

**A Phase 2, Multicenter, Open-label Study to Assess the Efficacy
and Safety of Enzalutamide with Trastuzumab in Subjects with
HER2+ AR+ Metastatic or Locally Advanced Breast Cancer**

Protocol for Phase 2 Study of Enzalutamide

ISN/Protocol 9785-CL-1121

Version 7.1

Incorporating Nonsubstantial Amendment 2 [See Attachment 1]

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Sponsor:

Astellas Pharma Global Development, Inc. (APGD)

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Table of Contents

I.	SIGNATURES	8
II.	CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL	10
III.	LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS	11
IV.	SYNOPSIS	16
V.	FLOW CHART AND SCHEDULE OF ASSESSMENTS	29
1	INTRODUCTION	34
1.1	Background	34
1.2	Nonclinical and Clinical Data	35
1.2.1	Nonclinical Studies	35
1.2.1.1	Pharmacology	35
1.2.1.2	Pharmacokinetics	36
1.2.1.3	Toxicology	37
1.2.2	Clinical Studies	37
1.2.2.1	Pharmacokinetics	37
1.3	Summary of Key Safety Information for Study Drugs	38
1.3.1	Enzalutamide	38
1.3.2	Trastuzumab	40
1.4	Risk-Benefit Assessment	40
2	STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS	40
2.1	Study Objectives	40
2.1.1	Primary Objective	40
2.1.2	Secondary Objectives	41
2.1.3	Exploratory Objectives	41
2.2	Study Design and Dose Rationale	41
2.2.1	Study Design	41
2.2.2	Dose Rationale	42
2.3	Endpoints	42
2.3.1	Primary Endpoint	42
2.3.2	Secondary Endpoints	42
2.3.2.1	Efficacy Endpoints	42
2.3.2.2	Safety Endpoints	43
2.3.3	Exploratory Endpoints	43

2.3.3.1	Pharmacokinetic Endpoints.....	43
2.3.3.2	Pharmacodynamic Endpoints	43
2.3.3.3	CCl	43
3	STUDY POPULATION	44
3.1	Selection of Study Population	44
3.2	Inclusion Criteria	44
3.3	Exclusion Criteria	46
4	TREATMENT(S)	48
4.1	Identification of Investigational Product(s)	48
4.1.1	Test Drug(s)	48
4.1.1.1	Enzalutamide	48
4.1.1.2	Trastuzumab	48
4.1.2	Comparative Drug(s)	49
4.2	Packaging and Labeling	49
4.2.1	Enzalutamide	49
4.2.2	Trastuzumab	49
4.3	Study Drug Handling	49
4.4	Blinding	50
4.5	Assignment and Allocation	50
4.5.1	Subject Registration	50
4.5.2	Subject Enrollment	50
4.5.3	Definition of Treated Subject	50
5	TREATMENTS AND EVALUATION	51
5.1	Dosing and Administration of Study Drug(s) and Other Medication(s)	51
5.1.1	Dose/Dose Regimen and Administration Period	51
5.1.1.1	Enzalutamide	51
5.1.1.2	Trastuzumab	51
5.1.2	Increase or Reduction in Dose of the Study Drug(s)	51
5.1.2.1	Enzalutamide	51
5.1.2.2	Trastuzumab	52
5.1.3	Previous and Concomitant Treatment (Medication and Nonmedication Therapy)	52
5.1.4	Treatment Compliance	53
5.1.5	Restrictions During the Study	53

5.2	Demographics and Baseline Characteristics	54
5.2.1	Demographics.....	54
5.2.2	Medical History.....	54
5.2.3	Diagnosis of the Target Disease, Severity, and Duration of Disease.....	54
5.2.4	Androgen Receptor, Estrogen Receptor and Progesterone Receptor Status.....	54
5.3	Efficacy Assessment	55
5.3.1	Radiographic Disease Assessment	55
5.3.2	Disease Assessment Methods	55
5.3.2.1	Chest/Abdominal/Pelvic Imaging and Other Measurements	55
5.3.2.2	Brain Imaging	56
5.3.2.3	Bone Imaging	56
5.3.2.4	Cutaneous and Subcutaneous Lesions.....	56
5.4	Safety Assessment	56
5.4.1	Height and Weight	56
5.4.2	Vital Signs.....	56
5.4.3	Adverse Events	56
5.4.3.1	Adverse Events of Possible Hepatic Origin	56
5.4.4	Laboratory Assessments	57
5.4.5	Physical Examination	57
5.4.6	Electrocardiogram (ECG)	57
5.4.7	Echocardiogram/MUGA	57
5.4.8	Performance Status	57
5.5	Adverse Events and Other Safety Aspects	57
5.5.1	Definition of Adverse Events (AEs)	57
5.5.2	Definition of Serious Adverse Events.....	58
5.5.3	Criteria for Causal Relationship to the Study Drug	59
5.5.4	Criteria for Defining the Severity of an Adverse Event	60
5.5.5	Reporting of Serious Adverse Events	60
5.5.6	Follow-up of Adverse Events	61
5.5.7	Monitoring of Common Serious Adverse Events	61
5.5.8	Procedure in Case of Pregnancy	61
5.5.9	Emergency Procedures and Management of Overdose	62
5.5.10	Supply of New Information Affecting the Conduct of the Study.....	62
5.5.11	Urgent Safety Measures	63
5.5.12	Reporting Urgent Safety Measures.....	63

5.6	Test Drug Concentration	63
5.6.1	Pharmacokinetic Assessments	63
5.7	Other Measurements, Assessments or Methods	64
5.7.1	Pharmacodynamic Assessments	64
5.7.1.1	Endocrine and Circulating Tumor Markers	64
5.7.1.2	CCI	64
5.7.2	Sample for the Analysis of Genes Related to Pharmacokinetics, Efficacy, and/or Safety	64
5.7.3	Blood Sample for Future Pharmacogenomic Analysis (Retrospective Pharmacogenomic Analysis)	65
5.8	Total Amount of Blood	65
6	DISCONTINUATION	66
6.1	Discontinuation of Individual Subject(s)	66
6.2	Discontinuation of the Site	66
6.3	Discontinuation of the Study	67
7	STATISTICAL METHODOLOGY	67
7.1	Sample Size	67
7.2	Analysis Set	67
7.2.1	Full Analysis Set (FAS)	68
7.2.2	Efficacy Evaluable Set (EES)	68
7.2.3	Per Protocol Set (PPS)	68
7.2.4	Safety Analysis Set (SAF)	68
7.2.5	Pharmacokinetic Analysis Set (PKAS)	68
7.2.6	Pharmacodynamic Analysis Set (PDAS)	68
7.3	Demographics and Other Baseline Characteristics	68
7.4	Analysis of Efficacy	68
7.4.1	Analysis of Primary Endpoint	69
7.4.1.1	Primary Analysis	69
7.4.1.2	Secondary Analysis	69
7.4.1.3	Subgroup Analysis	69
7.4.2	Analysis of Secondary Endpoints	69
7.4.3	Analysis of Exploratory Endpoints	69
7.5	Analysis of Safety	69
7.5.1	Adverse Events	69

7.5.2	Laboratory Assessments	70
7.5.3	Vital Signs.....	70
7.5.4	ECGs.....	70
7.5.5	LVEF	70
7.6	Analysis of Pharmacokinetics	70
7.6.1	Estimation of Pharmacokinetic Parameters	70
7.6.2	Concentration-Response Relationship Analysis	70
7.7	Analysis of Pharmacodynamics	70
7.7.1	Pharmacodynamic Analyses	70
7.7.2	CCIs	71
7.8	Protocol Deviations and Other Analyses	71
7.9	Interim Analysis (and Early Discontinuation of the Clinical Study).....	71
7.10	Handling of Missing Data, Outliers, Visit Windows, and Other Information	71
8	OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS	72
8.1	Procedure for Clinical Study Quality Control	72
8.1.1	Data Collection	72
8.1.2	Specification of Source Documents	72
8.1.3	Clinical Study Monitoring.....	73
8.1.4	Direct Access to Source Data/Documents.....	74
8.1.5	Data Management	74
8.1.6	Protocol Deviations	74
8.1.7	End of Trial in All Participating Countries.....	75
8.2	Ethics and Protection of Subject Confidentiality	75
8.2.1	Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Competent Authorities (CA)	75
8.2.2	Ethical Conduct of the Study.....	75
8.2.3	Informed Consent of Subjects	76
8.2.3.1	Subject Information and Consent	76
8.2.3.2	Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information	76
8.2.4	Subject Confidentiality	76
8.3	Administrative Matters	77
8.3.1	Arrangement for Use of Information and Publication of the Clinical Study	77
8.3.2	Documents and Records Related to the Clinical Study	77
8.3.3	Protocol Amendment and/or Revision	78

8.3.4	Insurance of Subjects and Others	78
8.3.5	Signatory Investigator for Clinical Study Report	78
9	QUALITY ASSURANCE	78
10	STUDY ORGANIZATION	79
10.1	Independent Data-Monitoring Committee (IDMC) Data and Safety Monitoring Board (DSMB)	79
10.2	Other Study Organization	79
11	REFERENCES	80
12	APPENDICES	82
12.1	List of Excluded Concomitant Medications	82
12.2	Liver Safety Monitoring and Assessment	83
12.3	Common Serious Adverse Events	86
12.4	Retrospective Pharmacogenomic Sub-Study	87
12.5	ECOG Performance Status	89
12.6	RECIST 1.1 Criteria	90
12.7	Laboratory Assessments	93
13	ATTACHMENT 1: NONSUBSTANTIAL AMENDMENT 2	94
14	SPONSOR'S SIGNATURE	96

List of Tables

Table 1	Schedule of Assessments	31
Table 2	Effect of Enzalutamide and Trastuzumab on Her2-amplified Breast Cancer Cell Lines	36
Table 3	Evaluation of Target Lesions	91
Table 4	Evaluation of Nontarget Lesions	91
Table 5	Evaluation of New Lesions	91
Table 6	Time Point Response	91
Table 7	Best Overall Response	92

I. SIGNATURES

1. SPONSOR'S SIGNATURES

Required signatures (e.g., Protocol authors, Sponsor's reviewers and contributors, etc.) are located in Section [14](#), Sponsor Signatures; e-signatures (when applicable) are located at the end of this document.

2. INVESTIGATOR'S SIGNATURE

A Phase 2, Multicenter, Open-label Study to Assess the Efficacy and Safety of Enzalutamide with Trastuzumab in Subjects with HER2+ AR+ Metastatic or Locally Advanced Breast Cancer

ISN/Protocol 9785-CL-1121

Version 7.1

Incorporating Nonsubstantial Amendment 2

10 Jan 2023

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulations. I will also ensure that Subinvestigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: _____

Date

Printed Name: _____

Address: _____

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24h-Contact for Serious Adverse Events (SAEs) See Section 5.5.5	Please fax or email the SAE Worksheet to: Astellas Pharma Global Development, Inc. Product Safety & Pharmacovigilance Fax numbers: <div>PPD</div> <div></div> <div></div> <div></div>
Medical Monitor/ Medical Expert:	<div>PPD</div> <div></div> <div>Astellas Pharma Global Development, Inc.</div> <div>PPD</div> <div></div>
Clinical Research Contact:	<div>PPD</div> <div></div> <div>Astellas Pharma, Inc.</div> <div>PPD</div> <div></div>

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse event
AI	Adrenal insufficiency
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (GPT)
ANC	Absolute neutrophil count
APEBV	Astellas Pharma Europe B.V.
APGD	Astellas Pharma Global Development, Inc.
AR	Androgen receptor
AREC	Astellas ethical committee
AST	Aspartate aminotransferase (GOT)
AUC	Area under the concentration curve
AUST	Astellas United States Technologies
BORR	Best overall response rate
CA	Competent authority
CBR	Clinical benefit rate
CR	Complete response
CRO	Contract research organization
CRF	Case report form
CRPC	Castration-resistant prostate cancer
CSR	Clinical study report
CT	Computed tomography
C _{trough}	Trough concentration
CTx	Chemotherapy
CYP	Cytochrome P450
D	Day
DHT	Dihydrotestosterone
DILI	Drug-induced liver injury
DOR	Duration of response
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
Echo	Echocardiogram
ECLIA	Electrochemiluminescence immunoassay
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
eCTD	Electronic common technical document
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid

Abbreviations	Description of abbreviations
EOT	End of treatment
ER	Estrogen receptor
FAS	Full analysis set
FDA	Food and Drug Administration
FDG-PET	Fluorodeoxyglucose positron emission tomography
FOXA1	Forkhead box protein A1
FSH	Follicle stimulating hormone
FU	Follow-up
GABA	Gamma aminobutyric acid
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
GnRH	Gonadotropin releasing hormone
GWAS	Genome-Wide Association Studies
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HER2 or HER2/neu	Human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive response technology
ISH	<i>in situ</i> hybridization
ISN	International study number
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
J-NDA	Japanese new drug application
LABC	Locally advanced breast cancer
LA-CRF	Liver abnormality case report form
LC-MS/MS	liquid chromatography – tandem mass spectrometry
LFT	Liver function tests or liver function testing
LH	Luteinizing hormone
LHRH	Luteinizing hormone releasing hormone

Abbreviations	Description of abbreviations
LVEF	Left ventricular ejection fraction
M	Month
MAA	Marketing Authorisation Application
MBC	Metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MPS	Myocardial perfusion scintigraphy
MRI	Magnetic resonance imaging
MUGA	Multi-gated acquisition scan
N/A	Not applicable
NASH	Nonalcoholic steatohepatitis
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NDA	New Drug Application
NE	Not evaluated
NYHA	New York Heart Association
OPT	Optional
ORR	Overall response rate
PD	Pharmacodynamic or progressive disease
PDAS	Pharmacodynamic analysis set
PET	Positron emission tomography
PFS	Progression free survival
PGx	Pharmacogenomics
PgR	Progesterone receptor
PHI	Protected health information
PK	Pharmacokinetic
PKAS	Pharmacokinetic analysis set
PPS	Per protocol set
PR	Partial response
PT	Preferred term
Q	Quarter or every
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Stable disease
SDF-1	Stromal cell-derived factor 1
SHBG	Sex hormone binding globulin
sHER2	Serum HER2
SPC	Summary of Product Characteristics
SOC	System organ class
SOP	Standard operating procedure
T	Testosterone

Abbreviations	Description of abbreviations
$t_{1/2}$	Apparent terminal elimination half-life
TEAE	Treatment emergent adverse event
TBL	Total bilirubin
TLF	Tables listings figures
t_{max}	Time after dosing when C_{max} occurs
TMF	Trial master file
TNBC	Triple negative breast cancer
TTP	Time to progression
TTR	Time to response
Tx	Treatment
ULN	Upper limit of normal
UNSCH	Unscheduled
USM	Urgent safety measure
W	Week
WHO	World Health Organization
%ΔTM	Percent change in tumor measurement

Definition of Key Study Terms

Terms	Definition of terms
Baseline	Observed values/findings which are regarded observed starting point for comparison. For this study, unless otherwise specified, Baseline finding are the findings observed just prior to the first dose of study drug (enzalutamide or trastuzumab).
Enroll	To enter into a clinical trial in order to begin treatment. Informed consent precedes enrollment.
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test drug or comparative drug is usually given to a subject, and continues until the last assessment after completing administration of the test drug or comparative drug. The Investigational period for this trial is from the time of enrollment through the end of treatment.
Post investigational period	Period of time after the Investigational period. Follow-up observations for sustained adverse events and/or survival are done in this period.
Screening period	Period of time before entering the investigational period, usually from the time of starting a subject signing consent until enrollment.
Screening	Process for checking the eligibility of subjects usually done during the Screening Period and prior to Enrollment.
Screen failure	Subject that was screened but did not fulfill protocol inclusion and/or exclusion criteria and failed to receive study treatment, or decided not to participate anymore (withdrew consent) prior to completing preinvestigational period.
Study drug	Agents given as part of the clinical trial. In this study, enzalutamide and trastuzumab are study drugs.
Study period	Period of time beginning with the first subject consented through to the last observation collected for the study.
Variable	Any quantity, attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Date and Version of Protocol Synopsis:	10 Jan 2023, Version 7.1
Sponsor: Astellas Pharma Global Development Inc (APGD)	Protocol Number: 9785-CL-1121
Name of Study Drugs: enzalutamide and trastuzumab	Phase of Development: Phase 2
Title of Study: A Phase 2, Multicenter, Open-label Study to Assess the Efficacy and Safety of Enzalutamide with Trastuzumab in Subjects with HER2+ AR+ Metastatic or Locally Advanced Breast Cancer	
Planned Study Period: From 2Q2014 to 1Q2025	
Study Objective(s): <u>Primary Objective:</u> To evaluate the efficacy of enzalutamide with trastuzumab in evaluable subjects with human epidermal growth factor receptor 2 positive (HER2+) and androgen receptor positive (AR+) metastatic or locally advanced breast cancer, as measured by Clinical Benefit Rate (CBR) (defined as the proportion of evaluable subjects with best objective response of confirmed CR or PR per RECIST 1.1, or prolonged SD (≥ 24 weeks)). <u>Secondary Objectives:</u> <ul style="list-style-type: none"> To evaluate the following efficacy measures: <ul style="list-style-type: none"> Best Overall Response Rate (BORR) Overall Response Rate (ORR) at 24 weeks Progression Free Survival (PFS) Time to Progression (TTP) Duration of Response (DOR) Time to Response (TTR) To evaluate safety and tolerability. <u>Exploratory Objectives:</u> <ul style="list-style-type: none"> CC/ 	
Planned Total Number of Study Centers and Location(s): Approximately 55 centers North America and Europe	
Study Population: Female subjects with HER2+ and AR+ metastatic or locally advanced breast cancer who have progressed on at least 1 prior line of anti-HER2 therapy in the metastatic or advanced setting. Subjects may be either ER/PgR positive or negative according to the local assessment for hormone receptor diagnostics. A line of therapy is defined as a course of treatment at the end of which there	

was disease progression toxicity, or in the Investigator's opinion, maximum benefit has been achieved.

Number of Subjects to be Enrolled/Randomized:

Approximately 80 subjects were planned to be enrolled to reach 66 evaluable AR+ subjects. 103 subjects were actually enrolled in the study.

Study Design Overview:

This is a multinational, multicenter, open-label, single-arm, 2-stage, Phase 2 study evaluating the efficacy, safety, and tolerability of enzalutamide with trastuzumab. A Simon's 2-stage design is implemented to allow for early termination if < 3 of 21 evaluable AR+ subjects show clinical benefit [confirmed complete response (CR), partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria or prolonged stable disease (SD) ≥ 24 weeks] at the analysis of the first stage. If ≥ 3 of 21 evaluable AR+ subjects show clinical benefit, then a second stage will continue to enroll a total of 66 evaluable AR+ subjects.

Subjects will enter the screening period up to 28 days prior to treatment start. Subjects will be allowed to prescreen under a separate consent form to enable testing of archival tissue for AR expression before initiation of other screening activities. After completion of screening assessments, eligible subjects will enter into the treatment phase to receive enzalutamide with trastuzumab. Study visits will take place every 3 weeks until week 16, then at weeks, 25, 34, 40, and 49, and then every 12 weeks thereafter until the subject meets discontinuation criteria or the study ends. Tumor assessments will be performed every 8 weeks up to week 49, and then every 12 weeks thereafter. Subjects will continue on treatment until disease progression, unacceptable toxicity, or any other discontinuation criteria are met.

Upon discontinuation of study drug, subjects will enter the follow-up period. An end of treatment visit will be performed within 7 days of the last dose of enzalutamide. The Follow-up Visit will be performed approximately 30 days after the last dose of enzalutamide or before initiation of subsequent treatment (whichever is first); this visit may be conducted by phone call if the subject is unable to return to the clinic. The treatment emergent period will be defined as the period of time from the first dose date of study drug to 30 days after the last dose date of study drug or the start of subsequent treatment (whichever occurs first). All adverse events (AEs) that occur during the collection period are to be followed until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

If the study is terminated early for reasons other than safety, and the subject is receiving clinical benefit per Investigator's judgment, the subject may continue on study medication until they have disease progression as defined per RECIST.

Inclusion/Exclusion Criteria:

Inclusion:

1. The subject has consented and signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act [HIPAA] for U.S. sites) prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. The subject is a female ≥ 18 years of age.
3. The subject has histologically or cytologically proven adenocarcinoma of the breast that is HER2+ defined as a score of 3+ for staining by immunohistochemistry (IHC), or IHC 2+ with HER2 gene amplification as determined by a locally approved *in situ* hybridization (ISH) assay, or (for patients without IHC data) HER2 gene amplification.

Inclusion continued

4. The subject has AR+ breast cancer, which is defined as any tumor cells with nuclear AR staining by immunohistochemistry (IHC). Enrollment may be based on the local pathologist's findings; however, tissue will be sent to a central pathology laboratory for assessment. NOTE: If a subject is enrolled in the study based on local pathologist results, but subsequent central assessment cannot confirm AR+ disease, the subject may remain in the study.
5. The subject has metastatic disease or has locally advanced disease that is not amendable to curative treatment.
6. The subject has measurable disease or nonmeasurable, evaluable disease per RECIST 1.1 (NOTE: pleural effusions, ascites or other third fluid space are not evaluable diseases per RECIST 1.1).
7. The subject has received at least 1 line of therapy in the metastatic or locally advanced disease setting:
 - A line of therapy is defined as a course of treatment at the end of which there was disease progression, toxicity, or in the Investigator's opinion, maximum benefit has been achieved. If the subject discontinued therapy due to any other reason but progressed without receiving other treatment, this would be considered a line of therapy.
 - The subject has been documented to have progressed by determination of the Investigator on a regimen containing an anti-HER2 agent (includes trastuzumab emtansine in countries where it is not approved) as the most recent regimen or the most recent anti-HER2 regimen was discontinued for any toxicity, with the exception of a cardiotoxicity.
 - Subjects who received < 28 days of therapy in the most recent regimen may be eligible upon approval from the medical monitor.
 - The subject progressed on a trastuzumab containing regimen. If progression occurred within 12 months after completing trastuzumab-containing adjuvant treatment, this counts as having received trastuzumab but not as a line of therapy.
8. The subject has adequately recovered from toxicities due to prior therapy.
9. The subject has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 at Screening and Day 1.
10. The subject has available at the site a representative, formalin-fixed, paraffin-embedded, tumor specimen that enabled the definitive diagnosis of breast cancer with adequate viable tumor cells in a tissue block (preferred) or ≥ 10 (20 preferred) freshly cut, unstained, serial slides and the associated pathology report:
 - Archival tissue from the most recent biopsy available is preferred.
 - For subjects who are known AR+ per local pathology report, a fresh biopsy can be done per Investigator's discretion, to obtain tissue for central AR confirmation if the archival specimen is insufficient or unavailable.
 - Cytological or fine-needle aspiration samples are not acceptable.
11. The subject has an estimated life expectancy of at least 6 months at Day 1, in the opinion of the Investigator.

Inclusion continued

12. The subject is either:

- Of nonchildbearing potential:
 - postmenopausal (defined as no spontaneous menses for at least 12 months prior to Screening with FSH > 40 IU/L for women < 55 years of age at Screening),
 - documented surgically sterile or status post hysterectomy (at least 1 month prior to Screening), or
- Or, if of childbearing potential,
 - must agree to not try to become pregnant during the study and for 5 half-lives (29 days) after the final study drug administration
 - must have a negative urine pregnancy test at Screening and at Day 1 before the first dose of study drug is administered,
 - must use 2 acceptable methods of birth control starting at Screening and through 6 months after the final study drug administration.

The 2 acceptable methods of birth control are as follows or per local guidelines where these require additional description of contraceptive methods:

- A barrier method (e.g., condom by a male partner) is required;
AND
- One of the following is required:
 - Placement of an intrauterine device (IUD) or intrauterine system (IUS);
 - Additional barrier method including occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository;
 - Vasectomy or other surgical castration at least 6 months before Screening.

13. The subject must not be breastfeeding at Screening or during the study period, and for 6 months after the final study drug administration.

14. The subject must be able to swallow enzalutamide and comply with study requirements.

15. The subject agrees not to participate in another interventional study while on treatment

Waivers to the inclusion criteria will **NOT** be allowed.

Exclusion:

Subject will be excluded from participation if any of the following apply:

1. The subject has a severe concurrent disease, infection, or comorbidity that, in the judgment of the Investigator, would make the subject inappropriate for enrollment.
2. The subject has current or previously treated brain metastasis or active leptomeningeal disease. Brain imaging is required during screening in all subjects to exclude the presence of unequivocal central nervous system disease.
3. The subject has a history of a nonbreast cancer malignancy with the following exceptions:
 - The subject with a previous history of a noninvasive carcinoma is eligible if in the opinion of the Investigator he/she has had successful curative treatment any time prior to Screening.
 - For all other malignancies, the subject is eligible if they have undergone potentially curative therapy and they have been considered disease free for at least 5 years prior to Screening.

Exclusion continued

4. The subject has inadequate marrow, hepatic, and/or renal function at the Screening Visit defined as:
 - Absolute neutrophil count $< 1.5 \times 10^9/L$ (< 1500 cells/mm³)
 - Platelet count $< 75 \times 10^9/L$ ($< 75,000$ cells/mm³)
 - Hemoglobin < 5.6 mmol/L (< 9 g/dL)
 - Total bilirubin $> 1.5 \times$ Upper Limit of Normal (ULN) unless there is an alternate nonmalignant etiology (e.g., Gilbert's syndrome).
 - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $> 3 \times$ ULN (or $> 5 \times$ ULN if hepatic metastasis is present).
 - Creatinine $> 1.5 \times$ ULN or Glomerular Filtration Rate (eGFR)/Creatinine Clearance (CrCL) < 30 mL/min, whichever is more restrictive.
 - NOTE: May not have received any growth factors or blood transfusions within 7 days before the hematology values obtained at screening
5. The subject has a history of seizure or any condition that may predispose to seizure (e.g., prior cortical stroke, significant brain trauma).
6. The subject has a history of loss of consciousness, cerebrovascular accident or transient ischemic attack within 12 months before the Day 1 visit.
7. The subject has had a hypoglycemic episode requiring medical intervention while on insulin (or other anti-diabetic) treatment within 12 months before Day 1.
8. The subject has clinically significant cardiovascular disease including:
 - Myocardial infarction within 6 months before the Day 1 visit.
 - Uncontrolled angina within 6 months before the Day 1 visit.
 - Congestive heart failure New York Heart Association (NYHA) Class III or IV or history of congestive heart failure NYHA Class III or IV in the past, unless a screening echocardiogram, myocardial perfusion scintigraphy (MPS), or multi-gated acquisition scan performed within 3 months before the Day 1 visit reveals a left ventricular ejection fraction that is $\geq 50\%$.
 - History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, Torsade de Pointes).
 - History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place.
 - Hypotension as indicated by systolic blood pressure < 86 mmHg on 2 consecutive measurements at the Screening visit.
 - Bradycardia (in the presence of known cardiovascular disease) as indicated by a heart rate of < 50 beats per minute on the Screening electrocardiogram (ECG) recording.
 - Uncontrolled hypertension as indicated by systolic blood pressure > 170 mmHg or diastolic blood pressure > 105 mmHg on 2 consecutive measurements at the Screening visit.
9. The subject has significant respiratory disease, including severe dyspnea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.
10. The subject has an active gastrointestinal disorder affecting absorption (e.g., gastrectomy, active peptic ulcer disease) within the 3 months prior to the Day 1 visit.
11. The subject had a major surgical procedure, substantial open biopsy, or significant traumatic experience within 28 days before the Day 1 visit, or anticipation of need for major surgical procedure during the course of the study.

12. The subject has had palliative radiation therapy to bone metastases within 14 days prior to the Day 1 visit (side effects from radiation must be resolved).

Exclusion continued

13. The subject has received chemotherapy, immunotherapy, or any other systemic anti-cancer therapy, with the exception of anti-HER2 therapy (e.g., trastuzumab and trastuzumab emtansine), within 14 days prior to the Day 1 visit.
14. The subject has been treated with any investigational drugs within 14 days prior to the Day 1 visit.
15. The subject has received treatment with any approved or investigational agent that either blocks androgen synthesis or targets the AR (e.g., abiraterone acetate, bicalutamide, enzalutamide, TAK-448, TAK-683, TAK-700, ARN-509, ODM-201, BMS-641988). Subjects who received treatment for < 28 days or placebo on an investigational study are acceptable.
16. The subject would, in the Investigator's opinion, benefit from estrogen receptor targeted therapy while on study.
17. The subject has used any of the following within 28 days before the Day 1 visit:
- 5- α reductase inhibitors
 - Systemic androgens and estrogens
18. The subject has a known history of positive test for Hepatitis B surface antigen (HBsAg) or hepatitis C antibody or history of positive test for Human Immunodeficiency Virus (HIV).
19. The subject has shown a hypersensitivity reaction to the active pharmaceutical ingredient or any of the enzalutamide capsule components, including Labrasol, butylated hydroxyanisole and butylated hydroxytoluene.
20. The subject has had a severe infusion reaction to trastuzumab or hypersensitivity to trastuzumab, and excipients including murine proteins, L-histidine, L-histidine hydrochloride monohydrate, α,α -trehalose dehydrate, L-methionine, and polysorbate.
21. The subject has any other condition or reason that, in the opinion of the Investigator, would make the subject ineligible to receive trastuzumab, interferes with the ability of the subject to participate in the trial, places the subject at undue risk, or complicates the interpretation of safety data.

Waivers to the exclusion criteria will **NOT** be allowed.

Investigational Product(s):

Enzalutamide 40 mg soft gelatin capsules

Trastuzumab 150 mg lyophilized sterile powder

Dose(s):

Enzalutamide 160 mg/day.

Trastuzumab infusion: 6 mg/kg every 21 days. For subjects whose last dose of anti-HER2 antibody was greater than 21 days prior to Day 1 or for subjects who were on weekly trastuzumab for ≤ 2 weeks, a loading dose of 8 mg/kg will be administered on Day 1, followed by 6 mg/kg every 21 days thereafter.

Trastuzumab subcutaneous: 600mg/5mL q3 weeks

Mode of Administration:

Enzalutamide capsules are administered orally with or without food.

Trastuzumab Infusion: Intravenous (IV) infusion is given over 30-90 minutes. For a loading dose, a 90 minute IV infusion is given or per local label.

Sub-cutaneous: subcutaneous injections should be given per local label.

Comparative Drug(s):

Not applicable.

Dose(s):

Not applicable.

Mode of Administration:

Not applicable.

Concomitant Medication Restrictions or Requirements:

Medications taken within 14 days before the Screening visit and up to the 30 Day Follow-Up visit will be documented on the appropriate case report form as concomitant medication.

All concomitant medication(s) must be reported on the appropriate case report form. Prior and concomitant medications include all vitamins, herbal remedies, over the counter, and prescription medications.

Concomitant administration of bisphosphonates or bone targeting agents are acceptable if the subject is on a stable regimen (per Investigator's judgement) prior to Day 1. The Investigator should consult with Medical Monitor if new use of bone-targeting agents is deemed necessary during the study.

Concomitant administration of enzalutamide with strong cytochrome P450 (CYP)2C8 inhibitors, strong or moderate CYP2C8 inducers, strong or moderate CYP3A4 inducers should be avoided.

Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4, CYP2C9, and CYP2C19 should be avoided.

Subjects should avoid use of any herbal medications or dietary supplements including products containing *Hypericum perforatum* (e.g., St. John's Wort).

The following medications or therapies are prohibited during the receipt of study drug:

- Medications, including herbal therapies, with an antitumor effect (medications used to induce menopause in women of child-bearing potential and are permitted).
- Any investigational agent
- AR antagonists (e.g., bicalutamide, flutamide, nilutamide)
- 5- α reductase inhibitors (e.g., finasteride, dutasteride)
- Systemic androgens and estrogens (vaginal estrogen creams are allowed)
- Megestrol acetate for appetite stimulation may be used at Investigator's discretion.

If it is anticipated that the subject may require radiation (e.g., painful boney metastases), Investigators are encouraged to have subjects complete any radiation therapy prior to entering the study, as concomitant radiation therapy may be cause for discontinuation from the study. During the course of the study the Medical Monitor must be contacted for approval prior to initiation of any radiation.

Duration of Treatment:

Until disease progression, unacceptable toxicity, or any other discontinuation criteria are met.

Formal Stopping Rules:

A Simon's 2-stage design is implemented to allow for termination if < 3 of 21 evaluable AR+ subjects show clinical benefit (defined as subjects with best objective response of confirmed CR or

PR per RECIST 1.1, or prolonged SD (≥ 24 weeks). If ≥ 3 of 21 evaluable AR+ subjects show clinical benefit, approximately 45 additional evaluable AR+ subjects will be enrolled, for a total of 66 evaluable AR+ subjects. Recruitment in Stage 1 will not be suspended to evaluate interim data.

Endpoints for Evaluation:

Primary

CBR defined as the proportion of evaluable subjects with best objective response of confirmed CR or PR per RECIST 1.1 criteria, or prolonged SD (≥ 24 weeks).

Secondary

Efficacy Endpoints:

- ORR (CR+PR) at 24 weeks according to RECIST 1.1 criteria.
- BORR according to RECIST 1.1.
- PFS is defined as the time from the date of first dose of enzalutamide (Study Day 1) until the date of disease progression per RECIST 1.1 or death from any cause on study, whichever occurs first.
- TTP is defined as the time from the first date of enzalutamide treatment until the date of disease progression per RECIST 1.1.
- DOR is defined as the time from the date first documentation of response (CR or PR) until the date of disease progression per RECIST 1.1.
- TTR is defined as the time from the first date of enzalutamide treatment to initial CR or PR.

Safety Endpoints:

Safety will be assessed on an ongoing basis by physical examination, measurement of vital signs, laboratory assessments, 12-lead ECGs, LVEF by echocardiogram or multi-gated acquisition scan (MUGA), and evaluation of AEs/serious adverse events.

Exploratory

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Statistical Methods:

Sample Size Justification:

The sample size is sufficient to determine the absence or presence of an efficacy signal. The sample sizes for the first and second stage were determined using Simon's 2-stage design. The null hypothesis that the true CBR is 10% will be tested against a 1-sided alternative at a 5% significance level. In the first stage, 21 evaluable AR+ subjects will be evaluated; the study will stop if < 3 evaluable subjects show confirmed CR or PR per RECIST 1.1, or prolonged SD (≥ 24 weeks). Otherwise, the study will continue to enroll up to 66 evaluable AR+ subjects. This design has a statistical power of 90% when the true CBR is 25%. To illustrate the precision with a total of 66 subjects: if the observed CBR is 40%, then the 90% confidence interval will be within the 30% to 50% range.

Taking into account an anticipated number of nonevaluable subjects, approximately 80 subjects were planned to be enrolled to achieve a data set with at least 66 evaluable AR+ subjects.

Efficacy:

The Efficacy Evaluable Set (EES) is a subset of the FAS defined as all enrolled subjects who have centrally assessed AR+ (defined as > 10% of tumor cells with nuclear expression), received at least 1 dose of study drug, and have at least 1 available post baseline tumor assessment.

The primary analyses will be done in the EES, while all efficacy analyses will be done in both the EES and Full Analysis Set (FAS). If more than 5 subjects are enrolled into the study but had less than 10% of tumor cells with nuclear expression, and received at least 1 dose of study drug, the efficacy analyses will also be conducted in this subset of FAS. Further details will be presented in the statistical analysis plan. Subjects whose disease is not confirmed to be AR+ upon central review may stay on study; however, they will not contribute to the primary and secondary efficacy analyses.

All variables will be presented as descriptive statistics. CBR, ORR, and BORR will be summarized including 95% 2-sided confidence intervals.

Kaplan-Meier methods will be used to estimate PFS, TTP, TTR, and DOR.

Pharmacokinetics:

PK analyses will be conducted using the pharmacokinetic analysis set (PKAS). The PKAS is defined as the subset of the safety analysis set (SAF) population for which at least 1 quantifiable enzalutamide N-desmethyl enzalutamide, or trastuzumab concentration value after Week 4 is available.

The enzalutamide, N-desmethyl enzalutamide, and trastuzumab concentration-time data will be summarized by descriptive statistics at each visit. Additional model-based analyses may be performed but will be reported separately.

Pharmacodynamics:

Pharmacodynamic:

Circulating hormones and protein markers will be expressed as the change in absolute value and percent change from baseline at each visit and presented using descriptive statistics.

Additional model-based analyses to explore PK-PD relationships may be performed.

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Safety:

Safety analyses will be conducted using the Safety Analysis Set (SAF). The SAF is defined as all subjects who have received at least partial or full dose of study drug. The treatment emergent period will be defined as the period of time from the first dose date of study drug to 30 days after the last dose date of study drug or the start of subsequent treatment (whichever is first). Safety will be assessed through descriptive statistics for the frequency of AEs by system organ class (SOC), preferred term (PT), and National Cancer Institute Common Terminology Criteria for Adverse

Events (NCI CTCAE) grade, the frequency of treatment discontinuations due to AEs, vital signs, ECG, LVEF, and laboratory evaluations.

The severity of all AEs is to be evaluated by the Investigator based on the NCI CTCAE, version 4.03. All AEs will be coded to preferred term and system organ class using Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment emergent adverse events will be presented by MedDRA system organ class and preferred term, relationship to study treatment, and NCI CTCAE grade. A subject reporting the same AE more than once is counted once and at the maximum severity or strongest relationship to study drug treatment, when calculating incidence.

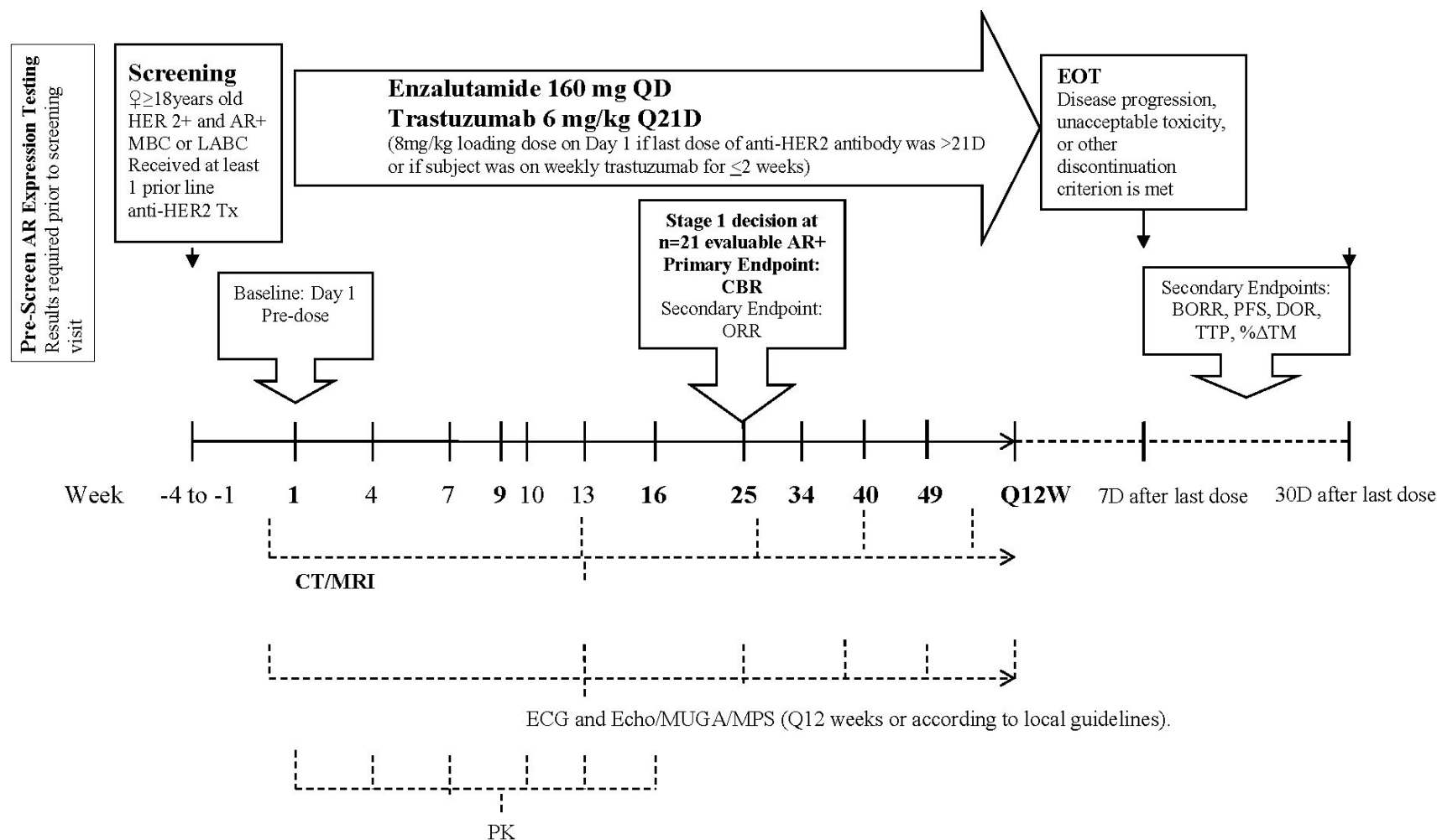
Laboratory data consist of hematology, chemistry, coagulation, and urine dipstick laboratory test results. Where applicable, NCI CTCAE version 4.03 will be used to categorize toxicity grades for the laboratory parameters. Laboratory shift tables compared to baseline results for each subsequent visit will be produced. For each laboratory parameter, the baseline laboratory value is defined as the last laboratory value collected on or prior to the first dose date of enzalutamide.

Interim Analyses:

Recruitment will continue if there are 3 or more subjects with clinical benefit in the first 21 evaluable AR+ subjects from the evaluable set. If there are less than 3 subjects who demonstrate confirmed CR or PR per RECIST 1.1, or prolonged SD \geq 24 weeks (using all available data), recruitment will be stopped.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart



Footnotes appear on next page

AR+ = androgen receptor positive, BORR = best overall response rate, CBR = clinical benefit rate, CT = computed tomography, CTx = chemotherapy, D = day, DOR = duration of response, Echo = echocardiogram, EOT = end of treatment, HER2+ = human epithelial growth factor receptor positive, LABC = locally advanced breast cancer, M = month, MBC = metastatic breast cancer, MPS= Myocardial Perfusion Scintigraphy, MRI = magnetic resonance imaging, MUGA = multi-gated acquisition scan, ORR = overall response rate, PFS = progression free survival, PK = pharmacokinetics, Q = every, TTP = time to progression, Tx = treatment, W = week, %ΔTM = percent change in tumor measurements.

Table 1 Schedule of Assessments

Assessments	Prescreen	Screen	Treatment											Follow-up	
Study Week/Visit	Prior to screen	-4 to -1	1	4	7	10	13	16	25	34	40	49 and Q12W	UNSCH	EOT	30D FU ¹
Study Day	N/A	-28 to -1	1	22	43	64	85	106	169	232	274	337+	N/A	≤ 7D after last dose	30D after last dose
Window (days)	N/A	N/A	0	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	N/A	N/A	+7
Informed Consent	X	X													
Initial AR expression testing ²	X														
Inclusion/Exclusion Criteria		X	X												
Return and/or Dispense Enzalutamide			X	X	X	X	X	X	X	X	X	X	X [OPT]	X	
Trastuzumab administration			To be administered Q3W												
Concomitant Medications ³		X	X	X	X	X	X	X	X	X	X	X	X	X	
Demographics, Medical and Disease History		X													
Radiographic Disease Assessment ⁴		X	To be performed Q8W (+/- 10 D)										X [OPT]		
Brain Imaging ⁵		X											X [OPT]		
Height		X													
Weight		X	X				X		X	X	X	X	X [OPT]	X	
Vital Signs		X	X	X	X	X	X	X	X	X	X	X	X [OPT]	X	
Adverse Events ⁶		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests ⁷		X ⁸	X ⁹	X	X	X	X	X	X	X	X	X	X [OPT]	X	
Urine Pregnancy Test ¹⁰		X	X		X		X	X	X	X	X	X	X [OPT]	X	X
Physical Examination ¹¹		X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG ¹²		X	To be performed Q12W (+/- 14D) or according to local guidelines										X [OPT]	X	
Echocardiogram/MUGA/MPS		X	To be performed Q12W (+/- 14D) or according to local guidelines										X [OPT]		
ECOG PS		X	X	X	X	X	X	X	X	X	X	X	X [OPT]	X	
Circulating Endocrine and Other Protein Markers ¹³			X	X	X	X	X	X	X	X	X				
PK Samples ¹⁴			X	X	X	X	X	X							
Dosing Diary Review ¹⁵			X	X	X	X	X	X							
Tumor Tissue Collection for Central Testing ¹⁶		X													
Blood Sample for Genotype Analysis ¹⁷			X												
Optional PGx Sample ¹⁸			X												

Footnotes appear on next page

Abbreviations: CT = computed tomography, D = day, DOR = duration of response, Echo = echocardiogram, ECG = electrocardiogram, EOT = end of treatment, FU = follow-up, MPS= Myocardial Perfusion Scintigraphy, MRI = magnetic resonance imaging, MUGA = multi-gated acquisition scan, N/A = not applicable, OPT = optional, PGx = pharmacogenomic, PK = pharmacokinetic, Q = every, UNSCH = unscheduled, W = week

1. Phone call may be conducted only if subject is unable to return to the clinic. Follow-up visit should occur approximately 30 days following the last dose of study drug, or before initiation of subsequent treatment (whichever is first).
2. Testing of archival tissue for AR expression can be done before initiation of other screening activities under a separate prescreen consent form. Results for AR expression from local pathology can be used for enrollment.
3. Medications taken within 14 days before the Screening visit and up to 30 Day-Follow-up visit will be collected.
4. CT/MRI of the chest/abdomen/pelvis as well as any other anatomical region appropriate for that subject's disease must be performed within 28 days prior to day 1. Results from CT/MRI assessments performed prior to consent and within 28 days of day 1 may be used for screening if available. All subjects should have bone imaging to assess metastasis to the bone within 6 months prior to the Day 1 visit. Thereafter, subjects without bone metastasis will have bone scans only if clinically indicated. PR and CR require confirmation with equivalent or improved assessment no less than 4 weeks after the date of scan that PR or CR was first observed.
 - a. Subjects with suspected bone-only, measurable lesions must have bone lesions assessed by CT with bone windows or by MRI within 12 weeks before Day 1. Thereafter, measureable lytic lesions should be followed as target lesions according to RECIST 1.1 using the same method.
 - b. Subjects with suspected bone-only, nonmeasurable disease should have had a bone assessment (e.g., scintigraphy or skeletal survey) performed within 12 weeks before Day 1.
 - c. Imaging of nonmeasurable, evaluable disease should be performed as clinically indicated, with a required assessment at Week 24.
 - d. Cutaneous and subcutaneous lesions should be assessed by physical examination with digital photographs that must include a metric ruler in the image. Photographs should be obtained in such a manner to protect subject privacy.
5. Brain imaging is required at Screening for all subjects to rule out central nervous system disease. A brain MRI with contrast enhancement is required unless it cannot be performed within 2 weeks prior to Day 1 due to feasibility or subject-specific contraindications. A head CT may be performed in these situations after discussion with the medical monitor or designee. Results from brain imaging performed prior to consent and within 28 days of Day 1 may be used for screening if available. Additional imaging to rule out CNS metastases should be performed as clinically indicated.
6. Adverse Events will be collected from the time of informed consent through 30 days following last dose of study drug or through the day prior to initiation of alternate treatment (whichever occurs first).
7. Clinical Laboratory Assessments include hematology, chemistry, and local urine dipstick. Coagulation panel will be performed at Screening for all subjects and only at each visit if subject is on anti-coagulant therapy.
8. Local FSH testing is required at screening for postmenopausal women who are < 55 years of age.
9. Day 1 clinical laboratory tests do not need to be repeated if Screening labs were performed within 7 days prior to Day 1.
10. Urine pregnancy test will be performed in women of child-bearing potential. Testing at treatment visits must occur prior to study drug administration.
11. Physical exam performed prior to ICF and within 7 days of the screening visit may be used for screening if available.

Footnotes continued on next page

12. All on-treatment ECGs will be obtained prior to drug administration. In addition, whenever a study procedure coincides with the scheduled time point for an ECG, the study activities should be undertaken in a fixed sequence if possible: ECGs first, vital signs second, and any type of blood draw as the last assessment.
13. Blood samples to measure circulating endocrine levels and other protein markers will be obtained. Blood sample should be obtained prior to study drug administration at the Day 1 visit and at approximately the same time of day at each following visit.
14. Predose plasma PK samples will be collected prior to enzalutamide intake and will be analyzed for enzalutamide and N-desmethyl enzalutamide. Predose serum PK samples will be collected prior to the start of the trastuzumab infusion and will be analyzed for trastuzumab. Enzalutamide and trastuzumab will be administered in clinic on PK days.
15. A dosing diary will be dispensed to the subject on Day 1. Date and time of enzalutamide dose will be recorded in the diary by the subject for the 2 days prior to each PK sample.
16. All subjects are required to have tissue sample available to send for central lab confirmation of AR expression at screening visit.
17. A blood sample is taken to allow evaluation of potential AR mutations and another sample is taken to allow for genotype analysis of relevant metabolism, transporter, PD, and/or safety genes, in the event of unusual PK/PD patterns or safety findings.
18. Optional exploratory retrospective, PGx for those subjects who consent to the sub-study.

1 INTRODUCTION

1.1 Background

Breast cancer is one of the most frequently diagnosed malignancies and the second most common cause of cancer deaths in women, despite improvements in screening and treatment regimens. According to the American Cancer Society, about 1.4 million women are diagnosed with breast cancer annually worldwide and about 458,400 will die from the disease [American Cancer Society, 2011]. In the United States, approximately 1 in 8 women (12%) will develop invasive breast cancer over their lifetimes, and about 39,510 women annually will die from the disease [Siegel et al, 2011].

Breast cancer is genetically heterogeneous and biologically diverse and it is no longer considered a single disease. The long recognized clinical and phenotypic differences have been shown to correlate with differences at the gene expression level [Sørlie et al, 2004; Perou et al, 2000]. Five distinct breast cancer molecular subtypes are defined by hierarchical cluster analyses of array gene expression data; they include luminal A, luminal B, human epidermal growth factor receptor 2 (HER2) amplified, basal-like and normal-like [Goldhirsch et al, 2011].

Approximately 20% of all breast cancers have gene amplification or overexpression (or both) of human epidermal growth factor receptor 2 (HER2), a tyrosine kinase transmembrane receptor, resulting in a more aggressive phenotype and a poor prognosis. Treatment with the anti-HER2 humanized monoclonal antibody trastuzumab in addition to chemotherapy, as compared with chemotherapy alone, significantly improves progression-free and overall survival among patients with HER2-positive metastatic breast cancer. Trastuzumab binds to subdomain intravenous (IV) infusion of the HER2 extracellular domain and exerts its antitumor effects by blocking HER2 cleavage, stimulating antibody-dependent, cell-mediated cytotoxicity and inhibiting ligand-independent, HER2-mediated mitogenic signaling. However, in most patients with HER2-positive metastatic breast cancer, the disease progresses, highlighting the need for new targeted therapies for advanced disease [Baselga et al, 2012]

Expression of the androgen receptor (AR) has been observed in the majority of breast cancer specimens. In studies evaluating over 3,000 breast tumor specimens, AR expression was observed in 77% of invasive breast tumors and its expression was observed across all molecular phenotypes [Collins et al, 2011; Goldhirsch et al, 2011; Niemeier et al, 2010]. In invasive carcinomas, AR expression was identified in 89% of luminal A, 66% of luminal B, 54% of HER2 amplified, 31% of triple negative breast cancer (TNBC) and 35% of unclassified breast cancers [Collins et al, 2011; Niemeier et al, 2010]. The role of AR signaling in patients with AR-positive (AR+) breast cancer remains to be elucidated through well conducted studies using selective and potent AR signaling inhibitors.

AR expression has been identified in over 50% of patients with HER2 positive/hormone receptor negative disease [Hu et al, 2011; Park et al, 2010]. An evaluation of published microarray data from 3 patient sets demonstrated that AR gene expression levels correlated

with HER2 amplification/ overexpression [Ni et al, 2011]. This is consistent with immunohistochemistry (IHC) observations of AR expression correlating with HER2 overexpression [Niemeier et al, 2010; Park et al, 2010; Agoff et al, 2003]. Prolonged AR stimulation in an AR+ cell line where ER is absent and HER2 is expressed but not amplified (MDA-MB-453) resulted in activation of HER2/HER3 signaling. Bicalutamide reversed this activation via reduction of total and phosphorylated HER3 protein and inhibited growth. The combination of lapatinib (a tyrosine kinase inhibitor with activity against HER1 and HER2) and bicalutamide was more active than either agent alone [Brown, 2011]. In vivo, dihydro-testosterone (DHT) enhanced tumor growth while bicalutamide caused tumor regression [Ni et al, 2011]. A similar mechanism of action may be occurring in AR+/ER- cell lines where HER2 is amplified. In BT474 cells (AR+/ER-/HER2+amplified), DHT treatment increases both total and phospho-HER3 protein [Richer AACR Advances in Breast Cancer meeting, 03 Oct, 2013]. In addition, the combination of enzalutamide and trastuzumab can reverse HER3 activation better than either agent alone and reduce cell growth [Richer AACR Advances in Breast Cancer meeting, 03 Oct, 2013]

Clinical evaluations of agents that interfere with HER2/HER3 crosstalk in patients with HER2 amplified breast cancer have yielded promising results [Baselga et al, 2012]. The combination of pertuzumab plus trastuzumab plus docetaxel, as compared with placebo plus trastuzumab plus docetaxel, when used as first-line treatment for HER2-positive metastatic breast cancer, significantly prolonged progression-free survival, with no increase in cardiac toxic effects. The median progression-free survival was 12.4 months in the control group, as compared with 18.5 months in the pertuzumab group. The interim analysis of overall survival showed a strong trend in favor of pertuzumab plus trastuzumab plus docetaxel. Median overall survival was 37.6 months in the placebo group but had not been reached in the pertuzumab group [Swain et al, 2013]. Taken together, these data warrant further clinical investigation of a possible link between AR and growth factor pathways in AR+/HER2+ breast cancer. The primary pharmacodynamic (PD) effect of enzalutamide is inhibition of the AR signaling pathway. Medivation and APGD are in a partnership to co-develop enzalutamide for the treatment of breast cancer.

1.2 Nonclinical and Clinical Data

1.2.1 Nonclinical Studies

1.2.1.1 Pharmacology

The primary PD effect of enzalutamide is inhibition of the AR signaling pathway. Primary PD has been defined in experiments that demonstrated inhibition of AR binding, inhibition of AR nuclear translocation, inhibition of AR chromatin association, inhibition of AR-dependent transcription and cancer cell proliferation, induction of cell death and tumor regression, and lack of agonist activity. On the whole, nonclinical data on the primary PD of enzalutamide shows that it is a potent AR inhibitor, and further that it is distinct from other anti-androgens in affecting multiple points in the AR signaling pathway.

A major human metabolite of enzalutamide, N-desmethyl enzalutamide, demonstrated key primary PD of similar potency to the parent molecule.

Two luminal AR+ and ER+ breast cancer cell lines, MCF7 and BCK4, were shown to proliferate in response to AR stimulation with DHT. Enzalutamide inhibited DHT-mediated cell growth in both cell lines. Enzalutamide also inhibited estradiol-mediated cell growth of MCF7 and BCK4 cells. In contrast, bicalutamide did not inhibit estradiol-mediated cell growth of MCF7 cells. Consistent with the inhibitory effect on estradiol-induced cell growth, enzalutamide also blocked estradiol-stimulated expression of 3 genes: Stromal Cell-Derived Factor-1 (SDF-1), the progesterone receptor (PgR), and the AR. As enzalutamide does not block binding of estradiol to the ER, these data suggest that AR and ER crosstalk, and AR signaling inhibition with enzalutamide has a dominant negative role on ER signaling. In AR+, ER-negative (ER-) breast cancer cells (MDA-kb2), enzalutamide inhibits DHT-induced viability at 10 µM.

The effect of enzalutamide on several Her2-amplified cell lines was evaluated in vitro. In some cases, DHT could enhance the growth of these cell lines. In the cell lines tested, either enzalutamide or trastuzumab inhibited cell growth in the presence or absence of DHT. In the cases where DHT was present, enzalutamide reduced cell number below nonDHT-treated levels. A similar observation was made with trastuzumab. When cells were treated with both agents, a further reduction in cell number was observed. The results are summarized in the table below.

Table 2 Effect of Enzalutamide and Trastuzumab on Her2-amplified Breast Cancer Cell Lines

Cell line	Receptor Status	Stimulated by DHT	Enz	Tras	Enz + Tras
SK-BR-3	ER-/PgR-	NT	R	R	E
SUM225*	ER-/PgR-	Y	R	R	E
ZR-75-30*	ER+/PgR-	N	R	R	E
UACC812	ER+/PgR+	NT	R	NT	NT
BT-474*	ER+/PgR+	Y	R	R	E

*Tested in the presence of DHT, Enz-enzalutamide, Tras-trastuzumab, R-reduced cell number, E-enhanced reduction in cell number beyond Enz or Tras alone, NT-not tested

Please refer to the Investigator's Brochure for more information.

1.2.1.2 Pharmacokinetics

Following oral administration in animals, enzalutamide is eliminated slowly from plasma with a long $t_{1/2}$ across species. In vitro studies show that enzalutamide is metabolized by human recombinant cytochrome P450 (CYP) isoenzymes CYP2C8 and CYP3A4/5.

Enzalutamide and/or its major human metabolites caused direct in vitro inhibition of multiple CYP enzymes including CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5; however, subsequent clinical data showed that enzalutamide is an inducer of CYP2C9, CYP2C19 and CYP3A4/5 and had no clinically meaningful effect on CYP2C8 (see Section 1.2.2.1). In vitro, enzalutamide caused time-dependent inhibition of CYP1A2. Based

on in vitro data, enzalutamide is a potential inducer of CYP3A4 and is not expected to induce CYP1A2 at therapeutically relevant concentrations.

In vitro data show that enzalutamide and its active metabolite N-desmethyl enzalutamide are potential inhibitors, but not substrates, of the efflux transporter P-glycoprotein (P-gp).

Please refer to the Investigator's Brochure for more information.

1.2.1.3 Toxicology

The species included in the toxicity program were mice, rats, dogs and cynomolgus monkeys.

Electrocardiogram (ECG) and cardiovascular assessments in a toxicity study in dogs showed no treatment related effects. In vivo and in vitro safety pharmacology studies also demonstrated the absence of cardiovascular enzalutamide-related effects.

Enzalutamide was non mutagenic in bacteria, nonclastogenic in mammalian cells and non genotoxic in vivo in mice. The 2 major human metabolites (N-desmethyl enzalutamide and an inactive carboxylic acid derivative) and a minor metabolite (M6) were negative for mutagenicity in the bacterial reverse mutation assay (Ames).

Overall, enzalutamide was generally well tolerated in pivotal nonclinical studies with rats and dogs with the most prominent effects occurring in reproductive and hormone-sensitive tissues.

Please refer to the Investigator's Brochure for more information.

1.2.2 Clinical Studies

1.2.2.1 Pharmacokinetics

The pharmacokinetics (PK) of oral enzalutamide is being investigated in a Phase 1 study in women with advanced breast cancer (MDV3100-08, NCT01597193). Preliminary data demonstrate similar PK of enzalutamide and N-desmethyl enzalutamide in women relative to men with CRPC.

The PK and metabolism of enzalutamide have been evaluated in more than 2500 patients with prostate cancer and in more than 200 volunteers, including healthy male subjects and subjects with mild or moderate hepatic impairment. Individual daily doses have ranged from 30 to 600 mg.

Oral absorption of enzalutamide, whether administered as single or multiple doses, is rapid and independent of dose. Peak concentration of enzalutamide is generally achieved 1 to 2 hours post dose in both patients and healthy subjects. Enzalutamide is well absorbed (estimated bioavailability based on mass balance data $\geq 84.2\%$). The mean $t_{1/2}$ is 5.8 days, and does not appear to be affected by dose. With daily administration, it takes approximately 1 month to reach steady state. The accumulation ratio is 8.3-fold. At steady state, enzalutamide shows approximately dose proportional PK over the range of 30 to 600 mg/day.

A mass balance and biotransformation study in healthy male volunteers showed that enzalutamide is primarily eliminated by hepatic metabolism.

A food-effects study showed that food does not have a clinically relevant effect on AUC of enzalutamide or N-desmethyl enzalutamide; therefore, enzalutamide can be taken with or without food.

A hepatic impairment study showed that the composite area under the curve (AUC) of enzalutamide plus N-desmethyl enzalutamide after single-dose enzalutamide was similar in subjects with baseline mild or moderate hepatic impairment (Child-Pugh Class A and B, respectively) relative to subjects with normal hepatic function, and no starting dose adjustment is needed.

A clinical drug-drug interaction study showed that enzalutamide can affect exposures to other co-medications. At steady state, enzalutamide did not have a clinically significant effect on exposure to pioglitazone (CYP2C8 substrate). Steady-state enzalutamide reduced the AUC of midazolam (CYP3A4 substrate), S-warfarin (CYP2C9 substrate) and omeprazole (CYP2C19 substrate) by 86%, 56% and 70%, respectively. Therefore, enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. Substrates of CYP3A4, CYP2C9 and CYP2C19 with a narrow therapeutic index are to be avoided, as enzalutamide may decrease plasma exposure of these drugs.

Another clinical drug-drug interaction study showed that concomitant medications can affect exposure to enzalutamide. Coadministration of gemfibrozil (a strong CYP2C8 inhibitor) increased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold; therefore, strong CYP2C8 inhibitors are to be avoided. If coadministration with a strong CYP2C8 inhibitor is necessary, the dose of enzalutamide is to be reduced to 80 mg once daily. Coadministration of itraconazole (strong CYP3A4 inhibitor) increased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 1.3-fold; as this small change is not clinically meaningful, no starting dose adjustment is needed when coadministering enzalutamide with CYP3A4 inhibitors.

Strong or moderate inducers of CYP3A4 or CYP2C8 are to be avoided as they can alter the plasma exposure to enzalutamide plus N-desmethyl enzalutamide.

1.3 Summary of Key Safety Information for Study Drugs

1.3.1 Enzalutamide

To date, limited safety data are available from the ongoing Phase 1 study of enzalutamide in women with breast cancer (MDV3100-08, NCT01597193). The dose-escalation portion of the study evaluated 80 and 160 mg/day, and 160 mg/day was determined to be the recommended Phase 2 dose. The dose-expansion portion of this study is evaluating enzalutamide at 160 mg/day as a single agent in women with AR+ breast cancer, and enzalutamide at 160 mg/day in combination with either anastrozole or exemestane in women with ER+ breast cancer. Preliminary data suggest a similar safety profile to that observed in men. In addition, enzalutamide is being evaluated in a Phase 2, single-arm, open-label study in AR+ TNBC patients, MDV3100-11 (NCT01889238), and in a Phase 2, randomized, double-blind, placebo-controlled study in combination with exemestane in ER+/PgR+ HER2-normal breast cancer patients, MDV3100-12.

As of 28 Feb 2015, over 3000 patients with prostate cancer, over 300 women with breast cancer and over 250 subjects with no known cancer, including healthy male subjects and subjects with hepatic impairment, have received at least 1 dose of enzalutamide in completed and ongoing clinical studies.

Enzalutamide 160 mg daily was generally well-tolerated in subjects with CRPC. The adverse events (AEs) occurring in at least 5% of the enzalutamide group and at an incidence at least 2% greater than in the placebo group included fatigue (37% vs. 30%), arthralgia (21% vs. 17%), diarrhea (20% vs. 18%), hot flush (20% vs. 10%), peripheral edema (16% vs. 13%), musculoskeletal pain (14% vs. 12%), headache (12% vs. 6%), muscular weakness (9% vs. 7%), insomnia (9% vs. 6%), hematuria (7% vs. 5%), hypertension (6% vs. 3%) and pollakiuria (5% vs. 3%).

Other AEs reported less commonly than 5% but that may be associated with enzalutamide treatment after careful assessment of the AEs include: falls (4.5% vs. 1.3%), nonpathologic fracture (4.0% vs. 0.8%), dry skin (3.6% vs. 1.3%) and pruritus (3.3% vs. 1.3%). A possible cognitive effect of enzalutamide was observed with a greater proportion of patients in the enzalutamide-treated group (4.5% vs. 1.8%) reporting the following AE terms: memory impairment, cognitive disorder, amnesia, disturbance of attention and dementia. In addition, event terms related to hallucination (visual hallucination, tactile hallucination, hallucination) were reported more frequently in the enzalutamide-treated group (1.6% vs. 0.3%).

In clinical studies, seizure was identified as a risk associated with enzalutamide treatment. In the controlled clinical study CRPC2, seizures occurred in 0.9% (7/800) of patients receiving enzalutamide 160 mg daily, whereas no seizures occurred in patients treated with placebo. Confounding factors may have contributed to the occurrence of seizures in several of these cases. Dose appears to be an important predictor of seizure, with a greater risk of seizure at daily doses higher than 160 mg. In a dose escalation study involving 140 patients, no patients experienced seizures at or below daily doses of 240 mg, whereas 3 seizures were reported, 1 each at 360, 480 and 600 mg/day. Caution should be used in administering enzalutamide to patients with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, stroke, primary brain tumors or brain metastases or alcoholism. In addition, the risk of seizure may be increased in patients receiving concomitant medications that may lower the seizure threshold. Enzalutamide should be permanently discontinued in patients who have a seizure while on treatment.

Enzalutamide should not be administered to any patient who has shown a hypersensitivity reaction to the active pharmaceutical ingredient or any of the enzalutamide capsule components, including Labrasol, butylated hydroxyanisole and butylated hydroxytoluene.

Concomitant administration of enzalutamide with strong CYP2C8 inhibitors, strong or moderate CYP2C8 inducers, strong or moderate CYP3A4 inducers should be avoided. Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4, CYP2C9, and CYP2C19 should be avoided. Subjects should avoid use of any herbal medications or dietary supplements including products containing *Hypericum perforatum* (e.g., St. John's Wort).

Food has no clinically significant effect on the extent of absorption. Enzalutamide may be taken with or without food.

1.3.2 Trastuzumab

Signs and symptoms of cardiotoxicity and cardiac dysfunction have been observed in patients treated with Trastuzumab, especially when used concurrently with anthracyclines.

Please refer to local prescribing information for key safety information.

1.4 Risk-Benefit Assessment

Although new therapies are available for patients with metastatic HER2+ breast cancer, this still remains an unmet medical need as patients will eventually progress on their treatments [Lin et al, 2004].

Enzalutamide given at 160 mg/day has been evaluated and found to be well tolerated in a Phase 3 study in men with prostate cancer. It is the dose approved by the Food and Drug Administration (FDA) and European Medicinal Agency (EMA) for use in men with castration-resistant prostate cancer after chemotherapy.

A Phase 1 dose escalation study in women with Stage IV and locally advanced unresectable breast cancer is ongoing. The dose of 160 mg daily has been found tolerable according to the protocol dose escalation criteria. To date, enzalutamide has been generally safe and well tolerated in breast cancer subjects.

This Phase 2 study represents a proof-of-concept study in women with HER2+/AR+ breast cancer. The patient population selected for this study is a standard population for the assessment of safety, tolerability, PK and anti-tumor activity in a Phase 2 breast cancer setting.

Restricting the HER2+ population to AR+ patients is to minimize exposure to potential toxicities in patients least likely to benefit from enzalutamide. Moreover, this study will enroll subjects who would be receiving a HER2-targeting agent (e.g., trastuzumab monotherapy) as part of their standard of care treatment.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

To evaluate the efficacy of enzalutamide with trastuzumab in evaluable subjects with human epidermal growth factor receptor 2 positive (HER2+) and androgen receptor positive (AR+) metastatic or locally advanced breast cancer, as measured by Clinical Benefit Rate (CBR) [defined as the proportion of evaluable subjects with best objective response of confirmed CR or PR per RECIST 1.1, or prolonged SD (≥ 24 weeks)].

2.1.2 Secondary Objectives

- To evaluate the following efficacy measures:
 - Best Overall Response Rate (BORR)
 - Overall Response Rate (ORR) at 24 weeks
 - Progression Free Survival (PFS)
 - Time to Progression (TTP)
 - Duration of Response (DOR)
 - Time to Response (TTR)
- To evaluate safety and tolerability.

2.1.3 Exploratory Objectives

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This is a multinational, multicenter, open-label, single-arm, 2-stage, Phase 2 study evaluating the efficacy, safety, and tolerability of enzalutamide with trastuzumab. The study population includes female subjects with HER2+ and AR+ metastatic or locally advanced breast cancer who have progressed on at least 1 prior line of anti-HER2 therapy in the metastatic or advanced setting. Subjects may be either ER/PgR positive or negative according to the local assessment for hormone receptor diagnostics. A line of therapy is defined as a course of treatment at the end of which there was disease progression, toxicity, or in the Investigator's opinion, maximum benefit has been achieved. Approximately 55 centers in North America and Europe will conduct the study. Approximately 80 subjects were planned to be enrolled to reach 66 evaluable AR+ subjects. 103 subjects were actually enrolled in the study.

A Simon's 2-stage design is implemented to allow for early termination if < 3 of 21 evaluable AR+ subjects show clinical benefit [confirmed complete response (CR), partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, criteria or prolonged stable disease (SD) \geq 24 weeks] at the analysis of the first stage. If \geq 3 of 21 evaluable AR+ subjects show clinical benefit, then a second stage will continue to enroll a total of 66 evaluable AR+ subjects.

Subjects will enter the screening period up to 28 days prior to treatment start. Subjects will be allowed to prescreen under a separate consent form to enable testing of archival tissue for AR expression before initiation of other screening activities. After completion of screening assessments, eligible subjects will enter into the treatment phase to receive enzalutamide with trastuzumab. Study visits will take place every 3 weeks until week 16, then at weeks 25, 34,

40, and 49, and then every 12 weeks thereafter until the subject meets discontinuation criteria or the study ends. Tumor assessments will be performed every 8 weeks through week 49, and then every 12 weeks thereafter. Subjects will continue on treatment until disease progression, unacceptable toxicity, or any other discontinuation criteria are met. Upon discontinuation of study drug, subjects will enter the follow-up period. An end of treatment visit will be performed within 7 days of the last dose of enzalutamide. The Follow-up Visit will be performed 30 days after the last dose of enzalutamide or before initiation of subsequent treatment (whichever occurs first); this visit may be conducted by phone call if the subject is unable to return to the clinic. The treatment emergent period will be defined as the period of time from the first dose date of study drug to 30 days after the last dose date of study drug or the start of subsequent treatment (whichever occurs first). All AEs that occur during the collection period are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

If the study is terminated early for reasons other than safety, and the subject is receiving clinical benefit per Investigator's judgment, the subject may continue on study medication until they have disease progression as defined per RECIST.

2.2.2 Dose Rationale

Enzalutamide given at 160 mg/day has been approved by the FDA and EMA for use in men with castration-resistant prostate cancer after docetaxel chemotherapy.

A Phase 1 dose escalation study in women with breast cancer (MDV3100-08) has identified the 160 mg/day dose as the recommended dose in women.

Trastuzumab will be given per local guidelines. Trastuzumab given as an 8mg/kg loading dose followed by 6 mg/kg every 21 days has been evaluated in numerous studies and remains standard of care treatment after first line therapy for advanced metastatic or locally advanced disease [NCCN, 2012; Cardoso et al, 2012]. Trastuzumab given every 21 days is preferred over the weekly schedule for subject convenience with similar safety and efficacy observed [Leyland-Jones et al, 2003].

2.3 Endpoints

2.3.1 Primary Endpoint

CBR defined as the proportion of evaluable subjects with best objective response of confirmed CR or PR per RECIST 1.1 or prolonged SD (≥ 24 weeks) criteria.

2.3.2 Secondary Endpoints

2.3.2.1 Efficacy Endpoints

Efficacy Endpoints include:

- Overall response rate (CR+PR) at 24 weeks according to RECIST 1.1 criteria.
- Best overall response rate according to RECIST 1.1.

- PFS is defined as the time from the date of first dose of enzalutamide (Study Day 1) until the date of disease progression per RECIST 1.1, or death from any cause on study, whichever occurs first.
- TTP is defined as the time from the first date of enzalutamide treatment until the date of disease progression per RECIST 1.1.
- DOR is defined as the time from the date of first documentation of response (CR or PR) until the date of disease progression per RECIST 1.1.
- TTR is defined as the time from the first date of enzalutamide treatment to initial CR or PR.

2.3.2.2 Safety Endpoints

Safety will be assessed on an ongoing basis by physical examination, measurement of vital signs, laboratory assessments, 12-lead ECGs, left ventricular ejection fraction (LVEF) by echocardiogram, myocardial perfusion scintigraphy (MPS) or multi-gated acquisition scan (MUGA), and evaluation of AEs/serious adverse events (SAEs).

2.3.3 Exploratory Endpoints

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3 STUDY POPULATION

3.1 Selection of Study Population

Subjects will be selected based on Inclusion and Exclusion Criteria listed. Waivers to eligibility criteria will not be allowed.

3.2 Inclusion Criteria

Subject is eligible for the study if all of the following apply:

1. The subject has consented and signed an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act [HIPAA] for U.S. sites) prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. The subject is a female ≥ 18 years of age.
3. The subject has histologically or cytologically proven adenocarcinoma of the breast that is HER2+ defined as a score of 3+ for staining by IHC, or IHC 2+ with HER2 gene amplification as determined by a locally approved *in situ* hybridization (ISH) assay, or (for patients without IHC data) HER2 gene amplification.
4. The subject has AR+ breast cancer, which is defined as any tumor cells with nuclear AR staining by IHC. Enrollment may be based on the local pathologist's findings; however, tissue will be sent to a central pathology laboratory for assessment. NOTE: If a subject is enrolled in the study based on local pathologist results, but subsequent central assessment cannot confirm AR+ disease, the subject may remain in the study.
5. The subject has metastatic disease or has locally advanced disease that is not amenable to curative treatment.
6. The subject has measurable disease or nonmeasurable, evaluable disease per RECIST 1.1 (NOTE: pleural effusions, ascites or other third fluid space are not evaluable diseases per RECIST 1.1).
7. The subject has received at least 1 line of therapy in the metastatic or locally advanced disease setting:
 - A line of therapy is defined as a course of treatment at the end of which there was disease progression, toxicity, or in the Investigator's opinion, maximum benefit has been achieved. If the subject discontinued therapy due to any other reason but progressed without receiving other treatment, this would be considered a line of therapy.
 - The subject has been documented to have progressed by determination of the Investigator on a regimen containing an anti-HER2 agent (includes trastuzumab emtansine in countries where it is not approved) as the most recent regimen or the most recent anti-HER2 regimen was discontinued for any toxicity, with the exception of a cardiotoxicity.

- Subjects who received < 28 days of therapy in the most recent regimen may be eligible upon approval from the medical monitor.
 - The subject has progressed on a trastuzumab containing regimen. If progression occurred within 12 months after completing trastuzumab-containing adjuvant treatment, this counts as having received trastuzumab but not as a line of therapy.
8. The subject has adequately recovered from toxicities due to prior therapy.
 9. The subject has an Eastern Cooperative Oncology Group performance (ECOG) status ≤ 1 at Screening and Day 1.
 10. The subject has available at the site a representative, formalin-fixed, paraffin-embedded, tumor specimen that enabled the definitive diagnosis of breast cancer with adequate viable tumor cells in a tissue block (preferred) or ≥ 10 (20 preferred) freshly cut, unstained, serial slides and the associated pathology report:
 - Archival tissue from the most recent biopsy available is preferred.
 - For subjects who are known AR+ per local pathology report, a fresh biopsy can be done, per Investigator's discretion, to obtain tissue for central AR confirmation if the archival specimen is insufficient or unavailable.
 - Cytological or fine-needle aspiration samples are not acceptable.
 11. The subject has an estimated life expectancy of at least 6 months at Day 1, in the opinion of the Investigator.
 12. The subject is either:
 - Of nonchildbearing potential:
 - postmenopausal (defined as no spontaneous menses for at least 12 months prior to Screening with FSH > 40 IU/L at Screening for women < 55 years of age),
 - documented surgically sterile or status post hysterectomy (at least 1 month prior to Screening),
 - Or, if of childbearing potential,
 - must agree to not try to become pregnant during the study and for 5 half-lives (29 days) after the final study drug administration
 - must have a negative urine pregnancy test at Screening and at Day 1 before the first dose of study drug is administered,
 - must use 2 acceptable methods of birth control starting at Screening and through 6 months after the final study drug administration.

The 2 acceptable methods of birth control are as follows or per local guidelines where these require additional description of contraceptive methods:

- A barrier method (e.g., condom by a male partner) is required; AND
- One of the following is required:
 - Placement of an intrauterine device (IUD) or intrauterine system (IUS);
 - Additional barrier method including occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository;
 - Vasectomy or other surgical castration at least 6 months before Screening.

13. The subject must not be breastfeeding at Screening or during the study period, and for 6 months after the final study drug administration.
14. The subject must be able to swallow study drug and comply with study requirements.
15. The subject agrees not to participate in another interventional study while on treatment.

Waivers to the inclusion criteria will **NOT** be allowed.

3.3 Exclusion Criteria

Subject will be excluded from participation if any of the following apply:

1. The subject has a severe concurrent disease, infection, or comorbidity that, in the judgment of the Investigator, would make the subject inappropriate for enrollment.
2. The subject has current or previously treated brain metastasis or active leptomeningeal disease. Brain imaging is required during screening in all subjects to exclude the presence of unequivocal central nervous system disease.
3. The subject has a history of a nonbreast cancer malignancy with the following exceptions:
 - The subject with a previous history of a noninvasive carcinoma is eligible if in the opinion of the Investigator he/she has had successful curative treatment any time prior to Screening.
 - For all other malignancies, the subject is eligible if they have undergone potentially curative therapy and they have been considered disease free for at least 5 years prior to Screening.
4. The subject has inadequate marrow, hepatic, and/or renal function at the Screening Visit defined as:
 - Absolute neutrophil count $< 1.5 \times 10^9/L$ (< 1500 cells/mm³)
 - Platelet count $< 75 \times 10^9/L$ ($< 75,000$ cells/mm³)
 - Hemoglobin < 5.6 mmol/L (< 9 g/dL)
 - Total bilirubin $> 1.5 \times$ Upper Limit of Normal (ULN) unless there is an alternate nonmalignant etiology (e.g., Gilbert's syndrome).
 - AST or alanine aminotransferase (ALT) $> 3 \times$ ULN (or $> 5 \times$ ULN if hepatic metastasis is present).
 - Creatinine $> 1.5 \times$ ULN or Glomerular Filtration Rate (eGFR)/Creatinine Clearance (CrCL) < 30 mL/min, whichever is more restrictive.
 - NOTE: May not have received any growth factors or blood transfusions within 7 days before the hematology values obtained at screening.
5. The subject has a history of seizure or any condition that may predispose to seizure (e.g., prior cortical stroke, significant brain trauma).
6. The subject has a history of loss of consciousness, cerebrovascular accident, or transient ischemic attack within 12 months before the Day 1 visit.

7. The subject has had a hypoglycemic episode requiring medical intervention while on insulin (or other anti-diabetic) treatment within 12 months before Day 1.
8. The subject has clinically significant cardiovascular disease including:
 - Myocardial infarction within 6 months before the Day 1 visit.
 - Uncontrolled angina within 6 months before the Day 1 visit.
 - Congestive heart failure New York Heart Association (NYHA) Class III or IV or history of congestive heart failure NYHA Class III or IV in the past, unless a screening echo-cardiogram, myocardial perfusion scintigraphy (MPS), or multi-gated acquisition scan performed within 3 months before the Day 1 visit reveals a left ventricular ejection fraction that is $\geq 50\%$.
 - History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, Torsade de Pointes).
 - History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place.
 - Hypotension as indicated by systolic blood pressure < 86 mmHg on 2 consecutive measurements at the Screening visit.
 - Bradycardia (in the presence of known cardiovascular disease) as indicated by a heart rate of < 50 beats per minute on the Screening ECG recording.
 - Uncontrolled hypertension as indicated by systolic blood pressure > 170 mmHg or diastolic blood pressure > 105 mmHg on 2 consecutive measurements at the Screening visit.
9. The subject has significant respiratory disease, including severe dyspnea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.
10. The subject has an active gastrointestinal disorder affecting absorption (e.g., gastrectomy, active peptic ulcer disease) within the 3 months prior to the Day 1 visit.
11. The subject had a major surgical procedure, substantial open biopsy, or significant traumatic experience within 28 days before the Day 1 visit, or anticipation of need for major surgical procedure during the course of the study.
12. The subject has had palliative radiation therapy to bone metastases within 14 days prior to the Day 1 visit (side effects from radiation must be resolved).
13. The subject has received chemotherapy, immunotherapy, or any other systemic anti-cancer therapy, with the exception of anti-HER2 therapy (e.g., trastuzumab), within 14 days prior to the Day 1 visit.
14. The subject has been treated with any investigational drugs within 14 days prior to the Day 1 visit.
15. The subject has received treatment with any approved or investigational agent that either blocks androgen synthesis or targets the AR (e.g., abiraterone acetate, bicalutamide, enzalutamide, TAK-448, TAK-683, TAK-700, ARN-509, ODM-201, BMS-641988).

Subjects who received treatment for < 28 days or placebo on an investigational study are acceptable.

16. The subject would, in the Investigator's opinion, benefit from estrogen receptor targeted therapy while on study.
17. The subject has used any of the following within 28 days before the Day 1 visit:
 - 5- α reductase inhibitors
 - Systemic androgens and estrogens
18. The subject has a known history of positive test for Hepatitis B surface antigen (HBsAg) or hepatitis C antibody or history of positive test for Human Immunodeficiency Virus (HIV).
19. The subject has shown a hypersensitivity reaction to the active pharmaceutical ingredient or any of the enzalutamide capsule components, including Labrasol, butylated hydroxyanisole and butylated hydroxytoluene.
20. The subject has had a severe infusion reaction to trastuzumab or hypersensitivity to trastuzumab, and excipients including murine proteins, L-histidine, L-histidine hydrochloride monohydrate, α,α -trehalose dehydrate, L-methionine, and polysorbate.
21. The subject has any other condition or reason that, in the opinion of the Investigator, would make the subject ineligible to receive trastuzumab, interferes with the ability of the subject to participate in the trial, places the subject at undue risk, or complicates the interpretation of safety data.

Waivers to the exclusion criteria will NOT be allowed.

4 TREATMENT(S)

4.1 Identification of Investigational Product(s)

4.1.1 Test Drug(s)

Enzalutamide and trastuzumab are components of the study regimen.

4.1.1.1 Enzalutamide

Enzalutamide is an opaque white to off-white oblong liquid filled soft gelatin capsule for oral administration. Each capsule contains 40 mg enzalutamide.

4.1.1.2 Trastuzumab

Trastuzumab may be given by IV infusion or sub-cutaneous injection.

IV infusion; Trastuzumab is a sterile, white to pale yellow, preservative-free, lyophilized powder for reconstitution to solution for IV infusion. Trastuzumab is supplied as vials containing 440 mg or 150 mg lyophilized powder. Please refer to the local prescribing information for specific information on identification [Herceptin Product Monograph, 2012; Herceptin Prescribing Information, 2010; Herceptin Summary of Product Characteristics, 2010].

4.1.2 Comparative Drug(s)

Not applicable.

4.2 Packaging and Labeling

4.2.1 Enzalutamide

Enzalutamide is supplied by APGD. Enzalutamide will be packaged in high-density polyethylene bottles with child-resistant induction seal closure. There are 124 capsules per bottle.

Enzalutamide will be prepared, packaged, and labeled under the responsibility of qualified staff at APGD-Astellas United States Technologies (AUST) or Sponsor's designee in accordance with APGD-AUST or Sponsor's designee Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines, and applicable local laws/regulations.

Each bottle will bear a label conforming to regulatory guidelines, Good Manufacturing Practice and local laws and regulations which identifies the contents as investigational drug.

A qualified person of Astellas Pharma Europe B.V. (APEBV) or Sponsor's designee will perform the final release of the medication according to Directive 2003/94/EC annex 13.

4.2.2 Trastuzumab

Trastuzumab will be supplied by the responsible site pharmacy of each investigational site or by the sponsor if applicable. If trastuzumab is supplied by the sponsor, trastuzumab used in the study will be labeled under the responsibility of AUST/APGD Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines, and applicable local laws/regulations.

4.3 Study Drug Handling

Enzalutamide will be stored in a secure location with limited access at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F). Subjects will be instructed to store study drug at room temperature and out of the reach of children.

Trastuzumab must be stored according to the product label. If provided by APGD, trastuzumab will be stored at 2-8°C (36-46°F) prior to reconstitution.

Current ICH GCP Guidelines require the Investigator to ensure that enzalutamide and trastuzumab (if supplied by APGD), deliveries from the Sponsor are received by the Investigator/or designee and

- that such deliveries are recorded,
- that study drug is handled and stored according to labeled storage conditions,
- that study drug with appropriate expiry/retest and is only dispensed to study subjects in accordance with the protocol, and
- that any unused study drug is returned to the Sponsor.

Drug inventory and accountability records for enzalutamide and trastuzumab (if supplied by APGD), will be kept by the Investigator/or designee. Enzalutamide accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The Investigator agrees not to supply enzalutamide to any persons except the eligible subjects in this study in accordance with the protocol.
- The Investigator or designee will keep the enzalutamide in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the Investigator to dispense enzalutamide.
- A study drug inventory will be maintained by the Investigator or designee. The inventory will include details of material received and a clear record of when it was dispensed and to which subject.
- At the conclusion or termination of this study, the Investigator or designee agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or returned medication. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.
- The site must return enzalutamide and trastuzumab (if supplied by APGD) to the Sponsor or designee at the end of the study or upon expiration.

4.4 Blinding

This section is not applicable as this is an open-label study.

4.5 Assignment and Allocation

All subjects will receive the same treatment. An Interactive Response Technology (IRT) system will be used to register subjects and to assign specific enzalutamide containers by packaging lot to subjects. Specific procedures for the IRT are contained in a separate IRT procedures manual.

4.5.1 Subject Registration

Subjects will be registered using the IRT at the time of informed consent signature for the main study. A subject number will be assigned and will be used throughout the study for that subject. Prescreen subjects should not be called into the IRT system.

4.5.2 Subject Enrollment

Subjects who are found to be eligible for treatment will be enrolled using the IRT at the Day 1 visit.

4.5.3 Definition of Treated Subject

Subjects will be considered as having entered treatment on Day 1 upon initiation of dosing with enzalutamide.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drug(s) and Other Medication(s)

5.1.1 Dose/Dose Regimen and Administration Period

5.1.1.1 Enzalutamide

Enzalutamide will be given as 160 mg/day (4 x 40 mg capsules) each day by mouth until any of the discontinuation criteria are met. Enzalutamide may be administered with or without food, and should be given around the same time each day.

Enzalutamide will be self-administered at home by the subject, except for visit days where PK samples are collected. On visit days with PK sampling, enzalutamide will be administered in clinic after the PK sample is collected. Subjects will keep a diary to record the date and time of enzalutamide dose on the 2 days before PK visit days.

Subjects should not make up missed or vomited doses; dosing should resume on the next calendar day unless otherwise instructed. For the purposes of this study, a “missed dose” is considered a dose not administered within 4 hours of the regular dosing time.

5.1.1.2 Trastuzumab

Trastuzumab should be administered as approved per local guidelines (IV infusion or subcutaneous injection).

Trastuzumab for infusion is typically given at a dose of 6 mg/kg every 21 days. For subjects whose last dose of anti-HER2 antibody was greater than 21 days prior to Day 1 (or for subjects who were on weekly trastuzumab for ≤ 2 weeks), a loading dose of 8 mg/kg will be administered on Day 1, followed by 6 mg/kg every 21 days thereafter until any of the discontinuation criteria are met.

Trastuzumab is given as an IV infusion over 30-90 minutes. For a loading dose, a 90 minute IV infusion is given or per local label. Premedication per institutional guidelines is permitted.

If trastuzumab is given via sub-cutaneous injection, local guidelines should be followed.

Refer to the package insert for specific preparation instructions.

5.1.2 Increase or Reduction in Dose of the Study Drug(s)

5.1.2.1 Enzalutamide

Enzalutamide treatment may be interrupted for subjects who experience a Grade ≥ 3 toxicity that is attributed to enzalutamide and cannot be ameliorated with adequate medical intervention. Enzalutamide may be resumed at the original dose (160 mg/day) or at a reduced dose (80 mg/day or 120 mg/day), per Investigator’s discretion. Treatment interruption for > 2 weeks must be discussed with the Medical Monitor. If the treatment interruption occurs for 4 weeks, the Medical Monitor must be contacted again for approval. Interruption of enzalutamide dosing for more than 4 weeks must be approved by the Medical Monitor, otherwise the subject will be discontinued. A dose adjustment should also be considered in subjects with Grade 2 toxicities that interfere with quality of life.

If coadministration with a strong CYP2C8 inhibitor is necessary, reduce the dose of enzalutamide to 80 mg once daily. If coadministration with the strong CYP2C8 inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the CYP2C8 inhibitor, or to 160 mg once daily if the subject was on the CYP2C8 inhibitor at the start of study treatment.

5.1.2.2 Trastuzumab

5.1.2.2.1 Dose Modification for Infusion Reaction

Infusion reactions will be managed according to the institution standard.

5.1.2.2.2 Dose Modification for Cardiomyopathy

Trastuzumab will be withheld for at least 4 weeks if either of the following occurs:

- ≥ 16 % absolute decrease in LVEF from baseline value

- LVEF below institutional limit of normal and ≥ 10% absolute decrease in LVEF from baseline value

Trastuzumab may be resumed if, within 4 to 8 weeks, the LVEF returns to normal limit and the absolute decrease from baseline is ≤ 15%. Trastuzumab should be discontinued for a persistent (> 8 weeks) LVEF decline or for suspension of dosing on more than 3 occasions for cardiomyopathy and the subject should be withdrawn from the study.

5.1.2.2.3 Dose Modification for All Other Toxicities

If a subject experiences an intolerable side effect, trastuzumab dosing may be held for up to 4 weeks or until symptoms improve. If the treatment interruption will occur for more than 4 weeks, the Medical Monitor must be contacted for approval. Interruption of trastuzumab dosing for more than 4 weeks for toxicity (other than for cardiomyopathy, see Section 5.1.2.2.2) must be approved by the Medical Monitor, otherwise the subject will be discontinued.

5.1.3 Previous and Concomitant Treatment (Medication and Nonmedication Therapy)

Medications taken within 14 days before the Screening visit up to the Study 30-Day Follow-up visit will be documented on the appropriate case report form as concomitant medication.

All concomitant medication(s) must be reported on the appropriate case report form. Prior and concomitant medications include all vitamins, herbal remedies, over the counter, and prescription medications.

Concomitant administration of bisphosphonates or bone-targeting agents are acceptable if the subject is on a stable regimen (per Investigator judgement) prior to Day 1. The Investigator should consult with Medical Monitor if new use of bone-targeting agents is deemed necessary during the study.

Concomitant administration of enzalutamide with strong CYP2C8 inhibitors, strong or moderate CYP2C8 inducers, strong or moderate CYP3A4 inducers should be avoided. Please see Section 5.1.2.1 for enzalutamide dose modifications when taking concomitant CYP2C8 inhibitors. Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4, CYP2C9, and CYP2C19 should be avoided. If enzalutamide is coadministered with warfarin (CYP2C9 substrate), additional international normalized ratio (INR) monitoring is to be conducted.

Subjects should avoid use of any herbal medications or dietary supplements including products containing *Hypericum perforatum* (e.g., St. John's Wort).

The following medications or therapies are prohibited during the receipt of study drug:

- Medications, including herbal therapies, with an antitumor effect (medications used to induce menopause in women of child-bearing potential are permitted).
- Any investigational agent
- AR antagonists (e.g., bicalutamide, flutamide, nilutamide)
- 5- α reductase inhibitors (e.g., finasteride, dutasteride)
- Systemic androgens and estrogens (vaginal estrogen creams are allowed)
- Megestrol acetate for appetite stimulation may be used at Investigator's discretion

5.1.4 Treatment Compliance

Study subjects should be counseled on the need to meet 100% compliance with study drug. Investigator or designee should ensure that study subjects meet this goal throughout the study period.

Treatment compliance should be monitored closely; sites will perform accountability of enzalutamide doses dispensed and returned, and deviations in overall compliance < 80% should be reported to the Sponsor. Greater than 1 consecutive missed cycle of Trastuzumab for reasons other than an adverse reaction should be reported to the Sponsor.

5.1.5 Restrictions During the Study

Subjects of childbearing potential must use 2 acceptable methods of birth control starting at Screening and through 6 months after the final study drug administration.

The 2 acceptable methods of birth control are as follows, or per local guidelines where these require additional description of contraceptive methods:

- A barrier method (e.g., condom by a male partner) is required; AND
- One of the following is required:
 - Placement of an IUD or intrauterine system IUS;
 - Additional barrier method including occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository;
 - Vasectomy or other surgical castration at least 6 months before Screening.

Subjects must not breastfeed from screening through 6 months after the last dose of study drug.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

Demographic information will be collected for all subjects and will include initials, age or date of birth, sex, race, and ethnicity, as local regulations allow.

5.2.2 Medical History

Medical history includes all significant medical conditions that have occurred or are currently ongoing. The condition, onset date, and recovery date will be collected. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade will be collected for conditions that are ongoing at the time of consent.

5.2.3 Diagnosis of the Target Disease, Severity, and Duration of Disease

Breast cancer diagnosis and studies related to breast cancer classification will be collected and will include date of diagnosis, histopathology, HER2+ status and testing method, ER and PgR status, details on prior therapies, and response to prior therapies.

5.2.4 Androgen Receptor, Estrogen Receptor and Progesterone Receptor Status

Subjects should have known ER and PgR status prior to screening for the study. Results for AR expression will be required for eligibility assessment. Enrollment may be based on the local pathologist's findings; however, tissue will be sent to a central pathology laboratory for confirmation. AR+ breast cancer for eligibility is defined as any tumor cell(s) with nuclear AR staining. If a subject is enrolled in the study based on local pathologist results, but subsequent central assessment cannot confirm AR+ disease, the subject may remain in the study per Investigator judgment. If sufficient tissue is available, expression levels of nuclear ER and PgR in tumor cells using standard assays will also be assessed.

A formalin-fixed paraffin-embedded tumor tissue block from the most recent biopsy available is preferred. If the archival specimen is insufficient or unavailable and the subject is known to be AR+ by local pathology report, a fresh biopsy can be done to obtain tissue for central AR confirmation. Tissue used for central confirmation will be shipped to and analyzed by a Sponsor-designated analytical laboratory. The laboratory will prepare slides for analysis, and then return the block to the Investigator. Tissue processing, storage, and shipment instructions are provided in the lab manual. If a tissue block is unavailable, then a minimum of 10 (preferably 20) unstained slides freshly prepared by the Institution will be sent to the Sponsor-designated analytical laboratory. The slides will not be returned.

Prescreening AR Assessment

Subjects with HER2+ breast cancer may be approached before screening for consent to submit archival tissue to test for AR expression. A separate prescreening consent will be available to enable testing of archival tissue for AR expression before initiating other screening activities. Patients must sign the separate prescreening consent form if archival tissue is to be analyzed before the protocol screening period (i.e., 28 days before day 1).

Subjects will not be allowed to undergo a biopsy for the sole purpose of determining eligibility for this study. For subjects who are known AR+ per local pathology report, a fresh biopsy can only be done, per Investigator's discretion, to obtain tissue for central AR confirmation if the archival specimen is insufficient or unavailable.

Furthermore, patients must be informed that analysis of tissue will not guarantee eligibility for this study, as patients found to have AR+ disease must meet all other eligibility criteria at the time of enrollment.

5.3 Efficacy Assessment

5.3.1 Radiographic Disease Assessment

Disease assessment will be based on RECIST v.1.1 criteria [Eisenhauer et al, 2009]. Disease assessment will be performed by the Investigator. Radiographic imaging technique will be dependent on the location and degree of disease, and must be performed using either diagnostic computed tomography (CT) scan, magnetic resonance imaging (MRI), and/or bone scan or skeletal survey. Imaging may be performed at any time to confirm suspected progression of disease. Assessment will include tumor measurements for target lesions, nontarget lesions, and assessment for any new lesions. An overall assessment will be characterized for each time point evaluation. At the end of study for that subject, the overall best response to the study regimen will be characterized. Refer to Appendix [12.6 RECIST Criteria](#) for more detail.

5.3.2 Disease Assessment Methods

Baseline evaluations (with the exception of bone imaging) will be performed within 4 weeks prior to day 1. Results from CT/MRI assessments performed prior to consent and within 28 days of day 1 may be used for screening if available. All patients should have bone imaging to assess metastasis to the bone within 6 months prior to the Day 1 visit.

Postbaseline evaluations including chest/abdominal/pelvic imaging will be performed every 8 weeks through 49, and then every 12 weeks thereafter. If a definitive new lesion is identified, remaining imaging is not required (for example, a CT of the chest, abdomen, and pelvis is not required if a new lesion is identified in the brain).

PR and CR require confirmation with equivalent or improved assessment no less than 4 weeks after the date of scan that PR or CR was first observed.

5.3.2.1 Chest/Abdominal/Pelvic Imaging and Other Measurements

Diagnostic CT, MRI, clinical measurement by caliper, and cytology/histology may be used to assess disease. CT/MRI of the chest/abdomen/pelvis as well as any other anatomical region appropriate for that subject's disease will be performed. CT or MRI with contrast should be used unless contraindicated. The same method of assessment should be used throughout the study.

NOTE: PET scans may not be used to assess response or progression; if PET-CT was performed, the CT component may be used if CT was obtained per RECIST 1.1 guidelines for gap thickness.

5.3.2.2 Brain Imaging

Brain imaging is required at Screening for all subjects to rule out central nervous system disease. A brain MRI with contrast enhancement is required unless it cannot be performed within 2 weeks prior to Day 1 due to feasibility or subject-specific contraindications. A head CT may be performed in these situations after discussion with the medical monitor or designee. Results from brain imaging performed prior to consent and within 28 days of Day 1 may be used for screening if available. Additional imaging to rule out CNS metastases should be performed as clinically indicated.

5.3.2.3 Bone Imaging

All subjects should have bone imaging to assess metastasis to the bone within 6 months prior to the Day 1 visit. Thereafter, subjects without bone metastasis will have bone scans only if clinically indicated. Subjects with suspected bone-only, measurable lesions must have bone lesions assessed by CT with bone windows or by MRI within 12 weeks before Day 1. Thereafter, measureable lytic lesions should be followed as target lesions according to RECIST 1.1 using the same method. Subjects with suspected bone-only, nonmeasurable disease should have had a bone assessment (e.g., scintigraphy or skeletal survey) performed within 12 weeks before Day 1. Thereafter, imaging of nonmeasurable, evaluable disease should be performed as clinically indicated, with a required assessment at Week 24.

5.3.2.4 Cutaneous and Subcutaneous Lesions

Cutaneous and subcutaneous lesions should be assessed by physical examination with digital photographs that must include a metric ruler in the image. Photographs should be obtained in such a manner to protect subject privacy.

5.4 Safety Assessment

5.4.1 Height and Weight

Height and weight will be measured using standard Institution practice and equipment.

5.4.2 Vital Signs

Vital signs will include systolic and diastolic blood pressure measured with standard sphygmo-manometer (mmHg), radial pulse (beats/min), and temperature (per institution standards). All vital signs will be measured with the subject in the sitting or supine position.

5.4.3 Adverse Events

See Section [5.5](#) Adverse Events and Other Safety Aspects for information regarding AE collection and data handling.

5.4.3.1 Adverse Events of Possible Hepatic Origin

See Appendix [12.2](#) Liver Safety Monitoring and Assessment for detailed information on liver abnormalities, monitoring and assessment, if the AE for a subject enrolled in a study and receiving study drug is accompanied by increases in liver function testing (LFT) (e.g., AST, ALT, bilirubin, etc.) or is suspected to be due to hepatic dysfunction.

5.4.4 Laboratory Assessments

Routine laboratory assessments for hematology, chemistry, coagulation, urinalysis, and urine pregnancy test will be collected and analyzed at the Institution's local laboratory. The local laboratory must be accredited to perform the protocol required tests and a certificate of accreditation and laboratory normal ranges must be provided to the Sponsor. Please refer to Appendix 12.7 Laboratory Assessments for a listing of analytes to be assessed.

5.4.5 Physical Examination

Standard, full physical examinations will be performed at Screening and Day 1 per Investigator's standard practice.

After Day 1, a brief symptom directed physical examination may be performed.

New or worsening clinically significant findings on physical exam will be recorded as AEs if they meet the criteria in Section 5.5.1 Definition of Adverse Events.

5.4.6 Electrocardiogram (ECG)

A 12-lead ECG will be performed on all subjects at the Institution and interpreted by the Institution's medically trained staff. Parameters that include heart rate, PR interval, RR interval, QRS interval, QT interval will be collected. Abnormalities and clinical significance as judged by the Investigator will be reported as well. It is recommended that ECG reports are printed in duplicate and photocopied to prevent fading.

ECG should be obtained after the subject has rested quietly and is awake in a fully supine position or semi-recumbent, if supine not tolerated) for 10 minutes.

All on-treatment ECGs will be obtained prior to drug administration. Whenever a study procedure coincides with the scheduled time point for an ECG, the study activities are ideally undertaken in a fixed sequence: ECG first, vital signs (blood pressure and heart rate) second, and any type of blood draws as the last assessment.

5.4.7 Echocardiogram/MUGA

Echocardiogram/MPS/MUGA will be used to measure LVEF. The same method used at baseline for each subject must be used throughout the study.

5.4.8 Performance Status

The ECOG scale [Oken et al, 1982] will be used to assess performance status. Refer to Appendix 12.5 ECOG Performance Status Scale.

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a subject administered a study drug or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal

laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

AEs are events that begin or worsen from the time of informed consent through the 30 Day Follow-up period. Treatment emergent adverse events (TEAEs) are events that begin or worsen from the date of first study drug administration through the 30 Day Follow-up period or start of subsequent treatment of an anti-neoplastic, whichever occurs first.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- The abnormality or investigational value is clinically significant in the opinion of the Investigator.

In the case of clinically disease progression, individual signs and symptoms that are secondary to disease progression will be collected as AEs. If disease progression is the cause of death, then “breast cancer progression” should be listed as the AE term with outcome as fatal.

5.5.2 Definition of Serious Adverse Events

An AE is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Results in death
- Is life threatening (an AE is considered “life-threatening” if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Safety events of interest on the medicinal products administered to the subject as part of the study (e.g., study drug, comparator, background therapy) that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of the medicinal product(s)
- Suspected abuse/misuse of the medicinal product(s)
- Inadvertent or accidental exposure to the medicinal product(s)
- Medication error involving the medicinal product(s) (with or without subject/patient exposure to the Sponsor medicinal product, e.g., name confusion)

All of the events of interest noted above should be recorded on the electronic case report form ([e]CRF). Any situation involving these events of interest that also meets the criteria for an SAE should be recorded on the AE page of the (e)CRF and marked 'serious' and the SAE worksheet.

The Sponsor has a list of events that they classify as "always serious" events. If an AE is reported that is considered to be an event per this classification as "always serious," additional information on the event may be requested.

5.5.3 Criteria for Causal Relationship to the Study Drug

Causal relationship will be assessed for enzalutamide and trastuzumab. Separate assessments for each agent will be obtained.

AEs that fall under either "Possible" or "Probable" should be defined as "AEs whose relationship to the study drugs could not be ruled out".

Causal relationship to the study drug	Criteria for causal relationship
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re- administration (rechallenge) or withdrawal (dechallenge).

5.5.4 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be graded using the NCI CTCAE (Version 4.03) [CTEP, 2010]. For terms not specified within NCI CTCAE, the following guidelines should be used to determine grade:

Grade	Assessment Standard
1	Mild; Asymptomatic, or mild symptoms, clinical or diagnostic observations noted; intervention not indicated.
2	Moderate; Local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
3	Severe or medically significant but not immediately life threatening, hospitalization or prolonged hospitalization indicated; disabling; limiting self-care activities of daily living.
4	Life threatening consequences, urgent intervention indicated
5	Death related to AE

5.5.5 Reporting of Serious Adverse Events

In the case of an SAE, the Investigator must contact the Sponsor by telephone or fax immediately (within 24 hours of awareness).

The Investigator should complete and submit an SAE Worksheet containing all information that is required by the Regulatory Authorities to the Sponsor by fax immediately (within 24 hours of awareness). If the faxing of an SAE Worksheet is not possible or is not possible within 24 hours, the local drug safety contact should be informed by phone.

For contact details, see Section II Contact Details of Key Sponsor's Personnel.

If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor/Expert or his/her designee (see Section II Contact Details of Key Sponsor's Personnel).

Follow-up information for the event should be sent promptly (within 7 days of the initial notification).

Full details of the SAE should be recorded on the medical records and on the (e)CRF.

The following minimum information is required:

- ISN/Study number,
- Subject number, sex and age,
- The date of report,
- A description of the SAE (event, seriousness of the event), and
- Causal relationship to the study drug.

The Sponsor or Sponsor's designee will submit expedited safety reports (i.e., Investigational New Drug (IND) Safety Reports) to the regulatory agencies (i.e., FDA) as necessary, and will inform the Investigators of such regulatory reports. Investigators must submit safety reports

as required by their IRB/IEC within timelines set by regional regulations (i.e., EU, electronic common technical document [eCTD], FDA). Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the site.

The Sponsor will notify all Investigators responsible for ongoing clinical studies with the study drug of all SAEs which require submission per local requirements IRB/IEC/head of the study site.

The Investigator should provide written documentation of IRB/IEC notification for each report to the Sponsor.

You may contact the Sponsor's Medical Monitor/Expert for any other problem related to the safety, welfare, or rights of the subject.

5.5.6 Follow-up of Adverse Events

All AEs occurring during the study (through the 30 Day Follow-up period or start of subsequent treatment of an anti-neoplastic, whichever occurs first) are to be followed until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

If during AE follow-up, the AE progresses to an "SAE," or if a subject experiences a new SAE, the Investigator must immediately report the information to the Sponsor.

Please refer to Appendix 12.2 Liver Safety Monitoring and Assessment for detailed instructions on Drug Induced Liver Injury (DILI).

5.5.7 Monitoring of Common Serious Adverse Events

Common SAEs are SAEs commonly anticipated to occur in the study population independent of drug exposure. SAEs classified as "common" are provided in Appendix 12.3 Common Serious Adverse Events for your reference. The list does NOT change your reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed above.

The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting by the Sponsor to the regulatory authorities based on the classification of "common SAEs" as specified in Appendix 12.3 Common Serious Adverse Events. The Sponsor will monitor these events throughout the course of the study for any change in frequency. Any changes to this list will be communicated to the participating investigational sites. Investigators must report individual occurrences of these events as stated in Section 5.5.5 Reporting of Serious Adverse Events.

5.5.8 Procedure in Case of Pregnancy

If a subject becomes pregnant during the study dosing period, study medication should be discontinued. If a subject becomes pregnant during the study dosing period or within 6 months from the discontinuation of dosing, the Investigator should report the information to the Sponsor as if it is an SAE. The expected date of delivery or expected date of the end of

the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

The Investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE and will report the outcome to the Sponsor.

The Investigator should report the outcome of the pregnancy (independent of outcome, e.g., full term delivery, preterm delivery, spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus), in accordance with the same reporting procedure as for SAEs. The date of outcome of the pregnancy, gestational age, date of birth and neonatal data, etc., should be included in this information. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

- "Spontaneous abortion" includes miscarriage, abortion and missed abortion
- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug
- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as "possible" by the Investigator
- In the case of a delivery of a living newborn, the "normality" of the infant is evaluated at the birth
- Unless a congenital anomaly are identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination

5.5.9 Emergency Procedures and Management of Overdose

If an overdose of enzalutamide occurs, the Medical Monitor must be contacted. An overdose is defined as at least 2 daily doses of study drug taken on the same calendar day. In the event of an overdose, stop treatment with study drug and initiate general supportive measures taking into consideration the enzalutamide $t_{1/2}$ of 5.8 days. The medical monitor must be contacted in the event of a study drug overdose.

Neither the effects of overdose of enzalutamide nor an antidote to overdose are known. Subjects may be at increased risk of seizures following an overdose of enzalutamide.

In the event of suspected trastuzumab overdose, refer to the approved Package Insert, Summary of Product Characteristics (SPC), or local product information supplied by the manufacturer.

5.5.10 Supply of New Information Affecting the Conduct of the Study

When new information becomes available that is necessary for conducting the clinical study properly, the Sponsor will inform all Investigators involved in the clinical study as well as the regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

5.5.11 Urgent Safety Measures

An Urgent Safety Measure (USM) is an intervention, which is not defined by the protocol and can be put in place with immediate effect without needing to gain prior approval by the sponsor, relevant Competent Authorities, IRB/IEC, where applicable, in order to protect study participants from any immediate hazard to their health and/or safety. Either the Investigator or the sponsor can initiate an USM. The cause of an USM can be safety, product or procedure related.

5.5.12 Reporting Urgent Safety Measures

In the event of a potential USM, the Investigator must contact the Astellas Study Physician (within 24 hours of awareness). Full details of the potential USM are to be recorded in the subject's medical records. The sponsor may request additional information related to the event to support their evaluation.

If the event is confirmed to be an USM the sponsor will take appropriate action to ensure the safety and welfare of the patients. These actions may include but are not limited to a change in study procedures or study treatment, halting further enrollment in the trial, or stopping the study in its entirety. The sponsor or sponsor's designee will notify Competent Authorities and concerned Ethics Committee within the timelines required per current local regulations, and will inform the Investigators as required. When required, Investigators must notify their IRB/IEC within timelines set by regional regulations.

5.6 Test Drug Concentration

5.6.1 Pharmacokinetic Assessments

Plasma samples will be analyzed to determine enzalutamide and N-desmethyl enzalutamide concentrations and serum samples will be analyzed to determine trastuzumab concentrations in all subjects treated in the study. PK samples will be obtained before enzalutamide and trastuzumab dosing in the clinic. Blood samples will be collected from a vein or port that is not used for drug infusions. Blood sampling, processing, storage and shipment instructions are provided in a lab manual. Samples will be shipped to and analyzed by a Sponsor designated analytical laboratory.

Subjects will keep a diary to record date and time of enzalutamide doses before PK visit days. The date and time that the subject took the previous 2 doses of study drug must be recorded at each PK sample collection visit. The PK sample will be collected even if the subject inadvertently took her daily dose of study drug earlier the same day. When this occurs, the dose that was taken on the same day will be recorded as one of the previous doses, and the subject will take no additional study drug that day.

5.7.1 Pharmacodynamic Assessments

5.7.1.1 CC/

5.7.2 Sample for the Analysis of Genes Related to Pharmacokinetics, Efficacy, and/or Safety

Knowledge of polymorphisms in the AR gene may help understand/explain observed differences in PK profiles, efficacy, and/or safety. After enrollment (see Schedule of Assessments), two 2 mL whole blood samples for the analysis of these genes will be collected into ethylenediaminetetraacetic acid (EDTA) containing polypropylene tubes. The first sample will be analyzed for polymorphisms of the AR gene. The second sample will be stored and may further be used for the exploratory analysis of relevant metabolism, transporter, PD and/or safety genes. Sample labels should uniquely identify each sample and contain at least: protocol number; subject ID; “genotyping” and biological matrix. The samples should be stored at -20°C or colder in the freezer or on dry ice for immediate shipment. For detailed sample collection, sample labeling and sample shipment procedures refer to the laboratory manual. All

samples will be transferred to the analytical laboratory. Samples will be analyzed using appropriate validated methods. The extracted deoxyribonucleic acid (DNA) will be stored at the analytical laboratory. A pharmacogenomics (PGx) analysis plan may be prepared, if necessary, and exploratory analysis will be carried out before the completion of the study. PGx samples will be disposed after the completion of the study. Genetic information which has an established relevance to an individual for prescription of approved medicines can be disclosed to subjects upon their request.

5.7.3 Blood Sample for Future Pharmacogenomic Analysis (Retrospective Pharmacogenomic Analysis)

PGx research may be conducted in the future to analyze or determine genes of relevance to clinical response, PK, and toxicity/safety issues. After enrollment (see Schedule of Assessments), a 5 mL sample of whole blood for possible retrospective PGx analysis will be collected using a vacutainer tube containing EDTA. After collection, gently invert the blood sample 8 to 10 times. The blood collection tube may either be stored upright at 4°C for up to 5 days prior to shipment or stored frozen at -20°C or below at the site for extended storage. Samples will be shipped to a Sponsor designated banking contract research organization (CRO).

Labels should uniquely identify each sample and contain at least:

- Protocol number (9785-CL-1121),
- Subject number, and
- Purpose and biological matrix (i.e., “biobanking,” “whole blood”).

Details on sample collection, labeling, storage and shipment procedures will be provided in a separate laboratory manual.

The results of the Retrospective PGx analysis will not be provided to any Investigators or subjects, nor can the results be requested at a later date.

See Appendix 12.4, Retrospective Pharmacogenomic Sub-study for further details on the banking procedures.

5.8 Total Amount of Blood

The total amount of blood for each subject will vary depending on the course of their disease, how long they stay on treatment, and local laboratory requirements. At any time during the study, if any laboratory abnormalities are found for a subject, additional blood may be drawn for monitoring.

The maximum amount of blood estimated for collection over any 1 month period is from Screening through the Week 4 visit where approximately 65mL may be drawn. The maximum amount of blood estimated over any approximate 3 month period is from Day 1 through Week 13 where approximately 106 mL may be drawn.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

A discontinuation is a subject who enrolled in the study and for whom study treatment is permanently discontinued for any reason.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The Investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

If a subject is discontinued from the study with an ongoing AE or an unresolved laboratory result that is significantly outside of the reference range, the Investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

Discontinuation Criteria from Treatment for Individual Subjects:

- Disease progression per RECIST 1.1;
- Subject develops an unacceptable AE including, but not limited to:
 - seizure
 - persistent (> 8 weeks) LVEF decline or for suspension of trastuzumab dosing on more than 3 occasions for cardiomyopathy
 - severe or life-threatening infusion reaction to trastuzumab
 - anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome due to trastuzumab
- Subject is lost to follow-up despite reasonable efforts by the Investigator to locate the subject
- Subject withdraws consent for further treatment
- Subject becomes pregnant

Discontinuation of treatment should be considered if:

- The subject experiences severe hepatic abnormalities as described in Appendix [12.2](#).
- There is a significant protocol violation or noncompliance that occurs with a subject that compromises study objectives or subject safety.

Discontinuation Criteria from Posttreatment Follow-up for Individual Subjects:

- Subject is lost to follow-up despite reasonable efforts by the Investigator to locate the subject
- Subject withdraws consent for further treatment
- Death
- 2 years has passed from the last dose

6.2 Discontinuation of the Site

If an Investigator intends to discontinue participation in the study, the Investigator must immediately inform the Sponsor.

6.3 Discontinuation of the Study

The Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the Sponsor terminates the study for safety reasons, the Sponsor will immediately notify the Investigator and subsequently provide written instructions for study termination.

7 STATISTICAL METHODOLOGY

The statistical analysis will be coordinated by the responsible biostatistician of APGD. A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures to be produced. The SAP will be drafted before first subject enrolled and finalized before the database soft lock. Any changes from the analyses planned in SAP will be justified in the Clinical Study Report (CSR).

Prior to Database Lock, a Final Review of Data and Tables, Listings and Figures (TLFs) Meeting will be held to allow a review of the clinical trial data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database lock.

In general, all data will be summarized with descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous endpoints, and frequency and percentage for categorical endpoints.

7.1 Sample Size

The sample size is sufficient to determine the absence or presence of an efficacy signal. The sample sizes for the first and second stage were determined using Simon's 2-stage design. The null hypothesis that the true CBR is 10% will be tested against a 1-sided alternative at a 5% significance level. In the first stage, 21 evaluable AR+ subjects will be evaluated; the study will stop if < 3 evaluable subjects show confirmed CR or PR per RECIST 1.1, or prolonged SD (≥ 24 weeks). Otherwise, the study will continue to enroll up to 66 evaluable AR+ subjects. This design has a statistical power of 90% when the true CBR is 25% (East version 5.4, Cytel Inc). To illustrate the precision with a total of 66 subjects: if the observed CBR is 40%, then the 90% confidence interval will be within the 30% to 50% range.

Taking into account the number of nonevaluable subjects, approximately 80 subjects were planned to be enrolled to get 66 evaluable AR+ subjects.

7.2 Analysis Set

Detailed criteria for analysis sets will be laid out in Classification Specifications and the allocation of subjects to analysis sets will be determined prior to database hard-lock.

The All Enrolled Subjects (AES) consists of all subjects who are found to be eligible for treatment and enrolled using the IRT at the day 1 visit.

7.2.1 Full Analysis Set (FAS)

The FAS is defined as all enrolled subjects who have centrally assessed AR+ breast cancer (defined as $\geq 10\%$ of tumor cells with nuclear expression), and received at least 1 dose of study drug.

7.2.2 Efficacy Evaluable Set (EES)

The Efficacy Evaluable Set (EES) is a subset of the FAS defined as all enrolled subjects who have centrally assessed AR+ (defined as $> 10\%$ of tumor cells with nuclear expression), received at least 1 dose of study drug, and have at least 1 available post baseline tumor assessment.

7.2.3 Per Protocol Set (PPS)

PPS is not defined for this study and separate analyses will not be performed on a PPS.

7.2.4 Safety Analysis Set (SAF)

For the statistical summary of the safety data, the safety analysis set (SAF) will be used. The SAF is defined as all subjects who have received at least partial or full dose of study drug.

7.2.5 Pharmacokinetic Analysis Set (PKAS)

The pharmacokinetic analysis set (PKAS) consists of the subset of the SAF population for which at least 1 quantifiable enzalutamide, N-desmethyl enzalutamide, or trastuzumab concentration value after Week 4 is available. Additional subjects may be excluded from the PKAS at the discretion of the pharmacokineticist. Any formal definitions for exclusion of subjects or time-points from the PKAS will be documented.

7.2.6 Pharmacodynamic Analysis Set (PDAS)

The pharmacodynamic analysis set (PDAS) will include the subjects from the SAF population for whom sufficient PD measurements (a baseline and at least 1 postbaseline sample after Week 4) were collected. The PDAS will be used for all analyses of PD data.

7.3 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized for the SAF. Descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum for continuous endpoints, and frequency and percentage for categorical endpoints.

7.4 Analysis of Efficacy

The primary analyses will be done in the EES, while all efficacy analyses will be done in both the EES and FAS. If more than 5 subjects are enrolled into the study but had less than 10% of tumor cells with nuclear expression, and received at least 1 dose of study drug, the efficacy analyses will also be conducted in this subset of FAS. Further details will be presented in the statistical analysis plan.

The totality of evidence from all primary and secondary efficacy variables on the EES will be used to evaluate the biologic activity of enzalutamide in combination with trastuzumab.

Subjects whose disease is not confirmed to be AR+ upon central review may stay on study; however, they will not contribute to the primary and secondary efficacy analyses.

7.4.1 Analysis of Primary Endpoint

7.4.1.1 Primary Analysis

The primary efficacy endpoint, (confirmed CR or PR according to RECIST 1.1 criteria or SD \geq 24 weeks) will be presented using descriptive statistics and will be summarized including 95% 2-sided exact confidence intervals.

7.4.1.2 Secondary Analysis

A secondary analysis is not planned.

7.4.1.3 Subgroup Analysis

A subgroup analysis will be conducted for the ER-/PgR- subjects. The details of any subgroup analyses will be included in the SAP.

7.4.2 Analysis of Secondary Endpoints

All variables will be presented as descriptive statistics. ORR, and BORR will be summarized including 95% 2-sided exact confidence intervals.

Kaplan-Meier methods will be used to estimate PFS, TTP, TTR, and DOR.

7.4.3 Analysis of Exploratory Endpoints

All variables will be presented as descriptive statistics.

7.5 Analysis of Safety

Safety analyses will be conducted using the SAF. The SAF is defined as all subjects who have initiated at least 1 or partial dose of study drug. The treatment emergent period will be defined as the period of time from the first dose date of study drug to 30 days after the last dose date of study drug or the start of subsequent treatment (whichever is first). Safety will be assessed through descriptive statistics for the frequency of AEs by system organ class (SOC), preferred term (PT), and NCI CTCAE grade, the frequency of treatment discontinuations due to AEs, vital signs, ECG, LVEF, and laboratory evaluations.

7.5.1 Adverse Events

The severity of all AEs is to be evaluated by the Investigator based on the NCI CTCAE, version 4.03. All AEs will be coded to preferred term and system organ class using Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with TEAEs will be presented by MedDRA system organ class and preferred term, relationship to study treatment, and NCI CTCAE grade. A subject reporting the same AE more than once is counted once and at the maximum severity or strongest relationship to study drug treatment, when calculating incidence.

7.5.2 Laboratory Assessments

Laboratory data consist of hematology, chemistry, coagulation, and urine dipstick laboratory test results. Where applicable, NCI CTCAE version 4.03 will be used to categorize toxicity grades for the laboratory parameters. Laboratory shift tables compared to baseline results for each subsequent visit will be produced. For each laboratory parameter, the baseline laboratory value is defined as the last laboratory value collected on or prior to the first dose date of enzalutamide.

7.5.3 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline by time point. Vital signs data will be displayed in listings.

7.5.4 ECGs

The 12-lead ECG results will be summarized by time point.

7.5.5 LVEF

Descriptive statistics will be used to summarize vital sign LVEF and changes from baseline by time point.

7.6 Analysis of Pharmacokinetics

PK analyses will be conducted using the PKAS.

The enzalutamide, N-desmethyl enzalutamide, and trastuzumab concentration-time data will be summarized by descriptive statistics at each visit. Additional model-based analyses may be performed and will be described in a separate population PK analysis plan.

7.6.1 Estimation of Pharmacokinetic Parameters

Enzalutamide and N-desmethyl enzalutamide concentration-time data may be incorporated in a population PK model. The analysis plan and results would be reported separately from the clinical study report. Similar analysis may be done on the trastuzumab levels, which will be reported separately too.

7.6.2 Concentration-Response Relationship Analysis

An exploratory population PK-PD analysis may be performed to investigate the relationship of enzalutamide and N-desmethyl enzalutamide exposure on circulating hormone concentrations, efficacy measures, and possibly safety endpoints. The details of the analysis would be provided in a separate population PK-PD analysis plan and the results will be reported separately from the clinical study report.

7.7 Analysis of Pharmacodynamics

7.7.1 Pharmacodynamic Analyses

CCI

Additional model-based analyses to explore PK-PD relationships may be performed.

CCI [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

7.8 Protocol Deviations and Other Analyses

Protocol deviations as defined in Section 8.1.6 Protocol Deviations will be summarized for all enrolled subjects by site. A data listing will be provided by site and subject.

The protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

7.9 Interim Analysis (and Early Discontinuation of the Clinical Study)

Recruitment will continue if there are 3 or more subjects with clinical benefit in the first 21 evaluable AR+ subjects from the evaluable set. If there are less than 3 subjects who demonstrate a confirmed CR or PR per RECIST 1.1, or prolonged SD of ≥ 24 weeks (using all available data), recruitment will be stopped. If the study is terminated early for reasons other than safety, and the subject is receiving clinical benefit per Investigator's judgment, the subject may continue on study medication until they have disease progression as defined per RECIST.

Tumor response will be monitored continuously throughout Stage 1, therefore it is expected that the decision to expand enrollment using the CBR after 24 weeks will be made before the 21st subject is evaluated.

7.10 Handling of Missing Data, Outliers, Visit Windows, and Other Information

As a general principle, no imputation of missing data will be done. Exceptions are the start and stop dates of AEs and concomitant medication. The imputed dates will be used to allocate the concomitant medication and AEs to a treatment period, in addition to determining whether an AE is/is not treatment emergent. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

See the SAP for details of the definitions for windows to be used for analyses by visit.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The Investigator or site designee will enter data collected using an Electronic Data Capture (EDC) system. The Investigator or site designee is responsible to ensure that all data in the (e)CRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

The monitor should verify the data in the (e)CRFs with source documents and confirm that there are no inconsistencies between them.

For Screen failures the demographic data, reason for failing, informed consent, inclusion and exclusion criteria and AEs will be collected in the eCRF.

Analytical laboratory tests for PK and PD measures will be collected and managed by Sponsor-designated vendors during the study. Data will be transferred electronically to the Sponsor at predefined intervals during the study. The external data vendors may provide the Data Manager with a complete and clean copy of the data, accompanied by a Quality Control statement.

8.1.2 Specification of Source Documents

Source data must be available at the site to document the existence of the study subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject. Source data may be in paper or electronic format.

Source documents will generally be in the institution's standard record format to avoid duplicate source. The sponsor may provide (or site can create) supplemental source tools to ensure all data elements are captured for assessments such as AEs (relationship, action taken, outcome, etc.) and disease assessment.

Source documents – whether paper or electronic must be:

- Attributable (distinguishable)
- Legible
- Contemporaneous (happening at the same period in time)
- Accurate
- Original (copies verified as identical, can replace the original)

A certified copy is a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original. A certified copy of electronic records may be used for monitoring purposes.

The following information should be included in the source medical records:

- Demographic data (age, sex, race, ethnicity, height and body weight)
- Target disease history. Photocopies or fax documents of original records are acceptable if obtained from an outside institution
- Inclusion and exclusion criteria details
- Participation in study and original signed and dated informed consent forms
- Visit dates
- Medical history and physical examination details
- Key efficacy and safety data, if applicable (as specified in the protocol)
- AEs and concomitant medication
- Results of relevant examinations (e.g., ECG charts, X-ray films, photographs, etc.)
- Laboratory results
- Dispensing and return of study drug details
- Reason for premature discontinuation (if applicable)
- Subject number
- Staff notes and subject contact records
- Significant medical records from other departments or hospitals, including discharge summaries, correspondence, etc., during the time the subject is on study. Photocopies or fax documents of original records are acceptable if obtained from an outside department or institution.

8.1.3 Clinical Study Monitoring

The Sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the Investigator/Subinvestigator are accurate and complete and that they are verifiable with study-related records such as source documents. The Sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The Investigator and the study site must accept monitoring and auditing by the Sponsor or delegated CRO as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents (refer to Section 8.1.2 "Specification of Source Documents") when they are requested by the Sponsor monitors and auditors, the IRB/IEC, or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

8.1.5 Data Management

Data Management will be coordinated by the Global Data Science department of the Sponsor in accordance with the standard operating procedures (SOPs) for data management. All study specific processes and definitions will be documented by Data Management. (e)CRF completion will be described in the (e)CRF instructions. Coding of medical terms and medications will be performed using MedDRA and World Health Organization (WHO) Drug Dictionary respectively.

8.1.6 Protocol Deviations

A protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The Investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to trial subjects.

A protocol waiver is a documented prospective approval of a request from an Investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

For the purposes of this protocol, deviations requiring notification to Sponsor are defined as any subject who:

- Entered into the study even though they did not satisfy entry criteria.
- Developed withdrawal criteria during the study and not withdrawn
- Received wrong treatment or incorrect dose.
- Received excluded concomitant treatment.

When one of the above deviations from the protocol is identified for an individual subject, the Investigator or designee must ensure the Sponsor is notified. The Sponsor will follow-up with the Investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the subject to determine subject continuation in the study.

If a deviation impacts the safety of a subject, the Investigator must contact the Sponsor immediately.

The Investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and

communications to the IRB/IEC and applicable regulatory authorities will be provided to the Sponsor and maintained within the Trial Master File (TMF).

NOTE: Other deviations outside of the categories defined above that are required to be reported by the IRB/IEC in accordance with local requirements will be reported, as applicable.

8.1.7 End of Trial in All Participating Countries

The end of trial in all participating countries is defined as the Last Subject's Last Visit (including follow-up contact if applicable).

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)/Competent Authorities (CA)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any substantial amendments to the protocol will require IEC/IRB approval prior to implementation of the changes made to the study design at the site. The Investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any SAEs that meet reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required. During the conduct of the study, the Investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to Sponsor.

If required by local regulations, the Investigator shall make accurate and adequate written progress reports to the IEC/IRB at appropriate intervals, not exceeding 1 year. The Investigator shall make an accurate and adequate final report to the IRB/IEC within 90 days after the close-out visit for APGD-sponsored studies.

8.2.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

The Investigator or his/her representative will explain the nature of the study to the subject or his/her guardian or legal representative, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject or his/her guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy. A prescreening consent form may be used to allow for testing of archival tissue samples for AR expression prior to the screening period (See Section 5.2.4 for details).

The signed consent forms will be retained by the Investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

The Investigator or his/her representative will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug adverse drug reaction). The communication must be documented in the subject's medical records and must document whether the subject is willing to remain in the study or not.

The Investigator must update their ICF and submit it for approval to the IRB/IEC. The Investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The Investigator or his/her designee must re-consent subjects with the updated ICF even if relevant information was provided orally. The Investigator or his/her representative who obtained the written informed consent and the subject should sign and date the informed consent form. A copy of the signed informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the re-consent process.

8.2.4 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The Sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

The Sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials will identify subject data retrieved by the Sponsor. However, the Sponsor requires the Investigator to permit the Sponsor, Sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The Sponsor will ensure that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (i.e., Health Insurance Portability and Accountability Act [HIPAA]).

8.3 Administrative Matters

8.3.1 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the Investigator's Brochure and other pertinent information is confidential and remains the property of the Sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The Investigator may use this information for the purpose of the study only. It is understood by the Investigator that the Sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical Investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide the Sponsor with all data obtained during the study.

Publication of the study results is discussed in the Clinical Study Agreement.

8.3.2 Documents and Records Related to the Clinical Study

The Investigator will archive all study data (e.g., Subject Identification Code List, source data, case report forms (CRFs), and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US sites, 2 years after approval of the New Drug Application (NDA) or discontinuation of the IND). The Sponsor will notify the site/Investigator if the NDA/Marketing Authorisation Application (MAA)/Japanese New Drug Application (J-NDA) is approved or if the Investigational New Drug application (IND)/Investigational Medical Product Dossier (IMPD)/Clinical Trial Notification (Chiken-Todoke) is discontinued. The Investigator agrees to obtain the Sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The Sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. All data will be entered on the (e)CRFs supplied for each subject.

The Investigator and Sponsor will mutually agree upon the storage format for the retention of electronic data.

8.3.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or nonsubstantial amendments.

Depending on the nature of the amendment, either IRB/IEC, Competent Authority approval or notification may be required. The changes will become effective only after the approval of the Sponsor, the Investigator, the regulatory authority, and the IRB/IEC (if applicable).

Amendments to this protocol must be signed by the Sponsor and the Investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented which affects subject safety or the evaluation of safety, and/or efficacy. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

If there are changes to the Informed Consent, written verification of IRB/IEC approval must be forwarded to the Sponsor. An approved copy of the new Informed Consent must also be forwarded to the Sponsor.

8.3.4 Insurance of Subjects and Others

The Sponsor has covered this study by means of an insurance of the study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's File.

8.3.5 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report which forms part of a marketing authorization application be signed by the representative for the Coordinating Investigator(s) or the Principal Investigator(s). The representative for the Coordinating Investigator (s) or the Principal Investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for Coordinating Investigator(s) or the Principal Investigator(s) will be selected from the participating Investigators by the Sponsor prior to database lock.

9 QUALITY ASSURANCE

The Sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The Sponsor or Sponsor's designee may arrange to audit the clinical study at any or all investigational sites and facilities. The audit may include on-site review of regulatory documents, case report forms, and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

10.1 Independent Data-Monitoring Committee (IDMC) | Data and Safety Monitoring Board (DSMB)

Not applicable. The study will undergo regular, data review by the internal study teams including but not limited to data management, clinical, medical, safety, etc.

10.2 Other Study Organization

Not applicable.

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12 APPENDICES

12.1 List of Excluded Concomitant Medications

The following medications or therapies are prohibited during the receipt of study drug:

- Medications, including herbal therapies, with an antitumor effect (Use of LHRH agonist used to induce menopause in women of child-bearing potential is permitted).
- Any investigational agent
- AR antagonists (e.g., bicalutamide, flutamide, nilutamide)
- 5- α reductase inhibitors (e.g., finasteride, dutasteride)
- Systemic androgens and estrogens
- Megestrol acetate for appetite stimulation may be used at Investigator's discretion.

12.2 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases (AT) to $> 3 \times \text{ULN}$ (to $> 5 \times \text{ULN}$ in subjects with liver metastases), or bilirubin $> 2 \times \text{ULN}$, should undergo detailed testing for liver enzymes (including at least ALT, AST, alkaline phosphatase (ALP), and total bilirubin [TBL]). Testing should be repeated within 48-72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central lab regarding moderate and severe liver abnormality to inform the Investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		Total Bilirubin
Moderate	$> 3 \times \text{ULN}$ (in patients without liver metastases), $> 5 \times \text{ULN}$ (in patients with liver metastases)	or	$> 2 \times \text{ULN}$
Severe*	$> 3 \times \text{ULN}$	and	$> 2 \times \text{ULN}$

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST $> 8 \times \text{ULN}$
- ALT or AST $> 5 \times \text{ULN}$ for more than 2 weeks (in the absence of liver metastases)
- ALT or AST $> 3 \times \text{ULN}$ and INR > 1.5 (If INR testing is applicable/evaluated)
- ALT or AST $> 3 \times \text{ULN}$ with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia ($> 5\%$).

The Investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site should complete the Liver Abnormality Case Report Form (LA-CRF) that has been developed globally and can be activated for any study or appropriate document. Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2 to 3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology may be considered an important medical event and may be reported as an SAE. The Sponsor

should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the Investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new onset-diseases should be recorded as 'AEs' on the AE page of (e)CRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis (NASH) is seen in obese hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels. The Investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use, and special diets. Medications, including dose, should be entered on the concomitant medication page of the (e)CRF. Information on alcohol, other substance use, and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the subject's history, other testing may be appropriate including:
 - acute viral hepatitis (A,B, C, D, E or other infectious agents)
 - ultrasound or other imaging to assess biliary tract disease
 - other laboratory tests including INR, direct bilirubin
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Discontinuation

In the absence of an explanation for increased LFT's, such as viral hepatitis, preexisting or acute liver disease, presence of liver metastases, or exposure to other agents associated with liver injury, the subject may be discontinued from the study. The Investigator may determine that it is not in the subject's best interest to continue study enrollment. Discontinuation of treatment should be considered if:

- ALT or AST $> 8 \times$ ULN
- ALT or AST $> 5 \times$ ULN for more than 2 weeks (in subjects without liver metastases)
- ALT or AST $> 3 \times$ ULN and TBL $> 2 \times$ ULN or INR > 1.5 (if INR testing is applicable/evaluated)
- ALT or AST $> 5 \times$ ULN and (TBL $> 2 \times$ ULN in patients with liver metastases)
- ALT or AST $> 3 \times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia ($> 5\%$).

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, drug should be discontinued.

*Hy's Law Definition-Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10 to 50% mortality (or transplant)." The 2 "requirements" for Hy's Law are: 1. Evidence that a drug can cause hepatocellular-type injury, generally has shown by an increase in transaminase elevations higher 3 times the upper limit of normal ("2 x ULN elevations are too common in treated and untreated patients to be discriminating"). 2. Cases of increased bilirubin (at least 2 x ULN) with concurrent transaminase elevations at least 3 x ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome [Temple R. Hy's law: predicting serious hepatotoxicity. *Pharmacoepidemiol Drug Saf.* 2006 Apr;15(4):241-3].

Reference

Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued by FDA on July 2009.

12.3 Common Serious Adverse Events

The following is a list of SAEs that the Sponsor considers to be associated with the disease state being studied. The list does NOT change your reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed in Section 5.5.2 Definition of Serious Adverse Events. The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of “common SAEs”. You are required to follow the requirements detailed in Section 5.5.5 Reporting of Serious Adverse Events.

For IND safety reporting, single occurrences of the following events may be excluded from expedited reporting to the FDA. If aggregate analyses of these events indicate they occur more frequently with study drug, an expedited IND safety report may be submitted to the FDA.

- Anorexia
- Asthenia/Fatigue
- Dyspnea
- Metastases to brain
- Metastases to bone
- Metastases to lung
- Metastases to liver
- Spinal cord compression
- Nausea
- Bone Pain
- Metastatic breast cancer
- Vomiting

12.4 Retrospective Pharmacogenomic Sub-Study

INTRODUCTION

PGx research aims to provide information regarding how naturally occurring changes in a subject's gene and/or expression based on genetic variation may impact what treatment options are best suited for the subject. Through investigation of PGx by technologies such as genotyping, gene sequencing, statistical genetics and Genome-Wide Association Studies (GWAS), the relationship between gene profiles and a drug's kinetics, efficacy or toxicity may be better understood. As many diseases may be influenced by 1 or more genetic variations, PGx research may identify which genes are involved in determining the way a subject may or may not respond to a drug.

OBJECTIVES

The PGx research that may be conducted in the future with acquired blood samples is exploratory. The objective of this research will be to analyze or determine genes of relevance to clinical response, pharmacokinetics, and toxicity/safety issues.

By analyzing genetic variations, it may be possible to predict an individual subject's response to treatment in terms of efficacy and/or toxicity.

SUBJECT PARTICIPATION

Subjects who have consented to participate in this study may participate in this PGx sub-study. As part of this sub-study, subjects must provide separate written consent prior to providing any blood samples that may be used at a later time for genetic analysis.

SAMPLE COLLECTION AND STORAGE

Subjects who consent to participate in this sub-study will provide one 5 ml tube of whole blood per Astellas' instructions. Each sample will be identified by the unique subject number (first code). Samples will be shipped frozen to a designated banking CRO either directly from site or via a central laboratory as directed by Astellas.

BANKING CRO STORAGE AND SAMPLE CODING

Once received at the banking CRO, the samples will be assigned a unique sample code (second code) and stored frozen. A table linking the subject number (first code) with the newly-assigned sample code (second code) will be kept by the banking CRO. PGx analysis will be conducted using the second code only.

PGx ANALYSIS

Details on the potential PGx analysis cannot be established yet. Astellas may initiate the PGx analysis in case evidence suggests that genetic variants may be influencing the drug's kinetics, efficacy and/or safety. Prior to initiating any analysis on the banked samples, the Astellas ethical committee (AREC) must approve the analysis plan.

DISPOSAL OF PGx SAMPLES/DATA

All PGx samples collected will be stored for a period of up to 15 years following study database hardlock. If there is no requirement for analysis, the whole blood sample will be destroyed after the planned storage period. The subject has the right to withdraw consent at any time. When a subject's withdraw notification is received, the PGx sample will be destroyed. The results of any PGx analysis conducted on a sample prior to its withdrawal will be retained at Astellas indefinitely.

INFORMATION DISCLOSURE TO THE SUBJECTS

Exploratory PGx analysis may be conducted following the conclusion of the clinical study, if applicable. The results of the genetic analysis will not be provided to any Investigators or subjects, nor can the results be requested at a later date. Any information that is obtained from the PGx analysis will be the property of Astellas.

12.5 ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, 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 only 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

12.6 RECIST 1.1 Criteria

The following is a summary of RECIST 1.1 criteria to be used for the study. Refer to Eisenhauer et al, 2009 for further details.

Baseline Evaluations

Assessment must occur during the Screening period.

- Measurable lesions at baseline: tumor lesions must be accurately measured in at least one dimension and have a minimum diameter of 10 mm by CT scan when slice thickness is 5 mm or less OR twice the slice thickness of scan if slice thickness is greater than 5 mm. A lesion that is 10 mm by caliper measurement by clinical exam may be considered measurable. Lymph nodes must have a minimum diameter of 15 mm in the short axis by CT scan when slice thickness is 5 mm or less.
- Target Lesions: a maximum of 5 lesions and maximum of 2 lesions per organ representative of all organs can be recorded.
- Nontarget lesions: all other lesions.

Assessment methods:

- CT, MRI: CT slice thickness should be 5 mm or less, however if it is greater than 5 mm, the minimum size of a measurable lesion at baseline is twice the slice thickness of the baseline scans.
- Clinical lesions: considered measurable at baseline if they are superficial and ≥ 10 mm in diameter. For cutaneous and subcutaneous lesions, digital photographs with a metric ruler in the image must be available. Photographs must be obtained in such a manner to protect subject privacy.
- Cytology, histology: may be used to determine if effusions are neoplastic in origin.

Special consideration is to be given for bone lesion:

- Bone scan, positron emission tomography (PET) scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability above.
- Blastic bone lesions are not measurable.

Time Point Evaluations

Each lesion identified at baseline must be continually tracked at each time point evaluation. The longest diameter for that lesion will be measured at each time point evaluation (with the exception of lymph nodes for which the short axis will be used in the sum of diameters). The sum of diameters will be recorded at each time point measurement. Lesions that become too small to measure must still have a numerical measurement provided. Lesions that disappear completely with no residual disease are to be recorded as 0 mm. Lymph nodes identified as

target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. If a lesion is still present but cannot be measured, then a default of 5 mm is to be recorded. If a lesion is less than 5 mm but can be measured, then the actual measurement is to be recorded.

Table 3 Evaluation of Target Lesions

Response	Definitions
Complete Response (CR)	Disappearance of all target lesions. Pathologic lymph nodes must have reduction in short axis to < 10 mm.
Partial Response (PR)	≥ 30% decrease in sum of diameters from baseline sum of target lesions.
Stable Disease (SD)	Neither PR nor PD.
Progressive Disease (PD)	≥ 20% increase in the sum of diameters from the smallest sum on study AND sum of diameters must be at least 5 mm increase from smallest sum on study.

Table 4 Evaluation of Nontarget Lesions

Response	Definitions
Complete Response (CR)	Disappearance of all non-target lesions. AND lymph nodes all < 10 mm in short axis.
Non-CR/Non-PD	Persistence of any nontarget lesions.
Progressive Disease (PD)	Unequivocal progression of nontarget lesions.

Table 5 Evaluation of New Lesions

Response	Definitions
Unequivocal New Lesion	Not attributable to scanning technique, imaging modality, or necrosis.
Equivocal New Lesion	Small lesion requiring follow-up scan, biopsy, or fluorodeoxyglucose positron emission tomography (FDG-PET) to confirm.
Absent	No new malignant lesions identified.

Table 6 Time Point Response

Target	Nontarget	New	Overall Response
CR	CR	Absent	CR
CR	Non-CR/Non-PD	Absent	PR
CR	Not evaluated	Absent	PR
PR	Non-PD OR not all evaluated.	Absent	PR
SD	Non-PD OR not all evaluated.	Absent	SD
Not all evaluated	Non-PD	Absent	NE
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Unequivocally present	PD

CR=complete response, PR=partial response, SD = stable disease, PD=progressive disease, NE=not evaluated.

Best Overall Response

Best overall response will be assessed at the end of study for a given subject and is the best response across all time points. PR and CR require confirmation with equivalent or improved assessment no less than 4 weeks after the date of scan that PR or CR was first observed. SD requires confirmation with equivalent or improved assessment no less than 8 weeks after enrollment.

Table 7 Best Overall Response

Overall Response First Time point	Overall Response Subsequent Time point	BEST Overall Response
CR	CR	CR
CR	PD	SD if ≥ 8 weeks after enrollment. Otherwise, PD.
CR	NE	SD if ≥ 8 weeks after enrollment. Otherwise, NE.
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD if ≥ 8 weeks after enrollment. Otherwise, PD.
PR	NE	SD if ≥ 8 weeks after enrollment. Otherwise, NE.
NE	NE	NE

CR and PR require minimum of 4 weeks duration to be considered a confirmed response.

Stable Disease requires a minimum of 8 weeks after enrollment above to be considered a confirmed response.

The only valid responses following an initial CR is CR, PD, and NE; otherwise the responses require review.

Date of Progression

Date of progression for all primary and secondary analyses will be the earliest date (either scan date or visit date) that PD has been documented by objective assessment. Clinical progression date will be collected (if applicable or if objective assessment is not available) for sensitivity analyses.

12.7 Laboratory Assessments

Panel/Assessment	Parameters to be Analyzed
Hematology	Red blood cell count Hemoglobin Hematocrit Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration Mean corpuscular volume White blood cell count Platelet count White blood cell count differential includes lymphocytes, monocytes, eosinophils, neutrophils, and basophils. ANC will be recorded. Follicle Stimulating Hormone (required at screening for postmenopausal women < 55 years of age)
Biochemistry	Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bicarbonate Blood urea nitrogen/Blood urea Serum Creatinine Calcium Chloride Glucose Lactate dehydrogenase Magnesium Phosphorus Potassium Sodium Total bilirubin (including direct and indirect if available) Total protein Uric acid
Coagulation Studies	International normalization ratio (with prothrombin time/prothrombin time percent if reported, or partial thromboplastin time ratio if reported) Activated partial thromboplastin time or partial thromboplastin time
Urinalysis – Standard dipstick urinalysis	Color Appearance Specific gravity pH Bilirubin Blood Glucose Ketones Leukocyte esterase Nitrite Protein Urobilinogen
Pregnancy test - urine	Human chorionic gonadotropin (hCG)

13 ATTACHMENT 1: NONSUBSTANTIAL AMENDMENT 2

I. The purpose of this amendment is:

Nonsubstantial Changes	
1. Update Key Sponsor Personnel	
DESCRIPTION OF CHANGE:	
Contact details for the medical monitor/medical expert and clinical research contact are updated.	
RATIONALE:	
These revisions are made based on changes to study personnel.	
2. Update Planned Study Period	
DESCRIPTION OF CHANGE:	
The completion date of the study is changed from 1Q2023 to 1Q2025.	
RATIONALE:	
The study period is updated to reflect the expected study completion date.	

II. Amendment Summary of Changes:

IIA. Nonsubstantial Changes

II Contact Details of Key Sponsor's Personnel	
WAS:	
Medical Monitor/ Medical Expert:	<div>PPD</div> <div></div> <div>Astellas Pharma Global Development, Inc.</div> <div>PPD</div> <div></div> <div></div>

IS AMENDED TO:	
Medical Monitor/ Medical Expert:	<p>PPD</p> <p></p> <p>Astellas Pharma Global Development, Inc.</p> <p>PPD</p> <p></p> <p></p> <p></p> <p></p> <p>Astellas Pharma Global Development, Inc.</p> <p>PPD</p> <p></p> <p></p>
WAS:	
Clinical Research Contact:	<p>PPD</p> <p></p> <p>Astellas Pharma Inc</p> <p>PPD</p> <p></p>
IS AMENDED TO:	
Clinical Research Contact:	<p>PPD</p> <p></p> <p>Astellas Pharma, Inc.</p> <p>PPD</p> <p></p> <p></p> <p></p> <p></p> <p>Astellas Pharma Inc</p> <p>PPD</p> <p></p>

IV Synopsis, Planned Study Period
WAS:
From 2Q2014 to 1Q2023
IS AMENDED TO:
From 2Q2014 to 1Q2023 1Q2025

14 SPONSOR'S SIGNATURE

Required sponsor signatures as required by ICH GCP 4.5.1 are located in the second attachment.

Attachment 2	Electronic Sponsor Signatures
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