



Clinical Trial Protocol

Study Title: 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)

Study Number: TRIO030

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TRIO030 Protocol v. 3.0 – Rationale for Amendment

TRIO030 protocol was amended due to the following reasons:

- Enrollment difficulties faced by participating sites in some of the cohorts defined in the study
- Updated data from the most current Investigator's Brochure
- Administrative changes, clarification and other minor edits

TRIO030 protocol was amended as follows:

- Sections 1.3.1, 3.1, 4.1, 4.2, 5.3.2.1, 5.3.3, 5.3.4, 5.4.1, 5.4.2, 5.5.2, 6.3, 6.4.3, 6.4.5, 6.5.7.1, 8.6, and Appendix 2: Wording modified to allow patients candidates for neoadjuvant therapy to participate on the trial, as long as patients and Investigators are willing to start such therapy once treatment with darolutamide is completed and to undergo a biopsy prior to starting neoadjuvant therapy.
- Sections 1.2 and 5.5.1: Sections have been updated as per safety data from Amendment 1 to Investigator's Brochure version 3.0, dated 22-Dec-2017.
- Sections 3.2, 6.3, and 6.5.7.1: Allowance of 2 cores for screening samples if 3 are not feasible.
- Sections 3.1, 3.2, 6.1.2.2: Allowance of a minimum of 8 evaluable patients per cohort.
- Sections 3.1, 6.3, and 6.4.1: Wording added to clarify that patients enrolled but never treated will be discontinued from study.
- Section 3.3: Potential reasons for the premature termination of the study by the sponsor were added.
- Sections 4.1 and 4.2: Criterion modified to allow patients with $T1 \geq 1.0$ cm.
- Section 4.2: Modifications done on exclusion criteria related to previous or concurrent anti-cancer treatments.
- Section 5.5.3: Conditions required to consider vasectomised male partner as a highly effective contraceptive method were added as a footnote.
- Sections 6.3 and 6.4.3: Wording added to allow Pre-surgery visit to take place the same day as BC surgery/pre-NAST biopsy.
- Section 6.4.3: Section was modified to request that laboratory safety tests are available and reviewed in the Pre-surgery visit before surgery is performed.
- Section 8.5: 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 have been enrolled and undergone the EoS as per protocol.
- Term darolutamide utilized throughout the protocol instead of ODM-201 for consistency with Investigator's Brochure.
- TRIO Project Team updated as per latest changes in its composition.

- Term “patient” utilized throughout the protocol to refer to women participating in the study, instead of other terms (e.g. “subject”).
- Abbreviation change (HR+ to substitute ER+ where applicable).
- Acronym “NAST” was utilized throughout the protocol to refer to Neoadjuvant Systemic Therapy.
- “Pre-NAST biopsy” utilized throughout the protocol to refer to biopsy to be performed prior to start of neoadjuvant treatment in patients who are candidates for such therapy.
- Figure 1: Surgery visit name changed to “BC surgery/pre-NAST biopsy”.
- Table 2: Schedule of Procedures: footnotes 1 and 12 revised to clarify the timelines for tumor samples collection at screening.

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INVESTIGATORS

Approximately 20 sites in North America and Europe will participate in the study. The list of Investigators participating in the study will be maintained in TRIO's Clinical Trial Management System.

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LIST OF ABBREVIATIONS

AE	Adverse Event
AI	Aromatase Inhibitors
ALT	Alanine Aminotransferase / GPT
ANC	Absolute Neutrophil Count
AR	Androgen Receptor
AST	Aspartate Transaminase / GOT
AUC	Area under the curve
BC	Breast Cancer
BCRP	Breast Cancer Resistance Protein
b.i.d.	Twice a Day
CIOMS	Council for International Organizations of Medical Sciences
C _{max}	Maximum Serum Concentration
CRPC	Castration-Resistant Prostate Cancer
CSR	Clinical Study Report
CYP	Cytochrome P
EBC	Early Breast Cancer
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EoS	End of Study
ER	Estrogen Receptor
FDA	Food and Drug Administration
g/dL	Grams per deciliter
GCP	Good Clinical Practices
HER2	Human Epidermal Growth Factor Receptor 2
HIPPA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Hormone Receptor
IB	Investigator's Brochure
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention-To-Treat
mCRPC	Metastatic Castration-Resistant Prostate Cancer
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
NAST	Neoadjuvant Systemic Therapy
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
npo	<i>nil per os</i> , nothing by mouth
NYHA	New York Heart Association
P-gp	P-Glycoprotein
PgR	Progesterone Receptor
PICF	Patient Informed Consent Form
PS	Performance status
PSA	Prostate-Specific Antigen
RDC	Remote Data Capture
SAE	Serious Adverse Event
SERM	Selective Estrogen Receptor Modulators
SLNB	Sentinel Lymph Node Biopsy
SoC	Standard of Care
SSC	Study Steering Committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNBC	Triple Negative Breast Cancer
TORL	Translational Oncology Research Laboratories
TRIO	Translational Research In Oncology
UCLA	University of California, Los Angeles
ULN	Upper Limit of Normal
US	United States
WBC	White Blood Cells

WoCBP	Women of Childbearing Potential
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PROTOCOL SYNOPSIS

Protocol Title	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)
Protocol #	TRIO030
Study Duration	Enrollment is expected to run over a 12-month period approximately. The overall study is expected to last around 14 months (from First Patient In until Last Patient Last Visit).
Sponsor/Study Chair	This is a TRIO-sponsored study which will be chaired by Dr. Dennis Slamon (Professor of Medicine, Chief, Division of Hematology-Oncology, UCLA's Department of Medicine, CA, USA). The study is financially supported by Bayer.
Participating Investigators/Sites	Approximately 20 sites in North America and Europe will participate in the study.
Target Population	Women with early-stage breast cancer (BC) candidates for surgery as primary treatment modality or candidates for neoadjuvant treatment who accept to undergo a second biopsy before starting such therapy.
Background and Rationale	<p>Despite progresses made in diagnostic techniques and treatments for BC, there is still a significant number of patients undergoing treatment for early BC (EBC) who will relapse or patients with advanced BC that do not respond or progress to their treatments. The medical need for new and potentially more active and better tolerated agents in BC remains very high.</p> <p>Endocrine treatment is one of the strategies with a major therapeutic value in patients with estrogen-receptor (ER) positive tumors. Although, the role of ER and progesterone receptor (PgR) is well established in BC as predictive and prognostic factors, little is known about the clinical significance of the androgen receptor (AR). Preclinical studies show that the androgen signaling pathway plays a critical role in the development of normal and malignant breast tissue. AR is expressed in approximately 80% and 60% of primary and metastatic BC, respectively. Its expression varies across the different subtypes, approximately 84-95% in ER+ tumors, 50-63% in ER-/HER2+ cases and 10-53% in TNBC.</p> <p>In ER+ BC it has been suggested that acquired resistance to antiestrogen therapies could result from adaptation from estrogen dependence to androgen dependence. Recently, clinical reports of AR antagonism have been promising, especially in TNBC. Bicalutamide and enzalutamide have been tested in phase II trials in TNBC and have shown promising clinical activity.</p> <p>These developments in combination with an improved understanding of AR signaling in different BC subtypes led to the renewed interest in targeting AR. However, the value of AR antagonists in the management of BC, the molecular alterations that occur after exposure to these agents and whether there are biomarkers useful to predict their effectiveness, still need to be fully elucidated. Increased understanding of AR blockade and its potential value in different BC subtypes and clinical testing of newer and more potent AR antagonists like darolutamide, is thus timely and necessary.</p> <p>The current study will enroll EBC female patients with differing BC subtypes, with the intent of characterizing the molecular alterations in BC tissue before and after a short-term exposure to darolutamide. Darolutamide is a new AR antagonist, that thus far has been found to be very well-tolerated.</p> <p>Studying the biological mechanisms in which darolutamide targets the AR in BC will be crucial in understanding its potential role in this disease, as well as providing the foundation for the rational development of darolutamide in the disease. Molecular profiling of tumor samples before and after darolutamide treatment may permit the identification of patients likely or unlikely to respond to the agent based on the biological and molecular characteristics of their tumors.</p> <p>Since it is essential to evaluate the molecular effects of darolutamide in tumors not exposed to chemotherapy or radiation, patients with untreated primary breast tumors amenable to a</p>

	<p>pre-treatment biopsy followed by a post-darolutamide sample at definitive surgery or prior to starting neoadjuvant systemic therapy (NAST) represent an ideal population to study. Although no direct benefit from the treatment with darolutamide is expected in the participating patients, the good tolerability and favourable safety profile of darolutamide at the selected dose, the proposed brief duration of treatment, and the fact that patients enrolled in the study will not be required to undergo any delay in definitive surgery/start of neoadjuvant therapy, should ensure the safety and ethical set-up of the trial.</p>
Objectives	<p>Primary Objective:</p> <ul style="list-style-type: none">▪ To identify the molecular alterations that occur in human BC tissue, following short-term exposure to darolutamide in female patients with EBC. <p>Secondary Objectives:</p> <ul style="list-style-type: none">▪ To evaluate the safety and tolerability of short-term exposure to darolutamide in female patients with EBC.
Study Design	<p>This is a multi-center, open-label, tissue-acquisition study involving up to 60 patients with early-stage invasive BC.</p> <p>Patients with (a) suspicion of invasive BC based on clinical and/or radiological findings, or (b) a confirmation of invasive BC based on previous cytology/core/incisional biopsy will be invited to participate in the study: (a) In cases without pathological confirmation of BC diagnosis, signature of patient informed consent form (PICF) before BC confirmation biopsy is preferred to allow the collection of study-specific biopsies to be conducted.</p> <p>(b) For patients who have already had a confirmatory biopsy, they may also participate in the study if willing to undergo a subsequent study-specific biopsy procedure according to the protocol or if their diagnostic biopsy has been done according to the protocol requirements (in terms of number of cores/tissue, fresh frozen collection, etc).</p> <p>At time of PICF signature, patients will be registered in the study. Primary tumor samples will be collected by core needle biopsy or incisional biopsy (excisional biopsy will not be allowed). A minimum of three cores of tissue using a 14-gauge needle is recommended (or equivalent amount with an incisional biopsy). Two of the cores will be snap-frozen and the third one should be prepared in paraffin according to site's practice. In cases, it is not possible to provide enough material, collection of 2 cores (or equivalent amount with incisional biopsy) will be acceptable: one core will be snap-frozen and the other one will be prepared in paraffin.</p> <p>To be able to assess the molecular alterations after darolutamide exposure in different BC subtypes, patients being either triple-negative, or HR+/HER2 negative, or HER2 positive will be enrolled in the study (up to 20 patients with each of these subtypes, with an acceptable minimum of 8 evaluable patients in each cohort if enrollment of recommended 20 patients is not feasible for any reason).</p> <p>Eligible patients will be enrolled and receive darolutamide at a dose of 600 mg (2 × 300 mg tablets) b.i.d. to a daily dose of 1,200 mg. Protocol treatment should start within 5 days of enrollment, and within 42 days of the study-specific tumor sample collection. Minimum duration of treatment with darolutamide is 14 days with a recommended maximum duration of 21 days. It is recommended that the BC surgery/pre-NAST biopsy date is defined prior to starting protocol treatment. The start date of darolutamide (Day 1) will be derived as minus 14 to 21 days from the scheduled BC surgery/pre-NAST biopsy date. If for some reason BC surgery/pre-NAST biopsy takes place more than 21 days after treatment start (e.g. scheduling issues, delays, etc.), it is acceptable that patient receives darolutamide for more than 21 days and up to a maximum of 35 days. Patient should continue protocol treatment until the day prior to BC surgery/pre-NAST biopsy or "nil per os" (npo) is ordered. In these cases it is strongly recommended to have BC surgery/pre-NAST biopsy performed as soon as possible after 21 days of treatment are completed. Also, in any case that treatment is extended beyond 21 days, TRIO Medical Monitor should be contacted to discuss continuation of treatment and the need for assessments.</p> <p>At the time of BC surgery (if NAST is not indicated), or before NAST starts if indicated, BC tissue will be collected: two cores (or an equivalent amount of tissue), one fresh-frozen and</p>

	<p>one paraffin-embedded.</p> <p>End of Study (EoS) visit will occur 30 days (+/- 3 days) after the patient's last intake of darolutamide.</p>
Eligibility Criteria	<p>Inclusion Criteria</p> <ol style="list-style-type: none">1. Signed and dated PICF obtained prior to initiation of any study-specific procedure and treatment.2. Female \geq 18 years old.3. Histologically proven invasive breast carcinoma (through either a core needle biopsy or an incisional biopsy) for which surgery is indicated as the primary treatment modality. Patients for which NAST is indicated are also eligible provided they are willing to undergo a biopsy after completing treatment with darolutamide and prior to NAST start.4. Known ER, PgR and HER2 statuses.5. Tumor must be confined to either the breast or to the breast and ipsilateral axilla (<i>Note: patients with multifocal/multicentric tumors are eligible</i>). Patient must have (according to TNM 7th edition rules):<ul style="list-style-type: none">▪ T1 with $T \geq 1.0$ cm, T2 or T3 by at least one radiographic or clinical measurement▪ Either clinically positive (N1 only) or clinically negative axillary nodes (N0)▪ M06. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.7. Adequate organ function within 28 days prior to enrollment, as defined by the following criteria:<ul style="list-style-type: none">▪ Hematology: Hemoglobin ≥ 9.0 g/dL, Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$, Platelet count $\geq 100 \times 10^9/L$▪ Liver function: Alanine aminotransferase (ALT) and aspartate transaminase (AST) $\leq 2.5 \times$ upper limit of normal (ULN), Total bilirubin $\leq 1.5 \times$ ULN (or ≤ 3 times ULN for patients with documented Gilbert's syndrome or for whom indirect bilirubin concentrations suggest an extra-hepatic source of elevation).▪ Renal function: Creatinine $\leq 2.0 \times$ ULN8. No more than 42 days should elapse from the day the study-specific tumor sample is taken at initial diagnosis (or subsequent procedure) to the day of the first intake of darolutamide.9. Women of childbearing potential (WoCBP) must agree to use acceptable non-hormonal contraceptive methods of birth control from the day of the screening pregnancy test and up to 3 months after the last intake of darolutamide.10. For WoCBP negative serum pregnancy test within 7 days of enrollment.11. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and biopsies as detailed in the protocol. <p>Exclusion Criteria</p> <ol style="list-style-type: none">1. Any T0, Tis, T1 < 1.0 cm, T4; or N2-3; or M1 BC.2. Bilateral invasive BC.3. Patient that underwent excisional biopsy of the primary tumor.4. Medical indication or patient desire to undergo BC surgery or start NAST prior to completing at least 14 days of treatment with darolutamide, and/or refusal of patient to undergo corresponding biopsy in case NAST is planned.5. Prior or concurrent systemic anticancer therapy for BC treatment (immunotherapy, biologic/targeted therapy, chemotherapy, investigational agents).6. Prior or concurrent ipsilateral radiation therapy for invasive or noninvasive BC.7. Prior or concurrent treatment or preventative use of any hormonal agent such as aromatase inhibitors (AI), fulvestrant, raloxifene, tamoxifen or other selective estrogen receptor modulators (SERM), or with any other hormonal agent used for the treatment or prevention of BC or for any other indication (e.g. osteoporosis).8. Concurrent use of ovarian hormone replacement therapy. Prior treatment should be stopped at least 28 days prior to registration.9. Prior or concurrent treatment with AR antagonists or CYP17 enzyme inhibitor.10. Use of other investigational drug within 28 days of enrollment.11. Major surgery within 28 days before enrollment.

	<ol style="list-style-type: none"> 12. Any concurrent or previous malignancy within 5 years prior to enrollment except for basal or squamous skin cancer, or carcinoma in situ of the cervix, or other non-invasive/in-situ neoplasm, all of which must have been adequately and radically treated. A patient with previous history of invasive malignancy (other than adequately and radically treated basal or squamous skin cancer) is eligible provided that she has been disease free for more than 5 years. 13. Severe or uncontrolled concurrent disease, infection or comorbidity. 14. Known active viral hepatitis, human immunodeficiency virus (HIV) or chronic liver disease. 15. Other serious illness or medical condition within 6 months before enrollment, including any of the following: Concurrent congestive heart failure New York Heart Association (NYHA) Class III or IV, severe/unstable angina pectoris, myocardial infarction, uncontrolled hypertension, coronary/peripheral artery bypass graft, high-risk uncontrolled arrhythmias, stroke. 16. Any contraindication to oral agents or gastrointestinal disorder or procedure which expects to interfere significantly with absorption of protocol treatment. 17. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating Investigator. 18. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. 19. Known allergy to darolutamide or any of the excipients. 20. Pregnant or lactating patients.
Protocol Treatment	<p>Darolutamide will be given at a dose of 600 mg (2 x 300 mg tablets) b.i.d. corresponding to a daily dose of 1,200 mg.</p> <p>The following timelines will be considered for darolutamide administration:</p> <ul style="list-style-type: none"> ▪ Darolutamide shall be administered starting within 5 days of enrollment. ▪ No more than 42 days should elapse from the day the study-specific tumor sample is taken at initial diagnosis (or in a subsequent procedure) to the day of the first intake of darolutamide. ▪ Minimum duration of treatment will be 14 days prior to BC surgery or to the pre-NAST biopsy (if NAST is indicated). ▪ A maximum duration of 21 days of treatment is recommended. It is recommended that the date of BC surgery/pre-NAST biopsy is defined prior to starting protocol treatment. The start date of darolutamide (Day 1) will be derived as minus 14 to 21 days from the scheduled BC surgery/pre-NAST biopsy date. ▪ Treatment will be given until the day prior to the BC surgery, or the day before pre-NAST biopsy or when npo is ordered, whichever occurs first. ▪ If for some reason BC surgery/pre-NAST biopsy takes place more than 21 days after treatment start, it is acceptable that patient receives darolutamide for more than 21 days and up to a maximum of 35 days; patient should continue protocol treatment until the day prior to BC surgery/pre-NAST biopsy or npo is ordered. In these cases it is strongly recommended to have BC surgery/pre-NAST biopsy done as soon as possible after 21 days of treatment are completed. Also, in any case that treatment is extended beyond 21 days, TRIO Medical Monitor should be contacted to discuss continuation of treatment and the need for assessments.

Visits and Assessments	Activity	Screening	Treatment Period	Pre-surgery	BC surgery/pre-NAST biopsy	End of Study	
	Informed consent/Registration and Enrollment	X					
	Demographics, medical, surgical, disease history	X					
	Complete physical examination	X		X			
	Symptom-directed physical examination		X			X	
	ECOG PS	X	X	X		X	
	Weight, height, blood pressure	X					
	Serum pregnancy test	X					
	Hematology, Blood chemistry	X		X		X	
	Treatment compliance assessment		X	X			
Statistical Methods	AEs assessments	X	X	X		X	
	Concomitant medication	X	X	X		X	
	Tumor sample	X			X		
	Up to 60 patients (a minimum of 8 evaluable patients and up to 20 patients in each breast cancer subtype: triple-negative, HR+/HER2 negative, HER2 positive) will be required for the performance of the molecular studies and possible hypothesis generation. A patient will be considered evaluable if the following criteria are met: <ul style="list-style-type: none">▪ Minimum duration of treatment with darolutamide is of 14 days, with a minimum of 10 consecutive days of treatment prior to the definitive BC surgery/pre-NAST biopsy.▪ Mandatory tumor tissue is collected at screening and at BC surgery/pre-NAST biopsy according to the protocol and submitted to the central lab.▪ Adequacy for molecular assessment of the tumor tissue collected before and after the protocol treatment initiation. The adequacy will be evaluated by the central lab. Assessment of patient evalability, safety and distribution of patients with respect to hormone receptor status and HER2 status will be performed by the Study Steering Committee (SSC) at given time points depending on the recruitment, primarily planned once 20, around 35 and once all patients have been enrolled and undergone the EoS per protocol. This will allow for the SSC to ascertain that the appropriate number of evaluable patients is being accrued, that more or less patients may be required, or in the extreme case, that accrual should close if the patient evalability rate is very low and/or safety concerns arise. The SSC will define the evalability of patients that discontinue treatment more than 3 days before surgery: molecular analyses may be taken into consideration for the decision about the evalability of such patients.						
Study Populations	Study Populations <ul style="list-style-type: none">▪ Intention-to-treat (ITT) Population: the ITT population includes all patients who are enrolled in the study regardless of whether they have been treated or not.▪ Safety Population: the Safety population includes all patients who have taken at least one						

	tablet of darolutamide.
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- Evaluable population: includes all patients who are considered evaluable per protocol.

1. BACKGROUND AND RATIONALE

1.1 Disease Overview

Breast cancer (BC) is the second most common cancer in the world and by far, the most frequent cancer among women.¹ In the United States (US), approximately 246,000 new BC cases and 40,000 deaths due to this disease are expected to occur in women during 2016. This represents 29% of all cancers diagnosed annually in women and 14% of deaths due to cancer annually in women.²

BC is a highly heterogeneous disease with marked differences regarding molecular, biological and clinical features. Molecular subtypes have been described with corresponding differences in prognosis and response to treatments. The current classification is based on the expression of estrogen and progesterone receptors (ER and PgR respectively) and HER2, and BC are broadly divided into three subtypes: HR+/HER2 negative, HER2+ and triple negative BC (TNBC). The characterization of which subtype of BC a patient has, allows to adapt the different treatment modalities due to their predictive value and has also prognostic implications.

Despite progress made in diagnostic techniques and treatments for BC, there is still a significant number of patients undergoing treatment for early BC (EBC) who will relapse or patients with advanced BC whose tumor will not respond to standard treatments or progress after them. The medical need for new and potentially more active and better tolerated agents in BC remains very high.

1.2 Investigational Medicinal Product Overview

Darolutamide (ODM-201) is a new AR antagonist that is being jointly developed by Bayer AG and Orion Corporation for the treatment of castration-resistant prostate cancer (CRPC). As of the version date of this protocol, it has not been marketed or authorized to be marketed in any country.

Darolutamide potently inhibits testosterone binding to AR and retains antagonistic properties in cells expressing increased AR levels better than bicalutamide. Darolutamide diminishes AR-signaling by inhibiting testosterone mediated nuclear localization of AR more efficiently than bicalutamide. It shows antiandrogenic and antitumor activity in *in vitro* and *in vivo* models of CRPC and in clinical studies in patients with metastatic CRPC (mCRPC).

Darolutamide is a 1:1 mixture of 2 pharmacologically active diastereomers: ORM-16497 and ORM-16555 which are able to interconvert. Steady-state plasma concentrations of darolutamide are reached by 7 days of repeated dosing. The mean elimination half-life is in the range of 11.5-16.1 hours.

Data from an *in vivo* mass balance study in rats suggests that about two-thirds of oral darolutamide dose is excreted in feces and the remaining amount in urine. After a single dose, excretion is almost complete by 48 hours post-dose.

In general, the potential for darolutamide to inhibit CYP reaction pathways *in vitro* in human liver microsomes is low. The CYP450 induction potential of darolutamide was evaluated *in vitro* in primary cultures of human hepatocytes and a risk of weak to moderate CYP3A4 induction by darolutamide was observed.

In vivo data from study 17726 indicates that co-administration of rifampicin -a strong CYP3A4 inducer- (600 mg, fasted state) and a single dose of darolutamide (600 mg; 2 tablets of 300 mg) together with food, resulted in a 3-and 2-fold decrease of AUC (0-72) and Cmax of darolutamide to 28% and 48% respectively. Therefore, repeated co-administration of strong or moderate CYP3A4 inducers (e.g. carbamazepine, phenobarbital, St. John's Wort) with darolutamide is expected to reduce darolutamide plasma concentrations. The concomitant intake of these substances during study treatment should hence be avoided.

In vitro data indicate that darolutamide is a substrate of P-glycoprotein (P-gp) and Breast cancer resistance protein (BCRP). Therefore administration of strong inhibitors of P-gp (e.g., verapamil, dronedarone) and BCRP (e.g., pantoprazole, eltrombopag) may increase the plasma concentrations of Darolutamide and should be used with caution. However, *in vivo* data from Study 17726 showed that co-administration of itraconazole –a strong CYP3A4 and P-gp inhibitor- (200 mg) and a single dose of darolutamide (600 mg; 2 tablets of 300 mg) together with food, resulted in a 1.7-fold increase in AUC (0-72) and a 1.4-fold increase of C max of darolutamide. This indicates that co-administration of darolutamide with a strong CYP3A4 or P-gp inhibitor does not result in a clinically relevant increase of darolutamide (ODM-201) plasma concentrations.

Plasma concentration of drugs that are sensitive P-gp or BCRP substrates might be increased by darolutamide. Medicinal products that are sensitive substrates for P-gp (e.g., digoxin) or BCRP (e.g., methotrexate) should be used with caution when co-administered with darolutamide. *In vivo* data shows that the administration of 600 mg of darolutamide b.i.d. over 4 days prior to administration of a single dose of 5 mg rosuvastatin, a BCRP substrate, together with food resulted in a 5.2-fold increase in mean exposure (AUC) of rosuvastatin and a 4.9-fold increase in maximum serum concentration (Cmax). This indicates that co-administration of darolutamide can increase the plasma concentrations of other concomitant BCRP substrates (e.g. methotrexate, sulfasalazine, fluvastatin, atorvastatin).

As of 04 January 2017, darolutamide has been given to 173 patients with CRPC. Until now, darolutamide has been studied in 6 clinical studies. The majority of the phase I/II studies were conducted in mCRPC patients. One phase I study was conducted in healthy male volunteers with a single administration of darolutamide. Non-metastatic CRPC patients are being investigated in an ongoing phase III study (ARAMIS trial).

Antitumor activity of darolutamide was evaluated in 3 studies in mCRPC. They have shown that darolutamide has antitumor activity at all dose levels as evaluated by Prostate Specific Antigen (PSA), circulating tumor cells and soft and bone lesion imaging. PSA decline \geq 50% was observed at 12 weeks in 74% of chemotherapy-naïve patients treated with darolutamide.

Darolutamide has thus far been found to be well-tolerated and to have negligible blood-brain barrier penetration. The integrated safety data from clinical trials showed 93.9% of patients developed at least 1 adverse event (AE) and grade 3 or higher AEs were reported in 28% of patients. The most common AEs have been fatigue in 26.8% of patients and back pain in 22% of patients. The most common AEs considered related to protocol treatment by the Investigator have been fatigue (9.8%) and hot flush (4.3%). The majority of AEs were classified as grade 1 (59.7% of the events) and grade 2 (31.2% of the events). Of the serious adverse events (SAEs) reported in clinical trials (27.4 %) none of them was considered related to the protocol treatment by the Investigator or by the Sponsor.

In summary, the results indicate that darolutamide exhibits a good safety and tolerability profile and promising antitumor activity in men with CRPC.

Additional information on the clinical efficacy, safety, pharmacology of darolutamide is provided in the darolutamide Investigator brochure (IB).

1.3 Rationale

1.3.1 Rationale for Conducting the Study

The androgen receptor (AR) is a member of the nuclear steroid hormone receptor family, which also includes ER and PgR. These are critical components of signaling pathways and regulate gene expression. AR expression in BC has long been noted and is the most common nuclear hormone receptor. AR is expressed in approximately 80% and 60% of primary and metastatic BC, respectively.³ Its expression varies across the different subtypes, approximately 84-95% in ER+ tumors, 50-63% in ER-/HER2+ cases and 10-53% in TNBC.³

The role of AR in BC still needs to be fully elucidated, differently from the well-known ER and PgR. Preclinical studies show that the androgen signaling pathway plays a critical role in the development of normal and malignant breast tissue. Epidemiologic studies suggest that increased levels of circulating androgens are associated with an increased risk for BC, primarily ER/PgR-positive BC.⁴

AR expression in ER+ BC associates with improved outcomes, but AR seems to be oncogenic in the tamoxifen-resistant setting.³ Approximately 30 to 50% of all ER+ BC tumors display *de novo* resistance to standard endocrine therapies and most metastatic ER+ tumors do eventually acquire resistance over time.⁵ AR positivity increases resistance to tamoxifen in BC models *in vitro* and *in vivo*.⁶ Thus, it is possible that acquired resistance to antiestrogen therapies could result from adaptation from estrogen dependence to androgen dependence.⁷

In the case of TNBC, signaling through the AR may play a role in pathogenesis. Studies which have focused on AR expression in TNBC have provided conflicting results in regards to the prognostic value of AR expression.⁸ While some studies suggest that AR expression is a favorable prognostic factor in patients with TNBC, others suggest that it predicts reduced survival in early TNBC.^{8, 9} Irrespective of this, AR might represent a new target in TNBC, which has so far a worse prognosis and very limited standard therapeutic options, none of them targeted.

As a result of these findings, AR has emerged as a potential useful marker for the further subclassification of BC and as a potential therapeutic target.

Modulation of AR signaling, either inhibitory or stimulatory, has previously been explored in BC with somewhat contrasting results. Androgen therapy has historically been used but largely abandoned in the 1970s due to its toxicity and the emergence of ER-directed therapies.

More recently, clinical reports of AR antagonism have been promising, especially in TNBC. Bicalutamide has been assessed in a phase II, single-arm trial in AR+, ER- advanced BC, and showed clinical benefit rate of 19% with a good safety profile.¹⁰ Some newer drugs like enzalutamide, have also been tested in TNBC. A phase II study in AR+ TNBC proved that this therapy was well-tolerated and showed promising clinical activity in selected patients.¹¹

These developments in combination with an improved understanding of AR signaling in different BC subtypes led to the renewed interest in targeting AR. However, the value of AR antagonists in the management of BC, the molecular alterations that occur after exposure to these agents and whether there are biomarkers useful to predict their effectiveness, still need to be fully elucidated. Increased understanding of AR blockade and its potential value in different BC subtypes and clinical testing of newer and more potent AR antagonists like darolutamide, is thus timely and necessary.

Translational Oncology Research Laboratories (TORL, at University of California Los Angeles, US) has conducted cell viability studies in 49 BC cell lines exposed to different concentrations of darolutamide. The studies have shown that cell lines belonging to each of the three BC subtypes (HR+, HER2+, TN) responded different to darolutamide. Responses are mainly seen in cell lines expressing AR but also in some lines that lack AR expression, suggesting that AR expression may not be the only biomarker predicting response to darolutamide (unpublished).

The current study will enroll EBC female patients with differing BC subtypes, with the intent of characterizing the molecular alterations in BC tissue before and after short-term exposure to the antiandrogen darolutamide. Studying the biological mechanisms in which darolutamide targets the AR in BC will be crucial in understanding its potential role in this disease, as well as providing the foundation for the rational development of darolutamide in the disease. Such information may suggest that darolutamide be combined with other modalities; for example, if treatment with the drug is discovered to affect multiple signaling pathways. Molecular profiling of tumor samples before and after darolutamide treatment may permit the identification of patients likely or unlikely to respond to the agent based on the biological and molecular characteristics of their tumors. Since it is essential to evaluate the molecular effects of darolutamide in tumors not previously exposed to chemotherapy or radiation, patients with untreated primary breast tumors amenable to a pre-

treatment biopsy followed by a post-darolutamide sample at definitive surgery or prior to starting neoadjuvant systemic therapy (NAST) represent an ideal population to study. Male patients will not be enrolled due to pathological and biological differences in male breast cancer.¹²

Although no direct benefit from the treatment with darolutamide is expected in the participating patients, the good tolerability and favourable safety profile of darolutamide at the selected dose, the proposed brief duration of treatment, and the fact that patients enrolled in the study will not be required to undergo any delay in definitive surgery or start of NAST if indicated, should ensure the safety and ethical set-up of the trial.

1.3.2 Rationale for Regimen and Dose Selection

In TRIO030, darolutamide will be given at a dose of 600 mg (2 × 300 mg tablets) b.i.d. to a daily dose of 1,200 mg. Darolutamide should be taken with food since exposure and C_{max} are reduced in fasting conditions.

Darolutamide has been studied in doses ranging from 100 mg to 900 mg b.i.d. in a phase I dose escalation and dose finding study. No dose-limiting toxicities were observed in this study and the maximum tolerated dose was not reached. Systemic exposure to darolutamide increased dose-proportionally in the dosing range from 100 to 700 mg b.i.d. At 900 mg b.i.d. dose there was no further increase in C_{max} or AUC observed when compared to 700 mg b.i.d. Based on the results of this phase I study, the recommended dose was 600 mg b.i.d. for further development. At the dose of 600 mg b.i.d. most AEs were grade 1-2 and assessed by the Investigators as not related to protocol treatment.

Therefore, the dose selected in the study is considered as safe and is the dose that is being used in current darolutamide trials in patients with other primary cancer sites.

2. OBJECTIVES

2.1 Primary Objective

- To identify the molecular alterations that occur in human BC tissue, following short-term exposure to darolutamide in female patients with EBC.

2.2 Secondary Objectives

- To evaluate the safety and tolerability of short-term exposure to darolutamide in female patients with EBC.

3. STUDY DESIGN

3.1 Overall Study Design and Plan: Description

This is a multi-center, open-label, tissue-acquisition study involving up to 60 patients with early-stage invasive BC.

Female patients with (a) suspicion of invasive BC based on clinical and/or radiological findings, or (b) those who have a confirmation of invasive BC based on previous cytology/core/incisional biopsy will be invited to participate in the study:

- (a) In cases without pathological confirmation of BC diagnosis, signature of patient informed consent form (PICF) before BC confirmation biopsy is preferred to allow the collection of study-specific biopsies to be conducted.

(b) For patients who have already had a confirmatory biopsy, they may also participate in the study if willing to undergo a subsequent study-specific biopsy procedure according to the protocol or if their diagnostic biopsy has been done according to the protocol requirements (in terms of number of cores/tissue, fresh frozen collection, etc.; refer to section 6.5.7.1).

At time of PICF signature, patients will be registered in the study. Primary tumor samples will be collected by core needle biopsy or incisional biopsy (excisional biopsy will not be allowed). A minimum of three cores of tissue using a 14-gauge needle is recommended (or equivalent amount with an incisional biopsy). Two of the cores will be snap-frozen and the third one should be prepared in paraffin according to site's practice. In cases that it is not possible to provide enough material, collection of 2 cores (or equivalent amount with incisional biopsy) will be acceptable; one core will be snap-frozen and the other one will be prepared in paraffin.

After all screening procedures and confirmation of eligibility, patients will be enrolled and will begin intake of darolutamide. To be able to assess the molecular alterations after darolutamide exposure in different BC subtypes, female patients being either triple-negative, or HR+/HER2 negative, or HER2 positive will be enrolled in the study. Up to 20 patients with each of these subtypes will be included (refer to section 6.1.2.2 for further details on the enrollment according to BC subtype). However, a minimum of 8 evaluable patients in each cohort is considered acceptable if enrollment of 20 patients is not feasible within a cohort for any reason.

Eligible patients will be enrolled and receive darolutamide at a dose of 600 mg (2 × 300 mg tablets) b.i.d. corresponding to a daily dose of 1,200 mg. Protocol treatment should start within 5 days of enrollment and within 42 days of the study-specific tumor sample collection. Patients enrolled, but not treated, will be discontinued from study and managed as per the site's standard of care (SoC). Minimum duration of treatment with darolutamide is 14 days with a recommended maximum duration up to 21 days. It is recommended that the BC surgery/pre-NAST biopsy date is defined prior to starting protocol treatment. The start date of darolutamide (Day 1) will be derived as minus 14 to 21 days from the scheduled BC surgery/pre-NAST biopsy date. Treatment will be taken until the day prior to the BC surgery (if NAST is not indicated) or the day before NAST starts if indicated; or when the patient is ordered to stop all oral intake, whichever occurs first (refer to section 5.3.2.1). If for some reason surgery takes place more than 21 days after treatment start (e.g. surgery scheduling issues, surgery delays, etc.) it is acceptable that patient receives darolutamide for more than 21 days and up to a maximum of 35 days. Patient should continue protocol treatment until the day prior to BC surgery/pre-NAST biopsy or "*nil per os*" (npo) is ordered. In these cases it is strongly recommended to have BC surgery/pre-NAST biopsy performed as soon as possible after 21 days of treatment are completed.

At the time of BC surgery (if NAST is not indicated), or before NAST starts if indicated, BC tissue will be collected: two cores (or an equivalent amount of tissue), one fresh-frozen and one paraffin-embedded.

End of Study (EoS) visit will occur 30 days (+/- 3 days) after the patient's last intake of darolutamide. In case protocol treatment-related AEs/SAEs ongoing at the time of the EoS visit, monitoring of these events will continue as clinically indicated until (a) the events have resolved or (b) the events have reached a status which, in the Investigator's opinion, is unlikely to resolve due to the nature of the condition and/or the patient's underlying disease.

Treatment for BC including NAST (if applicable), definitive surgery, and adjuvant therapy will be at the Investigator's discretion.

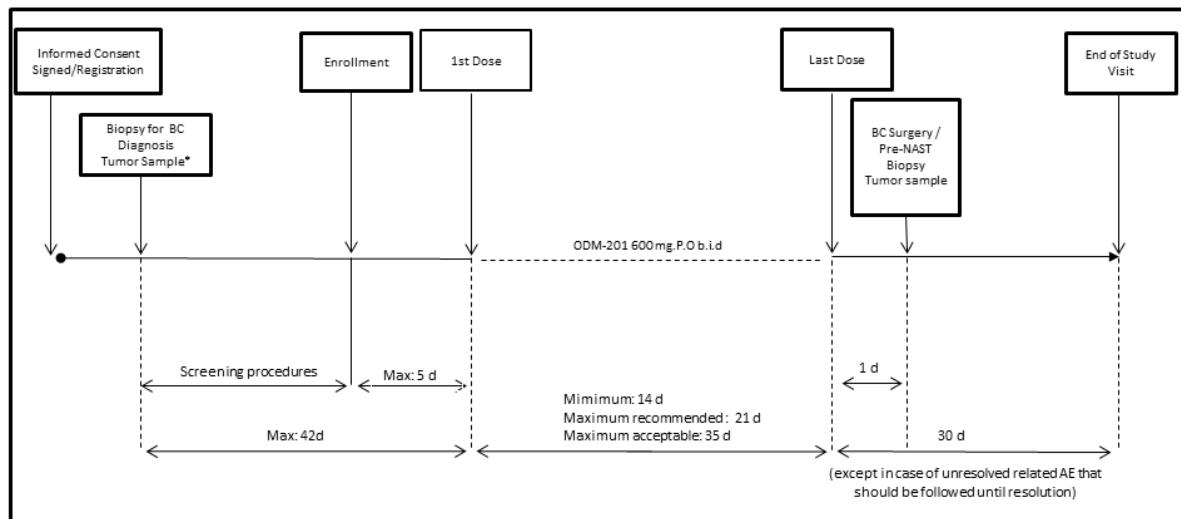


Figure 1: Study Schema

BC= Breast cancer

* In cases with absence of a pathological confirmation of BC diagnosis, PICF signature prior to the biopsy for BC confirmation is preferred. For patients who already had such confirmatory biopsy, they may also participate in the study if willing to undergo a subsequent study-specific biopsy procedure according to the protocol or if their diagnostic biopsy has been done according to the protocol requirements (in terms of number of cores/tissue, fresh frozen collection, etc.).

3.2 Number of Patients and Investigational Sites

Up to 60 patients will be enrolled in the study, from approximately 20 sites in North America and Europe, with an acceptable minimum of 8 evaluable patients in each if enrollment of 20 patients is not feasible within a cohort for any reason. The list of Investigators participating in the study will be maintained in TRIO's Clinical Trial Management System.

3.3 Study End

The study will end once the last patient undergoes the EoS visit and all data required for the analyses have been observed, collected and cleaned. The trial may be prematurely terminated at any time by Ethics Committees (EC)/Institutional Review Boards (IRB), competent authorities, or the sponsor. Potential reasons for premature termination of the study by the sponsor are (not exhaustive):

- Regulatory authority decision
- Change in opinion of the EC/IRB
- Drug safety concerns
- Manufacturer's decision to discontinue development of darolutamide
- Inability to run the study because of operational issues (e.g., low recruitment)

If the study is prematurely terminated or discontinued, TRIO will promptly notify the Investigators and all other relevant parties.

4. PATIENT SELECTION

Patients can be enrolled in the study only if the eligibility criteria are met. This study can fulfill its objectives only if appropriate patients are enrolled. Patients who fail to meet all inclusion criteria or fulfill at least one exclusion criteria cannot be enrolled in the study. The sponsor will not grant any eligibility waivers.

If a patient whom does not meet the eligibility criteria is incorrectly enrolled, the Investigator should immediately inform the Medical Monitor. The decision about the continuation or discontinuation of this patient on protocol treatment will be based on medical judgment, treatment benefit and safety risks for her.

4.1 Inclusion Criteria

1. Signed and dated PICF obtained prior to initiation of any study-specific procedure and treatment.
2. Female \geq 18 years old.
3. Histologically proven invasive breast carcinoma (through either a core needle biopsy or an incisional biopsy) for which surgery is indicated as the primary treatment modality. Patients for which NAST is indicated are also eligible provided they are willing to undergo a biopsy (as per requirements in section 6.5.7) after completing treatment with darolutamide and prior to NAST start.
4. Known ER, PgR and HER2 statuses.
5. Tumor must be confined to either the breast or to the breast and ipsilateral axilla (*Note: patients with multifocal/multicentric tumors are eligible*). Patient must have (according to TNM 7th edition rules):
 - T1 with T \geq 1.0 cm, T2 or T3 by at least one radiographic or clinical measurement
 - Either clinically positive (N1 only) or clinically negative axillary nodes (N0)
 - M0
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
7. Adequate organ function within 28 days prior to enrollment, as defined by the following criteria:
 - Hematology:
 - Hemoglobin \geq 9.0 g/dL,
 - ANC \geq 1.5 \times 10⁹/L,
 - Platelet count \geq 100 \times 10⁹/L
 - Liver function:
 - ALT and AST \leq 2.5 \times ULN,
 - Total bilirubin \leq 1.5 \times ULN (or \leq 3 times ULN for patients with documented Gilbert's syndrome or for whom indirect bilirubin concentrations suggest an extra-hepatic source of elevation)
 - Renal function: Creatinine \leq 2.0 \times ULN
8. No more than 42 days should elapse from the day study-specific tumor sample is taken at initial diagnosis (or subsequent procedure) to the day of the first intake of darolutamide.
9. WoCBP* must agree to use acceptable non-hormonal contraceptive methods of birth control from the day of the screening pregnancy test and up to 3 months after the last intake of darolutamide.
10. For WoCBP* negative serum pregnancy test within 7 days of enrollment.
11. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and biopsies as detailed in the protocol.

** Note: Women of childbearing potential (WoCBP) are any women between menarche and menopause who have not been permanently sterilized, capable of procreation. Permanent sterilization includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal ligation/occlusion. Postmenopause is defined as:*

- *Bilateral oophorectomy*
- *Age \geq 60*
- *Age < 60 and amenorrheic for ≥ 12 months in the absence of an alternative medical cause and FSH and estradiol in postmenopausal ranges.*

4.2 Exclusion Criteria

1. Any T0, Tis, T1 < 1.0 cm, T4; or N2-3; or M1 BC.
2. Bilateral invasive BC.
3. Patient that underwent excisional biopsy of the primary tumor.
4. Medical indication or patient desire to undergo BC surgery or start NAST prior to completing at least 14 days of treatment with darolutamide, and/or refusal of patient to undergo corresponding biopsy in case NAST is planned.
5. Prior or concurrent systemic anticancer therapy for BC treatment (immunotherapy, biologic/targeted therapy, chemotherapy, investigational agents).
6. Prior or concurrent ipsilateral radiation therapy for invasive or noninvasive BC.
7. Prior or concurrent treatment or preventative use of any hormonal agent such as aromatase inhibitors (AI), fulvestrant, raloxifene, tamoxifen or other SERM, or with any other hormonal agent used for the treatment or prevention of BC or for any other indication (e.g. osteoporosis).
8. Concurrent use of ovarian hormone replacement therapy. Prior treatment should be stopped at least 28 days prior to registration.
9. Prior or concurrent treatment with AR antagonists or CYP17 enzyme inhibitor.
10. Use of other investigational drug within 28 days of enrollment.
11. Major surgery* within 28 days before enrollment.
12. Any concurrent or previous malignancy within 5 years prior to enrollment except for basal or squamous skin cancer, or carcinoma in situ of the cervix, or other non-invasive/in-situ neoplasm, all of which must have been adequately and radically treated. A patient with previous history of invasive malignancy (other than adequately and radically treated basal or squamous skin cancer) is eligible provided that she has been disease free for more than 5 years.
13. Severe or uncontrolled concurrent disease, infection or comorbidity.
14. Known active viral hepatitis, HIV or chronic liver disease.
15. Other serious illness or medical condition within 6 months before enrollment, including any of the following: Concurrent congestive heart failure NYHA Class III or IV, severe/unstable angina pectoris, myocardial infarction, uncontrolled hypertension, coronary/peripheral artery bypass graft, high-risk uncontrolled arrhythmias, stroke.
16. Any contraindication to oral agents or gastrointestinal disorder or procedure which expects to interfere significantly with absorption of protocol treatment.
17. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration

of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating Investigator.

18. Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
19. Known allergy to darolutamide or any of the excipients.
20. Pregnant or lactating patients.

* Note: Major surgery defined as requiring a general anesthesia or respiratory assistance; involving openings into the great cavities of the body, organs removed, or normal anatomy altered; implying risks of severe hemorrhage; implying risk for life of the patient or severe disability.

5. TREATMENT

5.1 Protocol Treatment: Darolutamide

Darolutamide is the only protocol treatment in the trial and is considered an Investigational Medicinal Product (IMP). Darolutamide will be supplied to the investigational sites as 300 mg tablets, free of charge.

For the purpose of this trial, the Single Reference Document to be used for darolutamide is the IB.

5.2 Protocol Treatment Management

5.2.1 Packaging and Labeling

Darolutamide is provided as coated immediate-release 0.3 g (300 mg) tablets, in a high-density polyethylene (HDPE) white opaque plastic bottle containing 140 tablets.

Clinical supplies will be affixed with a clinical label in accordance with applicable regulatory requirements, and include a statement regarding its limitation to investigational use only.

5.2.2 Storage and Accountability

Study drugs must be stored according to labeled requirements, at room temperature not exceeding 30°C in a secure, limited-access location. Receipt and dispensing of trial medication must be recorded by an authorized person at the site. Clinical supplies may not be used for any purpose other than that stated in the protocol.

The Investigator/designee is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount administered or dispensed to and returned by the patients, and the amount remaining at the conclusion of the trial.

TRIO will provide appropriate documents that must be completed for drug accountability and destruction/return.

5.2.3 Drug Return/Destruction

Patients must return all unused medication and empty containers to the Investigator/designee. Unused/expired darolutamide should be destroyed locally (where requirements permit) once accountability is performed and drug supplies are reconciled. Procedures for proper disposal of darolutamide should be applied according to standards established at each site.

5.3 Protocol Treatment Administration

5.3.1 Pre-medication and Special Precautions

No specific pre-medication is required. Based on the available data on latest version of IB, there are no special warnings and precautions for use of darolutamide.

5.3.2 Standard Treatment Schedule

5.3.2.1 Dosage and Administration

Darolutamide will be given at a dose of 600 mg (2 × 300 mg tablets) b.i.d. to a daily dose of 1,200 mg.

The following timelines will be considered for darolutamide administration (refer to Figure 1: Study Schema):

- Darolutamide shall be administered starting within 5 days of enrollment.
- No more than 42 days should elapse from the day the study-specific tumor sample is taken at initial diagnosis (or in a subsequent procedure) to the day of the first intake of darolutamide (*Note: for patients who already had their initial diagnostic biopsy prior to registration and this procedure has been done according to the protocol requirements, the 42- day window should be counted from the date of such biopsy*).
- Minimum duration of treatment will be 14 days prior to BC surgery or to the pre-NAST biopsy (if NAST is indicated) (*Note: a day of treatment is considered as any day where the patient takes any darolutamide intake*)
- A maximum duration of 21 days of treatment is recommended. It is recommended that the date of BC surgery/pre-NAST biopsy is defined prior to starting protocol treatment. The start date of darolutamide (Day 1) will be derived as minus 14 to 21 days from the scheduled BC surgery/pre-NAST biopsy date.
- Treatment will be given until the day prior to the BC surgery, or the day before pre-NAST biopsy or when npo is ordered, whichever occurs first.
- If for some reason BC surgery/pre-NAST biopsy takes place more than 21 days after treatment start, it is acceptable that patient receives darolutamide for more than 21 days and up to a maximum of 35 days; patient should continue protocol treatment until the day prior to BC surgery/pre-NAST biopsy or npo is ordered. In these cases it is strongly recommended to have BC surgery/pre-NAST biopsy done as soon as possible after 21 days of treatment are completed. Also, in any case that treatment is extended beyond 21 days, TRIO Medical Monitor should be contacted to discuss continuation of treatment and the need for assessments.
- The first day of darolutamide administration in the study is considered Day 1. On or prior to Day 1 the patient will be provided with a bottle with 140 tablets containing 300 mg of darolutamide each (enough for 35 days of treatment at a daily dose of 1,200 mg). Patient will be instructed that the last protocol treatment intake should be the one in the morning of the Pre-surgery visit. The last darolutamide intake will be on the day prior to BC surgery, or the day before pre-NAST biopsy when the Pre-surgery visit should occur. Exceptions to this rule are when patient is ordered to stop oral intake before the day prior to BC surgery/pre-NAST biopsy, when BC surgery/pre-NAST biopsy is planned for a Monday or the day following a holiday, or in case that performing Pre-surgery visit on the same day of BC surgery/pre-NAST biopsy is required by site due to logistical reasons or patient's/physician's convenience (refer to section 6.4.3 for guidance).

Darolutamide should be taken approximately at the same time each day, twice a day. It is recommended that darolutamide be taken with food; recommendation is to take it with breakfast and dinner each day. Patients will ingest darolutamide whole tablets with water. No tablet should be ingested if it is broken, cracked, or otherwise not intact.

If the patient misses an intake or vomits following darolutamide administration, the missed/vomited dose should be skipped and the patient should take the next intake when scheduled. No “make-up dose” or increased dosing should occur.

If a patient accidentally or intentionally takes a higher daily dose than the one recommended per protocol and up to 1,800 mg (i.e. up to 6 × 300 mg tablets), protocol treatment should continue as scheduled without any dose reduction or skip. For example, if by mistake the patient takes 4 tablets in the first daily intake she can still take 2 tablets in the second daily intake since a total daily dose of 1,800 mg is not exceeded. The Medical Monitor should be contacted for any dose taken that exceeds 1,800 mg daily.

5.3.2.2 Treatment Compliance

The administration of the protocol treatment should be recorded in the appropriate sections of the electronic case report form (eCRF).

Additionally, treatment compliance will be assessed at each visit that may occur during treatment phase (see section 6.4.2) and at Pre-surgery visit, and it should be properly documented in source documents. Patients will complete a diary (Appendix 2) to document their daily intakes. They will be instructed to return all unused drugs (partially used and empty containers) and their diary at each visit during the treatment period (if any) and at Pre-surgery visit. Site staff will perform accountability of the returned drug and will assess compliance of the patient. Site staff must ensure that the patient clearly understands the directions for self-medication and follows the schedule adequately.

5.3.3 Protocol Treatment Discontinuation

Patients are treated until the day before BC surgery/pre-NAST biopsy (if NAST will be given), or when patient is ordered to stop oral intake, whichever occurs first.

The Investigator will also discontinue protocol treatment if any of the following conditions is met:

- Intercurrent illness or a change in patient’s condition or unacceptable toxicity that warrants protocol treatment discontinuation according to Investigator’s judgment
- Any event, condition, criterion which would warrant discontinuation of darolutamide as per section 5.4, including Grade 3 or higher protocol-treatment related AE
- Any event, condition, reason which would warrant darolutamide to be held for more than the maximum acceptable delay of 7 consecutive days
- Patient receives non-protocol anticancer therapy at any time during the protocol treatment
- Patient’s decision to withdraw protocol treatment
- Lost to follow up
- Death
- Pregnancy
- Investigator’s decision
- Discontinuation of the study by the sponsor (refer to section 3.3)

The reason and date of protocol treatment discontinuation for all patients will be documented in the eCRF (e.g. AE, lost to follow-up, etc.). The Investigator will attempt to complete all discharge procedures at the time a patient is discontinued from the study including an assessment of the AEs, collect all study-related materials from the patient (i.e. patient diary), and will complete the EoS form. Patients are free to discontinue their participation in the study at any time, without prejudice to further treatment.

5.3.4 Surgery and (Neo) Adjuvant Systemic Therapy

BC surgery, NAST and post surgical BC treatments are left at the discretion of the Investigator and are not considered protocol treatments.

5.4 Adverse Events Management and Treatment Schedule Adjustments

5.4.1 General Rules

Regular assessment and monitoring of AEs is required from PICF signature, throughout protocol treatment period and at least up until surgery or BC pre-NAST biopsy if patient will receive NAST.

Toxicity will be 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 guidance in section 5.4.2. 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.

All dose modifications should be based on the AE requiring the greatest modification and should be properly documented in source documents and the eCRF.

5.4.2 Guidance for Darolutamide Dose Modifications

A patient who experiences a treatment-related Grade 3 or higher AE must be withdrawn from protocol treatment and should proceed to surgery/pre-NAST biopsy, and undergo EoS visit.

In the case of a grade 1-2 treatment-related AE, the Investigator should contact the Medical Monitor in case it is considered that a dose reduction or treatment hold is required due to the related AE.

Refer to Table 1: Dose Modifications.

Table 1: Dose Modifications*

Severity grade of treatment-related AE	Dose modifications	Protocol treatment withdrawal
Grade 1-2	No dose modification required. Intake per regular schedule. Medical Monitor must be contacted in case the Investigator considers that a dose reduction or treatment hold is required due to a grade 1-2 treatment-related AE. After agreement with the Medical Monitor, treatment may be	Refer to Dose modifications on the left.

	held for a maximum of 7 consecutive days and/or dose reduced to 300 mg b.i.d. ^a Protocol treatment must be discontinued if further dose reduction is required or treatment is held for more than 7 consecutive days.	
Grade 3 or higher	No dose reduction or delay is permitted.	For any grade 3 AE or higher treatment-related AE, the patient must be withdrawn from treatment and should undergo BC surgery/pre-NAST biopsy.

* Excludes non-clinically significant and asymptomatic laboratory abnormalities.

^a In case of dose reduction, when AE returns to baseline or is resolved, dose escalation to 600 mg b.i.d. may be considered at the discretion of the Investigator.

5.5 Concomitant Medications and Procedures

Concomitant medications and procedures to be documented in patients' medical sources and collected in eCRF include any medication or therapeutic procedure (e.g. prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements, blood transfusions, etc.) used by a patient from 7 days prior to enrollment until the EoS visit.

Patients will be instructed to consult with the Investigator before taking any medications (including over-the-counter medications).

Supportive medications may be provided prophylactically or therapeutically per Investigator discretion.

Any concomitant treatment not listed in the section 5.5.2 is considered permitted in the study and may be prescribed as clinically appropriate during the study.

Concomitant therapies will be assessed at all visits and must be recorded on the appropriate eCRF according to the rules in section 6.5.4.

5.5.1 Precautions – Drug Interactions

- **Drugs metabolized via CYP3A4 enzyme:** Darolutamide may decrease the plasma concentrations of concomitantly given drugs which are mainly metabolized via CYP3A4 enzyme (e.g., simvastatin, verapamil, dronedarone). Although the clinical significance of this potential interaction is not fully known, the concomitant intake of these substances during study treatment should be avoided. In case patients must continue receiving them, they should be monitored for signs of decreased efficacy of these concomitant medications.

In vivo data from study 17726 indicates that co-administration of rifampicin -a strong CYP3A4 inducer- resulted in a significant decrease of darolutamide plasma concentrations. Therefore, repeated co-administration of strong or moderate CYP3A4 inducers (e.g. carbamazepine, phenobarbital, St. John's Wort) with darolutamide is expected to reduce darolutamide plasma concentrations. Thus, the concomitant intake of these substances during study treatment should also be avoided.

- **P-gp and BCRP inhibitors/substrates:** *In vitro* data indicate that darolutamide is a substrate of P-gp and BCRP. Therefore administration of strong inhibitors of P-gp (e.g. verapamil,

dronedarone) and BCRP (e.g., pantoprazole, eltrombopag) may increase the plasma concentrations of darolutamide and should be used with caution. Despite this fact, *in vivo* data from study 17726 showed that co-administration of darolutamide with itraconazole -a strong CYP3A4 and P-gp inhibitor- does not result in a clinically relevant increase of darolutamide plasma concentrations. In any case, caution is recommended.

Plasma concentration of drugs that are sensitive P-gp or BCRP substrates might be increased by darolutamide. Therefore sensitive substrates for P-gp (e.g., digoxin) should be used with caution when co-administered with darolutamide. Co-administration of darolutamide can also increase the plasma concentrations of other concomitant BCRP substrates (e.g. methotrexate, sulfasalazine, fluvastatin, atorvastatin). Therefore, the patients should be closely monitored for signs and symptoms of increased exposure to such BCRP substrates. Dose modification of BCRP substrates should be considered based on the prescriber information or such compounds should be avoided.

Refer to the section “Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers” of the FDA website for a list of potential interactions (as of the date of this protocol available at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm>

5.5.2 Prohibited Treatments and/or Procedures

Patients are prohibited from receiving the following therapies from the time of PICF signature until BC surgery/pre-NAST biopsy:

- Investigational agents other than the protocol treatment.
- Any additional standard or investigational anticancer agents, such as chemotherapy, immunotherapy, targeted/biologic therapy, endocrine therapy, etc., even if utilized as treatment of non-cancer indications. Darolutamide must be permanently discontinued upon initiation of a non-protocol standard or investigational antineoplastic therapy prior to BC surgery/pre-NAST biopsy.

5.5.3 Contraception

WoCBP must agree to use acceptable non-hormonal contraceptive methods of birth control from the day of the screening pregnancy test up to 3 months after the last intake of protocol treatment. Refer to section 4.1 for the definition of WoCBP.

Acceptable forms of contraception are:

(1) practice abstinence† from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity‡:

- Single method (one of the following is acceptable):
 - intrauterine device (IUD)
 - vasectomy of a female patient’s male partner¥
- Combination method (requires use of two of the following):
 - diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
 - cervical cap with spermicide (nulliparous women only)

- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the patient's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and Ethics Committees. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡ If a contraceptive method listed in this section is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for patients participating at sites in this country/region.

¥ Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WoCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

6. SCHEDULE OF VISITS AND PROCEDURES

6.1 Patient Inclusion

6.1.1 Informed Consent

A written, dated and signed and freely given informed consent must be obtained prior to any study-specific procedure.

Prior to any study-specific screening evaluation, the patient will be informed of the nature of the study and will be given pertinent information as to the intended purpose, possible benefits, and possible adverse experiences. The procedures and possible hazards to which the patient will be exposed will be explained.

An approved PICF will then be read and signed by the patient and, when required, a witness, and the Investigator or a person designated by the Investigator, as per local regulations. The patient will be provided with a copy of the signed PICF.

Patients with a suspicion of invasive BC based on clinical and/or radiological findings or those who have confirmation of invasive BC based on previous cytology/core/incisional biopsy deemed adequate candidate by the Investigator will be invited to participate in the study. In cases without pathological confirmation of BC diagnosis, signature of PICF before BC confirmation biopsy is an option to allow the collection of study-specific biopsies to be conducted at the same time as the diagnostic biopsy. For patients who have already had a confirmatory biopsy, they may participate in the study if their diagnostic biopsy has been done according to the protocol requirements. If their diagnostic biopsy has not been done according to the protocol requirement, they may also participate in the study if willing to undergo a subsequent study-specific biopsy procedure according to the protocol.

The patient may withdraw from the study at anytime without prejudicing future medical treatment. In any case, withdrawal should be documented on patient's clinical records.

If a potential patient is illiterate or visually impaired, the Investigator must provide an impartial witness to read the PICF to the patient and must allow for questions. Thereafter, the patient and the witness must sign the PICF to attest that informed consent was freely given and understood.

The PICF will include a statement by which the patient allows the Sponsor's duly authorized personnel, the EC/IRB, and the regulatory authorities to have direct access to her data that will be processed according to the confidentiality regulations.

If important new information becomes available that may be relevant to the patient's consent and willingness to continue participation in the study, the PICF will be revised and submitted to IRB/IEC and regulatory authorities (if applicable) for approval/favorable opinion. The new information will be then discussed with the patient in a timely manner and if she agrees to continue participation in the study, the revised PICF will be signed and dated and the patient will receive a copy.

In line with each local applicable regulations, the source should also support the documentation of the consent process, for each patient.

6.1.2 Registration and Enrollment

6.1.2.1 Registration and Enrollment Procedures

At time of PICF signature patients will be registered in the study and then will undergo screening procedures. After all screening procedures and confirmation of eligibility, patients will be enrolled.

The following steps for registering and enrolling a patient are chronologically performed:

1. The patient must provide written informed consent prior to performing any study-specific procedure not considered standard practice by the institution.
2. The site will ask TRIO for patient's registration immediately after signature of PICF. A unique registration number will be assigned to each patient in the study.
3. The site will proceed to perform the protocol-required biopsy and all screening procedures according to section 6.3. Upon completion of screening procedures, the Investigator or his/her delegate will check if the patient meets all eligibility criteria:
 - Patients who do not meet all eligibility criteria: sites will have the screen failure form completed in Remote Data Capture (RDC) with corresponding screen failure reason captured.
 - Patients who meet all eligibility criteria: sites will enter the screening data in RDC which will be reviewed centrally by TRIO. After the review of the eligibility criteria, TRIO may address, if necessary, some discrepancies that will have to be answered by the site. Once the eligibility central review is completed and discrepancies have been resolved (if applicable) TRIO will provide the confirmation that the patient is eligible and the site will be able to move forward with the patient's enrollment in RDC. The site will receive a confirmation of enrollment. If the patient is deemed not eligible following the central eligibility review, the site will be asked to report the screen failure reason in RDC.

6.1.2.2 Enrollment According to BC Subtype

To be able to assess the molecular alterations after darolutamide exposure in different BC subtypes, patients being either TNBC, or HR+/HER2-, or HER2+ will be enrolled in the study. Up to 20 patients with each of these subtypes will be included, with an acceptable minimum of 8 evaluable patients in each cohort if enrollment of recommended 20 patients is not feasible within a cohort for any reason.

Subtypes are defined based on local assessment as:

- TNBC: ER, PgR and HER2 negative
- HR+/HER2-: ER and/or PgR positive and HER2 negative
- HER2+: HER2 positive, irrespective of ER/PgR status

ER and PgR positivity is defined according to the American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations, as cases with $\geq 1\%$ of tumor cell nuclei that are immunoreactive.¹³

HER2 positivity is defined as IHC 3+ and/or ISH amplification. HER2 negativity is defined as IHC 0-1 and/or ISH non-amplification. In case HER2 status is Equivocal, patients will not be assigned to any cohort until central review is done and HER2 status is defined as either positive or negative.

Although patient inclusion in each of these three cohorts will be based on local testing, the central laboratory (TROL) will also test for ER, PgR and HER2. Assessment of distribution of patients with respect to centrally-assessed ER/PgR/HER2 will be done on an ongoing basis by the central laboratory and will also be performed by the Study Steering Committee (SSC) once the minimum requirement of patients in a cohort have undergone the EoS per protocol. This will allow the SSC to ascertain the rates of discordance between local and central testings and determine if more or less patients may be required in one or more cohort(s).

6.2 Study Participation Discontinuation

The Investigator has the right to discontinue a patient from protocol treatment or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue protocol treatment or withdraw from the study at any time for any reason.

6.2.1 Discontinuation from Protocol Treatment

Refer to section 5.3.3.

6.2.2 Discontinuation from Study Participation

The primary reason for study participation discontinuation should be documented on the eCRF. Reasons for patient's discontinuation from the study include (but may not be limited to):

- Patient is enrolled but does not receive protocol treatment for any reason
- Patient completes the study
- Death
- Consent withdrawal from entire study participation
- Patient non-compliance
- Lost to follow-up

Should a patient be enrolled, but has never started protocol treatment, she will be discontinued from the trial, and managed according to the site's SoC.

Should a patient decide to withdraw consent, all efforts will be made to complete and report the observations as thoroughly as possible. The Investigator should schedule a visit with the patient, or contact the patient by telephone to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study. After complete withdrawal of consent, no further study procedure is performed and no further data will be collected.

If a patient withdraws consent to the use of study-specific tumor samples:

- The Investigator has the responsibility to notify TRIO immediately.
- TRIO will ensure that the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are either returned to the study site, or disposed of/destroyed by the central laboratory as per site's request/local requirements, and the action documented by the central laboratory(ies).

In the event that analysis/research has already been performed, TRIO or its representatives, in strict compliance with the applicable local regulations, should retain the results and associated data for regulatory reasons but these will not be used in any subsequent analyses. In the case a patient does

not show up for study visits, site staff should make reasonable contact attempts before declaring the patient as lost to follow-up. These attempts need to be documented in the medical records.

6.3 Schedule of Procedures

All study visits and procedures are detailed in the table presented in this section. The detailed description of the study visits and assessments is in sections 6.4 and 6.5.

Table 2: Schedule of Procedures

Protocol Activities	Screening ¹	Treatment Period ²	Pre-surgery ³	BC surgery/pre-NAST biopsy	End of Study ⁴
Informed consent/Registration and Enrollment ⁵	X				
Demographics, medical, surgical, disease history	X				
Complete physical examination ⁶	X		X		
Symptom-directed physical examination		X			X
ECOG PS	X	X	X		X
Weight, height, blood pressure ⁷	X				
Serum pregnancy test	X ⁸				
Hematology, Blood chemistry ⁹	X		X		X
AEs assessments	X	X	X		X
Concomitant medication and therapeutic procedures ¹⁰	X	X	X		X
Treatment compliance assessment ¹¹		X	X		
Tumor sample ¹²	X			X	

Note: All assessments should be performed within 3 days of the scheduled visit, unless otherwise specified.

Footnotes:

1: Screening procedures (except PICF signature and screening tumor samples – see footnote 12) to be done within 28 days of enrollment, unless otherwise specified

2: Protocol treatment should begin within 5 days of enrollment and no more than 42 days after breast tissue collection. Treatment should last at least 14 days, and no more than 35 days (recommended maximum duration 21 days). The need for a clinic visit during this period will depend on the duration of protocol treatment. If duration of treatment with ODM-201 is 14 to 21 days only the Pre-surgery visit needs to be performed after Day 1, unless otherwise clinically indicated. If ODM-201 is taken/expected to be taken for > 21 days (due to planned date of surgery/pre-NAST biopsy, delay in surgery/pre-NAST biopsy, etc.) a visit is required as close as possible to Day 21 +/- 3 days (except in case the pre-surgery visit is planned within Day 21 + / - 3 days).

3: The Pre-surgery visit should be performed the day before BC surgery or the day before BC pre-NAST biopsy is performed. The only exceptions should be:

(a) If for some reason the patient is ordered to stop all oral intakes earlier than the day prior to BC surgery/pre-NAST biopsy, the Pre-surgery visit should be scheduled on the day patient is ordered to stop oral intake; (b) In case the BC surgery/pre-NAST biopsy is planned for a Monday or the day following a holiday; in such cases the Pre-surgery visit should be done on a working day as close as possible to the BC surgery/pre-NAST biopsy (e.g. on a Friday if surgery is scheduled on Monday); or (c) In case that performing Pre-surgery visit on the same day of BC surgery/pre-NAST biopsy is required by site due to logistical reasons or patient's/physician's convenience. Refer to section 6.4.3 for further guidance about the Pre-surgery visit planning and procedures.

4: End of Study visit must be scheduled 30 days (+/- 3 days) after the last intake of darolutamide, even for patients who did not complete the minimum 14 days of protocol treatment. The EoS will be the last study visit for patients. However, for patients experiencing protocol treatment-related AEs/SAEs that are ongoing at the time of the EoS visit, monitoring of these events will continue as clinically indicated until (a) the events have resolved or (b) the events have reached a status which, in the Investigator's opinion, is unlikely to resolve due to the nature of the condition and/or the patient's underlying disease. Frequency of visits will be according to Investigator's judgment.

5: There is no window to obtain the signed and dated PICF. Study-specific screening assessments not considered standard practice by the institution must start only once the PICF has been obtained. Registration takes place as soon as the patient signs the PICF. After screening procedures and if patient meets all eligibility criteria, enrollment will be done according to the process described in section 6.1.2.

6: Complete physical examination will include a complete assessment of body systems (i.e., general appearance, head, eyes, ears, nose, mouth, skin, heart, lungs, lymph nodes, gastrointestinal, genitourinary, skeletal, and neurologic). A complete examination of the breast and regional lymph nodes will also be done.

7: Weight, height and blood pressure must be assessed and collected during screening. Afterwards they will be assessed (as well as other vital signs) according to the SoC.

8: Within 7 days of enrollment, only in WoCBP.

9: Hematology: Hemoglobin, WBC, ANC, platelets. Blood chemistry: AST, ALT, total bilirubin, creatinine.

10: Concomitant medication and procedures include any medication or therapeutic procedure used by the patient within 7 days prior to enrollment until the EoS visit. Refer to section 6.5.4 for the reporting rules in the eCRF.

11: All unused drugs (partially used and empty containers) and the patient diary will be handed over to Investigators at each treatment visit (if any) and at the Pre-surgery visit.

12: Mandatory tissue collection:

- Pre-treatment: A breast tumor sample must be collected at the time of the initial diagnosis (or in a subsequent procedure) either by core needle or incisional biopsy. Excisional biopsy will not be allowed. A minimum of 3 core biopsies using a 14-gauge needle (or the equivalent with an incisional biopsy) is recommended (2 fresh-frozen + 1 paraffin-embedded). In cases it is not possible to provide enough material, collection of 2 cores (or equivalent amount with incisional biopsy) will be acceptable: one core will be snap-frozen and the other one will be prepared in paraffin. For patients who already had such confirmatory biopsy prior to registration, there is no need to repeat it provided that their diagnostic biopsy has been done according to the protocol requirements (in terms of number of cores/tissue, fresh frozen collection, etc.). The screening tumor samples must be collected before start of treatment with darolutamide at the latest.

- BC surgery/pre-NAST biopsy: Two cores (or equivalent amount) of breast tumor tissue must be collected at the time of the patient's surgery or before starting NAST if indicated (1 fresh-frozen + 1 paraffin-embedded).

6.4 Study Visits and Assessments/Investigations

During all visits below, assessments should be done according to the Schedule of Procedures (section 6.3).

6.4.1 Screening Period

The screening period starts with the registration (at time of PICF signature) and ends when the patient is enrolled (following eligibility central review and confirmation by TRIO) or screen failed. When scheduling the screening procedures it should be taken into account that treatment with darolutamide should start within 42 days of the study-specific tumor sample collection.

During the screening period the following assessments will be done:

- Demographics, medical, surgical, disease history
- Complete physical examination (including weight, height and blood pressure measurements)
- ECOG PS
- Serum pregnancy test: only in WoCBP, within 7 days of enrollment (refer to section 4.1 for the definition of WoCBP).
- Laboratory assessments:
 - Hematology: Hemoglobin, WBC, ANC and platelets
 - Blood chemistry: AST, ALT, total bilirubin and creatinine
- Adverse events assessment. For information on the assessment and collection of AEs refer to section 7 and to section 6.3
- Concomitant medications
- Tumor biopsy (refer to section 6.5.7)

Once all screening assessments have been conducted, the site will request enrollment of patients who meet all eligibility criteria through completion of all screening data in RDC (see section 6.1.2.1), and TRIO will review patient's eligibility. No enrollment must take place before formal confirmation of eligibility is provided by TRIO to the site.

Once the patient is enrolled, she will be instructed to begin protocol treatment with darolutamide. If for some reason the patient does not start their study treatment, she will be discontinued from study, and managed as per site's SoC.

If for some reason laboratory tests are repeated between these tests done at screening and treatment start, the most recent measurement obtained prior to treatment start must be within the required values according to the inclusion criteria, to begin protocol treatment.

6.4.2 Treatment Period Visits

Refer to section 5.3.2.1 for timelines regarding protocol treatment.

The need for a clinic visit during this period will depend on the duration of protocol treatment.

If duration of treatment with ODM-201 is 14 to 21 days, only the Pre-surgery visit needs to be performed after Day 1, unless otherwise clinically indicated.

If ODM-201 is taken/expected to be taken for > 21 days (due to planned date of BC surgery/pre-NAST biopsy, delay in BC surgery/pre-NAST biopsy, etc.) a visit is required as close as possible to Day 21 +/- 3 days (except in case the pre-surgery visit is planned within Day 21 + / - 3 days).

During the treatment period visit(s) (if any) the following will be assessed:

- Symptom-directed physical examination
- ECOG PS
- AEs
- Concomitant medication

6.4.3 Pre-surgery Visit

As a general rule, the Pre-surgery visit will be performed the day before BC surgery or the day before pre-NAST biopsy if NAST is indicated.* If after the Pre-surgery visit takes place, the BC surgery/pre-NAST biopsy planned for the following day is delayed for any reason, the Investigator should contact the Medical Monitor to discuss about potential continuation of darolutamide after the Pre-surgery visit.

During this visit the following assessments will be done:

- Complete physical examination
- ECOG PS
- Safety laboratory assessments:
 - Hematology: Hemoglobin, WBC, ANC and platelets
 - Blood chemistry: AST, ALT, total bilirubin and creatinine
- AEs
- Concomitant medication

Other pre-surgical assessments should be done according to the standard of care (SoC) at the site.

The only exceptions to scheduling the Pre-surgery visit on the day prior to BC surgery/pre-NAST biopsy will be in the following cases:

- a. If the patient is ordered to stop all oral intakes earlier than the day prior to BC surgery/pre-NAST biopsy. In such case the Pre-surgery visit should be scheduled on the day patient is ordered to stop oral intake and all test/assessments should be done at that point.
- b. In case the BC surgery/pre-NAST biopsy is planned for a Monday or the day following a holiday and the Pre-surgery visit cannot be scheduled the day prior to BC surgery/pre-NAST biopsy. In such case the following will be done:
 - The Pre-surgery visit should be done on a working day as close as possible to the BC surgery/pre-NAST biopsy (e.g. on a Friday if surgery is scheduled on Monday).
 - The patient will be instructed to continue with darolutamide intakes until the day prior to BC surgery/pre-NAST biopsy or when she is instructed to stop all oral intakes, whichever occurs first.

- c. In case that performing Pre-surgery visit on the same day of BC surgery/pre-NAST biopsy is required by site due to logistical reasons or patient's/physician's convenience. In such case, it is acceptable that Pre-surgery visit is performed on the same day that BC surgery/pre-NAST biopsy takes place, but before any of those procedures are performed. The results from the laboratory safety tests must be available and reviewed by the Investigator before the BC surgery takes place.

**Note: Should they coincide, it is acceptable for the Pre-surgery visit to take place on the day of a treatment period visit (if any). In such cases, assessments should be done according to the Pre-surgery visit requirements.*

6.4.4 BC Surgery/Pre-NAST biopsy

Surgery will be done according to site standards. In patients not receiving NAST, BC tissue will be collected at time of surgery according to section 6.5.7. In patients receiving NAST, a breast tumor sample will be collected during the pre-NAST biopsy (refer to section 6.5.7) after completing darolutamide and before NAST start. As much as possible, sites should avoid scheduling BC surgery/pre-NAST biopsy on Mondays or on the day following a holiday, so that Pre-surgery visit may take place the day prior to BC surgery/pre-NAST biopsy according to section 6.4.3.

In the event that a sentinel lymph node biopsy (SLNB) is performed, periareolar injection is to be conducted. The dye/colloid should not be injected into the tumor itself as this may alter the tissue and affect the molecular analyses to be performed on tumor tissue sample.

6.4.5 End of Study Visit

EoS visit must be scheduled 30 days (+/- 3 days) after the last intake of darolutamide, even for patients who did not complete the minimum 14 days of protocol treatment.

The primary purpose of this visit is to follow-up any AEs/laboratory abnormality ongoing at the time of protocol treatment discontinuation and to assess any new AEs/abnormality that may have occurred since protocol treatment discontinuation. Symptom-directed physical examination, ECOG PS assessment and hematology/blood chemistry should be done at this visit. All AEs will be collected (even if due to neoadjuvant treatment, surgery or adjuvant treatment, regardless of the relationship to darolutamide), as well as relevant concomitant treatment according to rules in section 6.5.4.

EoS will be the last study visit with the exception of patients with protocol treatment-related AEs/SAEs that are ongoing at the time of the EoS visit. In these cases, monitoring of these events will continue as clinically indicated until (a) the events have resolved or (b) the events have reached a status which, in the Investigator's opinion, is unlikely to resolve due to the nature of the condition and/or the patient's underlying disease. Frequency of visits will be according to Investigator's judgment.

6.4.6 Unscheduled Visit Procedures

Unscheduled visits may be performed any time to assess or follow AEs, to perform any clinically-indicated investigation, or at the request of the patient or Investigator.

6.5 Description of Assessments/Investigations

6.5.1 Demographics and Medical History

The Investigator will collect and report in the eCRF demographics and complete history of malignant and clinically-significant non-malignant diseases including known hypersensitivity reactions as well as clinically-significant symptoms.

6.5.2 Physical Examination and Vital Signs

At screening and at the Pre-surgery visit, physical examinations will include a complete assessment of body systems (i.e., general appearance, head, eyes, ears, nose, mouth, skin, heart, lungs, lymph nodes, gastrointestinal, genitourinary, skeletal, and neurologic) per SoC at the study site or as clinically indicated by symptoms. As well, a complete examination of the breast and regional lymph nodes will be done. Weight, height and blood pressure will also be measured at screening, and thereafter according to SoC.

During protocol treatment and EoS visits, a symptom-directed physical examination will be done.

6.5.3 ECOG Performance Status

Assessment of ECOG PS (Appendix 1) is required to assess patient's functional status for study eligibility purposes and will be performed throughout the study according to the section 6.3.

6.5.4 Adverse Events and Concomitant Treatments Assessment

- Adverse events assessment: For information on the assessment and collection of AEs refer to section 7 and to section 6.3.
- Concomitant Treatments: Concomitant treatment includes any medication or therapeutic procedure (e.g. prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements, blood transfusions, etc.) used by a patient from 7 days prior to enrollment until EoS. The concomitant treatments to be collected and reported in the eCRF are:
 - Any treatment used by the patient within 7 days prior to enrollment
 - After enrollment, only if:
 - Medication is given to treat an AE
 - Medication is listed in sections 5.5.1 or 5.5.2

6.5.5 Laboratory Assessments

At screening:

- Hematology: Hemoglobin, WBC, ANC and platelets
- Blood chemistry: AST, ALT, total bilirubin and creatinine
- Serum pregnancy test: within 7 days of enrollment, only in WoCBP

At the Pre-surgery and EoS visits:

- Hematology: Hemoglobin, WBC, ANC and platelets
- Blood chemistry: AST, ALT, total bilirubin and creatinine

6.5.6 Assessment of Efficacy

No efficacy assessments are planned in this study. With the exception of the examination of breast and regional lymph nodes according to section 6.5.2, disease assessments will be conducted according to the SoC at the study site.

6.5.7 Tumor Tissue Collection and Molecular Evaluation

All tumor samples will be submitted to the study Central Laboratory and will be stored for up to 20 years, unless otherwise required per local regulations, Investigator, IRB/IEC and/or the patient.

Full details on the analyses to be performed on the biologic samples and procedures for sample collection, labeling, storage and shipment/return of biological samples will be described in separate document(s) (e.g. Laboratory Manual, Samples Plan).

6.5.7.1 Breast Tumor Tissue Collection

Collection of the following samples is mandatory in the study:

- **Pre-treatment:** A breast tumor sample must be collected at the time of the initial diagnosis (or in a subsequent procedure) either by core needle or incisional biopsy. Excisional biopsy will not be allowed.

A minimum of 3 core biopsies using a 14-gauge needle (or the equivalent with an incisional biopsy) is recommended to perform the protocol-defined molecular analyses. Once the core biopsies have been removed, two of the cores (or equivalent amount of tumor) must be immediately snap-frozen using the procedure outlined in the study laboratory manual, then stored in liquid nitrogen or at -70 to -80 degrees Celsius at the site. The third sample should be prepared in paraffin according to site's practice. In cases it is not possible to provide enough material, collection of 2 cores (or equivalent amount with incisional biopsy) will be acceptable: one core will be snap-frozen and the other one will be prepared in paraffin.

In patients with multifocal or multicentric tumors, efforts will be made to obtain samples from each discrete lesion.

For patients who already had the confirmatory biopsy prior to registration, there is no need to repeat it provided that their diagnostic biopsy has been done according to the protocol requirements (in terms of number of cores/tissue, fresh frozen collection, etc.).

- **BC surgery/Pre-NAST biopsy:** An amount of BC tissue equivalent to two cores (or 2 cores of tissue) must be collected at the time of the patient's surgery (if no NAST indicated) or at time of the pre-NAST biopsy (if NAST is indicated). The pre-NAST biopsy should be done before NAST start. Half of the tissue will be prepared as fresh-frozen, the other half in paraffin.

6.5.7.2 Molecular Evaluation

The primary endpoint of the study is to explore and define the molecular alterations that may occur following darolutamide administration through comparisons of BC tissue before and after short-term exposure to darolutamide.

At least, the following markers will be assessed on the collected samples. In all experiments, appropriate positive and negative controls will be included.

- AR
- ER
- PgR
- HER2
- ki67
- Cytokeratins 5 and 6

Tissue microarrays will be developed from all tumor specimens. Other *in situ* assays for activated downstream signaling molecules will be performed using tissue sections and/or tissue microarrays. Promising candidate genes obtained from the microarray analysis will be validated using the frozen

tissue arrays generated above and using appropriate probes (i.e. antibodies, if available, or nucleic acid probes).

Additional assays in example but not limited to Reverse Phase Protein Analysis (RPPA), sequenciation of the RNA, immunohistochemistry (IHC) etc. may be performed based on the molecular analysis finding and/or in the future as new technology and data become available.

6.5.8 Other Procedures/Assessments

In addition to the protocol-required assessments, the Investigator may perform any clinically indicated test and procedure according to SoC (e.g. coagulation test prior to surgery, etc.) although these will not be collected in the eCRF.

7. SAFETY MONITORING

7.1 Definitions

7.1.1 Period of Observation

At each visit and any contact during the study and follow-up period, the Investigator or designee will inquire about the occurrence of AEs (and corresponding medications administered) and will document them in the eCRF.

For the purposes of this study, the period of observation for SAEs and AEs extends from the time the patient signs the PICF until the EOS, except for patients that are experiencing AEs or SAEs related to darolutamide ongoing at the time of EoS visit. In such cases, these events will be monitored beyond the EoS visit as clinically indicated until (a) the events have resolved or (b) the events have reached a status which, in the Investigator's opinion, is unlikely to resolve due to the nature of the condition and/or the patient's underlying disease.

The Investigator or designee will report the AEs/SAEs in the eCRF (and, if applicable, to TRIO Safety Department) when required as per the table below:

Table 3: Reporting Period of AEs/SAEs

Study period	AEs (non-serious)	SAEs
From PICF to 1 st intake	Only if related to study participation	All (regardless of relationship)
From 1 st intake until EoS visit	All (regardless of relationship)	All (regardless of relationship)
After the EoS visit	Only if related to protocol treatment	Only if related to protocol treatment

7.1.2 Adverse Event

An AE is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Worsening of pre-existing conditions: any pre-existing condition present at baseline, which remains unchanged during the trial, does not need to be recorded as an AE.

Any worsening of any pre-existing baseline condition should be reported as an AE in the eCRF. Examples of worsening of a preexisting condition that should be recorded as an AE are given below:

- Worsening of condition meets the criteria for an AE or SAE
- Action is taken with the investigational drug (e.g. dose is reduced or treatment is discontinued)
- Treatment is required (concomitant medication is added or changed)
- The Investigator believes a patient has shown a clear deterioration from baseline symptoms

Expected fluctuations or expected deterioration of the BC (symptoms of disease progression) should not be recorded as an AE.

Changes in vital signs, physical examination and laboratory test results: these will only be recorded as an AE in the eCRF if they are judged clinically relevant by the Investigator or led to protocol treatment modifications (dose delay or dose reduction).

Surgical procedures: these are not AEs *per se*; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not AEs.

Worsening of a sign or symptom of the condition under treatment: these situations (i.e. BC) should not be recorded as AEs.

7.1.3 Serious Adverse Events

A SAE is one that at any dose:

- Results in death
- Is life-threatening¹
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity²
- Is a congenital anomaly or birth defect
- Is an important medical event³

¹ “Life-threatening” means that the patient was at immediate risk of death at the time of the SAE; it does not refer to a SAE that hypothetically might have caused death if it were more severe.

² “Persistent or significant disability or incapacity” means that there is a substantial disruption of a person’s ability to carry out normal life functions.

³ Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, the development of drug dependency or drug abuse, etc.

7.1.3.1 Disease-related Events

An event that is part of the natural course of the disease under study (i.e. breast cancer) does not need to be reported as an SAE.

However, if the Investigator considers that there was a causal relationship between treatment with investigational product or protocol design/procedures and a disease progression, then this must be reported as an SAE. Any new primary cancer must be reported as an SAE.

7.1.3.2 Planned or Administrative Hospitalization

Patients may be hospitalized for administrative or social reasons during the trial (e.g. long distance from home to site, etc). These and other hospitalizations planned up to enrollment do not need to be reported as an SAE but should be properly documented in the source data.

7.1.4 Unexpected Adverse Event

The Darolutamide IB provides an overview of the AEs reported across each clinical trial.

Any SAE assessed as related to darolutamide but not presented in the IB section 8.6 Undesirable effects will be documented by TRIO as a suspected unexpected serious adverse reaction (SUSAR) and will be submitted according to applicable local regulations.

7.2 Performing Adverse Event Assessment

7.2.1 Collection of Adverse Event Information

The following information will be collected in the eCRF: Description of event (a single medical condition and not a collection of signs/symptoms), start/stop dates, worst grade experienced (severity/intensity), seriousness, action taken on protocol treatment and relationship to protocol treatment.

Intensity of AE: The intensity of AEs will be classified and recorded according to the NCI CTCAE version 4.03 in the eCRF, or according to the grading defined in section 5.4.1 if the AE is not specifically listed in NCI CTCAE.

All adverse clinical experiences, whether observed by the Investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug (refer to section 5.4.2 for recommendations on dose modifications), and the patient's outcome. The Investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The Investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the Investigator must provide details about the action taken with respect to the protocol treatments and about the patient's outcome.

7.2.2 Assessment of Causality

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship must be recorded for each adverse event.

Relationship to study drugs will be reported as either "Yes" or "No".

- Yes: there is a reasonable causal relationship between the IMP administered and the AE.
- No: there is no reasonable causal relationship between the IMP administered and the AE.

7.3 Reporting of Serious Adverse Events and Pregnancies

7.3.1 Reporting of Serious Adverse Events and Pregnancies from the sites to TRIO

SAEs and pregnancies will be reported within 24 hours of awareness by completing and emailing or faxing the SAE Reporting Form to TRIO Drug Safety Unit.

TRIO Drug Safety Unit contact information:

- Email: safety@trioncology.org
- Fax number: +1 780-702-2273

Table 4: SAE and Pregnancies Reporting Timelines

Type of Event	Initial Reports		Follow-up Information	
	Time Frame	Documents	Time Frame	Documents
All SAEs	Within 24 h of awareness	SAE reporting form	Within 24 h of awareness	SAE reporting form
Pregnancy	Within 24 h of awareness	Pregnancy reporting form	Within 24 h of awareness	Pregnancy reporting form

7.3.2 SAE information Provided by TRIO to the Manufacturer

TRIO will report all SAEs and pregnancies as well as follow up information for these events to Bayer by email or other secure method within 24 hours of awareness.

7.4 Management of Specific Cases

7.4.1 Medication Errors

In the event of a medication error, the patient should be observed closely for signs of toxicity. Medication errors include the accidental or intentional use of darolutamide in a daily dose greater than the protocol-specified daily dose. Appropriate supportive treatment should be provided if clinically indicated. In case of toxicity derived from the medication error, dose modification recommendations from section 5.4.2 should be followed.

The highest darolutamide dose administered in clinical trials is 1,800 mg daily, with no maximum tolerated dose achieved and no dose-limiting toxicity experienced by patients.

If an AE is associated with (“results from”) a medication error, the corresponding AE should be reported as SAE, even if no other seriousness criteria are met.

In cases of a medication error without any associated AE, the medication error should be reported as a non-serious AE, using terminology like “accidental or intentional overdose without adverse effect”, “medication error without adverse effect” or similar.

7.4.2 Pregnancy

Should a pregnancy occur, the Investigator must discontinue treatment immediately, capture any drug exposure during pregnancy, report the pregnancy through the Pregnancy Reporting Form and follow the pregnancy until outcome is known. Information related to outcome of the pregnancy, delivery, postpartum recovery and the clinical condition of the offspring during the neonatal period must also be collected.

Pregnancy is not automatically considered as a SAE, however, it must be reported following SAE timeline as detailed in section 7.3.

A SAE report must be forwarded to the TRIO if the outcome of the pregnancy results in an abortion/miscarriage or the occurrence of any other SAE(s).

7.5 Reporting to Ethics Committees, Regulatory Authorities and other Investigators

Prompt notification of SAEs by the Investigator to TRIO is essential so that legal obligations and ethical responsibilities towards the safety of patients are met.

TRIO will comply with local regulatory requirements relating to safety reporting to the regulatory authorities, IRB/IEC and Investigators.

TRIO will report SAEs and related safety information to the FDA as per the definitions and recommendations in 21 CFR 312 and per the FDA guidance for Industry and Investigators (available at <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM227351.pdf>).

Investigator safety reports are prepared for SUSARs according to local regulatory requirements and are forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from TRIO will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8. STATISTICAL CONSIDERATIONS

8.1 Study Populations

- Intention-to-treat (ITT) Population: The ITT population includes all patients who are enrolled in the study regardless of whether they have been treated or not.
- Safety Population: The Safety population includes all patients who have taken at least one tablet of darolutamide.
- Evaluable population: Includes all patients who satisfied all criteria in section 8.5.

8.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics data will be listed and summarized by each BC subtype using the ITT population.

8.3 Protocol Treatment

Duration of treatment, duration of exposure, cumulative dose and relative dose intensity will be summarized by each BC subtype using the Safety population. The patients with dose modifications will also be presented, along with reasons for the dose change.

8.4 Safety Evaluation

The assessment of safety will be made on the Safety population and will be based mainly on the frequency of AEs. The latest version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs to a preferred term and system organ class. AEs will be graded using the NCI CTCAE v4.03 or according to the applicable grading if the AE is not specifically listed in NCI CTCAE. Patient's incidence of AEs will be tabulated by system organ class, preferred term and toxicity grade for each BC subtype. AEs leading to death or drug discontinuation, drug related and SAEs will also be summarized.

Detailed listings for all AEs will also be provided.

Laboratory parameters: these will be summarized at baseline, along visits and at the EoS visit by each BC subtype, graded according to the NCI CTCAE v4.03. Tables of shifts in toxicity will also be provided.

Other Safety Data: ECOG will be summarized at baseline, along visits and at the EoS visit by BC subtype. Tables of shifts in toxicity will also be provided when applicable.

8.5 Sample Size

The primary objective of this trial is to evaluate molecular alterations occurring in BC tissue following short-term darolutamide administration.

Up to 60 patients (minimum of 8 but up to 20 patients in each BC subtype: triple-negative, HR+/HER2 negative, HER2 positive) will be required for the performance of the molecular studies and possible hypothesis generation.

A patient will be considered evaluable if the following criteria are met:

- Minimum duration of treatment with darolutamide is of 14 days, with a minimum of 10 consecutive days of treatment prior to the definitive BC surgery/pre-NAST biopsy.
- Mandatory tumor tissue is collected at screening and at BC surgery/pre-NAST biopsy according to the protocol and submitted to the central laboratory.
- Adequacy for molecular assessment of the tumor tissue collected before and after the protocol treatment initiation. The adequacy will be evaluated by the central laboratory.

Assessment of patient evaliability, safety and distribution of patients with respect to hormone receptor status and HER2 status will be performed by the SSC at given time points depending on the recruitment, for example once 20, around 35 and once all patients have been enrolled and undergone the EoS per protocol. This will allow SSC to ascertain that the appropriate number of evaluable patients is being accrued, that more or less patients may be required, or in the extreme case, that accrual should close if the patient evaliability rate is very low and/or safety concerns arise.

The SSC will define the evaliability of patients that discontinue treatment more than 3 days before BC surgery/pre-NAST biopsy; molecular analyses may be taken into consideration for the decision about the evaliability of such patients.

8.6 Molecular Analyses

The molecular analyses will be performed on the evaluable population. Descriptive statistics will be used to compare the pre-and post molecular findings.

A correlation analysis between the molecular alterations from the baseline tumor samples and the sample collected following administration of darolutamide, during the definitive BC surgery/pre-NAST biopsy will be conducted.

9. ADMINISTRATIVE, ETHICAL AND REGULATORY STANDARDS

9.1 Steering Committee

The SSC of the trial will be composed of the study Chair(s) and representatives from TRIO. The SSC will include also a number of study principal Investigators. Other members may be added after consultation with the SSC members. The SSC will be constituted prior to the enrollment of the first patient.

The SSC will have the sole responsibility for the scientific conduct and integrity of the trial. Responsibilities include development and approval of the protocol document, monitoring of accrual, compliance and safety during the conduct of the trial. The SSC will be solely responsible for the analysis, interpretation and public disclosure of the results of the trial in accordance with the statistical plan. The SSC should endeavor to ensure that the study is conducted at all times to the standards set out in Guidelines for Good Clinical Practice (GCP). In all of the deliberations of the SSC, the rights, safety and well being of the study participants are the most important considerations.

9.2 Ethical Conduct of the Study

This clinical study was designed and shall be implemented and reported in accordance with the clinical trial protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, applicable local regulations (including European Directives 2001/20/EC and 2005/28/EC and the US Code of Federal Regulations Title 21), the Council for International Organizations of Medical Sciences (CIOMS), and the ethical principles laid down in the Declaration of Helsinki. This study will be conducted under ethical, scientific and medical standards that protect the rights and welfare of participants.

9.3 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate IEC or IRB. The IEC/IRB decision concerning the conduct of the study will be made in writing and kept with the Investigator study file. A copy of this decision will also be provided to TRIO.

Particular attention is drawn to the Food and Drug Administration (FDA's requirements for IRBs under 21 CFR Part 56). By signing the "Statement of Investigator" form (Form FDA 1572), the Investigator provides TRIO with the necessary assurance that an IRB is responsible for the initial/continuing review and subsequent approval of the proposed clinical study in accordance with these regulations when applicable.

The Investigator will agree to make required progress reports to the IEC/IRB, as well as report any SAEs, life-threatening problems or deaths if applicable per local regulations. The IEC/IRB will be informed of SAEs in other clinical studies conducted with the study drug by the Investigator or the Sponsor according to the local regulations. The IEC/IRB must be informed by the Investigator of the termination of the study.

9.4 Compliance with the Protocol and Protocol Amendments

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the Investigator contact TRIO or its agents monitoring the trial, if any, to request approval of a protocol deviation, as no such authorized deviations are permitted.

If the Investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by TRIO and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the Clinical Study Report (CSR).

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by TRIO, and approved by the Ethics Committee/IRB and Health Authorities where required, prior to implementation. Only amendments that are required to eliminate an immediate hazard to patients for patient safety can

be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the Investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, TRIO should be notified of this action and the IRB/IEC at the study site should be informed.

9.5 Monitoring, Auditing and Inspecting

TRIO or its representatives must be allowed to visit all study site locations periodically to assess the data, quality, and study integrity. On site, they will notably review study records and directly compare them with source documents, review regulatory documents, discuss the conduct of the study with the Investigator, verify study drug accountability, and verify that the facilities remain acceptable.

9.6 Recording, Processing and Retention of Data

The Investigator is responsible for the preparation and maintenance of adequate case histories designed to record all observations and other relevant data. All patient data reported on the eCRF must be derived from source documents and as such be consistent with the source documents, or the discrepancies must be explained.

Data will be entered and collected via an electronic data capture system using eCRFs. RDC is a validated system designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). Study site staff will receive training and have access to a manual for appropriate eCRF completion. All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the Investigator or authorized designee. Only identified and trained users may view the data as their actions become part of the audit trial.

While study sites will be responsible for data entry, TRIO will be responsible for data management of this study, including quality checks.

The eCRF must be completed within 7 calendar days of data availability. All requested information must be entered on the eCRF. If an item is not available or is not applicable, it must be documented as such. The completed eCRF must be reviewed and approved by the Investigator or authorized designee. In the event of discrepant data, TRIO will request data clarification from the sites. The sites will resolve the discrepancy electronically in the RDC system. eCRF and data clarification documentation will be maintained in the RDC system's audit trail.

At the end of the study, the Investigator will receive patient data, for their site, in a readable format on CD, DVD, or other similar storage format that must be kept with the study records. Acknowledgement of receipt of the storage disc or similar is required.

The Investigator should retain the study documentation according to ICH-GCP, local regulations or as indicated in the contractual agreement whichever is longer.

9.7 Data Protection

Patient confidentiality is strictly held in trust by the participating Investigators, their staff, TRIO or affiliates. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participating patients.

Patient and Investigator personal data which may be included in the study database shall be treated in compliance with all applicable laws and regulations.

When archiving or processing personal data, TRIO shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval by TRIO.

The study monitor or TRIO's other authorized representatives will verify documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the patients in this study. The clinical study site will permit access to such records.

9.8 Confidentiality and Data Protection

All information concerning the study supplied by TRIO, in connection with this study and/or by any other party collaborating with TRIO, and not previously published, is considered confidential and proprietary information. This information includes but is not limited to the IB, clinical protocol, workbooks (if applicable), eCRFs, assay methods, TRIO technical methodology, and other technical and scientific data. This confidential information shall remain the sole property of TRIO and shall not be disclosed to others without prior written consent from TRIO. Information shall not be used except in the performance of this study.

9.9 Insurance of Liabilities

If required, the Investigator may forward to the IEC/IRB a copy of the insurance document required by TRIO, in order to cover his/her liabilities, and those of any other participating parties.

9.10 Use of Information and Publication

All information concerning the study drug or in connection with this study, supplied by TRIO and/or by any other party collaborating with TRIO within this study, and not previously published, is considered confidential and proprietary information. This information includes, but is not limited to, the IB, clinical protocol, workbooks (if applicable), eCRFs, assay methods, TRIO technical methodology, and basic scientific data. This confidential information shall remain the sole property of TRIO, the respective collaborating party, and shall not be disclosed to others without prior written consent from TRIO. Information shall not be used except in the performance of this study.

To allow for the use of the information derived from this clinical study and to ensure compliance to current regulations, the Investigator is obliged to provide TRIO with complete test results and all data developed in this study. No publication, abstract or presentation of the study will be made without the approval of the SSC. The SSC will review the manuscript to prevent forfeiture of patent rights to data not in the public domain. Prior to publication, the authorship list will be agreed upon by the SSC. For the purpose of analyses, the names on the author list will be given according to the participation in the concept of the study design as well as accrual input (number of eligible patients accrued) by the Investigators at each center. The maximum number of authors will be determined by the publication policy established by the targeted journal. Abstracts and publications will be submitted to the authors and to the SSC at least 30 days prior to the expected date of submission to the intended publisher.

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11. APPENDICES

Appendix 1: Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light and sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Appendix 2: Patient Diary Template

See next page. The remainder of this page is intentionally left blank.

Site Staff Instructions

Record the Patient ID.

Minimum duration of treatment with ODM-201 is 14 days, with a recommended maximum duration of 21 days. Treatment must not last more than 35 days.

Record in the below table, the calendar dates (dd/mmm/yyyy, Morning or Evening) corresponding to the initial treatment period with ODM-201 1200 mg per day (Sequence 1).

For grade 1-2 treatment-related AEs only: should any treatment interruption / dose modification take place (to be agreed on with TRIO Medical Monitor), please record in the subsequent row (Sequence 2) the treatment start / stop dates and treatment dose to be taken by the patient. Note: for grade ≥ 3 treatment-related AEs, treatment should be permanently discontinued.

Depending on the day / time when the patient is provided with the ODM-201 bottle, treatment may start with either a Morning or an Evening intake.

The last ODM-201 intake will be on the day prior to breast cancer surgery or before starting neoadjuvant treatment if indicated, in the morning of the Pre-surgery visit (except if the patient is ordered to stop oral intake earlier – please refer to protocol section 6.4.3 “Pre-surgery visit” for guidance).

Please refer to protocol sections 5.3 and 5.4.2 for more details.

Date of ODM-201 bottle dispensation: ____ / ____ / ____

(dd/mmm/yyyy)

Seq.	Treatment Period	Daily Dose	Study Treatment container
1	<p>From: _____ / _____ / _____ (dd/mmm/yyyy)</p> <p>To: _____ / _____ / _____ (dd/mmm/yyyy)</p>	<p><input type="checkbox"/> Morning <input type="checkbox"/> Evening</p> <p><input type="checkbox"/> Morning <input type="checkbox"/> Evening</p> <p>1200 mg 2 tablets twice a day (with food, at breakfast and dinner)</p>	<p>Bottle (containing 140 tablets of ODM-201 300 mg)</p>
2	<p>From: _____ / _____ / _____ (dd/mmm/yyyy)</p> <p>To: _____ / _____ / _____ (dd/mmm/yyyy)</p>	<p><input type="checkbox"/> Morning <input type="checkbox"/> Evening</p> <p><input type="checkbox"/> Morning <input type="checkbox"/> Evening</p> <p>1200 mg 2 tablets twice a day (with food, at breakfast and dinner)</p> <p>Or</p> <p><input type="checkbox"/> 600 mg</p> <p>1 tablet twice a day (with food, at breakfast and dinner)</p>	

Date of Pre-surgery visit: ____ / ____ / ____

–

(dd/mmm/yyyy)

Date of surgery: ____ / ____ / ____

(dd/mmm/yyyy)

Patient Instructions:

- **Swallow the ODM-201 whole tablets with water and do not chew them prior to swallowing.**
- **Take the tablets together with food if possible at approximately the same time twice a day (for example, with breakfast and dinner each day).**
- **Your study doctor may decide to reduce or hold your study treatment. Please follow his/her instructions carefully.**
- **If you miss an intake or vomit following ODM-201 intake, you should skip the missed/vomited intake and you should take the next one as scheduled. You should not make it up.**
- **If you inadvertently take more than the required number of tablets at a given intake, please take your next intake as scheduled. Please report this on your patient diary and inform your study doctor immediately.**
- **If a tablet is broken or damaged, the tablet should not be used. Inform your study doctor or nurse.**
- **If you lose a tablet accidentally (e.g. tablet drops in the sink, falls on the ground etc), please report it on your patient diary (in the section “Other comments”) and inform your study doctor or nurse.**
- **Keep the tablets in the bottle provided and do not transfer them to any other container.**
- **Record the number of tablets taken at each intake in the diary section below.**
- **To prevent any dosage error, you should complete your diary prior to taking the study treatment to ensure you will take the correct number of tablets.**
- **ALWAYS bring back the bottle and your completed diary to the clinic at each visit (treatment visit if any and Pre-surgery visit).**
- **In case of any question or problem please contact :**
 - **Name of study site staff: _____**
 - **Phone #:_____**

Patient Diary

DAY	DATE (dd/mmm/yyyy)	INTAKE	TIME Hour/Min (24:00 clock)	Number of tablets TAKEN	COMMENTS
Example: Day X	<i>Example:</i> 15/DEC/2016	<i>Morning intake</i>	8:00	2	
		<i>Evening intake</i>	19:00	1	<i>Only 1 tab taken, the other one was missed in error</i>
Day 1		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day 2		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day 3		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day 4		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day 5		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day 6		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day 7		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day 8		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day 9		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day 10		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day 11		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day 12		<i>Morning intake</i>			
		<i>Evening intake</i>			

DAY	DATE (dd/mmm/yyyy)	INTAKE	TIME Hour/Min (24:00 clock)	Number of tablets TAKEN	COMMENTS
				Report in the cells below the number of tablets taken (e.g. 2, 1 or 0) at each intake.	Please use this section to write down any side effects you are experiencing on a given day, explanation for any extra tablet taken or missed tablet, etc.
Day 13		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day 14		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day 15		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day 16		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day 17		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day 18		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day 19		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day 20		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day 21		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day __		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day __		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day __		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day __		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day __		<i>Morning intake</i>			
		<i>Evening intake</i>			

DAY	DATE (dd/mmm/yyyy)	INTAKE	TIME Hour/Min (24:00 clock)	Number of tablets TAKEN	COMMENTS
				Report in the cells below the number of tablets taken (e.g. 2, 1 or 0) at each intake.	Please use this section to write down any side effects you are experiencing on a given day, explanation for any extra tablet taken or missed tablet, etc.
Day __		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day __		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day __		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day __		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day __		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day __		<i>Morning intake</i>			
		<i>Evening intake</i>			
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Day __		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day __		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day __		<i>Morning intake</i>			
		<i>Evening intake</i>			
Day __		<i>Morning intake</i>			
		<i>Evening intake</i>			

Other comments (e.g.: lost or damaged tablets):

Signature Manifest

Document Number: TRIO030-MLD-0001

Revision: 03

Title: Clinical Trial Protocol

All dates and times are in Mountain Time.

Clinical Trial Protocol

Approval

Name/Signature	Title	Date	Meaning/Reason
Rodrigo Fresco (RFRESCO)		15 Feb 2018, 12:01:16 PM	Approved
Launa Aspeslet (LASPESLE)		15 Feb 2018, 12:21:43 PM	Approved
Valerie Bee (VBEE)		15 Feb 2018, 12:55:27 PM	Approved
Naouel Belhani (NBELHANI)		16 Feb 2018, 08:53:38 AM	Approved
Carlos Meyer (CMEYER)		20 Feb 2018, 04:30:20 AM	Approved

Set Effective Date

Name/Signature	Title	Date	Meaning/Reason
Carlos Meyer (CMEYER)		20 Feb 2018, 04:39:20 AM	Approved

Reapproval: TRIO030-MLD-0001

Reapproval

Name/Signature	Title	Date	Meaning/Reason
Carlos Meyer (CMEYER)		21 Feb 2018, 04:12:41 AM	Approved

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Reapproval

Name/Signature	Title	Date	Meaning/Reason
Carlos Meyer (CMEYER)		26 Feb 2018, 09:41:49 AM	Approved