Clinical trial results:
International, Multicenter, Open-label, Phase II Study to Investigate the Efficacy and Safety of Multiple Doses of IMAB362 in Patients With Advanced Adenocarcinoma of the Stomach or the Lower Esophagus

Summary

EudraCT number	2009-017365-36
Trial protocol	DE LV CZ LT AT BG
Global end of trial date	13 August 2015

Results information

Result version number	v1 (current)
This version publication date	10 April 2019
First version publication date	10 April 2019

Trial information

Trial identification

Sponsor protocol code	8951-CL-0201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01197885
WHO universal trial number (UTN)	-
Other trial identifiers	Protocol Number: GM-IMAB-001-02, Acronym: MONO

Notes:

Sponsors

Sponsor organisation name	Astellas Pharma Global Development
Sponsor organisation address	1 Astellas Way, Northbrook, IL, United States, 60062
Public contact	Clinical Trial Disclosure, Astellas Pharma Global Development, astellas.resultsdisclosure@astellas.com
Scientific contact	Clinical Trial Disclosure, Astellas Pharma Global Development, astellas.resultsdisclosure@astellas.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 August 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 August 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine antitumoral activity of zolbetuximab as monotherapy in patients with metastatic, refractory or recurrent disease of advanced adenocarcinoma of the stomach or the lower esophagus proven by histology.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 September 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Latvia: 10
Country: Number of subjects enrolled	Germany: 39
Country: Number of subjects enrolled	Switzerland: 5
Worldwide total number of subjects	54
EEA total number of subjects	49

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)	38
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This multinational, multicenter study was conducted at 21 contracted sites in 5 countries including Germany (13 sites), Bulgaria (3 sites), Latvia (3 sites), Lithuania (1 site) and Switzerland (1 site).

Pre-assignment

Screening details:

Prior to any screening procedures, all participants provided written informed consent to participate in the study. Screening evaluations were performed from 15 days to 1 day before (day -15 to day -1) administration of the study drug on visit 2. Eligible participants who met inclusion criteria and none of the exclusion criteria were enrolled.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: Zolbetuximab 300 mg/m^2

Arm description:

Participants received repeated doses of zolbetuximab at a lower dose level (300 mg/m^2 Body Surface Area (BSA)) every 2 weeks on visits 2, 5, 6, 7 and 8.

Arm type	Experimental
Investigational medicinal product name	Zolbetuximab
Investigational medicinal product code	IMAB362
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Zolbetuximab was administered to cohorts 1, 2 and 3 with the applicable dosage (antibody/body surface area) and in a sequential manner, i.e, the last participant in a prior cohort had to complete the 5 infusions before starting the infusion of the first participant in the next cohort. Zolbetuximab was administered as a 2-hour intravenous infusion, using an infusion system.

Arm title	Cohorts 2+3: Zolbetuximab 600 mg/m^2

Arm description:

Cohort 2 participants received repeated doses of zolbetuximab at a higher dose level (600 mg/m^2 BSA) every 2 weeks on visits 2, 5, 6, 7 and 8. Cohort 3 participants received repeated doses of zolbetuximab (600 mg/m^2 BSA) every 2 weeks on visits 2, 5, 6, 7 and 8.

Arm type	Experimental
Investigational medicinal product name	Zolbetuximab
Investigational medicinal product code	IMAB362
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Zolbetuximab was administered to cohorts 1, 2 and 3 with the applicable dosage (antibody/body surface area) and in a sequential manner, i.e, the last participant in a prior cohort had to complete the 5 infusions before starting the infusion of the first participant in the next cohort. Zolbetuximab was administered as a 2-hour intravenous infusion, using an infusion system.

Number of subjects in period 1	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2
Started	4	50
Treated	4	50
Completed	1	4
Not completed	3	46
Death	1	5
Miscellaneous	1	26
Adverse event	1	6
Withdrawal of consent	-	9

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: Zolbetuximab 300 mg/m^2
Reporting group description:	
Participants received repeated doses of zolbetuximab at a lower dose level (300 mg/m^2 Body Surface Area (BSA)) every 2 weeks on visits 2, 5, 6, 7 and 8.	
Reporting group title	Cohorts 2+3: Zolbetuximab 600 mg/m^2
Reporting group description:	
Cohort 2 participants received repeated doses of zolbetuximab at a higher dose level (600 mg/m^2 BSA) every 2 weeks on visits 2, 5, 6, 7 and 8. Cohort 3 participants received repeated doses of zolbetuximab (600 mg/m^2 BSA) every 2 weeks on visits 2, 5, 6, 7 and 8.	

Reporting group values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2	Total
Number of subjects	4	50	54
Age categorical Units: Subjects			
Age continuous			
The analysis population for the baseline characteristics consisted of the All-patients-treated set (APT), comprised of all participants who received at least 1 administration of study drug at any dose level and for any period of time.			
Units: years			
arithmetic mean	58.8	59.1	
standard deviation	± 9.5	± 10.6	-
Gender categorical Units:			
Male	1	36	37
Female	3	14	17
Race Units: Subjects			
White	4	50	54

End points

End points reporting groups

Reporting group title	Cohort 1: Zolbetuximab 300 mg/m^2
Reporting group description:	
Participants received repeated doses of zolbetuximab at a lower dose level (300 mg/m^2 Body Surface Area (BSA)) every 2 weeks on visits 2, 5, 6, 7 and 8.	
Reporting group title	Cohorts 2+3: Zolbetuximab 600 mg/m^2
Reporting group description:	
Cohort 2 participants received repeated doses of zolbetuximab at a higher dose level (600 mg/m^2 BSA) every 2 weeks on visits 2, 5, 6, 7 and 8. Cohort 3 participants received repeated doses of zolbetuximab (600 mg/m^2 BSA) every 2 weeks on visits 2, 5, 6, 7 and 8.	
Subject analysis set title	Cohort 1: KI 80 at baseline
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants with a KI of 80% at baseline, defined as normal activity with effort; some signs or symptoms of disease.	
Subject analysis set title	Cohort 2+3: KI 70 at baseline
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants with a KI of 70% at baseline, defined as cares for self; unable to carry on normal activity or to do active work.	
Subject analysis set title	Cohort 2+3: KI 80 at baseline
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants with a KI of 80% at baseline, defined as normal activity with effort; some signs or symptoms of disease.	
Subject analysis set title	Cohort 2+3: KI 90 at baseline
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants with a KI of 90% at baseline, defined as able to carry on normal activity; minor signs or symptoms of disease.	
Subject analysis set title	Cohort 2+3: KI 100 at baseline
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants with a KI of 100% at baseline, defined as normal, no complaints; no evidence of disease.	
Subject analysis set title	Cohort 1: ECOG Grade 1 at baseline
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants with a score of grade 1 at baseline, defined as restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	
Subject analysis set title	Cohort 2+3: ECOG Grade 0 at baseline
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants with a score of grade 0 at baseline, defined as fully active, able to carry on all pre-disease performance without restriction.	
Subject analysis set title	Cohort 2+3: ECOG Grade 1 at baseline
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants with a score of grade 1 at baseline, defined as restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	

Primary: Percentage of Participants with at Least 30% Decrease in Size of Lesions

End point title	Percentage of Participants with at Least 30% Decrease in Size of Lesions[1]

End point description:

Decrease of 30% size of lesions was defined as a 30% decrease from baseline of one-dimensional measure of tumor size without significant increasing of nontarget lesion and no new lesion, based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria determined by computed tomography (CT) or magnetic resonance imaging (MRI), i.e., the sum of the 5 longest tumor diameters at the target lesions. The sum of the longest diameters at visit 9 was used if available, if not available, the sum at visit 10 was used. Nontarget lesions with status "unequivocal progression" or "unknown" were regarded to be significant increasing. RECIST version 1.0 was used [Eisenhauer et al, 2000] and new version 1.1 [Eisenhauer et al, 2009] was accepted, if used for all examinations for a single participant. The analysis population consisted of the full analysis set (FAS), comprised of all participants who received at least 1 dose of study drug and for whom efficacy data upon treatment was available.

End point type	Primary

End point timeframe:

From first infusion until the end of study, maximum time on study was 36.4 months.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis is not applicable for this endpoint.

