Clinical trial results:
A multicentre phase IIa study to evaluate the efficacy and tolerability of ModraDoc006/r in patients with recurrent or metastatic HER-2 negative breast cancer, suitable for treatment with a taxane

Summary

EudraCT number	2018-003249-41
Trial protocol	BE DK ES
Global end of trial date	13 February 2020

Results information

Result version number	v1 (current)
This version publication date	06 November 2022
First version publication date	06 November 2022

Trial information

Trial identification

Sponsor protocol code	M18DMB

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03890744
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Modra Pharmaceuticals
Sponsor organisation address	Barbara Strozzilaan 201, Amsterdam, Netherlands, 1083 HN
Public contact	Project Director, Modra Pharmaceuticals, +31 2050188, info@modrapharmaceuticals.com
Scientific contact	Project Director, Modra Pharmaceuticals, +31 2050188, info@modrapharmaceuticals.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	12 May 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of ModraDoc006/r (oral docetaxel formulation given as ModraDoc006 10 mg tablets in combination with ritonavir 100 mg tablets) as measured by RECIST v1.1 criteria of objective response rate (ORR) in patients with histologically and cytologically confirmed, recurrent or metastatic HER-2 negative breast cancer suitable for treatment with a taxane.

Protection of trial subjects:

To minimize the risk to patients and maximize safety, the following factors were incorporated into the trial design:
• Detailed safety and laboratory assessments were be performed.
• As anti-emetic therapy, all subjects were given bi-daily 1 mg of granisetron 1 hour prior to oral ModraDoc006/r administration during the first two cycles. In subsequent cycles, granisetron premedication could be given if indicated. All subjects were provided by the site with a home prescription for anti-emetics (metoclopramide 10 mg maximum four times daily) and received instructions on how to use this medication in case nausea/vomiting occurred at home. If this proved insufficient, dexamethasone and lorazepam could be added as anti-emetic treatment. In case of vomiting after intake, the subjects did not take any new anti-emetic therapy
• Patients were provided with diet and hydration instructions and a home prescription for loperamide, with instructions on how to use this medication in case diarrhea occurred at home
• All clinical observations were evaluated by the Investigator on an ongoing basis.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 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	Belgium: 7
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Denmark: 4
Worldwide total number of subjects	13
EEA total number of subjects	13

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)	5
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Prior to obtaining informed consent, the purpose and nature of the trial as well as possible adverse effects resulting from trial drug administration were explained to each subject. Written informed consent was obtained, before any trial-specific procedures were performed.

Pre-assignment

Screening details:

Between 11Feb2019 and 09Jul2019, informed consent was obtained from 13 subjects with metastatic HER-2-negative breast cancer. One subject experienced elevated liver enzymes outside the allowed range for inclusion prior to investigational medicinal product (IMP) administration and was therefore excluded from receiving the trial drug.

Pre-assignment period milestones

Number of subjects started	13
Number of subjects completed	12

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 1

Period 1

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

Arms

Arm title	ModraDoc006/r

Arm description:

Patients received ModraDoc006 30 mg in combination with ritonavir 100 mg in the morning and ModraDoc006 20 mg in combination with 100 mg ritonavir in the afternoon (7 to 12 hours after the morning dose), on Day 1 of weekly cycles (BIDW: bi-daily once weekly dosing).

Arm type	Experimental
Investigational medicinal product name	ModraDoc006
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Bi-daily once weekly (BIDW) 30 mg in in the morning and 20 mg in the afternoon

Investigational medicinal product name	ritonavir
Investigational medicinal product code	/r
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Bi-daily once weekly (BIDW) 100 mg in the morning and 100 mg in the evening

Number of subjects in period 1[1]	ModraDoc006/r
Started	12
Completed	12

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One patient was enrolled, but did not start treatment due to elevated liver enzymes outside the allowed range for inclusion experienced prior to IMP administration.

Baseline characteristics

Reporting groups	
Reporting group title	Treated

Reporting group description: -

Reporting group values	Treated	Total	
Number of subjects	12	12	
Age categorical Units: Subjects			
Adults (18-64 years)	5	5	
From 65-84 years	7	7	
Age continuous Units: years			
median	66.0		
full range (min-max)	48 to 76	-	
Gender categorical Units: Subjects			
Female	12	12	
Male	0	0	
Child-bearing potential Units: Subjects			
Yes	0	0	
No	12	12	
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	
Not Hispanic or Latino	10	10	
Unknown	1	1	
Race Units: Subjects			
White	12	12	
Staging at primary cancer diagnosis Units: Subjects			
Ia	2	2	
II	2	2	
IIa	1	1	
IIb	1	1	
IIIa	3	3	
IV	2	2	
Missing	1	1	
Occurrence of metastasis Units: Subjects			
Yes	12	12	
No	0	0	
WHO Performance Status Units: Subjects			
PS 0	8	8	

PS 1	4	4	
Location of metastasis: Bone Units: Subjects			
Yes	9	9	
No	3	3	
Location of metastasis: Liver Units: Subjects			
Yes	4	4	
No	8	8	
Location of metastasis: Lungs Units: Subjects			
Yes	1	1	
No	11	11	
Previous cancer therapy: Radiotherapy Units: Subjects			
Yes	8	8	
No	4	4	
Previous cancer therapy: Surgery Units: Subjects			
Yes	9	9	
No	3	3	
Previous cancer therapy: Systemic regimen (adjuvant) Units: Subjects			
Yes	9	9	
No	3	3	
Previous cancer therapy: Systemic regimen (Metastatic) Units: Subjects			
Yes	11	11	
No	1	1	
Previous cancer therapy: Chemotherapy (adjuvant) Units: Subjects			
Yes	8	8	
No	4	4	
Previous cancer therapy: Chemotherapy (metastatic) Units: Subjects			
Yes	3	3	
No	9	9	
Previous cancer therapy: Taxane (adjuvant) Units: Subjects			
Yes	3	3	
No	9	9	
Height Units: centimetre			
median	157.5		
full range (min-max)	141 to 173	-	
Weight Units: kilogram(s)			
median	62.0		

full range (min-max)	38.4 to 83.0	-	
Body Mass Index (BMI) Units: kilogram(s)/square metre median full range (min-max)	 24.2 18.4 to 34.1	 -	
Body Surface Area (BSA) Units: square metre median full range (min-max)	 1.63 1.22 to 1.86	 -	
Median volumetric tumor size			
Sum of diameters of target lesions			
Units: millimetre(s) median full range (min-max)	 63.0 22.6 to 79.0	 -	
Median biomarker level CA 15-3 Units: unit(s)/millilitre median full range (min-max)	 224.35 21.48 to 447.30	 -	

End points

End points reporting groups

Reporting group title	ModraDoc006/r

Reporting group description:

Patients received ModraDoc006 30 mg in combination with ritonavir 100 mg in the morning and ModraDoc006 20 mg in combination with 100 mg ritonavir in the afternoon (7 to 12 hours after the morning dose), on Day 1 of weekly cycles (BIDW: bi-daily once weekly dosing).

Subject analysis set title	Evaluable for Radiological Response (ERR)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The population evaluable for radiological response (ERR) was defined as subjects who received at least six weekly administrations of ModraDoc006/r, who had measurable lesions according to RECIST v1.1, and whose response had been evaluated using RECIST v1.1

Primary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)[1]

End point description:

ORR according to RECIST v1.1

End point type	Primary

End point timeframe:

During study period; radiological assessment at baseline, Week 8 and 12, and every 6 weeks thereafter until the end of treatment.

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 objective response rate, ORR, was calculated as the proportion of subjects who achieved a CR or PR recorded from the start of the trial treatment until the end of treatment. ORR was summarised with 95% Clopper-Pearson Confidence Interval. PR = 37.5 % (8.52 – 75.5).

End point values	Evaluable for Radiological Response (ERR)			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: 0-12				
Complete response	0			
Partial response	3			
Stable disease	4			
Progressive disease	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

End point title	Duration of Response

End point description:

The DOR, calculated in the subpopulation of patients experiencing a CR or PR, is presented for patients that were evaluable for radiological response for the overall study.

End point type	Secondary

End point timeframe:

Overall study

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival

End point title	Progression Free Survival

End point description:

PFS was calculated as the time between the date of first dose of trial treatment (Day 1 of Cycle 1) and the first documented tumor progression or death from any cause. Tumor progression was defined as the occurrence of PD based on RECIST v1.1.

End point type	Secondary

End point timeframe:

Overall study

End point values	Evaluable for Radiological Response (ERR)			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: month				
median (full range (min-max))	5.7 (1.64 to 13.77)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were monitored and collected from the time the patient gave informed consent and throughout the study until 30 days after the last ModraDoc006/r administration.

Adverse event reporting additional description:

Safety analysis population assessed for all adverse events

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	5.0

Reporting groups

Reporting group title	Safety population (SAF)

Reporting group description: -

Serious adverse events	Safety population (SAF)		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 12 (33.33%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			

Chylothorax			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	1 / 12 (8.33%)		
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	Safety population (SAF)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 12 (41.67%)		
occurrences (all)	7		
Chest discomfort			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	17		
Localised oedema			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	4		
Mucosal toxicity			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	9		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	5		
Dysphonia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	10		
Epistaxis			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	8		
Nasal dryness			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Pleural effusion			
subjects affected / exposed	4 / 12 (33.33%)		
occurrences (all)	4		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Apathy			

subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Blood urine present			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Haematocrit decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Weight decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
White blood cell count decreased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			

Overdose subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all) Palpitations subjects affected / exposed occurrences (all) Ventricular arrhythmia subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all) Facial paralysis subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Hypoaesthesia subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all) Polyneuropathy subjects affected / exposed occurrences (all)	 5 / 12 (41.67%) 5 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 2 / 12 (16.67%) 5		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Lymphopenia	 4 / 12 (33.33%) 4		

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Neutropenia			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	4		
Thrombocytopenia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	4		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Eye disorders			
Eye pruritus			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Lacrimation increased			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	4		
Abdominal pain			
subjects affected / exposed	9 / 12 (75.00%)		
occurrences (all)	15		
Abdominal pain upper			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Anal fissure			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Aphthous ulcer			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	2		
Ascites			

subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	2			
Constipation				
subjects affected / exposed	6 / 12 (50.00%)			
occurrences (all)	10			
Diarrhoea				
subjects affected / exposed	10 / 12 (83.33%)			
occurrences (all)	21			
Dry mouth				
subjects affected / exposed	3 / 12 (25.00%)			
occurrences (all)	3			
Dysphagia				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	2			
Faeces soft				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Flatulence				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Gastrointestinal pain				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Gingival pain				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	2			
Mouth ulceration				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	2			
Nausea				
subjects affected / exposed	11 / 12 (91.67%)			
occurrences (all)	21			
Odynophagia				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Oral toxicity				

subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	2			
Stomatitis				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	7			
Tongue erythema				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Vomiting				
subjects affected / exposed	9 / 12 (75.00%)			
occurrences (all)	18			
Skin and subcutaneous tissue disorders				
Alopecia				
subjects affected / exposed	9 / 12 (75.00%)			
occurrences (all)	11			
Dry skin				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Madarosis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Nail discolouration				
subjects affected / exposed	2 / 12 (16.67%)			
occurrences (all)	2			
Nail ridging				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Nail toxicity				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Onycholysis				
subjects affected / exposed	1 / 12 (8.33%)			
occurrences (all)	1			
Palmar-plantar erythrodysaesthesia syndrome				

subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 9 3 / 12 (25.00%) 3		
Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all) Urinary incontinence subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 1 / 12 (8.33%) 2		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Dactylitis subjects affected / exposed occurrences (all) Groin pain subjects affected / exposed occurrences (all) Muscle fatigue subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 2 / 12 (16.67%) 3 1 / 12 (8.33%) 3 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 2 / 12 (16.67%) 2		
Infections and infestations			

Conjunctivitis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2		
Cystitis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 3		
Laryngitis subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Lung infection subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Paronychia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2		
Skin infection subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2		
Vaginal infection subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	9 / 12 (75.00%) 20		
Dehydration subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Hypocalcaemia			

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Hypoproteinaemia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported