Clinical trial results:
A MULTI-CENTER, OPEN-LABEL, PHASE 2 STUDY TO EVALUATE SAFETY AND EFFICACY OF U3-1402 IN SUBJECTS WITH ADVANCED OR METASTATIC COLORECTAL CANCER (CRC)

Summary

EudraCT number	2019-004418-32
Trial protocol	GB PL BE IT
Global end of trial date	03 February 2022

Results information

Result version number	v1 (current)
This version publication date	20 February 2023
First version publication date	20 February 2023

Trial information

Trial identification

Sponsor protocol code	U31402-A-U202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04479436
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo, Inc.
Sponsor organisation address	211 Mt. Airy Rd., Basking Ridge, United States, 07920
Public contact	Global Clinical Director, Daiichi Sankyo, Inc., +1 908-992-6400, CTRinfo@dsi.com
Scientific contact	Global Clinical Director, Daiichi Sankyo, Inc., +1 908-992-6400, CTRinfo@dsi.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	03 February 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 February 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the tolerability and antitumor activity of U3-1402 in subjects with advanced or metastatic CRC who are resistant, refractory, or intolerant to at least 2 prior lines of therapy

Protection of trial subjects:

The study protocol, amendments, the informed consent form(s) (ICF[s]), and information sheets were approved by the appropriate and applicable Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs). The study was conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 August 2020
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	United States: 30
Country: Number of subjects enrolled	Japan: 10
Worldwide total number of subjects	40
EEA total number of subjects	0

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)	30
From 65 to 84 years	10

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 40 participants were enrolled and treated at 12 sites in the United States and Japan.

Pre-assignment

Screening details:

60 participants were screened and 20 participants were screen failures. A total of 39 participants with high HER3 expression CRC were enrolled in Cohort 1 and 1 participant with low HER3 expression CRC was enrolled in Cohort 2.

Period 1

Period 1 title	Overall (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: HER3 High (IHC 3+, 2+)

Arm description:

Participants with high tumor expression levels of human epidermal receptor 3 (HER3) in a pre-treatment biopsy specimen who received 5.6 mg/Kg of U3-1402 intravenously (IV) on Day 1 of each 21-day cycle.

Arm type	Experimental
Investigational medicinal product name	U3-1402
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

U3-1402 will be dosed at 5.6 mg/kg as an intravenous (IV) infusion administered on Day 1 of each 21-day cycle.

Arm title	Cohort 2: HER3 Low/Negative (IHC 1+, 0)

Arm description:

Participants with low or negative tumor expression levels of human epidermal receptor 3 (HER3) in a pre-treatment biopsy specimen who received 5.6 mg/Kg of U3-1402 intravenously (IV) on Day 1 of each 21-day cycle.

Arm type	Experimental
Investigational medicinal product name	U3-1402
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

U3-1402 will be dosed at 5.6 mg/kg as an intravenous (IV) infusion administered on Day 1 of each 21-day cycle.

Number of subjects in period 1	Cohort 1: HER3 High (IHC 3+, 2+)	Cohort 2: HER3 Low/Negative (IHC 1+, 0)
Started	39	1
Completed	0	0
Not completed	39	1
Clinical progression	1	-
Physician decision	1	-
Adverse event, non-fatal	6	-
Progressive disease	26	1
Withdrawal by subject	5	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: HER3 High (IHC 3+, 2+)
Reporting group description:	
Participants with high tumor expression levels of human epidermal receptor 3 (HER3) in a pre-treatment biopsy specimen who received 5.6 mg/Kg of U3-1402 intravenously (IV) on Day 1 of each 21-day cycle.	
Reporting group title	Cohort 2: HER3 Low/Negative (IHC 1+, 0)
Reporting group description:	
Participants with low or negative tumor expression levels of human epidermal receptor 3 (HER3) in a pre-treatment biopsy specimen who received 5.6 mg/Kg of U3-1402 intravenously (IV) on Day 1 of each 21-day cycle.	

Reporting group values	Cohort 1: HER3 High (IHC 3+, 2+)	Cohort 2: HER3 Low/Negative (IHC 1+, 0)	Total
Number of subjects	39	1	40
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	30	0	30
From 65-84 years	9	1	10
85 years and over	0	0	0
Age continuous Units: years			
median	56	67	
full range (min-max)	40 to 74	67 to 67	-
Gender categorical Units: Subjects			
Female	13	1	14
Male	26	0	26
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	10	0	10
Native Hawaiian or Other Pacific Islander	3	0	3
Black or African American	0	0	0
White	26	1	27
More than one race	0	0	0
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Cohort 1: HER3 High (IHC 3+, 2+)

Reporting group description:

Participants with high tumor expression levels of human epidermal receptor 3 (HER3) in a pre-treatment biopsy specimen who received 5.6 mg/Kg of U3-1402 intravenously (IV) on Day 1 of each 21-day cycle.

Reporting group title	Cohort 2: HER3 Low/Negative (IHC 1+, 0)

Reporting group description:

Participants with low or negative tumor expression levels of human epidermal receptor 3 (HER3) in a pre-treatment biopsy specimen who received 5.6 mg/Kg of U3-1402 intravenously (IV) on Day 1 of each 21-day cycle.

Subject analysis set title	Cohort 1 & 2: HER3 High (IHC 3+, 2+) & HER3 Low/Negative (IHC)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants with high tumor expression & low or negative levels of human epidermal receptor 3 (HER3) low or negative and who received 5.6 mg/Kg of U3-1402 intravenously (IV) on Day 1 of each 21-day cycle (Safety Analysis Set).

Primary: Objective Response Rate (ORR) Based on Blinded Independent Central Review (BICR) Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer

End point title	Objective Response Rate (ORR) Based on Blinded Independent Central Review (BICR) Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer[1][2]

End point description:

The Objective Response Rate (ORR) was defined as the percentage of participants who achieved a best overall response of confirmed Complete Response (CR) or Partial Response (PR), assessed by blinded independent central review (BICR) based on RECIST version 1.1. CR was defined as a reduction of target lesions to non-measurable dimensions and PR was defined as at least a 30% decrease in the sum of diameters of target lesions. Confirmed ORR based on BICR is reported and was assessed in the Full Analysis Set.

End point type	Primary

End point timeframe:

From baseline up to disease progression by BICR, death, lost to follow up, or withdrawal of consent by subject (whichever occurs first), up to approximately 16.9 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: No further statistical analysis performed as this is a single arm study with no comparators.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only 1 participant was enrolled into cohort 2, data for this one participant was presented descriptively and was not summarized in aggregated form.

End point values	Cohort 1: HER3 High (IHC 3+, 2+)			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Percentage of Participants				
number (confidence interval 95%)	5.1 (0.6 to 17.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Based on Blinded Independent Central Review (BICR) and Investigator Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer

End point title	Duration of Response (DOR) Based on Blinded Independent Central Review (BICR) and Investigator Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer[3]

End point description:

Duration of Response (DOR) was defined as the time from the date of the first documentation of objective response (complete response [CR] or partial response [PR]) to the date of the first objective documentation of progressive disease (PD) or death due to any cause. DOR based on BICR and Investigator assessment and was calculated for responders (participants with CR/PR) only.

End point type	Secondary

End point timeframe:

From baseline up to disease progression by BICR, death, lost to follow up, or withdrawal of consent by subject (whichever occurs first), up to approximately 16.9 months

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only 1 participant was enrolled into cohort 2, data for this one participant was presented descriptively and was not summarized in aggregated form.

End point values	Cohort 1: HER3 High (IHC 3+, 2+)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: months				
median (confidence interval 95%)				
Duration of Response based on BICR	2.91 (2.79 to 3.02)			
Duration of Response based on Investigator	4.48 (2.56 to 6.41)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) Based on Investigator Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer

End point title	Objective Response Rate (ORR) Based on Investigator Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer[4]

End point description:

The Objective Response Rate (ORR) was defined as the percentage of participants who achieved a best overall response of confirmed Complete Response (CR) or Partial Response (PR), assessed by investigator assessment based on RECIST version 1.1.CR was defined as a reduction of target lesions to non-measurable dimensions and PR was defined as at least a 30% decrease in the sum of diameters of target lesions. Confirmed ORR based on investigator assessment is reported and was assessed in the Full Analysis Set.

End point type	Secondary

End point timeframe:

From baseline up to disease progression, death, lost to follow up, or withdrawal of consent by subject (whichever occurs first), up to approximately 16.9 months

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only 1 participant was enrolled into cohort 2, data for this one participant was presented descriptively and was not summarized in aggregated form.

End point values	Cohort 1: HER3 High (IHC 3+, 2+)			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Percentage of Participants				
number (confidence interval 95%)	5.1 (0.6 to 17.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) Based on Blinded Independent Central Review (BICR) and Investigator Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer

End point title	Disease Control Rate (DCR) Based on Blinded Independent Central Review (BICR) and Investigator Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer[5]

End point description:

Disease Control Rate (DCR) was defined as the proportion of participants who achieved a confirmed best overall response (BOR) of complete response (CR), partial response (PR), or stable disease (SD) as assessed by BICR or Investigator assessment. DCR was assessed in the Full Analysis Set.

End point type	Secondary

End point timeframe:

From baseline up to disease progression by BICR, death, lost to follow up, or withdrawal of consent by subject (whichever occurs first), up to approximately 16.9 months

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only 1 participant was enrolled into cohort 2, data for this one participant was presented descriptively and was not summarized in aggregated form.

End point values	Cohort 1: HER3 High (IHC 3+, 2+)			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Percentage of Participants				
number (confidence interval 95%)				
Disease Control Rate based on BICR	56.4 (39.6 to 72.2)			
Disease Control Rate based on Investigator	56.4 (39.6 to 72.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Tumor Response (TTR) Based on Blinded Independent Central Review (BICR) and Investigator Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer

End point title	Time to Tumor Response (TTR) Based on Blinded Independent Central Review (BICR) and Investigator Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer[6]

End point description:

Time to Tumor Response (TTR) was defined as the time from the start of study treatment to the date of the first documentation of objective response (CR or PR) that is subsequently confirmed. TTR based on BICR and Investigator assessment is reported and was calculated for responders only.

End point type	Secondary

End point timeframe:

From baseline up to disease progression by BICR, death, lost to follow up, or withdrawal of consent by subject (whichever occurs first), up to approximately 16.9 months

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only 1 participant was enrolled into cohort 2, data for this one participant was presented descriptively and was not summarized in aggregated form.

End point values	Cohort 1: HER3 High (IHC 3+, 2+)			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: months				
median (full range (min-max))				
Time to Tumor Response based on BICR	1.99 (1.4 to 2.6)			
Time to Tumor Response based on Investigator	1.53 (1.4 to 1.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) Based on Blinded Independent Central Review (BICR) and Investigator Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer

End point title	Progression-free Survival (PFS) Based on Blinded Independent Central Review (BICR) and Investigator Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer[7]

End point description:

Progression-free survival (PFS) was defined as the time from the date of enrollment to the earlier of the dates of the first objective documentation of disease progression (as per RECIST v1.1) or death due to any cause. Progressive disease was defined as at least a 20% increase in the sum of diameters of target lesions. PFS was assessed in the Full Analysis Set.

End point type	Secondary

End point timeframe:

From baseline until disease progression by BICR, death, lost to follow up, or withdrawal of consent by subject (whichever occurs first), up to approximately 16.9 months

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only 1 participant was enrolled into cohort 2, data for this one participant was presented descriptively and was not summarized in aggregated form.

End point values	Cohort 1: HER3 High (IHC 3+, 2+)			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: months				
median (confidence interval 95%)				
Progression Free Survival based on BICR	2.27 (1.51 to 2.96)			
Progression Free Survival based on Investigator	2.53 (1.64 to 3.71)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer

End point title	Overall Survival (OS) Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer[8]

End point description:

Overall survival (OS) was defined as the time from the date of first dose of study drug to the date of death due to any cause. OS was assessed in the Full Analysis Set.

End point type	Secondary

End point timeframe:

From baseline up to the date of death due to any cause, up to 16.9 months

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only 1 participant was enrolled into cohort 2, data for this one participant was presented descriptively and was not summarized in aggregated form.

End point values	Cohort 1: HER3 High (IHC 3+, 2+)			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: months				
median (confidence interval 95%)	10.58 (5.36 to 12.09)			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Treatment Emergent Adverse Events (TEAEs) Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer

End point title	Summary of Treatment Emergent Adverse Events (TEAEs) Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer

End point description:

A Treatment Emergent Adverse Events (TEAEs) was defined as an adverse event with start or worsening date from the first dose date of the study drug to 47 days after the last dose date of the study drug. TEAEs, study drug-related TEAEs, serious TEAEs, study drug-related TEAEs, and any Adverse Events of Special Interests (AESIs) are presented and were assessed in the Safety Analysis Set.

End point type	Secondary

End point timeframe:

From the signing of the main ICF to 47 days after the last dose of study drug, up to approximately 16.9 months

End point values	Cohort 1 & 2: HER3 High (IHC 3+, 2+) & HER3 Low/Negative (IHC)			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: Count of Participants				
number (not applicable)				
TEAEs	40			
Study drug-related TEAE	37			
Serious TEAE (SAE)	17			
Study drug-related SAE	9			
Any AESI	2			
Adjudicated Interstitial Lung Disease (ILD)	2			
Adjudicated Drug-Related Interstitial Lung Disease	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With HER3 Protein Expression Based on Immunohistochemistry (IHC) Assay

End point title	Number of Participants With HER3 Protein Expression Based on Immunohistochemistry (IHC) Assay[9]

End point description:

(HER3) protein expression will be measured by an investigational device (HER3 immunohistochemistry [IHC] assay). There is no scoring algorithm developed for the HER3 IHC assay in colon cancer; therefore, the American Society of Clinical Oncology guidelines for HER2 gastric cancer scoring were adopted for use in this study.

End point type	Secondary

End point timeframe:

At Baseline (archival and pre-treatment tumor biopsy) and at Cycle 2

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only 1 participant was enrolled into cohort 2, data for this one participant was presented descriptively and was not summarized in aggregated form.

End point values	Cohort 1: HER3 High (IHC 3+, 2+)			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Count of Participants				
number (not applicable)				
Archival: 0	0			
Archival: 1+	0			
Archival: 2+	12			
Archival: 3+	14			
Pre-treatment: 0	0			
Pre-treatment: 1+	0			
Pre-treatment: 2+	3			
Pre-treatment: 3+	36			
On-treatment: 0	2			
On-treatment: 1+	0			
On-treatment: 2+	6			
On-treatment: 3+	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Are Anti-Drug Antibody (ADA)-Positive

End point title	Percentage of Participants Who Are Anti-Drug Antibody (ADA)-Positive[10]

End point description:

Participants who are Anti-Drug Antibody (ADA)-Positive were defined as any participant having a confirmed positive ADA sample at any point in time. ADA titer will be determined for confirmed ADA-positive samples and assessed in the Full Analysis Set.

End point type	Secondary

End point timeframe:

From the start of study treatment to the end of treatment, up to approximately 16.9 months

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only 1 participant was enrolled into cohort 2, data for this one participant was presented descriptively and was not summarized in aggregated form.

End point values	Cohort 1: HER3 High (IHC 3+, 2+)			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Percentage of Participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Have Treatment Emergent Anti-Drug Antibody (ADA)

End point title	Percentage of Participants Who Have Treatment Emergent Anti-Drug Antibody (ADA)[11]

End point description:

Participants who are Treatment Emergent Anti-Drug Antibody (ADA) positive will be assessed in the Full Analysis Set.

End point type	Secondary

End point timeframe:

From the start of study treatment to the end of treatment, up to approximately 16.9 months

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only 1 participant was enrolled into cohort 2, data for this one participant was presented descriptively and was not summarized in aggregated form.

End point values	Cohort 1: HER3 High (IHC 3+, 2+)			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Percentage of Participants				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Serum Concentration (Cmax) of U3-1402 and Total Anti-HER3 Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer

End point title	Maximum Serum Concentration (Cmax) of U3-1402 and Total Anti-HER3 Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer[12]

End point description:

Maximum Plasma Concentration (Cmax) was defined as the maximum observed plasma concentration and was calculated using non-compartmental analysis. Cmax for U3-1402 and Total Anti-HER3 are presented and was assessed in the Pharmacokinetic Analysis Set. Cmax was evaluated at select time points.

End point type	Secondary

End point timeframe:

Cycle 1 & 3: Day(D)1 (Before Infusion [BI] & End of Infusion [EOI]), D8, D15; Cycle 2: D1 (BI & EOI), D3, D15; Cycle 4 and thereafter: BI & EOI; End of Treatment; 3 month Follow-up

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only 1 participant was enrolled into cohort 2, data for this one participant was presented descriptively and was not summarized in aggregated form.

End point values	Cohort 1: HER3 High (IHC 3+, 2+)			
Subject group type	Reporting group			
Number of subjects analysed	39[13]			
Units: ug/mL				
arithmetic mean (standard deviation)				
Cycle 1: U3-1402	155.67 (± 43.453)			
Cycle 3: U3-1402	159.80 (± 47.943)			
Cycle 1: Total Anti-HER3	154.08 (± 32.816)			
Cycle 3: Total Anti-HER3	153.86 (± 39.313)			

Notes:

[13] - Cycle 3: U3-1402, n=24; Cycle 3: Total Anti-HER3, n=24

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Serum Concentration (Cmax) of MAAA-1181 Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer

End point title	Maximum Serum Concentration (Cmax) of MAAA-1181 Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer[14]

End point description:

Maximum Serum Concentration (Cmax) was defined as the maximum observed serum concentration and was calculated using non-compartmental analysis. Cmax was assessed in the Pharmacokinetic Analysis Set. Cmax was evaluated at select time points.

End point type	Secondary

End point timeframe:

Cycle 1 & 3: Day(D)1 (Before Infusion [BI] & End of Infusion [EOI]), D8, D15; Cycle 2: D1 (BI & EOI), D3, D15; Cycle 4 and thereafter: BI & EOI; End of Treatment; 3 month Follow-up

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only 1 participant was enrolled into cohort 2, data for this one participant was presented descriptively and was not summarized in aggregated form.

End point values	Cohort 1: HER3 High (IHC 3+, 2+)			
Subject group type	Reporting group			
Number of subjects analysed	39[15]			
Units: ng/mL				
geometric mean (standard deviation)				
Cycle 1	38.09 (± 19.683)			
Cycle 3	16.13 (± 9.292)			

Notes:

[15] - Cycle 3, n=24

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Serum Concentration (Tmax) of U31402, Total Anti-HER3, and MAAA-1181 Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer

End point title	Time to Reach Maximum Serum Concentration (Tmax) of U31402, Total Anti-HER3, and MAAA-1181 Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer[16]

End point description:

Time of Maximum Serum Concentration (Tmax) was defined as the time of maximum observed serum concentration and was calculated using non-compartmental analysis. Tmax for U3-1402, Total Anti-HER3, and MAAA-1181 are presented and was assessed in the Pharmacokinetic Analysis Set. Tmax was evaluated at select time points.

End point type	Secondary

End point timeframe:

Cycle 1 & 3: Day(D)1 (Before Infusion [BI] & End of Infusion [EOI]), D8, D15; Cycle 2: D1 (BI & EOI), D3, D15; Cycle 4 and thereafter: BI & EOI; End of Treatment; 3 month Follow-up

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only 1 participant was enrolled into cohort 2, data for this one participant was presented descriptively and was not summarized in aggregated form.

End point values	Cohort 1: HER3 High (IHC 3+, 2+)			
Subject group type	Reporting group			
Number of subjects analysed	39[17]			
Units: hours				
median (full range (min-max))				
Cycle 1: U3-1402	2.42 (1.52 to 5.67)			

Cycle 3: U3-1402	4.39 (0.53 to 8.78)			
Cycle 1: Total Anti-HER3	1.72 (1.45 to 505.50)			
Cycle 3: Total Anti-HER3	3.86 (0.53 to 8.78)			
Cycle 1: MAAA-1181	5.28 (2.57 to 9.47)			
Cycle 3: MAAA-1181	4.45 (0.65 to 8.33)			

Notes:

[17] - Cycle 3: U3-1402, Total-Anti-HER3, and MAAA-1181, n=24

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Serum Concentration (Ctrough) of U3-1402 and Total Anti-HER3 Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer

End point title	Trough Serum Concentration (Ctrough) of U3-1402 and Total Anti-HER3 Following Administration of U3-1402 in Participants with Advanced or Metastatic Colorectal Cancer[18]

End point description:

Trough Serum Concentration (Ctrough) was calculated using non-compartmental analysis. Ctrough for U3-1402 and Total Anti-HER3 are presented and was assessed in the Pharmacokinetic Analysis Set. Ctrough was evaluated at select time points.

End point type	Secondary

End point timeframe:

Cycle 1 & 3: Day(D)1 (Before Infusion [BI] & End of Infusion [EOI]), D8, D15; Cycle 2: D1 (BI & EOI), D3, D15; Cycle 4 and thereafter: BI & EOI; End of Treatment; 3 month Follow-up

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only 1 participant was enrolled into cohort 2, data for this one participant was presented descriptively and was not summarized in aggregated form.

End point values	Cohort 1: HER3 High (IHC 3+, 2+)			
Subject group type	Reporting group			
Number of subjects analysed	39[19]			
Units: ug/mL				
arithmetic mean (standard deviation)				
Cycle 1: U3-1402	7.98 (± 24.200)			
Cycle 3: U3-1402	12.76 (± 9.185)			
Cycle 1: Anti-Total HER3	8.55 (± 29.614)			
Cycle 3: Anti-Total HER3	11.49 (± 9.254)			

Notes:

[19] - Cycle 1: U3-1402 & Total Anti-HER3, n=35; Cycle 3: U3-1402 & Total Anti-HER3, n=15

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Serum Concentration (Ctrough) of MAAA-1181 Following Administration in Participants with Advanced or Metastatic Colorectal Cancer

End point title	Trough Serum Concentration (Ctrough) of MAAA-1181 Following Administration in Participants with Advanced or Metastatic Colorectal Cancer[20]

End point description:

Trough Serum Concentration (Ctrough) was calculated using non-compartmental analysis. Ctrough is presented and was assessed in the Pharmacokinetic Analysis Set. Ctrough was evaluated at select time points.

End point type	Secondary

End point timeframe:

Cycle 1 & 3: Day(D)1 (Before Infusion [BI] & End of Infusion [EOI]), D8, D15; Cycle 2: D1 (BI & EOI), D3, D15; Cycle 4 and thereafter: BI & EOI; End of Treatment; 3 month Follow-up

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only 1 participant was enrolled into cohort 2, data for this one participant was presented descriptively and was not summarized in aggregated form.

End point values	Cohort 1: HER3 High (IHC 3+, 2+)			
Subject group type	Reporting group			
Number of subjects analysed	39[21]			
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1	0.49 (± 1.423)			
Cycle 3	0.68 (± 0.661)			

Notes:

[21] - Cycle 1, n=35; Cycle 3, n=16

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Serum Concentration-Time Curve up to Last Quantifiable Time (AUClast) and During Dosing Interval (AUCtau) of U3-1402 and Total Anti-HER3 Following Administration in Participants with Advanced or Metastatic Colorectal Cancer

End point title	Area Under the Serum Concentration-Time Curve up to Last Quantifiable Time (AUClast) and During Dosing Interval (AUCtau) of U3-1402 and Total Anti-HER3 Following Administration in Participants with Advanced or Metastatic Colorectal Cancer[22]

End point description:

Area under the concentration versus-time curve from time 0 to the last quantifiable concentration (AUClast) and during the dosing interval (AUCtau) was calculated using non-compartmental analysis. AUClast and AUCtau for U3-1402 and Total Anti-HER3 are presented and was assessed in the Pharmacokinetic Analysis Set at select time points.

End point type	Secondary

End point timeframe:

Cycle 1 & 3: Day(D)1 (Before Infusion [BI] & End of Infusion [EOI]), D8, D15; Cycle 2: D1 (BI & EOI), D3, D15; Cycle 4 and thereafter: BI & EOI; End of Treatment; 3 month Follow-up

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only 1 participant was enrolled into cohort 2, data for this one participant was presented descriptively and was not summarized in aggregated form.

End point values	Cohort 1: HER3 High (IHC 3+, 2+)			
Subject group type	Reporting group			
Number of subjects analysed	39[23]			
Units: day*ug/mL				
arithmetic mean (standard deviation)				
Cycle 1: U3-1402 (AUClast)	562.048 (± 246.928)			
Cycle 1: U3-1402 (AUCtau)	569.412 (± 191.026)			
Cycle 3: U3-1402 (AUCtau)	1230.441 (± 257.077)			
Cycle 1: Anti-HER3 (AUClast)	590.108 (± 279.670)			
Cycle 1: Anti-HER3 (AUCtau)	596.235 (± 217.231)			
Cycle 3: Anti-HER3 (AUCtau)	1104.218 (± 397.927)			

Notes:

[23] - C1:U3-1402 & Anti-HER3 (AUClast n=20)&(AUCtau n=18);C3:U3-1402 (AUCtau n=7)&Anti-HER3 (AUCtau n=9)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Serum Concentration-Time Curve up to Last Quantifiable Time (AUClast) and During Dosing Interval (AUCtau) of MAAA-1181 Following Administration in Participants with Advanced or Metastatic Colorectal Cancer

End point title	Area Under the Serum Concentration-Time Curve up to Last Quantifiable Time (AUClast) and During Dosing Interval (AUCtau) of MAAA-1181 Following Administration in Participants with Advanced or Metastatic Colorectal Cancer[24]

End point description:

Area under the concentration versus-time curve from time 0 to the last quantifiable concentration (AUClast) and during the dosing interval (AUCtau) was calculated using non-compartmental analysis. AUClast and AUCtau for MAAA-1181 is presented and was assessed in the Pharmacokinetic Analysis Set at select time points.

End point type	Secondary

End point timeframe:

Cycle 1 & 3: Day(D)1 (Before Infusion [BI] & End of Infusion [EOI]), D8, D15; Cycle 2: D1 (BI & EOI), D3, D15; Cycle 4 and thereafter: BI & EOI; End of Treatment; 3 month Follow-up

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only 1 participant was enrolled into cohort 2, data for this one participant was presented descriptively and was not summarized in aggregated form.

End point values	Cohort 1: HER3 High (IHC 3+, 2+)			
Subject group type	Reporting group			
Number of subjects analysed	39[25]			
Units: day*ng/mL				
arithmetic mean (standard deviation)				
Cycle 1: AUClast	89.963 (± 60.428)			
Cycle 1: AUCtau	92.814 (± 58.939)			
Cycle 3: AUCtau	78.680 (± 34.595)			

Notes:

[25] - Cycle 1: AUClast n=20; Cycle 1: AUCtau n=17; Cycle 3 AUCtau n=5

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AE) were collected from the date of signing the informed consent form up to 47 days after last dose of the study drug, up 16.9 months.

Adverse event reporting additional description:

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Overall

Reporting group description:

Participants with high tumor expression & low or negative levels of human epidermal receptor 3 (HER3) low or negative and who received 5.6 mg/Kg of U3-1402 intravenously (IV) on Day 1 of each 21-day cycle (Safety Analysis Set).

Serious adverse events	Overall		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 40 (42.50%)		
number of deaths (all causes)	23		
number of deaths resulting from adverse events	0		
Investigations			
International normalised ratio increased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cauda equina syndrome			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			

Febrile neutropenia				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Anaemia				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Disease progression				
subjects affected / exposed	3 / 40 (7.50%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	2 / 40 (5.00%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rectal obstruction				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 40 (2.50%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Hepatobiliary disorders			
Biliary obstruction			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperbilirubinaemia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	1 / 40 (2.50%)		
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 / 40 (5.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cytomegalovirus infection			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Liver abscess			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 40 (2.50%)		
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		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 40 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	24 / 40 (60.00%)		
occurrences (all)	30		
Oedema peripheral			
subjects affected / exposed	7 / 40 (17.50%)		
occurrences (all)	7		
Pyrexia			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	5		
Dyspnoea			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Epistaxis			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	4		
Hiccups			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Pulmonary embolism			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Psychiatric disorders			

Anxiety			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Blood bilirubin increased			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Lymphocyte count decreased			
subjects affected / exposed	8 / 40 (20.00%)		
occurrences (all)	10		
Neutrophil count decreased			
subjects affected / exposed	14 / 40 (35.00%)		
occurrences (all)	17		
Platelet count decreased			
subjects affected / exposed	12 / 40 (30.00%)		
occurrences (all)	19		
Weight decreased			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
White blood cell count decreased			
subjects affected / exposed	7 / 40 (17.50%)		
occurrences (all)	8		
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	6		
Headache			

subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	5		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 40 (35.00%)		
occurrences (all)	18		
Febrile neutropenia			
subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	2		
Neutropenia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	4		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Constipation			
subjects affected / exposed	11 / 40 (27.50%)		
occurrences (all)	11		
Diarrhoea			
subjects affected / exposed	15 / 40 (37.50%)		
occurrences (all)	17		
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 40 (10.00%)		
occurrences (all)	4		
Nausea			
subjects affected / exposed	22 / 40 (55.00%)		
occurrences (all)	24		
Stomatitis			
subjects affected / exposed	5 / 40 (12.50%)		
occurrences (all)	5		
Vomiting			
subjects affected / exposed	13 / 40 (32.50%)		
occurrences (all)	17		
Hepatobiliary disorders			

Hyperbilirubinaemia subjects affected / exposed occurrences (all)	4 / 40 (10.00%) 4		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 7 / 40 (17.50%) 7 2 / 40 (5.00%) 2 2 / 40 (5.00%) 2 8 / 40 (20.00%) 8		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Muscular weakness subjects affected / exposed occurrences (all)	 2 / 40 (5.00%) 2 2 / 40 (5.00%) 2		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	 2 / 40 (5.00%) 2		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Dehydration subjects affected / exposed occurrences (all) Hyperglycaemia	 17 / 40 (42.50%) 18 2 / 40 (5.00%) 2 		

subjects affected / exposed	2 / 40 (5.00%)		
occurrences (all)	3		
Hypokalaemia			
subjects affected / exposed	9 / 40 (22.50%)		
occurrences (all)	13		
Hypomagnesaemia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	6		
Hyponatraemia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 June 2020	This amendment provided revisions to the protocol design to enhance subject safety by implementing further guidance related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and also to ensure that subjects with a history of microsatellite instability-high (MSI-H) colorectal cancer have received immune checkpoint inhibitor therapy (if there were no contraindications) prior to enrollment into this study. Other minor editorial changes were provided to enhance clarity.
24 August 2020	This amendment provided revisions to the protocol design to enhance subject safety by clarifying that membrane transport inhibitors are permitted, and their use will be closely monitored. Other minor editorial changes were provided to enhance clarity.
24 November 2020	This amendment provided greater uniformity in the enrolled population by ensuring the prior use of a BRAF inhibitor in patients whose tumors expressed a BRAF V600E mutation. It also provided further specification regarding the required antibody washout period, conditions under which tumor assessments should be conducted, screening, rescreening, and study closure procedures. Other minor editorial changes were provided to enhance clarity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
03 February 2022	Study was terminated early given the Interim Analysis for Part 1 (signal finding) did not meet pre-specified criteria and will not proceed to Part 2. Sponsor will proceed closing the study.	-

Notes:

Limitations and caveats

None reported