assessment using the RANO criteria. RANO criteria define disease progression as >/= 25% increase in enhancing lesions or significant increase in non-enhancing T2-FLAIR lesions, not attributable to other non-tumour causes or any new lesions as assessed by MRI. ITT population included all randomised subjects with subjects allocated to the treatment arm to which they were randomised. Only subjects with Met+ glioblastoma tumours were included in this analysis.

End point type	Primary

End point timeframe:

Up to approximately 18 months

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This endpoint was not analysed, because the prevalence rate of Met+ glioblastoma was too low.

End point values	Placebo + Bevacizumab Met+	Onartuzumab + Bevacizumab Met+		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[3]	0[4]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[3] - No analyses were done for the Met+ subgroup, because the prevalence rate was too low.

[4] - No analyses were done for the Met+ subgroup, because the prevalence rate was too low.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) Rate at 9 Months (OS-9) in ITT Population

End point title	Overall Survival (OS) Rate at 9 Months (OS-9) in ITT Population

End point description:

OS-9 was defined as the percentage of subjects who were alive at 9 months after randomisation. ITT population included all randomised subjects with subjects allocated to the treatment arm to which they were randomised.

End point type	Secondary

End point timeframe:

From baseline up to 9 months

End point values	Placebo + Bevacizumab	Onartuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	64		
Units: Unitless (percentage)				
number (not applicable)	57.2	49.7		

Statistical analyses

No statistical analyses for this end point

Secondary: OS-9 in Subjects with Met+ Glioblastoma Tumours

End point title	OS-9 in Subjects with Met+ Glioblastoma Tumours

End point description:

OS-9 was defined as the percentage of subjects who were alive at 9 months after randomisation. ITT population included all randomised subjects with subjects allocated to the treatment arm to which they were randomised. Only subjects with Met+ glioblastoma tumours are included in this analysis.

End point type	Secondary

End point timeframe:

From baseline up to 9 months

End point values	Placebo + Bevacizumab Met+	Onartuzumab + Bevacizumab Met+		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[5]	0[6]		
Units: Unitless (percentage)				
number (not applicable)				

Notes:

[5] - No analyses were done for the Met+ subgroup, because the prevalence rate was too low.

[6] - No analyses were done for the Met+ subgroup, because the prevalence rate was too low.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of OS in ITT Population

End point title	Duration of OS in ITT Population

End point description:

OS was defined as the time from randomisation until death from any cause. ITT population included all randomised subjects with subjects allocated to the treatment arm to which they were randomised. 9999 = NE = Not Estimable

End point type	Secondary

End point timeframe:

Up to approximately 18 months

End point values	Placebo + Bevacizumab	Onartuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	64		
Units: months				
median (confidence interval 95%)	12.6 (7.5 to 9999)	8.8 (7 to 11.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of OS in Subjects with Met+ Glioblastoma Tumours

End point title	Duration of OS in Subjects with Met+ Glioblastoma Tumours

End point description:

OS was defined as the time from randomisation until death from any cause. ITT population included all randomised subjects with subjects allocated to the treatment arm to which they were randomised. Only subjects with Met+ glioblastoma tumours were included in this analysis.

End point type	Secondary

End point timeframe:

Up to approximately 18 months

End point values	Placebo + Bevacizumab Met+	Onartuzumab + Bevacizumab Met+		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[7]	0[8]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[7] - No analyses were done for the Met+ subgroup, because the prevalence rate was too low.

[8] - No analyses were done for the Met+ subgroup, because the prevalence rate was too low.

Statistical analyses

No statistical analyses for this end point

Secondary: PFS Rate at 6 Months (PFS-6) in ITT Population

End point title	PFS Rate at 6 Months (PFS-6) in ITT Population

End point description:

PFS-6 was defined as the percentage of subjects who were alive and progression free at 6 months after randomization. Disease progression was determined on the basis of investigator assessment using the RANO criteria. RANO criteria define disease progression as >/= 25% increase in enhancing lesions or significant increase in non-enhancing T2-FLAIR lesions, not attributable to other non-tumour causes or any new lesions as assessed by MRI. ITT population included all randomised subjects with subjects allocated to the treatment arm to which they were randomised.

End point type	Secondary

End point timeframe:

From randomisation up to 6 months

End point values	Placebo + Bevacizumab	Onartuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	64		
Units: Unitless (percentage)				
number (not applicable)	29	33.9		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS-6 in Subjects with Met+ Glioblastoma Tumours

End point title	PFS-6 in Subjects with Met+ Glioblastoma Tumours

End point description:

PFS-6 was defined as the percentage of subjects who were alive and progression free at 6 months after randomization. Disease progression was determined on the basis of investigator assessment using the RANO criteria. RANO criteria define disease progression as >/= 25% increase in enhancing lesions or significant increase in non-enhancing T2-FLAIR lesions, not attributable to other non-tumour causes or any new lesions as assessed by MRI. ITT population included all randomised subjects with subjects allocated to the treatment arm to which they were randomised. Only subjects with Met+ glioblastoma tumours were included in this analysis.

End point type	Secondary

End point timeframe:

From randomisation up to 6 months

End point values	Placebo + Bevacizumab Met+	Onartuzumab + Bevacizumab Met+		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[9]	0[10]		
Units: Unitless (percentage)				
number (not applicable)				

Notes:

[9] - No analyses were done for the Met+ subgroup, because the prevalence rate was too low.

[10] - No analyses were done for the Met+ subgroup, because the prevalence rate was too low.

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) in Subjects Within ITT Population with Measurable Disease at Baseline

End point title	Objective Response Rate (ORR) in Subjects Within ITT Population with Measurable Disease at Baseline

End point description:

ORR was defined as the percentage of subjects enrolled in each treatment arm who were judged by the investigators to have an objective response as determined using the RANO criteria. Analysis population included subjects within ITT population with measurable disease at baseline. ITT population included all randomised subjects with subjects allocated to the treatment arm to which they were randomised.

End point type	Secondary

End point timeframe:

Up to approximately 18 months

End point values	Placebo + Bevacizumab	Onartuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	54		
Units: Unitless (percentage)				
number (not applicable)	23.7	22.2		

Statistical analyses

No statistical analyses for this end point

Secondary: ORR in Subjects with Met+ Glioblastoma Tumours

End point title	ORR in Subjects with Met+ Glioblastoma Tumours

End point description:

ORR was defined as the percentage of subjects enrolled in each treatment arm who were judged by the investigators to have an objective response as determined using the RANO criteria. ITT population included all randomised subjects with subjects allocated to the treatment arm to which they were randomised. Only subjects with Met+ glioblastoma tumours were included in this analysis.

End point type	Secondary

End point timeframe:

Up to approximately 18 months

End point values	Placebo + Bevacizumab Met+	Onartuzumab + Bevacizumab Met+		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[11]	0[12]		
Units: Unitless (percentage)				
number (not applicable)				

Notes:

[11] - No analyses were done for the Met+ subgroup, because the prevalence rate was too low.

[12] - No analyses were done for the Met+ subgroup, because the prevalence rate was too low.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) in Responders Within ITT Population

End point title	Duration of Response (DOR) in Responders Within ITT Population

End point description:

DOR was defined as the time from the first occurrence of a documented objective response to disease progression (as determined by the investigator using the RANO criteria) or death from any cause during the study. RANO criteria define disease progression as >/= 25% increase in enhancing lesions or significant increase in non-enhancing T2-FLAIR lesions, not attributable to other non-tumour causes or any new lesions as assessed by MRI. The analysis population included responders within the ITT population. ITT population included all randomised subjects with subjects allocated to the treatment arm to which they were randomised. 9999 = NE = Not Estimable

End point type	Secondary

End point timeframe:

Up to approximately 18 months

End point values	Placebo + Bevacizumab	Onartuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	12		
Units: months				
median (confidence interval 95%)	9.7 (6.9 to 9999)	6.4 (5.6 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: DOR in Responders with Met+ Glioblastoma Tumours

End point title	DOR in Responders with Met+ Glioblastoma Tumours

End point description:

DOR was defined as the time from the first occurrence of a documented objective response to disease progression (as determined by the investigator using the RANO criteria) or death from any cause during the study. RANO criteria define disease progression as >/= 25% increase in enhancing lesions or significant increase in non-enhancing T2-FLAIR lesions, not attributable to other non-tumour causes or any new lesions as assessed by MRI. Analysis population included responders with Met+ glioblastoma tumours within the ITT population. ITT population included all randomised subjects with subjects allocated to the treatment arm to which they were randomised.

End point type	Secondary

End point timeframe:

Up to approximately 18 months

End point values	Placebo + Bevacizumab Met+	Onartuzumab + Bevacizumab Met+		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[13]	0[14]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[13] - No analyses were done for the Met+ subgroup, because the prevalence rate was too low.

[14] - No analyses were done for the Met+ subgroup, because the prevalence rate was too low.

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity: Percentage of Subjects with Anti-Therapeutic Antibodies Against Onartuzumab

End point title	Immunogenicity: Percentage of Subjects with Anti-Therapeutic Antibodies Against Onartuzumab

End point description:

Safety population included all subjects who were randomised and received at least one dose of study treatment with subjects allocated to the treatment arm associated with the regimen actually received.

End point type	Secondary

End point timeframe:

Up to approximately 18 months

End point values	Placebo + Bevacizumab	Onartuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	64[15]		
Units: Unitless (percentage)				
number (not applicable)	0	0		

Notes:

[15] - In this arm 65 subjects were included in analysis population based on treatment actually received.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Minimum Concentration (Cmin) of Onartuzumab

End point title	Pharmacokinetics: Minimum Concentration (Cmin) of Onartuzumab[16]

End point description:

Cmin of onartuzumab in serum before the first infusion on Day 1 of Cycles 1, 2, 3, and 4 and at the study drug discontinuation visit. Analysis population included treated subjects with pharmacokinetic draw according to treatment actually received. The number (n) of subjects analysed at each time point is indicated in each category title. 9999 indicates not recorded.

End point type	Secondary

End point timeframe:

Before first infusion on Day 1 of Cycles 1 (Day 1), 2 (Day 22), 3 (Day 43), 4 (Day 64) and at the study drug discontinuation visit (up to approximately 18 months)

Notes:

[16] - 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: Onartuzumab was only measured in the arm that received onartuzumab.

End point values	Onartuzumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	64[17]			
Units: micrograms/millilitre (mcg/mL)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=62)	9999 (± 9999)			
Cycle 2 Day 1 (n=55)	68.196 (± 113.569)			
Cycle 3 Day 1 (n=44)	75.811 (± 96.987)			
Cycle 4 Day 1 (n=42)	95.837 (± 145.663)			
Study Drug Discontinuation Visit (n=32)	57.603 (± 27.418)			

Notes:

[17] - In this arm 65 subjects were included in analysis population based on treatment actually received.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Maximum Concentration (Cmax) of Onartuzumab

End point title	Pharmacokinetics: Maximum Concentration (Cmax) of Onartuzumab[18]

End point description:

Cmax of onartuzumab after last infusion on Day 1 of Cycles 1, 2, 3, and 4. Analysis population included treated subjects with pharmacokinetic draw according to treatment actually received. The number (n) of subjects analysed at each time point is indicated in each category title.

End point type	Secondary

End point timeframe:

After last infusion on the first day of Cycles 1 (Day 1), 2 (Day 22), 3 (Day 43), and 4 (Day 64)

Notes:

[18] - 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: Onartuzumab was only measured in the arm that received onartuzumab.

End point values	Onartuzumab + Bevacizumab			
Subject group type	Reporting group			
Number of subjects analysed	64[19]			
Units: mcg/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=59)	404.441 (± 144.234)			
Cycle 2 Day 1 (n=57)	463.374 (± 157.67)			
Cycle 3 Day 1 (n=45)	496.667 (± 124.805)			
Cycle 4 Day 1 (n=42)	510.929 (± 165.083)			

Notes:

[19] - In this arm 65 subjects were included in analysis population based on treatment actually received.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Cmin of Bevacizumab

End point title	Pharmacokinetics: Cmin of Bevacizumab

End point description:

Cmin of bevacizumab in serum before the first infusion on Day 1 of Cycles 1, 2, 3, and 4 and at the study drug discontinuation visit. Analysis population included treated subjects with pharmacokinetic draw according to treatment actually received. 9999 indicates not recorded.

End point type	Secondary

End point timeframe:

Before first infusion on Day 1 of Cycles 1 (Day 1), 2 (Day 22), 3 (Day 43), 4 (Day 64) and at the study drug discontinuation visit (up to approximately 18 months)

End point values	Placebo + Bevacizumab	Onartuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[20]	64[21]		
Units: mcg/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=61, 63)	9999 (± 9999)	9999 (± 9999)		
Cycle 2 Day 1 (n=62, 55)	86.248 (± 23.177)	100.851 (± 59.667)		
Cycle 3 Day 1 (n=53, 45)	134.281 (± 58.65)	145.387 (± 34.887)		
Cycle 4 Day 1 (n=49, 44)	155.916 (± 56.136)	168.759 (± 38.138)		
Study Drug Discontinuation Visit (n=35, 32)	169.546 (± 57.67)	172.488 (± 74.133)		

Notes:

[20] - The number (n) of subjects analysed is indicated in each category title.

[21] - In this arm 65 subjects were included in analysis population based on treatment actually received.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Cmax of Bevacizumab

End point title	Pharmacokinetics: Cmax of Bevacizumab

End point description:

Cmax of onartuzumab after last infusion on Day 1 of Cycles 1, 2, 3, and 4. Analysis population included treated subjects with pharmacokinetic draw according to treatment actually received.

End point type	Secondary

End point timeframe:

After last infusion on the first day of Cycles 1 (Day 1), 2 (Day 22), 3 (Day 43), and 4 (Day 64)

End point values	Placebo + Bevacizumab	Onartuzumab + Bevacizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64[22]	64[23]		
Units: mcg/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=63, 61)	339.572 (± 96.936)	336.902 (± 82.52)		
Cycle 2 Day 1 (n=62, 57)	461.989 (± 168.306)	451.677 (± 96.006)		
Cycle 3 Day 1 (n=50, 46)	466.04 (± 139.575)	482.37 (± 132.188)		
Cycle 4 Day 1 (n=49, 43)	495.898 (± 145.273)	516.047 (± 146.121)		

Notes:

[22] - The number (n) of subjects analysed is indicated in each category title.

[23] - In this arm 65 subjects were included in analysis population based on treatment actually received.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 30 days after the last dose of study drug (approximately 19 months)

Adverse event reporting additional description:

Safety population included all subjects who were randomised and received at least one dose of study treatment with subjects allocated to the treatment arm associated with the regimen actually received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Placebo + Bevacizumab

Reporting group description:

Bevacizumab and matching placebo to onartuzumab were administered once every 3 weeks (q3w) up till primary analysis of the progression-free survival endpoint (up to approximately 18 months).

Reporting group title	Onartuzumab + Bevacizumab

Reporting group description:

Onartuzumab and bevacizumab were administered q3w up till primary analysis of the progression-free survival endpoint (up to approximately 18 months).

Serious adverse events	Placebo + Bevacizumab	Onartuzumab + Bevacizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 64 (32.81%)	20 / 65 (30.77%)	
number of deaths (all causes)	45	43	
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 64 (0.00%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 64 (3.13%)	3 / 65 (4.62%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemia			

subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	3 / 64 (4.69%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	3 / 64 (4.69%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	2 / 64 (3.13%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			

subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	5 / 64 (7.81%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal perforation			
subjects affected / exposed	0 / 64 (0.00%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Large intestine perforation			
subjects affected / exposed	0 / 64 (0.00%)	2 / 65 (3.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 64 (1.56%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			

subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 64 (3.13%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 65 (1.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	1 / 64 (1.56%)	0 / 65 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Bevacizumab	Onartuzumab + Bevacizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 64 (96.88%)	56 / 65 (86.15%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	21 / 64 (32.81%)	8 / 65 (12.31%)	
occurrences (all)	34	10	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	13 / 64 (20.31%)	16 / 65 (24.62%)	
occurrences (all)	16	19	
Fatigue			
subjects affected / exposed	14 / 64 (21.88%)	10 / 65 (15.38%)	
occurrences (all)	15	10	
Gait disturbance			
subjects affected / exposed	7 / 64 (10.94%)	1 / 65 (1.54%)	
occurrences (all)	7	1	
Oedema peripheral			
subjects affected / exposed	10 / 64 (15.63%)	29 / 65 (44.62%)	
occurrences (all)	12	44	
Pyrexia			
subjects affected / exposed	1 / 64 (1.56%)	4 / 65 (6.15%)	
occurrences (all)	1	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 64 (7.81%)	5 / 65 (7.69%)	
occurrences (all)	5	5	
Dysphonia			

subjects affected / exposed	6 / 64 (9.38%)	3 / 65 (4.62%)	
occurrences (all)	6	3	
Epistaxis			
subjects affected / exposed	8 / 64 (12.50%)	4 / 65 (6.15%)	
occurrences (all)	9	4	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	4 / 64 (6.25%)	1 / 65 (1.54%)	
occurrences (all)	4	1	
Depression			
subjects affected / exposed	4 / 64 (6.25%)	2 / 65 (3.08%)	
occurrences (all)	4	2	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 64 (6.25%)	5 / 65 (7.69%)	
occurrences (all)	4	5	
Weight decreased			
subjects affected / exposed	4 / 64 (6.25%)	1 / 65 (1.54%)	
occurrences (all)	6	2	
Weight increased			
subjects affected / exposed	2 / 64 (3.13%)	7 / 65 (10.77%)	
occurrences (all)	2	7	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	7 / 64 (10.94%)	3 / 65 (4.62%)	
occurrences (all)	8	4	
Nervous system disorders			
Aphasia			
subjects affected / exposed	6 / 64 (9.38%)	3 / 65 (4.62%)	
occurrences (all)	7	3	
Headache			
subjects affected / exposed	15 / 64 (23.44%)	10 / 65 (15.38%)	
occurrences (all)	18	14	
Hemiparesis			
subjects affected / exposed	5 / 64 (7.81%)	1 / 65 (1.54%)	
occurrences (all)	6	1	

Memory impairment			
subjects affected / exposed	4 / 64 (6.25%)	3 / 65 (4.62%)	
occurrences (all)	4	3	
Paraesthesia			
subjects affected / exposed	4 / 64 (6.25%)	1 / 65 (1.54%)	
occurrences (all)	4	1	
Partial seizures			
subjects affected / exposed	4 / 64 (6.25%)	1 / 65 (1.54%)	
occurrences (all)	4	1	
Seizure			
subjects affected / exposed	5 / 64 (7.81%)	4 / 65 (6.15%)	
occurrences (all)	10	4	
Somnolence			
subjects affected / exposed	2 / 64 (3.13%)	5 / 65 (7.69%)	
occurrences (all)	2	5	
Tremor			
subjects affected / exposed	0 / 64 (0.00%)	5 / 65 (7.69%)	
occurrences (all)	0	5	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 64 (1.56%)	4 / 65 (6.15%)	
occurrences (all)	1	4	
Constipation			
subjects affected / exposed	9 / 64 (14.06%)	9 / 65 (13.85%)	
occurrences (all)	9	9	
Diarrhoea			
subjects affected / exposed	3 / 64 (4.69%)	7 / 65 (10.77%)	
occurrences (all)	5	8	
Nausea			
subjects affected / exposed	7 / 64 (10.94%)	2 / 65 (3.08%)	
occurrences (all)	11	2	
Vomiting			
subjects affected / exposed	6 / 64 (9.38%)	3 / 65 (4.62%)	
occurrences (all)	6	3	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	7 / 64 (10.94%)	5 / 65 (7.69%)	
occurrences (all)	8	7	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	7 / 64 (10.94%)	4 / 65 (6.15%)	
occurrences (all)	10	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 64 (15.63%)	7 / 65 (10.77%)	
occurrences (all)	11	8	
Back pain			
subjects affected / exposed	6 / 64 (9.38%)	5 / 65 (7.69%)	
occurrences (all)	7	5	
Muscular weakness			
subjects affected / exposed	2 / 64 (3.13%)	5 / 65 (7.69%)	
occurrences (all)	2	6	
Myalgia			
subjects affected / exposed	2 / 64 (3.13%)	4 / 65 (6.15%)	
occurrences (all)	2	5	
Pain in extremity			
subjects affected / exposed	2 / 64 (3.13%)	4 / 65 (6.15%)	
occurrences (all)	2	4	
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 64 (6.25%)	3 / 65 (4.62%)	
occurrences (all)	4	3	
Nasopharyngitis			
subjects affected / exposed	4 / 64 (6.25%)	2 / 65 (3.08%)	
occurrences (all)	4	2	
Upper respiratory tract infection			
subjects affected / exposed	2 / 64 (3.13%)	4 / 65 (6.15%)	
occurrences (all)	2	4	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	6 / 64 (9.38%)	7 / 65 (10.77%)	
occurrences (all)	6	9	
Hyperglycaemia			
subjects affected / exposed	5 / 64 (7.81%)	2 / 65 (3.08%)	
occurrences (all)	5	2	
Hypoalbuminaemia			
subjects affected / exposed	1 / 64 (1.56%)	8 / 65 (12.31%)	
occurrences (all)	1	8	
Hypokalaemia			
subjects affected / exposed	6 / 64 (9.38%)	6 / 65 (9.23%)	
occurrences (all)	7	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 August 2012	To comply with updated regulations, serious adverse events (SAEs) and pregnancies should be reported within 24 hours. Instructions were provided on how to record when a previously recorded non-serious adverse event becomes an SAE. Clarification was provided regarding assessments to be performed at the study drug discontinuation visit for subjects who have been unblinded for potential crossover and are subsequently treated with bevacizumab in the study. To allow sufficient time to address certain adverse events and to monitor the effect of medical management, the maximum time allowed for delay of study drug administration was extended from 7 days to 21 days. The window for pregnancy testing at screening was changed from 48 hours to 7 days to ensure that the test is performed prior to study drug administration and to align with the protocol's schedule of assessments. The instructions for study drug delay/discontinuation due to proteinuria were corrected to align with the rest of the protocol as well as the bevacizumab Summary of Product Characteristics. The specific instructions for study drug discontinuation due to fistula were clarified.
18 January 2013	The enrollment into Treatment Arm C (onartuzumab + placebo) was permanently discontinued. A temporary suspension of enrollment into Arm C was announced via a letter to investigators dated 21 September 2012, pending the investigation of a potential safety concern of cerebral oedema in four out of five subjects in Arm C. During the suspension, randomisation to Treatment Arm A (bevacizumab + placebo) and Arm B (bevacizumab + onartuzumab) continued. On 17 October 2012, the Internal Monitoring Committee (IMC) and Scientific Oversight Committee (SOC) concluded that the cerebral oedema events reported in these subjects were findings consistent with the documented progression of their underlying glioblastoma and that there was no clear attribution to study drug. It was then determined that an insufficient number of subjects would be enrolled in Arm C compared to the other two arms by the targeted enrollment completion of March 2013 while maintaining a 1:1:1 randomisation.. Based on this assessment, the Sponsor decided to permanently discontinue enrollment into Arm C.
06 June 2014	Amendments were made to reduce the protocol-specified assessments for subjects who were either receiving study treatment or were in the survival follow-up period following the primary efficacy analysis and unblinding of treatment assignments. The Sponsor recommended that subjects continuing to receive study treatment discontinue onartuzumab. The decision to continue or discontinue treatment with onartuzumab was at the discretion of the investigator in consultation with the subject. Bevacizumab treatment could continue until there was evidence of progressive disease, until treatment-limiting toxicity developed, until the treating physician considered the subject to no longer be achieving benefit, or until the patient decided to withdraw, whichever occurred first. This protocol amendment reduced the number and type of assessments required for evaluation of study treatment but retained the requirements for submission of serious adverse event data. Important safety information regarding venous thrombosis and embolism was updated. The signs and symptoms of venous thrombosis and embolism were to be carefully monitored. The investigator was responsible for instructing subjects to seek medical care if they developed symptoms, such as shortness of breath, chest pain, or arm or leg swelling. Thromboprophylaxis had to be considered after careful assessment of an individual subject's underlying risk factors. Any thromboprophylaxis had to follow the current institutional guidelines and best practice.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported