Clinical trial results:
A single arm phase II, open-label, multicenter trial to investigate the clinical activity and safety of avelumab in combination with cetuximab in subjects with unresectable stage III or stage IV cutaneous squamous cell carcinoma (cSCC)

Summary

EudraCT number	2018-001708-12
Trial protocol	DE
Global end of trial date	04 April 2024

Results information

Result version number	v1 (current)
This version publication date	04 June 2025
First version publication date	04 June 2025

Trial information

Trial identification

Sponsor protocol code	4518000

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	DRKS: DRKS00017255

Notes:

Sponsors

Sponsor organisation name	Alcedis GmbH
Sponsor organisation address	Winchesterstraße 3, 35394, Germany, Gießen
Public contact	Universitätsklinik für Dermatologie, Johannes Wesling Klinikum Minden, +49 5717904500, ralf.gutzmer@muehlenkreiskliniken.de
Scientific contact	Universitätsklinik für Dermatologie, Johannes Wesling Klinikum Minden, +49 5717904500, ralf.gutzmer@muehlenkreiskliniken.de

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	11 December 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate efficacy in terms of objective response rate (ORR) after 3 months of combination therapy of avelumab and cetuximab according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)

Protection of trial subjects:

The treatment should be conducted as described in the protocol. Any protocol deviations were reported. The recommendations of Good Clinical Practice (see ICH-GCP: International Conference on Harmonisation - Good Clinical Practice), valid since 17.1.1997, were met. Throughout the study, participating patients were under close observation.

Background therapy:

Any medications (other than those excluded by the clinical trial protocol) that were considered necessary for the patients' welfare and did not interfere with the trial drug could be given at the investigator's discretion.
At least 1 hour prior to the first infusion of cetuximab, patients had to be pretreated with an antihistamine and a corticosteroid. This premedication was also recommended prior to all subsequent infusions.
Palliative bone-directed radiotherapy could be administered during the trial. Short-term administration of systemic steroid (that is, for allergic reactions or the management of irAEs) was allowed.
Erythropoietin and darbepoietin alpha could be prescribed at the Investigator's discretion.
Bisphosphonate treatment was permitted if it had been started more than 14 days before the first administration of the study drug.

Evidence for comparator:

As this was a single arm trial, no comparator was used.

Actual start date of recruitment	03 June 2019
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 49
Worldwide total number of subjects	49
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)	11
From 65 to 84 years	33
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

After obtaining signed informed consent, screening evaluations were performed to confirm eligibiliy. Between 03-Jun-2019 (first patient in) and 12-Apr-2021 (last patient in), 70 pts were screened by 10 German hospitals; 49 pts were registered by 9 sites. A two-stage design (Simon) was used: the first 15 pts were analyzed after 3 months of therapy.

Pre-assignment

Screening details:

The patients were selected by the investigator according to the inclusion and exclusion criteria after they had been informed about the study in writing and orally and had signed an informed consent form. The baseline examinations had to be performed within 28 days prior to date of registration.

Period 1

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

Blinding implementation details:

Not blinded

Arms

Arm title	Cetuximab + Avelumab

Arm description:

Biweekly Cetuximab in combination with Avelumab.

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

Dosage and administration details:

Cetuximab was supplied as 20 mL vials with 100 mg Cetuximab (each mL of solution for infusion contained 5 mg). Patients received Cetuximab 500 mg/m² as an intravenous infusion on day 1 every 2 weeks. The recommended infusion period for the first infusion was 180 minutes. The following biweekly infusions were administerd as 120-minute iv infusions with the infusion rate not exceeding 10 mg/min. Dose modifications (reductions or escalations) were not allowed. Doses could be delayed for drug-related AEs until improvement to NCI grade ≤1.

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

Dosage and administration details:

Avelumab was supplied in 10 mL single-use glass vials containing 200 mg Avelumab (each mL conained 20 mg Avelumab). Patients received 10 mg/kg body weight once every 2 weeks on the same day as the Cetuximab infusion. Avelumab was administered with a break of at least 60 minutes after the Cetuximab infusion. Dose modifications (reductions or escalations) were not allowed. Doses could be delayed for drug-related AEs until improvement to NCI grade ≤1.

Number of subjects in period 1	Cetuximab + Avelumab
Started	49
Completed	49

Baseline characteristics

Reporting groups

Reporting group title	Treatment period (overall period)

Reporting group description: -

Reporting group values	Treatment period (overall period)	Total	
Number of subjects	49	49	
Age categorical			
Male and female patients aged ≥ 18 years could be enrolled. There was no maximum age limit. Age of patients was calculated by subtracting year of birth from year of enrolment.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	11	11	
From 65-84 years	33	33	
85 years and over	5	5	
Age continuous			
Male and female patients aged ≥ 18 years could be enrolled. There was no maximum age limit. Age of patients was calculated by subtracting year of birth from year of enrolment.			
Units: years			
median	76		
full range (min-max)	46 to 90	-	
Gender categorical			
There was no preferred enrolment of men or women within this study since both drugs have not shown gender specific mode of action. However, pregnant or breast-feeding women were excluded from participation.			
Units: Subjects			
Female	16	16	
Male	33	33	
AJCC stage at initial diagnosis			
Tumor history prior to study enrollment			
Units: Subjects			
Stage 0	1	1	
Stage I	8	8	
Stage II	5	5	
Stage III	15	15	
Stage IV	15	15	
Unknown	5	5	

Subject analysis sets

Subject analysis set title	ITT+Safety
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients received at least one dose of Cetuximab and Avelumab.

Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

Patients received the study combination therapy for at least 12 weeks (= until the first planned assessment of efficacy) and had no major violation of inclusion/exclusion criteria.

Reporting group values	ITT+Safety	PP	
Number of subjects	49	37	
Age categorical			
Male and female patients aged ≥ 18 years could be enrolled. There was no maximum age limit. Age of patients was calculated by subtracting year of birth from year of enrolment.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	11	8	
From 65-84 years	33	25	
85 years and over	5	4	
Age continuous			
Male and female patients aged ≥ 18 years could be enrolled. There was no maximum age limit. Age of patients was calculated by subtracting year of birth from year of enrolment.			
Units: years			
median	76	77	
full range (min-max)	46 to 90	46 to 90	
Gender categorical			
There was no preferred enrolment of men or women within this study since both drugs have not shown gender specific mode of action. However, pregnant or breast-feeding women were excluded from participation.			
Units: Subjects			
Female	16	12	
Male	33	25	
AJCC stage at initial diagnosis			
Tumor history prior to study enrollment			
Units: Subjects			
Stage 0	1	1	
Stage I	8	6	
Stage II	5	4	
Stage III	15	12	
Stage IV	15	9	
Unknown	5	5	

End points

End points reporting groups

Reporting group title	Cetuximab + Avelumab
Reporting group description: Biweekly Cetuximab in combination with Avelumab.	
Subject analysis set title	ITT+Safety
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients received at least one dose of Cetuximab and Avelumab.	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description: Patients received the study combination therapy for at least 12 weeks (= until the first planned assessment of efficacy) and had no major violation of inclusion/exclusion criteria.	

Primary: Objective response rate after 3 months of combination therapy of avelumab and cetuximab according to RECIST v1.1

End point title	Objective response rate after 3 months of combination therapy of avelumab and cetuximab according to RECIST v1.1[1]

End point description:

Tumor assessments using computed tomography scan or magnetic resonance imaging of chest, abdomen and pelvis as well as of other tumor bearing areas were performed at screening and every 12 weeks during study treatment and during 3-monthly follow-up visits based on the German Guidelines for Diagnosis and Management of cSCC.
Clinical assessment of cutaneous tumor lesions, including photography, had to be performed at screening and every 6 weeks during treatment period.
Response evaluation was performed by the investigator according to RECIST v1.1 criteria. The overall response rate includd all patients with CR or PR at the respective time point.
A non-interesting response rate of p0 = 30% and a target response rate of p1 = 50% were assumed. The hypotheses H0: $p \leq p0$ versus H1: $p \geq p1$ were tested with a first-type error rate of $\alpha = 0.05$. At least 19 patients with objective responses (CR + PR) were required in 46 evaluable patients to reject $p \leq p0$.

End point type	Primary

End point timeframe:

Response assessment at week 12 (+/- 2 weeks) after start of study therapy

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: Analyses were descriptive only. No statistical analyses were planned.

End point values	Cetuximab + Avelumab	ITT+Safety	PP	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	49	49	37	
Units: number of subjects	15	15	15	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival

End point title	Progression-free survival

End point description:

End point type	Secondary

End point timeframe:

From start of study treatment (date of first administration of study drug) until the first documented tumor progression (PD) or death by any cause whichever occurred first.

End point values	ITT+Safety	PP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	49	37		
Units: months				
median (confidence interval 95%)	8.35 (4.64 to 10.39)	9.24 (6.15 to 15.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

DOR was calculated among the responders (i.e. patients showing CR or PR) as time (in months) from first PR or CR (date of first unconfirmed documentation of CR or PR) until first documented tumor progression (date of progression). For patients without progress, DOR was censored at the last known event-free date.

End point type	Secondary

End point timeframe:

From first PR or CR (date of first unconfirmed documentation of CR or PR) until first documented tumor progression (date of progression).

End point values	ITT+Safety	PP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20[2]	20[3]		
Units: months				
median (confidence interval 95%)	16.69 (7.00 to 30.38)	16.69 (7.00 to 30.38)		

Notes:

[2] - 29 patients did not have CR or PR.

[3] - 17 patients did not have CR or PR.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

From start of study treatment (date of first administration of study drug) until documented death (date of death).

End point values	ITT+Safety	PP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	48[4]	37		
Units: months				
median (confidence interval 95%)	23.08 (13.45 to 33.11)	25.42 (14.37 to 35.55)		

Notes:

[4] - One patient has been documented as deceased without a documented date of death.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From date of signing the informed consent until 30 days after date of last administration of study therapy.

Adverse event reporting additional description:

Toxicities were defined according to the NCI-CTC-Toxicity criteria version 5.0. From 30 days after the last administration of the study therapy until the end of the follow-up period for each patient, only AEs with a causal relationship to the study drugs had to be documented, as well as SAEs irrespective of causality.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	ITT+Safety

Reporting group description:

All patients who received at least one dose of cetuximab and / or avelumab were included in the safety analysis.

Serious adverse events	ITT+Safety		
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 49 (87.76%)		
number of deaths (all causes)	31		
number of deaths resulting from adverse events	30		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasm progression			
subjects affected / exposed	6 / 49 (12.24%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 6		
Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Pancreatic cystadenoma			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transitional cell carcinoma			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour pain			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Blepharorrhaphy			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stoma creation			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Death			
subjects affected / exposed	10 / 49 (20.41%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 10		
Disease progression			
subjects affected / exposed	7 / 49 (14.29%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 7		
General physical health deterioration			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Hypoxia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumothorax			

subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary haemorrhage				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Rhinorrhoea				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Delirium				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Suicide attempt				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Fracture				

subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Coronary artery stenosis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune-mediated myocarditis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Basal ganglia haemorrhage			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Syncope			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anemia of malignant disease			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hilar lymphadenopathy				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lymphadenopathy				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Eye disorders				
Ectropion				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhoea				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Skin and subcutaneous tissue disorders				
Actinic keratosis				
subjects affected / exposed	1 / 49 (2.04%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dermatitis acneiform				

subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Eczema			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pemphigoid			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 49 (4.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Soft tissue necrosis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infection			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Medical device site infection			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Staphylococcal infection			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

Hypercalcaemia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 49 (2.04%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	ITT+Safety		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 49 (100.00%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Hypertension			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Fatigue			
subjects affected / exposed	5 / 49 (10.20%)		
occurrences (all)	7		
Pain			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	6		
Respiratory, thoracic and mediastinal disorders			

Dyspnoea subjects affected / exposed occurrences (all)	5 / 49 (10.20%) 6		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	4 / 49 (8.16%) 4		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	4 / 49 (8.16%) 5		
Amylase increased subjects affected / exposed occurrences (all)	4 / 49 (8.16%) 4		
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	4 / 49 (8.16%) 4		
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	8 / 49 (16.33%) 8		
Blood creatinine increased subjects affected / exposed occurrences (all)	5 / 49 (10.20%) 5		
Electrocardiogram QT prolonged subjects affected / exposed occurrences (all)	9 / 49 (18.37%) 14		
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	7 / 49 (14.29%) 9		
Lipase increased subjects affected / exposed occurrences (all)	5 / 49 (10.20%) 10		
Lymphocyte count decreased subjects affected / exposed occurrences (all)	5 / 49 (10.20%) 7		
Injury, poisoning and procedural			

complications			
Infusion related reaction			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Headache			
subjects affected / exposed	7 / 49 (14.29%)		
occurrences (all)	7		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 49 (10.20%)		
occurrences (all)	8		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	8 / 49 (16.33%)		
occurrences (all)	8		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	5		
Diarrhoea			
subjects affected / exposed	6 / 49 (12.24%)		
occurrences (all)	7		
Nausea			
subjects affected / exposed	6 / 49 (12.24%)		
occurrences (all)	7		
Oral dysaesthesia			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Stomatitis			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Vomiting			

subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	29 / 49 (59.18%)		
occurrences (all)	44		
Dry skin			
subjects affected / exposed	13 / 49 (26.53%)		
occurrences (all)	13		
Eczema			
subjects affected / exposed	7 / 49 (14.29%)		
occurrences (all)	8		
Erythema			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	5		
Intertrigo			
subjects affected / exposed	7 / 49 (14.29%)		
occurrences (all)	7		
Pruritus			
subjects affected / exposed	5 / 49 (10.20%)		
occurrences (all)	6		
Rash			
subjects affected / exposed	3 / 49 (6.12%)		
occurrences (all)	3		
Rash maculo-papular			
subjects affected / exposed	5 / 49 (10.20%)		
occurrences (all)	5		
Skin fissures			
subjects affected / exposed	6 / 49 (12.24%)		
occurrences (all)	8		
Skin ulcer			
subjects affected / exposed	4 / 49 (8.16%)		
occurrences (all)	5		
Renal and urinary disorders			
Haematuria			

subjects affected / exposed occurrences (all)	6 / 49 (12.24%) 9		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 3 / 49 (6.12%) 3		
Infections and infestations Conjunctivitis subjects affected / exposed occurrences (all) Folliculitis subjects affected / exposed occurrences (all) Paronychia subjects affected / exposed occurrences (all) Rash pustular subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	 5 / 49 (10.20%) 6 3 / 49 (6.12%) 6 7 / 49 (14.29%) 9 3 / 49 (6.12%) 4 10 / 49 (20.41%) 14		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hyperkalaemia subjects affected / exposed occurrences (all) Hypomagnesaemia subjects affected / exposed occurrences (all)	 3 / 49 (6.12%) 4 5 / 49 (10.20%) 11 7 / 49 (14.29%) 10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 June 2019	Amendment 1 (protocol version 3.0, dated 07.06.2019) included changes in wording requested by the competent authority and ethics committee as well as a change to treatment schedule, addition of an exclusion criterion and an update of justification for dose.
04 January 2021	Amendment 2 (protocol version 4.0, dated 04.01.2021) included an update of study timelines due to prolongation of recruitment, administrative corrections and clarifications as well as minor corrections of cross-references to literature index.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported