Clinical trial results:
A Presurgical Tissue-Acquisition Study to Evaluate Molecular Alterations in Human Breast Cancer Tissue Following Short-Term Exposure to the Androgen Receptor Antagonist Darolutamide (ODM-201)

Summary

EudraCT number	2016-004151-79
Trial protocol	DE
Global end of trial date	13 March 2019

Results information

Result version number	v1 (current)
This version publication date	11 March 2020
First version publication date	11 March 2020

Trial information

Trial identification

Sponsor protocol code	TRIO030

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03004534
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Translational Research In Oncology (TRIO)
Sponsor organisation address	Suite 1100 9925-109 Street , Edmonton, Canada, T5K 2J8
Public contact	Project Management, Translational Research In Oncology (TRIO), 33 158 10 09 09, 030@trioncology.org
Scientific contact	Project Management, Translational Research In Oncology (TRIO), 33 158 10 09 09, 030@trioncology.org

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 March 2019
Global end of trial reached?	Yes
Global end of trial date	13 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To identify the molecular alterations that occur in human breast cancer (BC) tissue, following short-term exposure to darolutamide in female subjects with early breast cancer (EBC).

Protection of trial subjects:

Regular assessment and monitoring of adverse events (AEs) is required from Patient Informed Consent Form (PICF) signature, throughout the protocol treatment period and at least up until surgery or BC pre-NAST biopsy if patient will receive NAST.

Toxicity was assessed utilizing the National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE) v4.03. For toxicities not specifically listed in the NCI CTCAE, the following grading will apply for assessing severity:

Grade 1: Mild
Grade 2: Moderate
Grade 3: Severe
Grade 4: Life-threatening
Grade 5: Death related to AE

Patients will be instructed to notify their physician immediately for any and all AEs.

Doses of protocol treatment may be modified (delayed or reduced) in case of clinically significant toxicities that are considered by the Investigator to be related to protocol treatment, according to the protocol. Assessment of causality (chronology, confounding factors, concomitant medications, diagnostic tests, and previous experience with the protocol treatment) should be conducted by the Investigator prior to dose modification and/or delay whenever possible.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 July 2017
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	Canada: 8
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	36
EEA total number of subjects	7

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)	20
From 65 to 84 years	16
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were registered in the study once the Patient Informed Consent Form (PICF) signature was received.
Pre-treatment tumor samples were collected at screening.
After all screening procedures, and confirmation of eligibility, patients were enrolled and started oral intake of darolutamide.

Pre-assignment

Screening details:

The screening period starts with registration (which is the time of informed consent signature) and ends when the patient is enrolled (following eligibility central review and confirmation by TRIO) or screen failed.

Period 1

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

Blinding implementation details:

This was an open label study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Triple Negative Breast Cancer (TNBC)

Arm description:

There were a total of 3 cohorts, organized by breast cancer sub-types:

- HR+/HER2 negative
- HER2 positive
- Triple-negative

All patients received darolutamide at a dose of 600 mg (2 × 300 mg tablets) twice daily (b.i.d.) by mouth, corresponding to a daily dose of 1200 mg.

Arm type	Breast Cancer Sub-type
Investigational medicinal product name	Darolutamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received darolutamide at a dose of 600 mg (2 × 300 mg tablets) twice daily (b.i.d.) by mouth, corresponding to a daily dose of 1200 mg.

Arm title	HER2 Positive

Arm description:

There were a total of 3 cohorts, organized by breast cancer sub-types:

- HR+/HER2 negative
- HER2 positive
- Triple-negative

All patients received darolutamide at a dose of 600 mg (2 × 300 mg tablets) twice daily (b.i.d.) by mouth, corresponding to a daily dose of 1200 mg.

Arm type	Breast Cancer Sub-type

No investigational medicinal product assigned in this arm

Arm title	HR+/HER2 Negative

Arm description:

There were a total of 3 cohorts, organized by breast cancer sub-types:

- HR+/HER2 negative
- HER2 positive
- Triple-negative

All patients received darolutamide at a dose of 600 mg (2 × 300 mg tablets) twice daily (b.i.d.) by mouth, corresponding to a daily dose of 1200 mg.

Arm type	Breast Cancer Sub-type

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Triple Negative Breast Cancer (TNBC)	HER2 Positive	HR+/HER2 Negative
Started	7	9	20
Completed	7	9	20

Baseline characteristics

Reporting groups

Reporting group title	Triple Negative Breast Cancer (TNBC)

Reporting group description:

There were a total of 3 cohorts, organized by breast cancer sub-types:

- HR+/HER2 negative
- HER2 positive
- Triple-negative

All patients received darolutamide at a dose of 600 mg (2 × 300 mg tablets) twice daily (b.i.d.) by mouth, corresponding to a daily dose of 1200 mg.

Reporting group title	HER2 Positive

Reporting group description:

There were a total of 3 cohorts, organized by breast cancer sub-types:

- HR+/HER2 negative
- HER2 positive
- Triple-negative

All patients received darolutamide at a dose of 600 mg (2 × 300 mg tablets) twice daily (b.i.d.) by mouth, corresponding to a daily dose of 1200 mg.

Reporting group title	HR+/HER2 Negative

Reporting group description:

There were a total of 3 cohorts, organized by breast cancer sub-types:

- HR+/HER2 negative
- HER2 positive
- Triple-negative

All patients received darolutamide at a dose of 600 mg (2 × 300 mg tablets) twice daily (b.i.d.) by mouth, corresponding to a daily dose of 1200 mg.

Reporting group values	Triple Negative Breast Cancer (TNBC)	HER2 Positive	HR+/HER2 Negative
Number of subjects	7	9	20
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)	4	6	10
From 65-84 years	3	3	10
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	58.3	61.8	61.0
standard deviation	± 17.7	± 11.7	± 8.1

Gender categorical Units: Subjects			
Female	7	9	20
Male	0	0	0

Reporting group values	Total		
Number of subjects	36		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	20		
From 65-84 years	16		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	36		
Male	0		

End points

End points reporting groups

Reporting group title	Triple Negative Breast Cancer (TNBC)

Reporting group description:

There were a total of 3 cohorts, organized by breast cancer sub-types:

- HR+/HER2 negative
- HER2 positive
- Triple-negative

All patients received darolutamide at a dose of 600 mg (2 × 300 mg tablets) twice daily (b.i.d.) by mouth, corresponding to a daily dose of 1200 mg.

Reporting group title	HER2 Positive

Reporting group description:

There were a total of 3 cohorts, organized by breast cancer sub-types:

- HR+/HER2 negative
- HER2 positive
- Triple-negative

All patients received darolutamide at a dose of 600 mg (2 × 300 mg tablets) twice daily (b.i.d.) by mouth, corresponding to a daily dose of 1200 mg.

Reporting group title	HR+/HER2 Negative

Reporting group description:

There were a total of 3 cohorts, organized by breast cancer sub-types:

- HR+/HER2 negative
- HER2 positive
- Triple-negative

All patients received darolutamide at a dose of 600 mg (2 × 300 mg tablets) twice daily (b.i.d.) by mouth, corresponding to a daily dose of 1200 mg.

Primary: Breast Cancer Tissue Androgen Receptor Gene Expression

End point title	Breast Cancer Tissue Androgen Receptor Gene Expression[1]

End point description:

AR levels were measured in patients following darolutamide treatment and patients were characterized into 3 groups, AR down regulated, AR up-regulated and AR unchanged. There was a stronger concordance between IHC measurements and transcript level of AR versus protein AR measurements.

End point type	Primary

End point timeframe:

Assessment performed once all patients have completed the trial as per protocol (all patients have completed their End of Study visit).

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 grouping into 3 groups based on the AR level changes induced by darolutamide (up, down, no change) was using an arbitrary 1.2 fold cut-off in order to make at least 3 different groups for data analysis by ANOVA. No statistical analysis was conducted to compare the number of patients with the different AR level changes within each breast cancer subtype. This decision is due to the small sample size that prevented statistical analysis.

End point values	Triple Negative Breast Cancer (TNBC)	HER2 Positive	HR+/HER2 Negative	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	8[2]	19[3]	
Units: Patients				
Androgen Receptor - Up	1	3	3	
Androgen Recepto - No Change	2	2	7	
Androgen Receptor - Down	4	3	9	

Notes:

[2] - Assay from one patient was not obtained.

[3] - Assay from one patient was not obtained.

Statistical analyses

No statistical analyses for this end point

Primary: Breast Cancer Tissue Androgen Receptor Protein Level

End point title	Breast Cancer Tissue Androgen Receptor Protein Level[4]

End point description:

AR levels were measured in patients following darolutamide treatment and patients were characterized into 3 groups, AR down regulated, AR up-regulated and AR unchanged. There was a stronger concordance between IHC measurements and transcript level of AR versus protein AR measurements.

End point type	Primary

End point timeframe:

Assessment performed once all patients have completed the trial as per protocol (all patients have completed their End of Study visit).

Notes:

[4] - 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 grouping into 3 groups based on the AR level changes induced by darolutamide (up, down, no change) was using an arbitrary 1.2 fold cut-off in order to make at least 3 different groups for data analysis by ANOVA. No statistical analysis was conducted to compare the number of patients with the different AR level changes within each breast cancer subtype. This decision is due to the small sample size that prevented statistical analysis.

End point values	Triple Negative Breast Cancer (TNBC)	HER2 Positive	HR+/HER2 Negative	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	7	8[5]	19[6]	
Units: Patients				
Androgen Receptor - Up	1	3	8	
Andorgen Receptor - No Change	6	3	2	
Andorgen Receptor - Down	0	2	10	

Notes:

[5] - Assay from one patient was not obtained.

[6] - Assay from one patient was not obtained.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Regular assessment and monitoring of adverse events (AEs) is required from informed consent signature, throughout the protocol treatment period, and at least up until surgery, or breast cancer pre-NAST biopsy (if the patient received NAST).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Triple Negative Breast Cancer (TNBC)

Reporting group description:

There were a total of 3 cohorts, organized by breast cancer sub-types:

- HR+/HER2 negative
- HER2 positive
- Triple-negative

All patients received darolutamide at a dose of 600 mg (2 × 300 mg tablets) twice daily (b.i.d.) by mouth, corresponding to a daily dose of 1200 mg.

Reporting group title	HER2 Positive

Reporting group description:

There were a total of 3 cohorts, organized by breast cancer sub-types:

- HR+/HER2 negative
- HER2 positive
- Triple-negative

All patients received darolutamide at a dose of 600 mg (2 × 300 mg tablets) twice daily (b.i.d.) by mouth, corresponding to a daily dose of 1200 mg.

Reporting group title	HR+/HER2 Negative

Reporting group description:

There were a total of 3 cohorts, organized by breast cancer sub-types:

- HR+/HER2 negative
- HER2 positive
- Triple-negative

All patients received darolutamide at a dose of 600 mg (2 × 300 mg tablets) twice daily (b.i.d.) by mouth, corresponding to a daily dose of 1200 mg.

Serious adverse events	Triple Negative Breast Cancer (TNBC)	HER2 Positive	HR+/HER2 Negative
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	0 / 20 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Triple Negative Breast Cancer (TNBC)	HER2 Positive	HR+/HER2 Negative
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 7 (71.43%)	6 / 9 (66.67%)	15 / 20 (75.00%)
Vascular disorders			
Hot flush			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 7 (28.57%)	4 / 9 (44.44%)	2 / 20 (10.00%)
occurrences (all)	2	4	2
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	0 / 20 (0.00%)
occurrences (all)	1	1	0
Breast discomfort			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Breast oedema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Vulval disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Vulvovaginal dryness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0

Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Blood creatinine increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
White blood cell count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Seroma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Thrombocytopenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Eye disorders			
Lacrimation increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Vitreous detachment			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	2 / 20 (10.00%)
occurrences (all)	0	1	2
Diarrhoea			
subjects affected / exposed	1 / 7 (14.29%)	1 / 9 (11.11%)	1 / 20 (5.00%)
occurrences (all)	1	1	1
Nausea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	2 / 20 (10.00%)
occurrences (all)	1	0	2
Flatulence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Gingival bleeding			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Gingival pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 9 (11.11%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Rash pruritic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Renal and urinary disorders			

Dysuria			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Endocrine disorders			
Thyroid pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Limb discomfort			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Eyelid infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Postoperative wound infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 9 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 February 2018	-Wording modified to allow patients candidates for neoadjuvant therapy to participate on the study, as long as patients and Investigators were willing to start such therapy once treatment with darolutamide was completed and a biopsy would be undergone prior to starting neoadjuvant therapy. -Sections updated as per safety data from Amendment 1 to Investigator's Brochure version 3.0, dated 22-Dec-2017. -Allowance of 2 cores for screening samples if 3 were not feasible (i.e. allow collection of 1 FFT core if not possible to provide 2 FFT cores) -Allowance of a minimum of 8 evaluable patients per cohort. -Wording added to clarify that patients enrolled but never treated would be discontinued from study. -Potential reasons for the premature termination of the study by the sponsor added. -Inclusion criterion modified to allow patients with T1 ≥ 1.0 cm (instead of ≥ 1.5 cm) -Modifications done on exclusion criteria related to previous or concurrent anti-cancer treatments. -Conditions required to consider vasectomised male partner as a highly effective contraceptive method added. -Wording added to allow Pre-surgery visit to take place the same day as BC surgery/pre-NAST biopsy. -Wording modified to request that laboratory safety tests be available and reviewed in the Pre-surgery visit before surgerywas performed. -Wording modified to perform interim review of data at given time points depending on the recruitment, for example once 20, around 35 and once all patients had been enrolled and undergone the EoS as per protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported