Clinical trial results:
A Phase IIa Exploratory Study of CriPec® docetaxel Monotherapy in Subjects with Platinum Resistant Ovarian Cancer.

Summary

EudraCT number	2018-002117-36
Trial protocol	NL BE GB
Global end of trial date	06 July 2020

Results information

Result version number	v1 (current)
This version publication date	08 January 2021
First version publication date	08 January 2021
Summary attachment (see zip file)	SMS-0423_CINOVA_Synopsis final CSR_01Dec2020_signed (SMS-0423_CINOVA_Synopsis final CSR_01Dec2020_signed.pdf)

Trial information

Trial identification

Sponsor protocol code	CT-CL02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03742713
WHO universal trial number (UTN)	-
Other trial identifiers	SMS-oncology study number: SMS-0423

Notes:

Sponsors

Sponsor organisation name	Cristal Therapeutics
Sponsor organisation address	Oxfordlaan 55, Maastricht, Netherlands, 6229 EV
Public contact	Rob Hanssen, Cristal Therapeutics, info@cristaltherapeutics.com
Scientific contact	Rob Hanssen, Cristal Therapeutics, info@cristaltherapeutics.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	01 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 July 2020
Global end of trial reached?	Yes
Global end of trial date	06 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the Objective Response Rate (ORR) as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 of CriPec® docetaxel monotherapy in subjects with ovarian cancer who are resistant to prior platinum-based therapy.

Protection of trial subjects:

Corticosteroid pre-medication was administered to prevent skin toxicities.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 October 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Belgium: 15
Worldwide total number of subjects	25
EEA total number of subjects	25

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	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This trial was conducted in 8 centers divided over 3 countries: The Netherlands, Belgium and the United Kingdom. 6 out of 8 centers recruited patients. First patient was included 19Oct2018. Last study visit before database lock was 06Jul2020.

Pre-assignment

Screening details:

Patients with ovarian and peritoneal cancer resistant to prior platinum-based therapy. Total number of patients was 25 with 25 being part of the safety set population, and 23 being part of the per protocol set.

Stage 1: first 13 patients included
Stage 2: altered inclusion criteria to match those of hallmark Docetaxel trials

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Received at least one dose CriPec©docetaxel

Arm description:

Subjects eligible for the trial received CriPec®docetaxel Q3W at the RP2D of 60 mg/m2. Each treatment cycle consisted of 21 days. On Day 1 of each cycle, a single dose of CriPec®docetaxel was administered IV at a constant rate for ~1 hour. Pre-treatment with dexamethasone 8.0 mg orally was given three times before each CriPec®docetaxel administration (night before, morning and 1 hour before treatment).

Stage 1: (N=13) Simon 2-stage design.
Stage 2: (N=12). Simon 2-stage design no longer applicable. Maximum allowed treatment lines reduced from 3 to 2 lines, in both cases of which one could have been taxane-based. Life expectancy requirement extended from 12 weeks to 5 months.

Arm type	Experimental
Investigational medicinal product name	CriPec©docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The dose selection for CT-CL02 was based on previous experience from trial CT-CL01, where the R2PD of 60 mg/m2 with corticosteroid premedication was selected based on the following:
• There was a significant decrease of skin toxicities (all severity grades) comparing 70 mg/m2 to 60 mg/m2 dose level at the Q3W schedule;
• Addition of corticosteroid premedication to the 60 mg/m2/Q3W regimen prevented acute skin reactions. Also, at the 60 mg/m2 dose plus corticosteroids, overall less AEs have been reported;
• The average length of therapy at 60 mg/m2 plus corticosteroids was longer (~5.2 treatment cycles) than without co-medication (~3.2 treatment cycles);

The complete dose of CriPec®docetaxel had to be administered via IV infusion. Start and stop times had to be noted. If the administration was interrupted and subsequently restarted, the start and stop times of the re-administration must have also been noted.

Number of subjects in period 1	Received at least one dose CriPec©docetaxel
Started	25
Completed	25

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description:

Q3W IV CriPec©docetaxel administration at 60mg/m2, with corticosteroid premedication (three times 8.0 mg oral dexamethasone before each CriPec®docetaxel dose).

* Stage 1 (N=13): There was no limit to the number of previous treatment lines, but a maximum of 3 lines of therapy for platinum-resistant disease, of which one could have been taxane-based. Life expectancy required of at least 12 weeks.

* Stage 2: Subjects who have received a maximum of 2 prior treatment lines, of which one could have been taxane-based. Life expectancy required of at least 5 months.

Reporting group values	Overall trial	Total	
Number of subjects	25	25	
Age categorical 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	14	14	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	25	25	
Male	0	0	
Number of previous treatment lines			
PD was recorded in all subjects who had previously received four or five lines of therapy (four lines: three subjects in Stage 1 and one subject in Stage 2; five lines: three subjects in Stage 1). Previous treatment lines include: Platinum compounds, Taxanes, Anthracyclines and related, Monoclonal antibodies, Other antineoplastic agents, Pyrimidine analogues, Aromatase inhibitors, Investigational drugs and Antineoplastic agents.			
Units: Subjects			
1 treatment line	1	1	
2 treatment lines	9	9	
3 treatment lines	8	8	
4 treatment lines	4	4	
5 treatment lines	3	3	

Subject analysis sets	
Subject analysis set title	Stage 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

There was no limit to the number of previous treatment lines, but a maximum of 3 lines of therapy for platinum-resistant disease, of which one could have been taxane-based. Life expectancy required of at least 12 weeks.

Subject analysis set title	Stage 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who have received a maximum of 2 prior treatment lines, of which one could have been taxane-based. Life expectancy required of at least 5 months.

Reporting group values	Stage 1	Stage 2	
Number of subjects	13	12	
Age categorical			
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)	9	2	
From 65-84 years	4	10	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	13	12	
Male	0	0	
Number of previous treatment lines			
PD was recorded in all subjects who had previously received four or five lines of therapy (four lines: three subjects in Stage 1 and one subject in Stage 2; five lines: three subjects in Stage 1). Previous treatment lines include: Platinum compounds, Taxanes, Anthracyclines and related, Monoclonal antibodies, Other antineoplastic agents, Pyrimidine analogues, Aromatase inhibitors, Investigational drugs and Antineoplastic agents.			
Units: Subjects			
1 treatment line	0	1	
2 treatment lines	0	9	
3 treatment lines	7	1	
4 treatment lines	3	1	
5 treatment lines	3	0	

End points

End points reporting groups

Reporting group title	Received at least one dose CriPec©docetaxel

Reporting group description:

Subjects eligible for the trial received CriPec®docetaxel Q3W at the RP2D of 60 mg/m2. Each treatment cycle consisted of 21 days. On Day 1 of each cycle, a single dose of CriPec®docetaxel was administered IV at a constant rate for ~1 hour. Pre-treatment with dexamethasone 8.0 mg orally was given three times before each CriPec®docetaxel administration (night before, morning and 1 hour before treatment).

Stage 1: (N=13) Simon 2-stage design.
Stage 2: (N=12). Simon 2-stage design no longer applicable. Maximum allowed treatment lines reduced from 3 to 2 lines, in both cases of which one could have been taxane-based. Life expectancy requirement extended from 12 weeks to 5 months.

Subject analysis set title	Stage 1
Subject analysis set type	Sub-group analysis

Subject analysis set description:

There was no limit to the number of previous treatment lines, but a maximum of 3 lines of therapy for platinum-resistant disease, of which one could have been taxane-based. Life expectancy required of at least 12 weeks.

Subject analysis set title	Stage 2
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects who have received a maximum of 2 prior treatment lines, of which one could have been taxane-based. Life expectancy required of at least 5 months.

Primary: ORR as assessed by RECISTV1.1 calculated as proportion of subjects who achieved CR or PR

End point title	ORR as assessed by RECISTV1.1 calculated as proportion of subjects who achieved CR or PR[1]

End point description:

ORR as assessed by RECISTV1.1

End point type	Primary

End point timeframe:

At any time point prior to end of trial (when the subject had either discontinued trial treatment or received six cycles of treatment, whichever occurred first).

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: The analysis of the primary endpoint was descriptive i.e. no statistical hypothesis test was performed.

End point values	Received at least one dose CriPec©docetaxel	Stage 1	Stage 2	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	20	13	7	
Units: Best overall response				
CR	0	0	0	
PR	0	0	0	
SD	7	3	4	
PD	13	10	3	
Objective response rate	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Safety, evaluated by means of physical examinations, body weight, vital signs, ECOG, lab, ECG and AEs

End point title	Safety, evaluated by means of physical examinations, body weight, vital signs, ECOG, lab, ECG and AEs

End point description:

For physical examinations, body weight, vital signs lab, and ECG parameters no clear impact on safety could be detected. For an overview of the Adverse Events, please refer to the Adverse Event section of this report.

ECOG changes during the trial to higher grades were generally recorded for higher numbers of subjects in Stage 2 than in Stage 1.

End point type	Secondary

End point timeframe:

Safety parameters were recorded from screening until day 22 of the last cycle (EOT). Both ECOG and vital signs were additionally recorded at the safety follow-up visit 28 days after EOT. SAEs regarded related to IMP were followed until end of study.

End point values	Received at least one dose CriPec©docetaxel	Stage 1	Stage 2	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	13	12	
Units: ECOG worsening				
Baseline ECOG 0 - No worsening	6	6	0	
Baseline ECOG 0 - Worsening to ECOG 1	6	2	4	
Baseline ECOG 0 - Worsening to ECOG 2	2	1	1	
Baseline ECOG 0 - Worsening to ECOG 3	1	0	1	
Baseline ECOG 1 - No worsening	5	3	2	
Baseline ECOG 1 - Worsening to ECOG 2	2	0	2	
Baseline ECOG 1 - Worsening to ECOG 3	2	1	1	
No post-baseline ECOG assessment performed	1	0	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Subjects were monitored for AEs from screening and during each subject visit until 22 days after last CriPec©docetaxel administration (EOT visit). In addition, ongoing SAEs were assessed at the 28-day FU, regardless of its relationship to the IMP.

Adverse event reporting additional description:

AEs occurring after EOT and coming to the attention of the Investigator must be recorded only if they are considered (in the opinion of the Investigator) related to CriPec©docetaxel.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Overall trial

Reporting group description:

Subjects eligible for the trial received CriPec®docetaxel Q3W at the RP2D of 60 mg/m2. Each treatment cycle consisted of 21 days. On Day 1 of each cycle, a single dose of CriPec®docetaxel was administered IV at a constant rate for ~1 hour. Pre-treatment with dexamethasone 8.0 mg orally was given three times before each CriPec®docetaxel administration (night before, morning and 1 hour before treatment).

Stage 1: (N=13) Simon 2-stage design.
Stage 2: (N=12). Simon 2-stage design no longer applicable. Maximum allowed treatment lines reduced from 3 to 2 lines, in both cases of which one could have been taxane-based. Life expectancy requirement extended from 12 weeks to 5 months.

Serious adverse events	Overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 25 (64.00%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events	1		
Investigations			
Medical observation			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant ascites			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
T-cell prolymphocytic leukaemia			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Social circumstances			
Social stay hospitalisation			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Faecaloma			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic ascites			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
General physical health deterioration			
subjects affected / exposed	6 / 25 (24.00%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic kidney disease			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Empyema			

subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 25 (4.00%)		
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	Overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 25 (100.00%)		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	11 / 25 (44.00%)		
occurrences (all)	17		
Oedema peripheral			
subjects affected / exposed	6 / 25 (24.00%)		
occurrences (all)	7		

Malaise subjects affected / exposed occurrences (all)	4 / 25 (16.00%) 4		
Peripheral swelling subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Pyrexia subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	5 / 25 (20.00%) 10		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 3		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	12 / 25 (48.00%) 18		
Vomiting subjects affected / exposed occurrences (all)	9 / 25 (36.00%) 15		
Ascites subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Small intestinal obstruction subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Intestinal obstruction subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3		
Haemorrhagic ascites subjects affected / exposed occurrences (all)	1 / 25 (4.00%) 1		
Diarrhoea			

subjects affected / exposed	5 / 25 (20.00%)		
occurrences (all)	9		
Abdominal pain			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	5		
Constipation			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	5		
Abdominal pain upper			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Abdominal discomfort			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	4		
Dyspnoea			
subjects affected / exposed	10 / 25 (40.00%)		
occurrences (all)	12		
Cough			
subjects affected / exposed	4 / 25 (16.00%)		
occurrences (all)	4		
Dysphonia			
subjects affected / exposed	2 / 25 (8.00%)		
occurrences (all)	2		
Epistaxis			

subjects affected / exposed occurrences (all)	3 / 25 (12.00%) 3		
Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all) Alopecia subjects affected / exposed occurrences (all)	 3 / 25 (12.00%) 3 2 / 25 (8.00%) 3 2 / 25 (8.00%) 2		
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) Chronic kidney disease subjects affected / exposed occurrences (all)	 1 / 25 (4.00%) 1 1 / 25 (4.00%) 1		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	 1 / 25 (4.00%) 1		
Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all)	 2 / 25 (8.00%) 3 2 / 25 (8.00%) 2		
Infections and infestations Cystitis subjects affected / exposed occurrences (all) Oral candidiasis	 2 / 25 (8.00%) 2		

subjects affected / exposed occurrences (all)	2 / 25 (8.00%) 2		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hyperkalaemia subjects affected / exposed occurrences (all) Hypoalbuminaemia subjects affected / exposed occurrences (all)	 9 / 25 (36.00%) 15 2 / 25 (8.00%) 4 3 / 25 (12.00%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 September 2018	Protocol V3.0_25Sep2018 (NL, UK) and V2.0_11Sep2018 (Belgium-specific). For both UK and BE these protocols were approved under the Initial study approval. For NL it has been an amendment (SA01). The changes compared to V1.0_01Jun2018 include administrative changes and changes as directed by the CA of BE: -Frequency of pregnancy tests increased for women of childbearing potential -Further specification of footnotes of the schedule of assessments -Removal of some biochemistry parameters -Specification of the moment of EOT -Specification about SAE FU at safety FU visit
28 May 2019	Protocol V4.0_20May2019 & Protocol V5.0_24Jun2019 after comments of the CA of NL The protocol was amended after data review of the first stage of the trial. The following changes were applied in protocol V4.0: - Modification of inclusion criterion maximum number of treatment lines allowed to match those of landmark docetaxel trials -Required life expectancy increased from 12 weeks to 5 months -Therefore no longer a Simon 2-stage study design -Updated dose modification criteria -Introduction of possibility to replace subjects under certain conditions -Change of scan interval changed from: SCR, after 6 weeks and every 12 weeks thereafter, to: SCR, after 9 weeks and every 9 weeks thereafter; -Updated safety information from previous trials IB V5.0; -Introduction of slot reservation process prior to subject registration; -Cap of 2 patients per site for the first 8 included patients to ensure balanced recruitment. In protocol V5.0, a limit to the number of patients that may be replaced (max. 7) was introduced following comments from the CA in NL. Protocol V5.0 was submitted as a notification to UK and BE to ensure the same protocol version was used in all participating countries.
17 March 2020	Investigator's Brochure March2020 -Updated trial status -Updated reference safety information

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

16 March 2020	In light of the COVID-19 pandemic and the increased pressure on sites because of this, recruitment of patients was halted as of 16Mar2020. On 14May2020 it was subsequently decided that recruitment would not be resumed for the rest of the trial. The latter decision was communicated to sites on 18May2020, and was based on a DRC meeting held in April 2020, where efficacy signals were not considered strong enough to substantiate continuation. Patients that were on treatment during the time of the recruitment stop that was announced 16Mar2020 continued to receive treatment per protocol. At the time of the definitive recruitment closure on 18May2020, active patients (n=1) were informed of the limited efficacy signals and were given the choice to either continue or stop the treatment.	-

Notes:

Limitations and caveats

None reported