Clinical trial results:
A Randomized, Placebo-controlled, Double-blind, Multicenter Phase II Trial of Intravenous GC33 at 1600 mg Q2W in Previously Treated Patients with Unresectable Advanced or Metastatic Hepatocellular Carcinoma (HCC)

Summary

EudraCT number	2011-003574-84
Trial protocol	BE GB ES DE IT
Global end of trial date	20 August 2015

Results information

Result version number	v2 (current)
This version publication date	02 February 2020
First version publication date	18 July 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	NP27884

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01507168
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	20 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 August 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the efficacy of GC33 in previously treated subjects with unresectable advanced or metastatic hepatocellular carcinoma.

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	02 February 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	42 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	Italy: 16
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Hong Kong: 10
Country: Number of subjects enrolled	Japan: 23
Country: Number of subjects enrolled	Korea, Republic of: 19
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Taiwan: 18
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	United States: 21
Country: Number of subjects enrolled	United Kingdom: 12
Worldwide total number of subjects	185
EEA total number of subjects	89

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)	101
From 65 to 84 years	84
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 6 European, 5 Asian countries, New Zealand and the USA.

Pre-assignment

Screening details:

Subjects with previously treated unresectable advanced or metastatic hepatocellular carcinoma (HCC) with tumour expression of GPC3 determined on tumour biopsy were randomised in a GC33:placebo ratio of 2:1.

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	Placebo

Arm description:

Subjects were administered matching placebo on Days 1 and 8, and every 2 weeks thereafter.

Arm type	Placebo
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:

Intravenous (IV) infusion of matching placebo was administered on Days 1 and 8, and every 2 weeks thereafter.

Arm title	GC33

Arm description:

Subjects were administered GC33 on Days 1 and 8, and every 2 weeks thereafter.

Arm type	Experimental
Investigational medicinal product name	GC33
Investigational medicinal product code	
Other name	RO5137382
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous (IV) infusion of 1600 mg GC33 was administered on Days 1 and 8, and every 2 weeks thereafter.

Number of subjects in period 1	Placebo	GC33
Started	60	125
Safety Population	60	121
Completed	60	121
Not completed	0	4
Did not receive study medication	-	4

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects were administered matching placebo on Days 1 and 8, and every 2 weeks thereafter.	
Reporting group title	GC33
Reporting group description:	
Subjects were administered GC33 on Days 1 and 8, and every 2 weeks thereafter.	

Reporting group values	Placebo	GC33	Total
Number of subjects	60	125	185
Age Categorical Units: Subjects			

Age Continuous			
All Randomised subjects were included.			
Units: years arithmetic mean standard deviation	 61.0 ± 11.1	 61.9 ± 11.9	 -
Gender Categorical			
All Randomised subjects were included.			
Units: Subjects			
Female	15	19	34
Male	45	106	151

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects were administered matching placebo on Days 1 and 8, and every 2 weeks thereafter.	
Reporting group title	GC33
Reporting group description:	
Subjects were administered GC33 on Days 1 and 8, and every 2 weeks thereafter.	
Subject analysis set title	Cohort A (GPC3 IHC 2+/3+): Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
GPC3 IHC 2+/3+ subjects were administered matching placebo on Days 1 and 8, and every 2 weeks thereafter.	
Subject analysis set title	Cohort A (GPC3 IHC 2+/3+): GC33
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
GPC3 IHC 2+/3+ subjects were administered GC33 on Days 1 and 8, and every 2 weeks thereafter.	
Subject analysis set title	Cohort A (GPC3 IHC 2+/3+)+B (GPC3 IHC 1+): Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
This included subjects from both cohort A (GPC3 IHC 2+/3+) and cohort B (GPC3 IHC 1+). The subjects were administered matching placebo on Days 1 and 8, and every 2 weeks thereafter.	
Subject analysis set title	Cohort A (GPC3 IHC 2+/3+)+B (GPC3 IHC 1+): GC33
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
his included subjects from both cohort A (GPC3 IHC 2+/3+) and cohort B (GPC3 IHC 1+). The subjects were administered GC33 on Days 1 and 8, and every 2 weeks thereafter.	

Primary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)
End point description:	
PFS was defined as time between randomization and the first documentation of progression by Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria or death (if death occurs earlier than progression). Disease progression was defined as at least a 20% increase in the sum of the longest diameter (LD) of the target lesions (TLs), taking as reference the smallest sum LD recorded since the treatment started or appearance of one or more new lesions or unequivocal progression of existing non-target lesions. Participants who did not progress or die were censored on the date of the last valid tumor assessment. For participants who had no tumor assessment and no clinical progression post baseline and who did not die, PFS was assigned a value of one day and was censored in the analysis.	
End point type	Primary
End point timeframe:	
From the time of randomisation up to progression or death, whichever occurred first up to the cut-off date for the analysis of 13 June 2013 (up to approximately 16 months)	

End point values	Placebo	GC33	Cohort A (GPC3 IHC 2+/3+): Placebo	Cohort A (GPC3 IHC 2+/3+): GC33
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	60	125	35	70
Units: Months				
median (confidence interval 95%)	1.5 (1.5 to 2.8)	2.6 (1.5 to 3.0)	1.5 (1.4 to 2.8)	2.6 (1.4 to 3.7)

End point values	Cohort A (GPC3 IHC 2+/3+)+B (GPC3 IHC 1+): Placebo	Cohort A (GPC3 IHC 2+/3+)+B (GPC3 IHC 1+): GC33		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	106		
Units: Months				
median (confidence interval 95%)	1.6 (1.5 to 2.8)	2.6 (1.5 to 3.0)		

Statistical analyses

Statistical analysis title	Placebo vs GC33
Comparison groups	Placebo v GC33
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8667
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.39

Statistical analysis title	Cohort Placebo vs Cohort A: GC33
Comparison groups	Cohort A (GPC3 IHC 2+/3+): Placebo v Cohort A (GPC3 IHC 2+/3+): GC33
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9885
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.64

Statistical analysis title	Cohort A+B: Placebo vs Cohort A+B: GC33
Comparison groups	Cohort A (GPC3 IHC 2+/3+)+B (GPC3 IHC 1+): Placebo v Cohort A (GPC3 IHC 2+/3+)+B (GPC3 IHC 1+): GC33
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9313
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.45

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the interval of time from randomization to date of death due to any cause. Participants who were alive at the time of analysis
were censored at the last documented date that they were known to be alive. Participants without follow up assessment were censored at the day of last dose and the participants with no post baseline information were censored at the date of randomization.

End point type	Secondary

End point timeframe:

From the time of randomization to the date of death due to any cause up to the cut-off date for the analysis of 11 April 2014 (up to approximately 26 months)

End point values	Placebo	GC33	Cohort A (GPC3 IHC 2+/3+): Placebo	Cohort A (GPC3 IHC 2+/3+): GC33
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	60	125	35	70
Units: months				
median (confidence interval 95%)	10.0 (5.9 to 11.2)	8.7 (6.8 to 11.3)	6.7 (5.3 to 11.4)	8.9 (6.8 to 11.8)

End point values	Cohort A (GPC3 IHC 2+/3+)+B (GPC3 IHC 1+): Placebo	Cohort A (GPC3 IHC 2+/3+)+B (GPC3 IHC 1+): GC33		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	106		
Units: months				
median (confidence interval 95%)	7.6 (5.8 to 11.4)	8.9 (7.4 to 11.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression (TTP)

End point title	Time to progression (TTP)

End point description:

TTP was defined as the time from randomization to the first documented disease progression. Only radiologically documented progression of tumor was considered as disease progression. Clinical progression as judged by the investigators was not considered as progressive disease, unless accompanied by radiological progression.

End point type	Secondary

End point timeframe:

From the time of randomization to disease progression up to the cut-off date for the analysis of 13 June 2013 (up to approximately 16 months)

End point values	Placebo	GC33	Cohort A (GPC3 IHC 2+/3+): Placebo	Cohort A (GPC3 IHC 2+/3+): GC33
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	60	125	35	70
Units: months				
median (confidence interval 95%)	1.7 (1.5 to 2.8)	2.9 (1.5 to 3.6)	1.9 (1.5 to 2.8)	2.9 (1.4 to 3.9)

End point values	Cohort A (GPC3 IHC 2+/3+)+B (GPC3 IHC 1+): Placebo	Cohort A (GPC3 IHC 2+/3+)+B (GPC3 IHC 1+): GC33		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	106		
Units: months				
median (confidence interval 95%)	1.9 (1.5 to 2.8)	2.8 (1.5 to 3.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

The DCR was defined as the percentage of participants who had a best response of complete response (CR), partial Response (PR), or stable disease (SD) lasting at least 6 weeks. CR was defined as the disappearance of all target lesions; for non-target lesions disappearance of lesions and normal tumour marker levels. PR was defined as at least a 30% decrease in the sum of LD of target lesions, using as reference the Baseline sum LD. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started; for non-target lesions persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.

End point type	Secondary

End point timeframe:

From the time of randomization to disease progression up to the cut-off date for the analysis of 13 June 2013 (up to approximately 16 months)

End point values	Placebo	GC33		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	125		
Units: percentage of subjects				
number (not applicable)	38.3	43.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AEs)

End point title	Number of Subjects With Adverse Events (AEs)

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a participant who was administered a study treatment, regardless of whether or not the event had a causal relationship with the treatment. An AE, therefore, could be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study treatment, whether or not related to the treatment. The safety population included all subjects who received at least one dose or part of one
dose of study medication.

End point type	Secondary

End point timeframe:

Up to approximately 42 months

End point values	Placebo	GC33		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	121		
Units: subjects	59	114		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Serum Concentration (Cmax) of GC33

End point title	Maximum Serum Concentration (Cmax) of GC33[1]

End point description:

The PK evaluable population included subjects who received at least one dose of GC33 and provided at least PK samples up to Day 3 of Cycle 1.

End point type	Secondary

End point timeframe:

Cycles 1 and 6, Day 1: prior to infusion, end of infusion, at 24 hours (h) and 96 h (approximately first 40 subjects) or at 48 h (sparse sampling after first 40 subjects).

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: Pharmacokinetic endpoint is only reported for the arm treated with GC33.

End point values	GC33			
Subject group type	Reporting group			
Number of subjects analysed	119			
Units: mcg/mL				
arithmetic mean (standard deviation)				
Cycle 1 (n=119) Cycle 6 (n=56)	515 (± 140) 715 (± 212)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Serum Concentration (Cmin) of GC33

End point title	Trough Serum Concentration (Cmin) of GC33[2]

End point description:

The PK evaluable population included subjects who received at least one dose of GC33 and provided at least PK samples up to Day 3 of Cycle 1.

End point type	Secondary

End point timeframe:

Cycle 1, Day 8 and Cycle 7, Day 1: prior to infusion

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic endpoint is only reported for the arm treated with GC33.

End point values	GC33			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: mcg/ml				
arithmetic mean (standard deviation)				
Cycle 1	175 (± 56.0)			
Cycle 6	258 (± 97.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Serum Concentration (Tmax) of GC33

End point title	Time to Reach Maximum Serum Concentration (Tmax) of

End point description:

The PK evaluable population included subjects who received at least one dose of GC33 and provided at least PK samples up to Day 3 of Cycle 1.

End point type	Secondary

End point timeframe:

Cycles 1 and 6, Day 1: prior to infusion, end of infusion, at 24 h and 96 h (approximately first 40 subjects) or at 48 h (sparse sampling after first 40 subjects).

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic endpoint is only reported for the arm treated with GC33.

End point values	GC33			
Subject group type	Reporting group			
Number of subjects analysed	119			
Units: day				
median (full range (min-max))				
Cycle 1 (n=119)	0.0722 (0.00 to 8.98)			
Cycle 6 (n=56)	0.116 (0.00 to 1.15)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-time Curve to Last Measurable Concentration (AUClast) of GC33

End point title	Area Under the Concentration-time Curve to Last Measurable

	Concentration (AUClast) of GC33[4]

End point description:

AUClast is the area under the concentration-time curve from time of dosing to the last measurable concentration from the same Cycle. The PK evaluable population included subjects who received at least one dose of GC33 and provided at least PK samples up to Day 3 of Cycle 1.

End point type	Secondary

End point timeframe:

Cycles 1 and 6, Day 1: prior to infusion, end of infusion, at 24 h and 96 h (approximately first 40 subjects) or at 48 h (sparse sampling after first 40 subjects).

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic endpoint is only reported for the arm treated with GC33.

End point values	GC33			
Subject group type	Reporting group			
Number of subjects analysed	119			
Units: day*mcg/ mL				
arithmetic mean (standard deviation)				
Cycle 1 (n=119) Cycle 6 (n=14)	1980 (± 649) 6420 (± 2060)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (CL) of GC33

End point title	Clearance (CL) of GC33[5]

End point description:

The PK evaluable population included subjects who received at least one dose of GC33 and provided at least PK samples up to Day 3 of Cycle 1.

End point type	Secondary

End point timeframe:

Cycle 1, Day 1: prior to infusion, end of infusion, at 24 h and 96 h.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic endpoint is only reported for the arm treated with GC33.

End point values	GC33			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: mL/day				
arithmetic mean (standard deviation)				
Cycle 1	889 (± 407)			

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (Vz) of GC33

End point title	Volume of Distribution (Vz) of GC33[6]

End point description:

Cycle 1, Day 1: prior to infusion, end of infusion, at 24 h and 96 h. The PK evaluable population included subjects who received at least one dose of GC33 and provided at least PK samples up to Day 3 of Cycle 1.

End point type	Secondary

End point timeframe:

Cycle 1, Day 1: prior to infusion, end of infusion, at 24 h and 96 h

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Pharmacokinetic endpoint is only reported for the arm treated with GC33.

End point values	GC33			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: mL				
arithmetic mean (standard deviation)				
Cycle 1	4200 (± 1000)			

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation Ratio for Cmax of GC33

End point title	Accumulation Ratio for Cmax of GC33[7]

End point description:

Accumulation ratio for Cmax was calculated as Cmax observed at steady state in Cycle 6 divided by Cmax after first dose in Cycle 1. The PK evaluable population included subjects who received at least one dose of GC33 and provided at least PK samples up to Day 3 of Cycle 1.

End point type	Secondary

End point timeframe:

Cycles 1 and 6, Day 1: prior to infusion, end of infusion, at 24 hours (h) and 96 h (approximately first 40 subjects) or at 48 h (sparse sampling after first 40 subjects).

Notes:

[7] - 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: Pharmacokinetic endpoint is only reported for the arm treated with GC33.

End point values	GC33			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: unitless ratio				
arithmetic mean (standard deviation)	1.42 (± 0.482)			

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation Ratio for AUC(0-8 days) of GC33

End point title	Accumulation Ratio for AUC(0-8 days) of GC33[8]

End point description:

Accumulation ratio for AUC(0-8 days) was calculated as AUC(0-8 days) at steady state in Cycle 6 divided by AUC(0-8 days) after first dose in Cycle 1. The PK evaluable population included subjects who received at least one dose of GC33 and provided at least PK samples up to Day 3 of Cycle 1.

End point type	Secondary

End point timeframe:

Cycles 1 and 6, Day 1: prior to infusion, end of infusion, at 24 h and 96 h (approximately first 40 subjects) or at 48 h (sparse sampling after first 40 subjects), Cycles 1 and 6, Day 8.

Notes:

[8] - 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: Pharmacokinetic endpoint is only reported for the arm treated with GC33.

End point values	GC33			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: unitless ratio				
arithmetic mean (standard deviation)	1.93 (± 0.330)			

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation Ratio for Cmin of GC33

End point title	Accumulation Ratio for Cmin of GC33[9]

End point description:

Accumulation ratio for Cmin was calculated as Cmax observed at steady state prior to infusion at Cycle 7, Day divided by Cmax after first dose and prior to infusion at in Cycle 1, Day 8. The PK evaluable population included subjects who received at least one dose of GC33 and provided at least PK samples up to Day 3 of Cycle 1.

End point type	Secondary

End point timeframe:

Cycle 1, Day 8 and Cycle 7, Day 1: prior to infusion.

Notes:

[9] - 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: Pharmacokinetic endpoint is only reported for the arm treated with GC33.

End point values	GC33			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: unitless ratio				
arithmetic mean (standard deviation)	1.59 (± 0.841)			

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Elimination Half-life (t1/2) of GC33

End point title	Terminal Elimination Half-life (t1/2) of GC33[10]

End point description:

The PK evaluable population included subjects who received at least one dose of GC33 and provided at least PK samples up to Day 3 of Cycle 1.

End point type	Secondary

End point timeframe:

Cycle 1, Day 1: prior to infusion, end of infusion, at 24 hours (h) and 96 h (approximately first 40 subjects) or at 48 h (sparse sampling after first 40 subjects) and prior to next infusion Cycle 1, Day 8.

Notes:

[10] - 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: Pharmacokinetic endpoint is only reported for the arm treated with GC33.

End point values	GC33			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: day				
arithmetic mean (standard deviation)				
Cycle 1	3.74 (± 1.39)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of GC33 at the Time of Tumor Progression (Cprog)

End point title	Serum Concentration of GC33 at the Time of Tumor Progression (Cprog)[11]

End point description:

The PK evaluable population included subjects who received at least one dose of GC33 and provided at least PK samples up to Day 3 of Cycle 1.

End point type	Secondary

End point timeframe:

Cycle 1, Day 8 to Cycle 18, Day 1

Notes:

[11] - 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: Pharmacokinetic endpoint is only reported for the arm treated with GC33.

End point values	GC33			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: mcg/mL				
arithmetic mean (standard deviation)	135 (± 87.6)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to approximately 42 months	
Adverse event reporting additional description:	
The safety population included all subjects who received at least one dose or part of one dose of study medication.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects were administered matching placebo on Days 1 and 8, and every 2 weeks thereafter.	
Reporting group title	GC33
Reporting group description:	
Subjects were administered GC33 on Days 1 and 8, and every 2 weeks thereafter.	

Serious adverse events	Placebo	GC33	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 60 (31.67%)	32 / 121 (26.45%)	
number of deaths (all causes)	42	76	
number of deaths resulting from adverse events	3	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic Pain			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour Rupture			
subjects affected / exposed	1 / 60 (1.67%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive Crisis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Chest Pain			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General Physical Health Deterioration			
subjects affected / exposed	1 / 60 (1.67%)	2 / 121 (1.65%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	1 / 1	1 / 1	
Generalised Oedema			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza Like Illness			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury Associated With Device			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 60 (5.00%)	5 / 121 (4.13%)	
occurrences causally related to treatment / all	0 / 3	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			

subjects affected / exposed	1 / 60 (1.67%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural Effusion			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	1 / 60 (1.67%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed Suicide			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Investigations			
Aspartate Aminotransferase Increased			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood Bilirubin Increased			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Infusion Related Reaction			

subjects affected / exposed	0 / 60 (0.00%)	2 / 121 (1.65%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius Fracture			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	1 / 60 (1.67%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral Haemorrhage			
subjects affected / exposed	1 / 60 (1.67%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous System Disorder			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy Peripheral			
subjects affected / exposed	1 / 60 (1.67%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	1 / 60 (1.67%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	2 / 60 (3.33%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	1 / 60 (1.67%)	3 / 121 (2.48%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal Pain Upper			
subjects affected / exposed	1 / 60 (1.67%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 60 (1.67%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric Haemorrhage			
subjects affected / exposed	1 / 60 (1.67%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Gastric Ulcer Haemorrhage			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Haemorrhage			
subjects affected / exposed	1 / 60 (1.67%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 60 (1.67%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Gastrointestinal Haemorrhage			
subjects affected / exposed	0 / 60 (0.00%)	2 / 121 (1.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic Haemorrhage			
subjects affected / exposed	2 / 60 (3.33%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice Cholestatic			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 60 (1.67%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Nephrolithiasis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure			
subjects affected / exposed	1 / 60 (1.67%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial Nephritis			

subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back Pain			
subjects affected / exposed	1 / 60 (1.67%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopathy			
subjects affected / exposed	1 / 60 (1.67%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 121 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis Bacterial			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 60 (0.00%)	3 / 121 (2.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Streptococcal Infection			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 121 (0.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	GC33	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 60 (86.67%)	105 / 121 (86.78%)	
Vascular disorders			
Hot Flush			
subjects affected / exposed	3 / 60 (5.00%)	0 / 121 (0.00%)	
occurrences (all)	3	0	
Hypertension			
subjects affected / exposed	6 / 60 (10.00%)	6 / 121 (4.96%)	
occurrences (all)	6	7	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 60 (3.33%)	20 / 121 (16.53%)	
occurrences (all)	2	24	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	3 / 60 (5.00%)	6 / 121 (4.96%)	
occurrences (all)	4	9	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 60 (20.00%)	13 / 121 (10.74%)	
occurrences (all)	12	19	
Chills			
subjects affected / exposed	3 / 60 (5.00%)	12 / 121 (9.92%)	
occurrences (all)	4	12	
Fatigue			
subjects affected / exposed	12 / 60 (20.00%)	36 / 121 (29.75%)	
occurrences (all)	12	46	
Influenza Like Illness			
subjects affected / exposed	2 / 60 (3.33%)	9 / 121 (7.44%)	
occurrences (all)	2	11	
Oedema Peripheral			
subjects affected / exposed	8 / 60 (13.33%)	16 / 121 (13.22%)	
occurrences (all)	10	16	
Pyrexia			
subjects affected / exposed	6 / 60 (10.00%)	49 / 121 (40.50%)	
occurrences (all)	11	58	
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	4 / 60 (6.67%)	5 / 121 (4.13%)	
occurrences (all)	4	5	
Abdominal Pain			
subjects affected / exposed	10 / 60 (16.67%)	15 / 121 (12.40%)	
occurrences (all)	11	15	
Abdominal Pain Upper			
subjects affected / exposed	2 / 60 (3.33%)	7 / 121 (5.79%)	
occurrences (all)	2	7	
Ascites			
subjects affected / exposed	6 / 60 (10.00%)	7 / 121 (5.79%)	
occurrences (all)	9	7	
Constipation			

subjects affected / exposed	9 / 60 (15.00%)	17 / 121 (14.05%)	
occurrences (all)	10	21	
Diarrhoea			
subjects affected / exposed	10 / 60 (16.67%)	18 / 121 (14.88%)	
occurrences (all)	14	19	
Dyspepsia			
subjects affected / exposed	3 / 60 (5.00%)	4 / 121 (3.31%)	
occurrences (all)	4	5	
Nausea			
subjects affected / exposed	5 / 60 (8.33%)	21 / 121 (17.36%)	
occurrences (all)	5	27	
Vomiting			
subjects affected / exposed	1 / 60 (1.67%)	15 / 121 (12.40%)	
occurrences (all)	1	17	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 60 (8.33%)	15 / 121 (12.40%)	
occurrences (all)	5	18	
Dyspnoea			
subjects affected / exposed	3 / 60 (5.00%)	9 / 121 (7.44%)	
occurrences (all)	3	9	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	6 / 60 (10.00%)	14 / 121 (11.57%)	
occurrences (all)	8	16	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	5 / 60 (8.33%)	7 / 121 (5.79%)	
occurrences (all)	5	7	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	8 / 60 (13.33%)	10 / 121 (8.26%)	
occurrences (all)	9	12	
Musculoskeletal Chest Pain			
subjects affected / exposed	3 / 60 (5.00%)	2 / 121 (1.65%)	
occurrences (all)	3	3	

Myalgia subjects affected / exposed occurrences (all)	1 / 60 (1.67%) 1	7 / 121 (5.79%) 7	
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	3 / 60 (5.00%) 3	3 / 121 (2.48%) 3	
Metabolism and nutrition disorders Decreased Appetite subjects affected / exposed occurrences (all)	9 / 60 (15.00%) 9	19 / 121 (15.70%) 28	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 June 2012	Amendment allowed an increase of the number of subjects in cohort C, GPC3-negative [IHC 0] from 6 to 21. These subjects were to be randomized in a 2:1 fashion (GC33: Placebo). Additional changes to the protocol: 1) Warning about non-steroidal anti-inflammatory drugs (NSAIDs) used; use of ibuprofen prohibited, 2) Submission of tumour tissue for GPC3 IHC could be done up to 4 weeks prior to the 28-day screening period (ICF must have been previously signed). Collection of the tumor tissue could be done within approximately 12 months (the sponsor to be contacted if the collection exceeded 12 months), 3) The QTc (machine reading) was not collected for the study. QTc to be calculated internally, 4) Timing of reporting of Serious Adverse Events and Pregnancy were updated, 5) Statistical Analyses were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 August 2015	A protocol-specified analysis was triggered on 06 May 2013, after 128 progression-free survival events had been observed. This unblinded data review suggested that improved efficacy would not be observed, regardless of patients' GPC3 expression level, after treatment with GC33. Consequently, treatment of the remaining subjects in the study was unblinded, and the study was stopped by the Sponsor. Although the study was discontinued, subjects were given the option to continue receiving treatment at the discretion of the Principal Investigator. One subject remained on treatment and continued to receive GC33 for an additional 16 months up to the global interruption date.	-

Notes:

Limitations and caveats

None reported