End point values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	36		
Units: percentage of participants				
number (not applicable)	0.0	5.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs)

End point title	Number of Participants with Adverse Events (AEs)

End point description:

An AE is any untoward medical occurrence in a participant administered a study drug and which does not necessarily have to have a causal relationship with this treatment, and includes an abnormal laboratory finding or test. A treatment-emergent adverse event (TEAE) was defined as any adverse event with a start date on or after the date of the first infusion and until 28 days after the last infusion. A serious adverse event (SAE) was defined as any untoward medical occurrence that: ●Resulted in death ●Was life-threatening ●Required hospitalization or prolongation of an existing hospitalization ●Resulted in disability/incapacity or ●Was a congenital anomaly/birth defect in the offspring of a study participant ●Was another medically important condition. The analysis population consisted of the APT.

End point type	Secondary

End point timeframe:

From start of first infusion up to until 28 days after the last infusion; Up to 35.71 months.

End point values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	50		
Units: participants				
Any TEAE	4	48		
Adverse reactions (ARs) or Drug-related TEAEs	3	41		
Deaths	0	10		
Serious TEAEs	1	24		
Serious ARs (SARs) or Drug-related Serious TEAEs	1	4		
TEAEs Leading to Study Drug Discontinuation	1	10		
ARs or Drug-related TEAEs Leading to Drug Disc.	0	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS was defined as the time between start of first infusion and date of first observed disease progression according to the overall response or death due to any cause. PFS was calculated and plotted using Kaplan-Meier estimation with 95% confidence interval (CI). Participants with no baseline and postbaseline tumor assessments, no progression or death reported, discontinued study other than death or progressive disease and progression or death after 2 or more consecutive missed CT scans were censored. The analysis population consisted of the FAS.

End point type	Secondary

End point timeframe:

From first infusion until the end of study, maximum time on study was 36.4 months.

End point values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	35		
Units: weeks				
median (confidence interval 95%)	10.00 (10.000 to 11.000)	10.00 (8.600 to 10.100)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Anti-Zolbetuximab (IMAB362) Antibodies

End point title	Number of Participants with Anti-Zolbetuximab (IMAB362) Antibodies

End point description:

The analysis population consisted of the APT.

End point type	Secondary

End point timeframe:

From first infusion until the end of study, maximum time on study was 36.4 months.

End point values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	50		
Units: participants	0	0		

Statistical analyses

No statistical analyses for this end point

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

End point title	Change from Baseline in Quality of Life (QoL) per European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30 (EORTC QLQ-C30)

End point description:

The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients. It is supplemented by a disease-specific module (QLQ-STO22). EORTC QLQ-C30 (version 3) was analyzed according to the scoring manual. All of the scales and single-item measures range from 0 to 100 by applying a linear transformation to standardize the raw score. A high scale score represents a higher response level: A high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/QoL scale represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems. The analysis population consisted of the FAS with data available at baseline and visit 10. N is the number of participants with available data. Data not available/applicable is denoted as "99999."

End point type	Secondary

End point timeframe:

Baseline and X (where X is a time point 7-9 weeks after last treatment)

End point values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	24		
Units: scores on a scale				
arithmetic mean (standard deviation)				

Global health status [N=0, 24]	99999 (± 99999)	-3.7 (± 19.6)		
Physical functioning [N=1, 12]	0.0 (± 99999)	-15.8 (± 23.5)		
Role functioning [N=1, 12]	0.0 (± 99999)	-16.7 (± 27.4)		
Emotional functioning [N=0, 11]	99999 (± 99999)	-8.5 (± 15.8)		
Cognitive functioning [N=0, 11]	99999 (± 99999)	-10.6 (± 13.5)		
Social functioning [N=0, 11]	99999 (± 99999)	-13.5 (± 24.7)		
Fatigue [N=1, 12]	34.0 (± 99999)	9.2 (± 29.2)		
Nausea and vomiting [N=1, 12]	50.0 (± 99999)	29.1 (± 37.7)		
Pain [N=1, 12]	0.0 (± 99999)	11.3 (± 25.9)		
Dyspnoea [N=0, 11]	99999 (± 99999)	6.0 (± 25.0)		
Insomnia [N=1, 12]	34.0 (± 99999)	16.8 (± 22.5)		
Appetite loss [N=1, 12]	33.0 (± 99999)	27.9 (± 37.2)		
Constipation [N=1, 12]	-100.0 (± 99999)	13.9 (± 33.2)		
Diarrhoea [N=0, 11]	99999 (± 99999)	3.1 (± 18.0)		
Financial difficulties [N=0, 11]	99999 (± 99999)	-3.2 (± 31.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in QoL per Quality of Life Questionnaire Gastric Cancer Module (QLQ-STO22)

End point title	Change from Baseline in QoL per Quality of Life Questionnaire Gastric Cancer Module (QLQ-STO22)

End point description:

The QLQ-STO22 is a disease-specific module. All of the scales and single-item measures range from 0 to 100 by applying a linear transformation to standardize the raw score. A high scale score represents a higher response level: A high score for a functional scale represents a high/healthy level of functioning but a high score for a symptom scale/item represents a high level of symptomatology/problems. The analysis population consisted of the FAS with data available at baseline and visit 10. N is the number of participants with available data. Data not available/applicable is denoted as "99999."

End point type	Secondary

End point timeframe:

Baseline and X (where X is a time point 7-9 weeks after last treatment)

End point values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	12		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Dysphagia [N=1, 12]	-6.0 (± 99999)	13.0 (± 33.1)		

Pain [N=1, 12]	25.0 (± 99999)	7.0 (± 26.8)		
Reflux symptoms [N=1, 12]	27.0 (± 99999)	11.0 (± 34.4)		
Eating restrictions [N=1, 12]	17.0 (± 99999)	11.9 (± 32.9)		
Anxiety [N=1, 12]	0.0 (± 99999)	5.9 (± 26.0)		
Dry Mouth [N=1, 12]	-34.0 (± 99999)	8.5 (± 29.1)		
Taste [N=1, 12]	34.0 (± 99999)	11.1 (± 25.8)		
Body image [N=1, 12]	0.0 (± 99999)	-5.7 (± 23.9)		
Hair loss [N=1, 12]	-33.0 (± 99999)	-18.1 (± 38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Change from Baseline in Karnofsky Index (KI)

End point title	Percentage of Participants with Change from Baseline in Karnofsky Index (KI)

End point description:

Karnofsky Index: 100 Normal, no complaints; no evidence of disease. 90 Able to carry on normal activity; minor signs or symptoms of disease. 80 Normal activity with effort; some signs or symptoms of disease. 70 Cares for self; unable to carry on normal activity or to do active work. 60 Requires occasional assistance, but is able to care for most of his personal needs. 50 Requires considerable assistance and frequent medical care. 40 Disabled; requires special care and assistance. 30 Severely disabled; hospital admission is indicated although death not imminent. 20 Very sick; hospital admission necessary; active supportive treatment necessary. 10 Moribund; fatal processes progressing rapidly. 0 Dead. The analysis population consisted of the FAS participants with KI of 80% at baseline for cohort 1 and 70-100% at baseline for cohort 2 and 3.

End point type	Secondary

End point timeframe:

Baseline and X (where X is a time point 7-9 weeks after last treatment)

End point values	Cohort 1: KI 80 at baseline	Cohort 2+3: KI 70 at baseline	Cohort 2+3: KI 80 at baseline	Cohort 2+3: KI 90 at baseline
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	1	5	7
Units: percentage of participants				
number (not applicable)				
KI 60 at Visit 10	0	0	13.3	6.7
KI 70 at Visit 10	100.0	6.7	6.7	0
KI 80 at Visit 10	0	0	0	13.3
KI 90 at Visit 10	0	0	6.7	13.3
KI 100 at Visit 10	0	0	6.7	13.3

End point values	Cohort 2+3: KI 100 at baseline			

Subject group type	Subject analysis set			
Number of subjects analysed	2			
Units: percentage of participants				
number (not applicable)				
KI 60 at Visit 10	0			
KI 70 at Visit 10	0			
KI 80 at Visit 10	0			
KI 90 at Visit 10	13.3			
KI 100 at Visit 10	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Change from Baseline in Eastern Cooperative Oncology Group (ECOG) Performance Status

End point title	Percentage of Participants with Change from Baseline in Eastern Cooperative Oncology Group (ECOG) Performance Status

End point description:

ECOG Performance Status Grades: 0 Fully active, able to carry on all pre-disease performance without restriction. 1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work. 2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. 3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. 4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. 5 Dead. The analysis population consisted of the FAS participants with a score of 1 at baseline for cohort 1 and a score of 0 or 1 at baseline for cohort 2 and 3.

End point type	Secondary

End point timeframe:

Baseline and X (where X is a time point 7-9 weeks after last treatment)

End point values	Cohort 1: ECOG Grade 1 at baseline	Cohort 2+3: ECOG Grade 0 at baseline	Cohort 2+3: ECOG Grade 1 at baseline	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	1	7	8	
Units: percentage of participants				
number (not applicable)				
Grade 0 at Visit 10	0	26.7	6.7	
Grade 1 at Visit 10	100.0	13.3	26.7	
Grade 2 at Visit 10	0	6.7	20.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Clinical Benefit According to RECIST

End point title	Overall Clinical Benefit According to RECIST

End point description:

Clinical benefit was defined as a participant's response of complete remission (CR), partial remission (PR), and stable disease (SD) according to RECIST. Clinical benefit was determined at visit 9. The analysis population consisted of the FAS. Data not calculated is denoted as "99999." There were no participants for cohort 1 who achieved CR, PR or SD and is also denoted as "99999."

End point type	Secondary

End point timeframe:

From first infusion until the end of study, maximum time on study was 36.4 months.

End point values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	26		
Units: percentage of participants				
number (confidence interval 95%)	99999 (99999 to 99999)	34.6 (17.21 to 55.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response According to RECIST

End point title	Best Overall Response According to RECIST

End point description:

Best overall response was determined as PR, SD and progressive disease (PD) according to RECIST. Best overall response was determined based on visit 9 and/or end-of study visit 10. The analysis population consisted of the FAS.

End point type	Secondary

End point timeframe:

From first infusion until the end of study, maximum time on study was 36.4 months.

End point values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	40		
Units: percentage of participants				
number (not applicable)				
PR	0	10.0		
SD	0	15.0		
PD	100.0	70.0		
Not evaluable	0	5.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Objective Response According to RECIST

End point title	Overall Objective Response According to RECIST

End point description:

Objective response was defined as a participant's response of CR or PR according to RECIST. Objective response was determined at visit 9. The analysis population consisted of the FAS. Data not calculated is denoted as "99999." There were no participants for cohort 1 who achieved CR or PR, and is also denoted as "99999."

End point type	Secondary

End point timeframe:

From first infusion until the end of study, maximum time on study was 36.4 months.

End point values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	26		
Units: percentage of participants				
number (confidence interval 95%)	99999 (99999 to 99999)	7.7 (0.95 to 25.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve from the Time of Dosing to Day 14 After End of Infusion (AUC0-14day)

End point title	Area Under the Concentration-Time Curve from the Time of Dosing to Day 14 After End of Infusion (AUC0-14day)

End point description:

The analysis population consisted of the pharmacokinetic analysis set (PKAS; comprised of all participants who received study drug at least once and for whom at least 1 pharmacokinetic measurement upon treatment was available) with participants who had available data.

End point type	Secondary

End point timeframe:

Day 1 to Day 14

End point values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	38		
Units: day*µg/mL				
arithmetic mean (standard deviation)	776 (± 83.0)	1450 (± 408)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve from the Time of Dosing to the Last Measurable Concentration (AUClast)

End point title	Area Under the Concentration-Time Curve from the Time of Dosing to the Last Measurable Concentration (AUClast)

End point description:

The analysis population consisted of the PKAS.

End point type	Secondary

End point timeframe:

Day 1 to Day 14

End point values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	40		
Units: day*ug/mL				
arithmetic mean (standard deviation)	795 (± 117)	1230 (± 533)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve from the Time of Dosing Extrapolated to Time Infinity (AUCinf)

End point title	Area Under the Concentration-Time Curve from the Time of Dosing Extrapolated to Time Infinity (AUCinf)

End point description:

The analysis population consisted of the PKAS with participants who had available data.

End point type	Secondary

End point timeframe:

Day 1 to Day 14

End point values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	33		
Units: day*ug/mL				
arithmetic mean (standard deviation)	1030 (± 256)	1930 (± 922)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of the Area Under the Concentration-Time Curve from the Time of Dosing to Time Infinity Due to Extrapolation from the Last Measurable Concentration to Time Infinity (AUCinf_%Extrap)

End point title	Percentage of the Area Under the Concentration-Time Curve from the Time of Dosing to Time Infinity Due to Extrapolation from the Last Measurable Concentration to Time Infinity (AUCinf_%Extrap)

End point description:

The analysis population consisted of the PKAS with participants who had available data.

End point type	Secondary

End point timeframe:

Day 1 to Day 14

End point values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	33		
Units: percentage extrapolated				
arithmetic mean (standard deviation)	21.4 (± 8.16)	26.6 (± 15.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Concentration (Cmax)

End point title	Maximum Concentration (Cmax)

End point description:

The analysis population consisted of the PKAS.

End point type	Secondary

End point timeframe:

Day 1 to Day 14

End point values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	40		
Units: µg/mL				
arithmetic mean (standard deviation)	288 (± 68.6)	355 (± 69.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Last Measurable Concentration (Clast)

End point title	Last Measurable Concentration (Clast)

End point description:

The analysis population consisted of the PKAS.

End point type	Secondary

End point timeframe:

Day 1 to Day 14

End point values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	40		
Units: µg/mL				
arithmetic mean (standard deviation)	28.3 (± 8.48)	94.7 (± 79.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration Immediately Prior to Dosing at Multiple Dosing (Ctrough)

End point title	Concentration Immediately Prior to Dosing at Multiple Dosing (Ctrough)

End point description:

The analysis population consisted of the PKAS. N is the number of participants with available data.

End point type	Secondary

End point timeframe:
Days 15, 29, 43, 57, and 71

End point values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	34		
Units: µg/mL				
arithmetic mean (standard deviation)				
Day 15 [N= 4, 34]	22.5 (± 10.5)	47.3 (± 28.8)		
Day 29 [N= 4, 29]	34.9 (± 15.8)	90.4 (± 57.9)		
Day 43 [N= 3, 24]	44.9 (± 14.5)	123 (± 76.2)		
Day 57 [N= 3, 19]	46.1 (± 18.5)	143 (± 90.4)		
Day 71 [N= 3, 18]	34.5 (± 12.2)	164 (± 98.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time of the Maximum Concentration (Tmax)

End point title	Time of the Maximum Concentration (Tmax)
End point description: The analysis population consisted of the PKAS.	
End point type	Secondary
End point timeframe: Day 1 to Day 14	

End point values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	40		
Units: days				
median (full range (min-max))	0.205 (0.153 to 0.378)	0.148 (0.0833 to 0.340)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time of the Last Measurable Concentration (Tlast)

End point title	Time of the Last Measurable Concentration (Tlast)
End point description: The analysis population consisted of the PKAS.	
End point type	Secondary
End point timeframe: Day 1 to Day 14	

End point values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	40		
Units: days				
arithmetic mean (standard deviation)	12.0 (± 3.86)	9.62 (± 4.80)		

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Elimination Half-Life (T1/2)

End point title	Terminal Elimination Half-Life (T1/2)
End point description: The analysis population consisted of the PKAS with participants who had available data.	
End point type	Secondary
End point timeframe: Day 1 to Day 14	

End point values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	33		
Units: days				
arithmetic mean (standard deviation)	5.83 (± 2.70)	5.38 (± 2.56)		

Statistical analyses

No statistical analyses for this end point

Secondary: Total Clearance After Intravenous Dosing (CL)

End point title	Total Clearance After Intravenous Dosing (CL)

End point description:

The analysis population consisted of the PKAS with participants who had available data.

End point type	Secondary

End point timeframe:

Day 1 to Day 14

End point values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	33		
Units: L/day				
arithmetic mean (standard deviation)	0.496 (± 0.153)	0.718 (± 0.366)		

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution (Vd)

End point title	Volume of Distribution (Vd)

End point description:

The analysis population consisted of the PKAS with participants who had available data.

End point type	Secondary

End point timeframe:

Day 1 to Day 14

End point values	Cohort 1: Zolbetuximab 300 mg/m^2	Cohorts 2+3: Zolbetuximab 600 mg/m^2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	33		
Units: liters				
arithmetic mean (standard deviation)	3.77 (± 1.33)	4.61 (± 1.30)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of first infusion up to until 28 days after the last infusion; Up to 35.71 months.

Adverse event reporting additional description:

The total number of deaths (all causes) includes deaths reported after the time frame above.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Cohorts 2+3: Zolbetuximab 600 mg/m^2

Reporting group description:

Cohort 2 participants received repeated doses of zolbetuximab at a higher dose level (600 mg/m^2 BSA) every 2 weeks on visits 2, 5, 6, 7 and 8. Cohort 3 participants received repeated doses of zolbetuximab (600 mg/m^2 BSA) every 2 weeks on visits 2, 5, 6, 7 and 8.

Reporting group title	Cohort 1: Zolbetuximab 300 mg/m^2

Reporting group description:

Participants received repeated doses of zolbetuximab at a lower dose level (300 mg/m^2 BSA) every 2 weeks on visits 2, 5, 6, 7 and 8.

Serious adverse events	Cohorts 2+3: Zolbetuximab 600 mg/m^2	Cohort 1: Zolbetuximab 300 mg/m^2	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 50 (48.00%)	1 / 4 (25.00%)	
number of deaths (all causes)	23	3	
number of deaths resulting from adverse events	10	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	5 / 50 (10.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 5	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 50 (2.00%)	0 / 4 (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	1 / 50 (2.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	5 / 50 (10.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 50 (0.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 50 (2.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	3 / 50 (6.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 50 (6.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 50 (2.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vomiting			
subjects affected / exposed	3 / 50 (6.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	3 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 50 (2.00%)	0 / 4 (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	3 / 50 (6.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 50 (2.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 50 (2.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 50 (2.00%)	0 / 4 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 50 (2.00%)	1 / 4 (25.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	1 / 50 (2.00%)	0 / 4 (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			
Hyperglycaemia			
subjects affected / exposed	1 / 50 (2.00%)	0 / 4 (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	Cohorts 2+3: Zolbetuximab 600 mg/m^2	Cohort 1: Zolbetuximab 300 mg/m^2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 50 (94.00%)	4 / 4 (100.00%)	
Investigations			
Weight decreased			
subjects affected / exposed	8 / 50 (16.00%)	0 / 4 (0.00%)	
occurrences (all)	8	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 50 (2.00%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Tumour pain			
subjects affected / exposed	3 / 50 (6.00%)	3 / 4 (75.00%)	
occurrences (all)	3	3	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 50 (6.00%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 50 (10.00%)	1 / 4 (25.00%)	
occurrences (all)	7	1	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	12 / 50 (24.00%)	0 / 4 (0.00%)	
occurrences (all)	15	0	
Chills			
subjects affected / exposed	3 / 50 (6.00%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Fatigue			
subjects affected / exposed	22 / 50 (44.00%)	1 / 4 (25.00%)	
occurrences (all)	39	1	
Feeling hot			
subjects affected / exposed	3 / 50 (6.00%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
General physical health deterioration			
subjects affected / exposed	7 / 50 (14.00%)	0 / 4 (0.00%)	
occurrences (all)	8	0	
Oedema peripheral			
subjects affected / exposed	12 / 50 (24.00%)	0 / 4 (0.00%)	
occurrences (all)	16	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 50 (14.00%)	0 / 4 (0.00%)	
occurrences (all)	8	0	
Abdominal pain upper			
subjects affected / exposed	8 / 50 (16.00%)	0 / 4 (0.00%)	
occurrences (all)	10	0	
Ascites			
subjects affected / exposed	5 / 50 (10.00%)	1 / 4 (25.00%)	
occurrences (all)	7	1	
Constipation			
subjects affected / exposed	13 / 50 (26.00%)	1 / 4 (25.00%)	
occurrences (all)	21	1	
Diarrhoea			
subjects affected / exposed	11 / 50 (22.00%)	0 / 4 (0.00%)	
occurrences (all)	12	0	
Dyspepsia			

subjects affected / exposed	3 / 50 (6.00%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Dysphagia			
subjects affected / exposed	4 / 50 (8.00%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Flatulence			
subjects affected / exposed	3 / 50 (6.00%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Nausea			
subjects affected / exposed	32 / 50 (64.00%)	2 / 4 (50.00%)	
occurrences (all)	91	4	
Retching			
subjects affected / exposed	3 / 50 (6.00%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Salivary hypersecretion			
subjects affected / exposed	3 / 50 (6.00%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Vomiting			
subjects affected / exposed	29 / 50 (58.00%)	2 / 4 (50.00%)	
occurrences (all)	80	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 50 (6.00%)	0 / 4 (0.00%)	
occurrences (all)	4	0	
Dyspnoea			
subjects affected / exposed	8 / 50 (16.00%)	0 / 4 (0.00%)	
occurrences (all)	9	0	
Pleural effusion			
subjects affected / exposed	3 / 50 (6.00%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	2 / 50 (4.00%)	1 / 4 (25.00%)	
occurrences (all)	2	1	
Psychiatric disorders			

Agitation			
subjects affected / exposed	1 / 50 (2.00%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Anxiety			
subjects affected / exposed	1 / 50 (2.00%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Sleep disorder			
subjects affected / exposed	7 / 50 (14.00%)	0 / 4 (0.00%)	
occurrences (all)	8	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 50 (2.00%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Back pain			
subjects affected / exposed	5 / 50 (10.00%)	0 / 4 (0.00%)	
occurrences (all)	5	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 50 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Infections and infestations			
Oesophageal candidiasis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Oral candidiasis			
subjects affected / exposed	0 / 50 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 50 (6.00%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 50 (32.00%)	0 / 4 (0.00%)	
occurrences (all)	23	0	
Dehydration			
subjects affected / exposed	4 / 50 (8.00%)	0 / 4 (0.00%)	
occurrences (all)	5	0	

Hypoalbuminaemia subjects affected / exposed occurrences (all)	3 / 50 (6.00%) 4	0 / 4 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 May 2010	Amendment 1 (Protocol version 2.0) was issued to implement the Data Safety Monitoring Board (DSMB) Working Procedure. The infusion interval was changed from once weekly to once every 2 weeks due to the availability of new human pharmacokinetic data. The study duration was increased as a consequence, with infusions taking place on days 1, 15, 29, 43 and 57 as opposed to the previously proposed days 1, 8, 15, 22 and 29.
02 March 2011	Amendment 2 (Protocol version 3.0) was issued to add language to the introduction section as per the recommendations of German Competent Authority (Paul-Ehrlich-Institute) after the sponsor presented results from a mouse study, which showed acute severe allergic reactions in some animals following administration of a murinized variant of chimeric zolbetuximab, obtained by a different purification process with different pharmacokinetic properties. Changes were also made to update screening procedures, blood sample collection and to analyze more laboratory parameters for better patient monitoring.
09 June 2011	Amendment 3 (Protocol version 4.0) was issued to provide continued access to treatment after a patient showed no tumor remission but showed stable disease conditions. The preconditions for continued treatment were changed to enable patients with stable disease to enter the continued treatment phase.
27 July 2011	Amendment 4 (Protocol version 5.0) was issued since new batches of study drug were manufactured using a different manufacturing process to meet the increased demand from the high rate of patient drop-out and continued treatment of patients with stable disease. Furthermore, the first 3 patients dosed with the newly produced study drug in cohort 3 were to be monitored after receiving all 5 infusions, followed by DSMB review and pharmacokinetic analysis, and a decision was to be made for continuation of treatment.
13 September 2011	Amendment 5 (Protocol version 6.0) was issued to improve the observation of tumor status and quality of life (QoL) of patients included in the continued treatment phase by measuring body weight, conducting computed tomography (CT)/magnetic resonance imaging (MRI), requesting European Organisation for Research and Treatment of Cancer (EORTC) questionnaires and taking blood samples for analysis of tumor markers. Additional blood sampling was added before and after each infusion during the continued treatment phase for pharmacokinetic analysis.
08 November 2011	Amendment 6 (Protocol version 7.0) was issued to obtain more pharmacokinetic data. Pharmacokinetic evaluation was to be performed for all patients during the study treatment phase to account for inter-individual differences.
11 January 2012	Amendment 7 (Protocol version 8.0) was issued to clarify that safety of the study drug manufactured by the new process was considered assessable after the first 3 patients of cohort 3 received at least 4 infusions (as opposed to all 5 infusions as previously proposed), before more patients could be treated in cohort 3.
12 November 2012	Amendment 8 (Protocol version 9.0) was issued to change the duration of treatment for responders in the continued treatment phase from about 6 months (12 further infusions) to more than 6 months, until the time of disease progression, unacceptable toxicity or withdrawal of consent.

30 October 2013	Amendment 9 (Protocol version 10.0) was issued to introduce additional antidrug antibody (ADA) measurements on samples initially collected for pharmacokinetic analysis in order to increase patient safety. Administrative changes were also made (contract research organization [CRO] was changed and safety reporting was to be covered by the sponsor), and 20R size vials were introduced as drug product containers in addition to the previously used 6R vials.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This study was conducted by Ganymed AG, a company that was acquired by Astellas in December of 2016.

Notes: