Protocol of Post-marketing Clinical Study on Enzalutamide

—A Randomized Phase IV Study Comparing Enzalutamide versus Flutamide in CRPC Patients Who Have Failed Combined Androgen Blockade Therapy with Bicalutamide plus ADT—

ISN/Protocol 9785-MA-3051

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I. SIGNATURES

1. AGREEMENT BETWEEN THE SPONSOR'S RESPONSIBLE PERSON AND THE INVESTIGATOR

This clinical study will be conducted in adherence to GCP, ICH Guidelines and applicable laws and regulatory requirements, as well as this study protocol. As the evidence of the agreement, the investigator (CHIKEN SEKININ ISHI) and responsible person of the Sponsor (CHIKEN IRAI SEKININSHA) inscribe in the bipartite agreement.

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

Contact Information for the Sponsor

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Location: 2-5-1, Nihonbashi-Honcho, Chuo-ku, Tokyo

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Fax: [redacted]

Sponsor's personnel: [redacted]

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III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AAT	Alternative Antiandrogen Therapy
ADT	Androgen Deprivation Therapy
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AR	Androgen Receptor
AST	Aspartate Aminotransferase
BFI	Brief Fatigue Inventory
BPI-SF	Brief Pain Inventory-Short Form
BUN	Blood Urea Nitrogen
CAB	Combined Androgen Blockade
CRF	Case Report Form
CRO	Contract Research Organization
CRPC	Castration-Resistant Prostate Cancer
CSR	Clinical Study Report
CT	Computerized Axial Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DES	Diethylstilbestrol
DHEA	Dihydroepiandrosterone
DILI	Drug-induced Liver Injury
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EQ-5D-5L	European Quality of Life-5 Dimension-5 Level Instruments
FACT–P	Functional Assessment of Cancer Therapy–Prostate
FDA	Food and Drug Administration
GABA	Gamma Amino Butyric Acid
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
GnRH	Gonadotropin Releasing Hormone
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IRB	Institutional Review Board
ISN	International Study Number
ITT	Intent-to-Treat
IUD	Intrauterine Device
IUS	Intrauterine System
LA-CRF	Liver Abnormality Case Report Form
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviations	Description of abbreviations
MFS	Metastasis-Free Survival
MRI	Magnetic Resonance Imaging
NASH	Non-Alcoholic Steatohepatitis
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PCWG2	Prostate Cancer Clinical Trials Working Group 2
PDAS	Pharmacodynamic Analysis Set
P-gp	P-glycoprotein
PKAS	Pharmacokinetic Analysis Set
PSA	Prostate-Specific Antigen
QOL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	Radiographic Progression-Free Survival
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SFL	Screen Failure Log
SOP	Standard Operating Procedure
$t_{1/2}$	Terminal Elimination Half-life
TTF1	Time to Treatment Failure 1
TTF2	Time to Treatment Failure 2
TTPP1	Time to PSA Progression 1
TTPP2	Time to PSA Progression 2
2nd TTPP	2nd Time to PSA Progression
ULN	Upper Limit of Normal
WHODDE	WHO Drug Dictionary Enhanced
γ-GTP	γ-gultamyltranspeptidase

Definition of Key Study Terms

Terms	Definition of terms
Baseline	Observed values/findings that are considered as observed starting point for comparison. The baseline of individual endpoints is defined as data from the following period: ● Prostate-specific antigen (PSA), subject reported outcome, vital signs, laboratory test values, Eastern Cooperative Oncology Group (ECOG) Performance Status: Week 1 (Day 1) of 1st line AAT and 2nd line AAT ● Diagnostic imaging: Screening period
Enroll	To register or enter into a clinical trial. NOTE: Once a subject has been enrolled, the clinical trial protocol applies to the subject.
Intervention	The drug, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study. (e.g., health-related quality of life, efficacy, safety, pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test drug or comparative drug (sometimes without randomization) is usually given to a subject, and continues until the last assessment after completing administration of the test drug or comparative drug.
Post investigational period	Period of time after the last assessment of the protocol. 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 the informed consent form until the initial administration of the test drug or comparative drug (sometimes without randomization) is given to a subject.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screen failure	Potential subject who did not meet one or more criteria required for participation in a trial.
1st line AAT period	Period from starting the first study drug (test drug or comparative drug) after randomization to the end of last assessment at completion or discontinuation of treatment with 1st line AAT or to start the second study drug (test drug or comparative drug).
2nd line AAT period	Period from starting the second study drug (test drug or comparative drug) to the end of last assessment at completion or discontinuation of treatment with 2nd line AAT.
Safety follow-up period	28 days from final administration of the study drug.
Adverse Event	Any untoward medical occurrence in a subject administered a study drug and which does not necessarily have a causal relationship with the study treatment.
Subject	An individual who participates in a clinical trial, and receives or is to receive the study drug.
Subject Number, Subject ID Code	A number given to an individual subject who agrees to participate in the study and signs an informed consent form.

Terms	Definition of terms
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Date and Version # of Protocol Synopsis: 03 August, 2016, Version 2.0	
Sponsor: Astellas Pharma Inc (API)	**Protocol Number:** 9785-MA-3051
Name of Study Drug: Enzalutamide	**Phase of Development:** Phase 4
Title of Study: Post-marketing clinical study on enzalutamide —A Randomized Phase IV Study Comparing Enzalutamide versus Flutamide in CRPC Patients Who Have Failed Combined Androgen Blockade Therapy with Bicalutamide plus ADT—	
Planned Study Period: From October 2016 to March 2020	
Study Objective(s): To compare the efficacy and safety of the combination therapy with enzalutamide + ADT and the combination therapy with flutamide + ADT in patients with castration resistant prostate cancer that relapsed during combined androgen blockade (CAB) therapy with bicalutamide and androgen deprivation therapy (ADT). To investigate the order of alternative antiandrogen therapy (AAT) by changing the 1st line medication after progression of prostate-specific antigen (PSA). **Primary objective:** ● To determine the benefit of enzalutamide + ADT therapy as compared to flutamide + ADT therapy as assessed by time to PSA progression with 1st line AAT (time to PSA progression 1 [TTPP1]). **Secondary objectives:** ● To determine the order of AAT treatment as assessed by time to PSA progression with 1st line AAT + 2nd line AAT (time to PSA progression 2 [TTPP2]). ● To determine the benefit of enzalutamide + ADT therapy as compared to flutamide + ADT therapy as assessed by PSA response rate to 1st line AAT (proportion of subjects with a decrease by at least 50% or 90% from baseline irrespective of the timing). ● To determine the benefit of enzalutamide + ADT therapy as compared to flutamide + ADT therapy as assessed by PSA response rate to 1st line AAT at Week 13 (proportion of subjects with a decrease by at least 50% or 90% from baseline). ● To determine the benefit of enzalutamide + ADT therapy as compared to flutamide + ADT therapy as assessed by time to PSA decrease by 50% from baseline with 1st line AAT. ● To determine the benefit of enzalutamide + ADT therapy as compared to flutamide + ADT therapy as assessed by time to discontinuation of 1st line AAT (time to treatment failure 1 [TTF1]). ● To determine the order of AAT treatment as assessed by time to discontinuation of 2nd line AAT (time to treatment failure 2 [TTF2]). ● To determine the benefit of enzalutamide + ADT therapy as compared to flutamide + ADT therapy as assessed by radiographic progression-free survival (rPFS).	

Safety objective:

- To determine the safety of enzalutamide + ADT therapy as compared to flutamide + ADT therapy.

Exploratory objectives:

- To evaluate time to PSA progression with 2nd line AAT (2nd time to PSA progression [2nd TTPP]).
- To evaluate PSA response rate to 2nd line AAT.
- To determine the benefit of enzalutamide + ADT therapy as compared to flutamide + ADT therapy as assessed by metastasis-free survival (MFS).
- To evaluate Quality of Life (QOL) on 1st line AAT and 2nd line AAT using Functional Assessment of Cancer Therapy–Prostate (FACT–P) and European Quality of Life 5-Dimension-5 Level instruments (EQ-5D-5L).
- To evaluate Brief Pain Inventory-Short Form (BPI-SF) with 1st line AAT and 2nd line AAT.
- To evaluate Brief Fatigue Inventory (BFI) with 1st line AAT and 2nd line AAT.
- To determine the benefit of enzalutamide + ADT therapy as compared to flutamide + ADT therapy as assessed by objective response rate (ORR) in soft tissue with 1st line AAT based on the best overall response in RECIST guidelines.
- To evaluate the efficacy in subgroups according to disease-related patient demographics.

Planned Total Number of Study Centers and Location(s):
Approximately 40 centers
Japan

Study Population:
Patients with castration resistant prostate cancer that relapsed during CAB therapy with bicalutamide

Number of Subjects to be Enrolled / Randomized:
200 subjects (1st line AAT enzalutamide group: 100, 1st line AAT flutamide group: 100)

Study Design Overview:
This is a randomized, open-label, comparative study on enzalutamide and flutamide.
Patients with M0 or M1 castration resistant prostate cancer that relapsed during CAB therapy with bicalutamide will be randomized to Groups A or B. Randomization will be stratified according to the stages shown below (M0/N0, M0/N1, or M1):

- M0/N0: No distant metastasis, and no lymph node metastasis
- M0/N1: Without distant metastasis, but with metastasis in lymph nodes distal to the aortic bifurcation
- M1: With distant metastasis (including metastasis in lymph nodes proximal to the aortic bifurcation)

For subjects in Group A, enzalutamide is administered as the 1st line AAT. After the confirmation of PSA progression, medication is changed from enzalutamide to flutamide as the 2nd line AAT.
For subjects in Group B, flutamide is administered as the 1st line AAT. After the confirmation of PSA progression, medication is changed from flutamide to enzalutamide as the 2nd line AAT. The treatment period with each drug should not be more than 2 years from the enrollment of the last subjects.
PSA progression will be defined according to the consensus guidelines of PCWG2. For patients with PSA declines at Week 13, the PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained 3 or more weeks later. For patients with no PSA decline at

Week 13, the PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the baseline is documented.
Data for the analysis of primary endpoint TTPP1 will be cut-off if not less than 135 events of PSA progression occurred in association with the 1st line AAT.
After the discontinuation of the 1st line AAT due to PSA progression or other reasons, the 2nd line AAT will be started. Subjects who discontinued the 1st line AAT due to PSA progression will start the 2nd line AAT within 6 weeks after the date of examination that identified PSA progression. Subjects who discontinued the 1st line AAT due to other reasons will start the 2nd line AAT within 6 weeks from the day when the investigator or subinvestigator decided the discontinuation.
A safety follow-up visit should be performed wherever possible in 28 days from the final study treatment, or before starting other study drugs, or before starting other treatment for prostate cancer, whichever comes first. If subjects do not show up on the safety follow-up visit, confirm adverse events by the telephone wherever possible.

Inclusion/Exclusion Criteria:

Inclusion:

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

1. Subject must have submitted an informed consent form approved by the institutional review board (IRB) established at each study center prior to the study.
2. Age ≥20 years at the time of signing the informed consent form.
3. Subject is diagnosed with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small-cell histology.
4. Subject on continuous ADT with GnRH agonist/antagonist or bilateral orchiectomy (surgical or chemical castration).
5. Subject for whom treatment with effective GnRH agonist/antagonist is to be continued during the study period if bilateral orchiectomy is not performed.
6. Serum testosterone level ≤1.73 nmol/L (50 ng/dL or 0.5 ng/mL) at screening visit.
7. Subject with no change in the dose of bisphosphonate preparation or denosumab for at least 4 weeks if these drugs are used.
8. Subject with asymptomatic or mildly symptomatic prostate cancer (BPI-SF score is <4 to Question 3 “the worst pain within 24 hours”).
9. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
10. Subject has an estimated life expectancy of ≥12 months.
11. Subject is able to swallow the study drug, and comply with procedures required by the study.
12. Subject has progression of the disease that falls under at least one of the following 3 criteria during CAB therapy in combination of bicalutamide and ADT.
    - PSA increase should be confirmed at least 2 timepoints with an interval of ≥1 week. In at least 6 weeks after the last dose of bicalutamide, PSA should be confirmed higher than the highest PSA measured after the nadir was confirmed during administration of bicalutamide. PSA at screening visit should be ≥2 ng/mL (2 μg/L).
    - Soft tissue disease progression defined by RECIST guidelines (version 1.1).
    - Progression of ≥2 bone lesions defined as new lesions in bone scintigraphy by PCWG2.
13. A sexually active male subject and his female partner who is of childbearing potential must use 2 acceptable birth control methods shown below (1 of which must include a condom as a barrier method of contraception) from screening to 3 months after the last dose of the study drug.

- A male or female condom as a barrier method of contraception;
- Consistent and correct usage of established, proper use of oral contraceptives;
- Established intrauterine device or intrauterine system by the female partner;
- Tubal ligation in the female partner performed at least 6 months prior to subject's screening visit;
- Vasectomy or other procedure resulting in infertility (e.g., bilateral orchiectomy) performed at least 6 months prior to screening;
- Calendar-based contraceptive methods (Knaus-Ogino or rhythm method).

14. Subject must use a condom throughout the study if engaging in sexual intercourse with a pregnant woman.
15. Subject must agree not to donate sperm from screening to 3 months after the last dose of the study drug.
16. 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 the study if any of the following apply:

1. Subject with severe concurrent diseases, infections, or complications, which are considered inappropriate for enrollment by the investigator or subinvestigator.
2. Subject with confirmed or suspected brain metastasis or active leptomeningeal metastasis.
3. Subject with a history of malignant tumor other than prostate cancer in the past 5 years (except for non-melanoma skin cancer cured with radical therapy).
4. Subject hypersensitive to the ingredients of enzalutamide capsules or flutamide tablets.
5. Subject with a history of seizure, or any condition that may predispose to seizure.
6. Subject with liver disorder such as viral hepatitis and hepatic cirrhosis, or subject with AST and ALT at screening visit higher than the upper limit of normal.
7. Subject on warfarin.
8. Subject received treatment for prostate cancer with cytocidal chemotherapy that includes anti-androgenic agents other than bicalutamide (e.g., enzalutamide, flutamide), abiraterone, or estramustine.
9. Subject participated in a clinical trial on a drug other than GnRH agonist/antagonist in prostate cancer.
10. Subject received treatment with herbal medications that may have hormonal anti-prostate cancer activity or herbal medications (saw palmetto) that may decrease PSA levels; subject received treatment for prostate cancer with systemic corticosteroids, or treatment for other diseases with systemic corticosteroids greater than the equivalent of 10 mg per day of prednisone (Decadron 1 mg/day) within 4 weeks prior to enrollment (Day 1).
11. Subject received treatment with bicalutamide within 6 weeks prior to enrollment (Day 1).
12. Subject received treatment with 5-α reductase inhibitors (finasteride, dutasteride), estrogens, or drugs with anti-tumor action other than GnRH agonists/antagonists within 4 weeks prior to enrollment (Day 1).
13. Subject received treatment with opioid analgesic for pains associated with prostate cancer

within 4 weeks prior to enrollment (Day 1).

14. Subject participated or is currently participating in a clinical trial or a post-marketing clinical study on other ethical drugs (excluding GnRH agonist/antagonist) or medical devices within 12 weeks or 5 half lives (in case of ethical drugs), whichever is longer, prior to screening.
15. Subject received treatment for primary or metastatic lesion with surgery or radiation therapy within 4 weeks prior to enrollment (Day 1).
16. Subject with unstable psychiatric disease (e.g., schizophrenia, dementia, uncontrollable depression/bipolar disorder).
17. Subject with a disease or reason unsuitable for participation in the study, which is considered by the investigator or subinvestigator to cause excessive risk to the subject or make the interpretation of safety data difficult.

Waivers to the exclusion criteria will NOT be allowed.

Criteria to shift from 1st line AAT to 2nd line AAT:
If any of the following is satisfied, the study drug will be shifted to the 2nd line AAT after the discontinuation of the1st line AAT:

1. PSA progression
2. In case where the 1st line AAT is to be discontinued due to adverse events, but the investigator or subinvestigator considers that there is no problem in the subject tolerance to transition to the 2nd line AAT.
3. In case where the 1st line AAT is to be discontinued due to progression of disease other than PSA progression, but the investigator or subinvestigator considers that there is no problem in the subject tolerance to transition to the 2nd line AAT.

In any of the following cases, study treatment will be discontinued without shifting to the 2nd line AAT:

1. In case of enzalutamide as 2nd line AAT, subjects with seizure as an adverse event
2. In case of flutamide as 2nd line AAT, subjects with the latest AST or ALT exceeding the upper limit of normal
3. Other cases that the investigator or subinvestigator considers unsuitable for study continuation

Investigational Product(s):
Enzalutamide capsule 40 mg
Dose(s):
160 mg once daily (160 mg/day)
Mode of Administration:
Oral

Comparative Drug(s):
Flutamide tablets 125 mg
Dose(s):
125 mg × 3 times daily (375 mg/day)
Mode of Administration:
Oral

Drug(s) for Screening:
Not applicable

Rescue Therapy: Not applicable

Enzalutamide Dose Reduction/Adjustment
If a study drug associated adverse reaction occurs, is evaluated as Grade 3 or higher according to the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, and is not improved by proper medical intervention, stop the treatment for a week or until the severity of the adverse reaction improves to Grade 2 or lower. After the improvement, treatment may be restarted with the original or reduced dose at the discretion of the investigator or subinvestigator.
If a strong CYP2C8 inhibitor (e.g., gemfibrozil) should be concurrently used, reduce the dose of enzalutamide to 80 mg once daily. When the CYP2C8 inhibitor is discontinued, return the dose of enzalutamide to the original dose.

Flutamide Dose Reduction/Adjustment
If a study drug associated adverse reaction occurs, is evaluated as Grade 3 or higher according to the NCI-CTCAE version 4.0, and is not improved by proper medical intervention, stop the treatment for a week or until the severity of the adverse reaction improves to Grade 2 or lower. After the improvement, treatment may be restarted with the original or reduced dose at the discretion of the investigator or subinvestigator.

Concomitant Medication Restrictions or Requirements:
Required concomitant medications:
All subjects must undergo continuous ADT with GnRH agonist/antagonist or bilateral orchiectomy during the study period. GnRH agonist/antagonist will be prepared and administered by the study center. Do not change the medications in principle.

Prohibited concomitant medications:
The use of the following drugs and therapies are prohibited during the study treatment and in the period from the end of the 1st line AAT to the start of the 2nd line AAT:

- anti-androgenic agents (steroid or non-steroid) other than study drugs such as chlormadinone and bicalutamide
- CYP17 inhibitor (abiraterone)
- cytocidal chemotherapy that includes estramustine
- systemic corticosteroids for prostate cancer or systemic corticosteroids greater than the equivalent of 10 mg per day of prednisone (Decadron 1 mg/day) for other diseases
- 5-α reductase inhibitors (finasteride, dutasteride)
- estrogen or progesterone agents such as medroxyprogesterone and diethylstilbestrol (DES)
- biological agents or other drugs with anticancer activity to prostate cancer
- herbal medications that may have hormonal anti-prostate cancer activity or herbal medications (saw palmetto) that may decrease serum PSA levels
- androgen (e.g., testosterone, dehydroepiandrosterone [DHEA])
- study drugs for prostate cancer
- surgery or radiation therapy for primary lesion
- warfarin

Precautions for concomitant medication with enzalutamide (drug interactions):
Enzalutamide may affect the exposure to other medications. Other medications may also affect the exposure to enzalutamide.

- Concomitant use with strong CYP2C8 inhibitors (e.g., gemfibrozil) may elevate the plasma concentration of enzalutamide. Therefore, it is desirable to avoid the concomitant use. If the subject needs a strong CYP2C8 inhibitor, reduce the dose of enzalutamide to 80 mg once

daily, and return the dose of enzalutamide to the original dose when the combination use is discontinued.

- Strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, and rifampicin) or moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin, and hypericum erectum) may decrease the plasma concentration of enzalutamide. Therefore, it is desirable to avoid the concomitant use. It is recommended to select a drug that is less likely to induce CYP3A4, or minimizes the induction.
- Enzalutamide is a strong inducer of CYP3A4, and moderate inducer of CYP2C9 and CYP2C19. Enzalutamide decreases the exposure to drugs of CYP3A4 substrate with a small therapeutic range (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus), drugs of CYP2C9 substrate with a small therapeutic range (e.g., phenytoin and warfarin), drugs of CYP2C19 substrate with a small therapeutic range, and drugs of UGT1A1 substrate with a small therapeutic range (e.g., S-mephenytoin). Therefore, it is desirable to avoid the concomitant use.
- Enzalutamide is an inhibitor of human P-glycoprotein (P-gp) and may increase the exposure to drugs of P-gp substrate. Precaution is required for the combination use of drugs of P-gp substrate with a small therapeutic range (e.g., digoxin, colchicine, and dabigatran etexilate) with enzalutamide.

Duration of Treatment:

- The administration of the 1st line AAT will be continued until the case falls under the criteria for shifting from the1st line AAT to 2nd line AAT or the discontinuation criteria, or for 2 years from the enrollment of the last subject.
- After the discontinuation of the 1st line AAT due to PSA progression or other reasons, the 2nd line AAT will be started. Subjects who discontinued the 1st line AAT due to PSA progression will start the 2nd line AAT within 6 weeks after the date of examination that identified PSA progression. Subjects who discontinued the 1st line AAT due to other reasons will start the 2nd line AAT within 6 weeks from the day when the investigator or subinvestigator decided the discontinuation.
- The administration of the 2nd line AAT will be continued until PSA progression or until the case falls under the discontinuation criteria, or for 2 years from the enrollment of the last subject.

Discontinuation Criteria:
The study will be discontinued in case of any of the following events:

1. Adverse events (excluding events in the discontinuation criteria 2 and 3) that are intolerable for the subject, and are not improved by proper medical intervention or reduction of the study drug; or adverse events, which the investigator or subinvestigator considers that the continuation of the study drug may cause an excessive risk to subjects.
2. Seizure during the treatment period of enzalutamide (subjects who had seizure on the1st line AAT may be shifted to the 2nd line AAT.)
3. Liver disorder during the treatment period of flutamide (AST or ALT that exceeds 3 fold of the upper limit of normal) or interstitial pneumonia (subjects who had a case on the 1st line AAT may be shifted to the 2nd line AAT.)
4. With or without PSA progression, the investigator or subinvestigator considers that the study should be discontinued due to the progression of the disease.
5. Subject withdraws the informed consent.
6. Observation cannot be continued (e.g., subject stops study visit; subject is lost to contact)
7. The sponsor, investigator, or subinvestigator considers that the study should be discontinued due to deviation from the protocol (excluding the discontinuation criterion 8).
8. It turns out after the enrollment that the subject did not satisfy the inclusion criteria at the time of enrollment, or met the exclusion criteria, and the continuation of the study is judged inappropriate.
9. Other
   For reasons other than those mentioned above, the investigator or subinvestigator considers that the study should be discontinued.

For discontinuation after the start of the study drug, a discontinuation examination/observation will be conducted wherever possible immediately after the decision of discontinuation.

Endpoints for Evaluation:
Primary:

- Time to PSA progression with 1st line AAT (TTPP1)

Secondary:

- Time to PSA progression with 1st line AAT + 2nd line AAT (TTPP2)
- PSA response rate to 1st line AAT (decrease by at least 50% or 90% from baseline)
- PSA response rate to 1st line AAT at Week 13 (decrease by at least 50% or 90% from baseline)
- Time to PSA decrease by 50% from baseline with 1st line AAT
- Time to discontinuation of 1st line AAT (TTF1)
- Time to discontinuation of 2nd line AAT (TTF2)
- rPFS

Safety:

- Characteristics, frequency, and severity of adverse events
- Safety-related laboratory tests (biochemistry and hematology)
- Vital signs (blood pressure and pulse rate)

- ECOG Performance Status

Exploratory:

- Time to PSA progression with 2nd line AAT (2nd TTPP)
- PSA response rate to 2nd line AAT (decrease by at least 50% or 90% from baseline)
- MFS
- QOL assessment with 1st line AAT and 2nd line AAT by FACT–P and EQ-5D-5L
- BPI-SF with 1st line AAT and 2nd line AAT
- BFI with 1st line AAT and 2nd line AAT
- ORR in best overall soft tissue response of RECIST guidelines with 1st line AAT
- Efficacy assessment by subgroups according to disease-related patient demographics

Statistical Methods:

Sample size justification:

The sample size for evaluation will be approximately 200 subjects (1st line AAT enzalutamide group: 100, 1st line AAT flutamide group: 100).

The sample size to evaluate the time to PSA progression with 1st line AAT (TTPP1) was calculated in consideration of the following points:

- Median TTPP1 with enzalutamide: 10.5 months.
  [redacted]
- Median TTPP1 with flutamide: 6 months.
  Values reported in the literature: 5 months according to [Okihara et al., 2007]; 6.25 months according to [Narimoto et al., 2010].
- The ratio of randomization of 1st line AAT enzalutamide and flutamide groups is 1:1.
- Subject enrollment period is 12 months, and the observation period is 24 months from the enrollment of the last subject.
- Type I error of the two-sided test is 0.05, and power is 90%.
- A log-rank test with the TTPP1 parameters shown above requires 135 events. The necessary number of subjects calculated based on the required number of events is 74 subjects per group.
- Considering the dropout rate of approximately 25%, 100 subjects are to be enrolled in each group.

Efficacy:
Efficacy analysis will be performed on Intent-to-Treat (ITT) defined as all the randomized subjects.

Primary endpoint:
Time to PSA progression with 1st line AAT (TTPP1)

- Time to PSA progression with 1st line AAT is defined as the period from randomization to the first day when PSA progression is objectively identified. Convention of censoring is specified in Section 7.10.
- The benefit of enzalutamide as compared to flutamide will be assessed with stratified log-rank test as the primary efficacy analysis. The significance level is 0.05 (two-sided). The stratification factor will be the disease stages (M0/N0, M0/N1, or M1) used as stratification factor for allocation.
- The benefit of enzalutamide as compared to flutamide will be also assessed with hazard ratio and its 95% CI based on Cox proportional hazards model. Disease stages (M0/N0, M0/N1, or M1) will be used as a covariate for adjustment.
- Furthermore, the distribution of time to PSA progression will be estimated using the Kaplan–Meier method. The median time to PSA progression will be estimated using the 50 percentile value of the Kaplan–Meier curve. The two-sided 95% CI will be calculated based on the estimation.

Secondary endpoints:
Time to PSA progression with 1st line AAT + 2nd line AAT (TTPP2)

- Time to PSA progression with 2nd line AAT is defined as the period from Day 1 of 2nd line AAT to the date of PSA progression with 2nd line AAT. The total of time to PSA progression with 1st line AAT and time to PSA progression with 2nd line AAT will be evaluated. Convention of censoring is specified in Section 7.10.
- The distribution of the period of TTPP2 will be estimated using the Kaplan–Meier method. The median period of TTPP2 will be estimated using the 50 percentile value of the Kaplan–Meier curve. The two-sided 95% CI will be calculated based on the estimation. The benefit of enzalutamide as compared to flutamide will be descriptively assessed.

PSA response rate to 1st line AAT (decrease by at least 50% or 90% from baseline)

- PSA response rate decreasing by at least 50% will be calculated by treatment groups of subjects with baseline PSA value and PSA measured at least once after baseline. For the comparison of response rate between the enzalutamide and flutamide groups, the stratified Cochran–Mantel–Haenszel test will be used. The stratification factor will be the disease stages (M0/N0, M0/N1, or M1) used as stratification factor for allocation.
- PSA decrease by at least 90% will also be compared at the 0.05 significance level (two-sided) between the enzalutamide and flutamide groups using stratified Cochran–Mantel–Haenszel test.

PSA response rate to 1st line AAT at Week 13 (decrease by at least 50% or 90% from baseline)

- PSA response rate decreasing by at least 50% (or at least 90%) will be calculated by treatment groups of subjects with baseline PSA value and PSA measured at Week 13. Response rate between the enzalutamide and flutamide groups will be compared using the stratified Cochran–Mantel–Haenszel test. The stratification factor will be the disease stages (M0/N0, M0/N1, or M1) used as stratification factor for allocation.

Time to PSA decrease by 50% from baseline with 1st line AAT

- The time to PSA decrease by 50% with 1st line AAT is defined as the period from randomization to the day when the decrease of PSA from baseline by 50% is first identified. Convention of censoring is specified in Section 7.10.
- The benefit of enzalutamide as compared to flutamide will be assessed by the stratified log-rank test. The significance level is 0.05 (two-sided). The stratification factor will be the disease stages (M0/N0, M0/N1, or M1) used as stratification factor for allocation.
- The distribution of the period where PSA decreases by 50% will be estimated using the Kaplan–Meier method. The median period where PSA decreases by 50% will be estimated using the 50 percentile value of the Kaplan–Meier curve. The two-sided 95% CI will be calculated based on the estimation.

Time to discontinuation of 1st line AAT (TTF1)

- The time to discontinuation of 1st line AAT will be calculated as the period from randomization to the date of discontinuation of 1st line AAT. Convention of censoring is specified in Section 7.10.
- The benefit of enzalutamide as compared to flutamide will be assessed with the stratified log-rank test. The significance level is 0.05 (two-sided). The stratification factor will be the disease stages (M0/N0, M0/N1, or M1) used as stratification factor for allocation.
- The distribution of the time to discontinuation of 1st line AAT will be estimated using the Kaplan–Meier method. The median time to discontinuation of 1st line AAT will be estimated using the 50 percentile value of the Kaplan–Meier curve. The two-sided 95% CI will be calculated based on the estimation.

Time to discontinuation of 2nd line AAT (TTF2)

- The time to discontinuation of 2nd line AAT will be calculated as the period from randomization to the date of discontinuation of 2nd line AAT. Convention of censoring is specified in Section 7.10.
- The distribution of the period of TTF2 will be estimated using the Kaplan–Meier method. The median period of TTF2 will be estimated using the 50 percentile value of the Kaplan–Meier curve. The two-sided 95% CI will be calculated based on the estimation. The benefit of enzalutamide as compared to flutamide will be descriptively assessed.

Radiographic progression-free survival (rPFS)

- rPFS will be assessed using the same method as that with the time to PSA progression with 1st line AAT (TTPP1) in subjects with distant metastasis confirmed at baseline.

Explorative endpoint:
Time to PSA progression with 2nd line AAT (2nd TTPP)

- Time to PSA progression with 2nd line AAT is defined as the period from the start of 2nd line AAT to the first day when PSA progression is objectively identified. Convention of censoring is specified in Section 7.10.
- The distribution of the time to PSA progression with 2nd line AAT will be estimated using the Kaplan–Meier method. The median time to discontinuation of 2nd line AAT will be estimated using the 50 percentile value of the Kaplan–Meier curve. The two-sided 95% CI will be calculated based on the estimation. The benefit of enzalutamide as compared to flutamide will be descriptively assessed.

PSA response rate to 2nd line AAT

- PSA response rate to 2nd line AAT will be assessed using the same method as that with PSA response rate to 1st line AAT.

Metastasis-free survival (MFS)

- MFS will be assessed using the same method as that with 2nd TTPP in subjects without distant metastasis at baseline.

FACT–P and EQ-5D-5L with 1st line AAT and 2nd line AAT

- For FACT–P and EQ-5D-5L, summary statistics will be calculated at each assessment.

Brief Pain Inventory-Short Form (BPI-SF) with 1st line AAT and 2nd line AAT

- For BPI-SF, summary statistics will be calculated at each assessment.

Brief Fatigue Inventory (BFI) with 1st line AAT and 2nd line AAT

- For BFI, summary statistics will be calculated at each assessment.

Objective response rate (ORR) in best overall soft tissue response of RECIST guidelines with 1st line AAT

- ORR will be assessed using the same method as that with PSA response rate.

Pharmacokinetics:
Not applicable

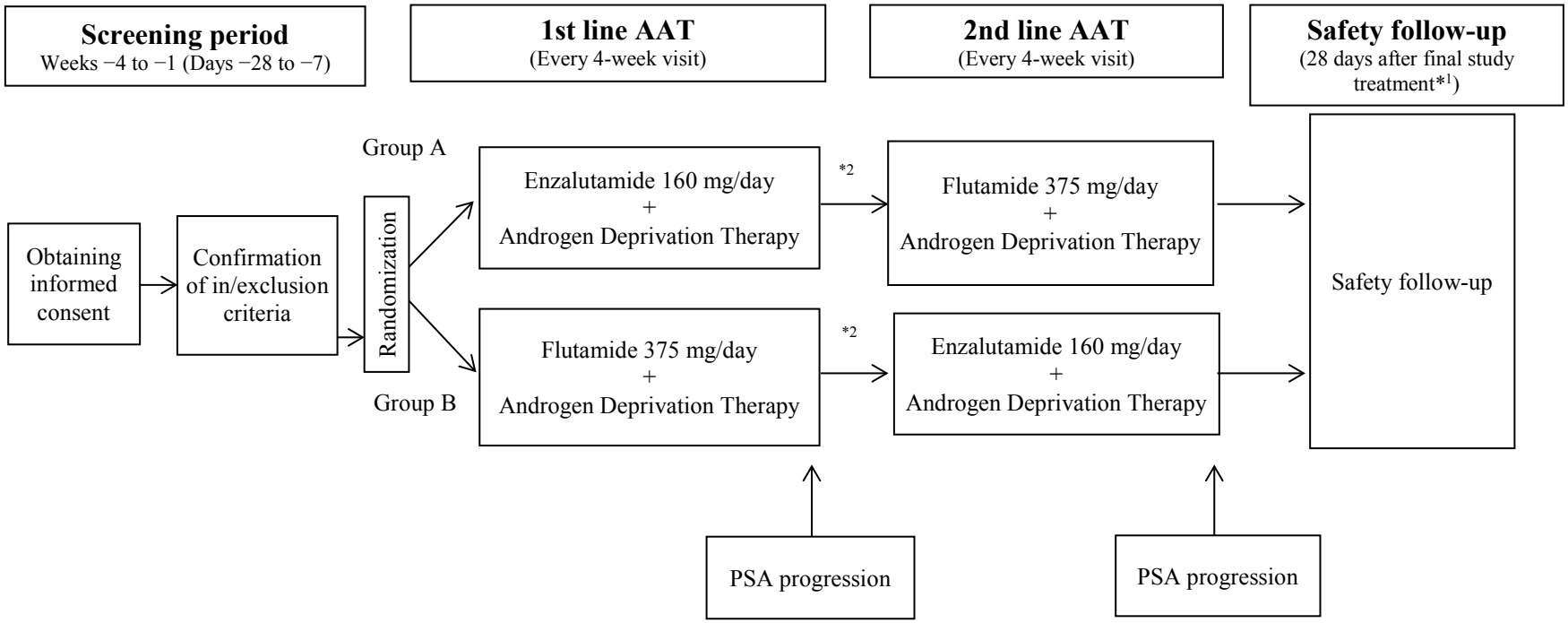
Pharmacodynamics:
Not applicable

Safety:
For frequency and severity of adverse events, safety-related laboratory tests, and vital signs, summary statistics will be calculated. For ECOG Performance Status, frequency distribution will be calculated.

Interim analyses:
Not applicable

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart



*1: 28 days after final study treatment, or before starting other study drugs, or before starting other treatment for prostate cancer, whichever comes first

*2: Subjects who discontinued the 1st line AAT due to PSA progression will start the 2nd line AAT within 6 weeks after the date of examination that identified PSA progression. Subjects who discontinued the 1st line AAT due to other reasons will start the 2nd line AAT within 6 weeks from the day when the investigator or subinvestigator decided the discontinuation.

Table 1: Schedule of Assessments

1st line AAT

	Screening period	1st line AAT					Unscheduled[*a]
Visit Days	Days −28 to −7	1	29	57	85 and every subsequent 84 days	113 and every subsequent 28 days	–
Visit Weeks	−4 to −1	1	5	9	13 and every subsequent 12 weeks	17 and every subsequent 4 weeks	–
Allowed visit window (days)	–	–	± 7	± 7	± 7	± 7	–
Informed consent[*b]	X [*b]						
Subject background survey	X						
Confirmation of in/exclusion criteria	X	X					
Randomization/enrollment		X [*c]					
Vital signs[*d]	X	X	X	X	X	X	X
Height/body weight	X						
Laboratory tests[*e]	X	X	X	X	X	X	X
PSA	X	X			X	X	X
Abdominopelvic CT/MRI and bone scintigraphy (every 3 months)	X [*f]				X		X
Chest CT	X [*f]				X [*g]		X
ECOG Performance Status	X	X	X	X	X	X	X
FACT–P		X			X		
EQ-5D-5L		X			X		
Brief Pain Inventory-Short Form (BPI-SF)[*h]	X	X			X		
Brief Fatigue Inventory (BFI)	X	X			X		
Adverse event survey[*i]		X	X	X	X	X	X
Survey on previous/concomitant medication	X	X	X	X	X	X	X
Study drug prescription (every month)		X	X	X	X	X	

CT: Computed Tomography, ECOG: Eastern Cooperative Oncology Group, FACT–P: Functional Assessment of Cancer Therapy–Prostate

*a: Unscheduled visit may be made whenever adverse events should be assessed, or PSA progression and disease progression should be confirmed. Laboratory tests, PSA measurement, and diagnostic imaging will be performed when assessment is required.

*b: Informed consent will be obtained within 42 days before enrollment (Day 1) and before initiating the scheduled study procedures.

*c: Randomization should be performed on Day 1 after the confirmation of eligibility.

*d: Measure vital signs (blood pressure and pulse rate) at each visit.
*e: Laboratory tests include hematology, biochemistry, blood glucose test, and urinalysis.
*f: Imaging diagnosis performed before informed consent and within 42 days before randomization can be used as baseline data.
*g: Not required if no chest metastasis is identified in the screening chest CT.
*h: Instruct subjects to assess prostate cancer-related pains.
*i: Collect all adverse events in the period from the start of study treatment to the date of safety follow-up visit.

2nd line AAT

	2nd line AAT					Unscheduled[*1]	At the end or discontinuation[*2]	Safety follow-up
Visit Days	1	29	57	85 and every subsequent 84 days	113 and every subsequent 28 days	–	–	–
Visit Weeks	1	5	9	13 and every subsequent 12 weeks	17 and every subsequent 4 weeks	–	Final treatment	28 days after final treatment[*3]
Allowed visit window (days)	–	± 7	± 7	± 7	± 7	–	Within 7 days after final treatment[*11]	± 7
Enrollment	X						X	
Vital signs[*4]	X	X	X	X	X	X	X	X
Laboratory tests [*5]	X	X	X	X	X	X	X	X
PSA	X			X	X	X	X	X
Abdominopelvic CT/MRI and bone scintigraphy (every 3 months)				X [*6]		X	X [*12]	
Chest CT				X [*6,7]		X	X [*12]	
ECOG Performance Status	X	X	X	X	X	X	X	X
FACT–P	X [*8]			X [*8]			X [*12]	
EQ-5D-5L	X [*8]			X [*8]			X [*12]	
Brief Pain Inventory-Short Form (BPI-SF) [*9]	X [*8]			X [*8]			X [*12]	
Brief Fatigue Inventory (BFI)	X [*8]			X [*8]			X [*12]	
Adverse event survey[*10]	X	X	X	X	X	X	X	X
Previous/concomitant medication	X	X	X	X	X	X	X	X
Study drug prescription (every month)	X	X	X	X	X			

CT: Computed Tomography, ECOG: Eastern Cooperative Oncology Group, FACT–P: Functional Assessment of Cancer Therapy–Prostate

*1: Unscheduled visit may be made during the study period whenever adverse events should be assessed, or PSA progression and disease progression should be confirmed. Laboratory tests, PSA measurement, and diagnostic imaging will be performed when assessment is required. If the study is discontinued at an unscheduled visit, perform laboratory tests, PSA measurement, and diagnostic imaging wherever possible.

*2: For subjects who finished or discontinued the study with the 1st line AAT or 2nd line AAT, immediately perform examination/observation wherever possible.

*3: Conduct a visit for safety follow-up 28 days after the final study treatment, or before start of cytocidal chemotherapy, or before start of other new treatment for prostate cancer, whichever comes first.

*4: Measure vital signs (blood pressure and pulse rate) at each visit.

*5: Laboratory tests include hematology, biochemistry, blood glucose test, and urinalysis.

*6: Perform diagnostic imaging every 12 weeks after Day 1 of 1st line AAT, independently from switching medications.

*7: Not required if no chest metastasis is identified in screening chest CT.

*8: Start the evaluation after switching the drugs on Day 1 of 2nd line AAT, and implement every subsequent 12 weeks.

*9: Instruct subjects to assess prostate cancer-related pains.

*10: Collect all adverse events until the date of safety follow-up visit. If there is no safety follow-up visit, collect adverse events until 28 days after the final study treatment. If subjects do not show up on the safety follow-up visit, confirm adverse events by the telephone wherever possible.

*11: For subjects who discontinued the study treatment after the treatment interruption due to adverse events, adopt data within 7 days after the final study treatment as discontinuation data. If no data is available in the period within 7 days after the final study treatment, perform a discontinuation examination/observation immediately after the decision of discontinuation.

*12: Not required if it occurs within 28 days from the latest measurement.

VI. ACCEPTABLE RANGE OF SCHEDULE OF ASSESSMENTS

The acceptable time ranges of the examinations, observations, etc. specified in the schedule are as follows.

[Acceptable Time Ranges of Efficacy Tests]

(1) PSA

1st line AAT

Study Visit	Reference Date	Acceptable Range
Screening visit	−28 days to −7 days	28 days to 7 days before randomization
Week 1 (Day 1)	1	-
Week 13 (Day 85)	85	Reference date ± 7 days
Week 17 (Day 113)	113	Reference date ± 7 days
Every subsequent 4 weeks	Every subsequent 28 days	Reference date ± 7 days

2nd line AAT

Study Visit	Reference Date	Acceptable Range
Week 1 (Day 1)	1	-
Week 13 (Day 85)	85	Reference date ± 7 days
Week 17 (Day 113)	113	Reference date ± 7 days
Every subsequent 4 weeks	Every subsequent 28 days	Reference date ± 7 days
At completion or discontinuation	Final study treatment	Reference date + 7 days
Safety follow-up	Final study treatment + 28 days	Reference date ± 7 days

(2) Abdominopelvic CT/MRI, Bone scintigraphy, Chest CT

Study Visit	Reference Date	Acceptable Range
Screening visit[*1]	−28 days to −7 days	28 days to 7 days before randomization
Week 13 (Day 85)	85	Reference date ± 14 days
Every subsequent 12 weeks[*2]	Every subsequent 84 days	Reference date ± 14 days
At completion or discontinuation[*3]	Final study treatment	Reference date + 14 days

*1: Images taken within 42 days before randomization as part of daily consultation before informed consent may be used as data in the screening period.

*2: Perform every 12 weeks, irrespective of switching medications.

*3: Not required if it occurs within 28 days from the latest measurement.

(3) FACT–P[*1], EQ-5D-5L[*1], BPI-SF, BFI

1st line AAT

Study Visit	Reference Date	Acceptable Range
Screening visit	−28 days to −7 days	28 days to 7 days before randomization
Week 1 (Day 1)	1	-
Week 13 (Day 85)	85	78 days to 92 days
Every subsequent 12 weeks	Every subsequent 84 days	Reference date ± 7 days

2nd line AAT

Study Visit	Reference Date	Acceptable Range
Week 1 (Day 1)	1	-
Week 13 (Day 85)	85	78 days to 92 days
Every subsequent 12 weeks	Every subsequent 84 days	Reference date ± 7 days
At completion or discontinuation[*2]	Final study treatment	Reference date + 7 days

*1: Do not perform on screening visit.

*2: Not required if it occurs within 28 days from the latest measurement.

[Acceptable Time Ranges of Safety Tests]

Laboratory test (biochemistry, hematology, and urinalysis), Vital signs (blood pressure and pulse rate), ECOG Performance Status

1st line AAT

Study Visit	Reference Date	Acceptable Range
Screening visit	−28 days to −7 days	28 days to 7 days before randomization
Week 1 (Day 1)	1	-
Week 5 (Day 29)	29	Reference date ± 7 days
Week 9 (Day 57)	57	Reference date ± 7 days
Week 13 (Day 85)	85	Reference date ± 7 days
Every subsequent 4 weeks	Every subsequent 28 days	Reference date ± 7 days

2nd line AAT

Study Visit	Reference Date	Acceptable Range
Week 1 (Day 1)	1	-
Week 5 (Day 29)	29	Reference date ± 7 days
Week 9 (Day 57)	57	Reference date ± 7 days
Week 13 (Day 85)	85	Reference date ± 7 days
Every subsequent 4 weeks	Every subsequent 28 days	Reference date ± 7 days
At completion or discontinuation	Final study treatment	Reference date + 7 days
Safety follow-up	Final study treatment + 28 days	Reference date ± 7 days

1 INTRODUCTION

1.1 Background

Worldwide, prostate cancer ranks second in cancer incidence (2012) [Torre et al., 2015], and ranks second in Japan as well (2011) [Matsuda et al., 2013]. In 2020, prostate cancer is expected to be at the top in male cancer incidence [Sobue et al., 2012].

Since prostate cancer exhibits androgen-dependent growth, androgen deprivation therapy (ADT) by surgical or chemical castration is widely conducted, and is positioned as a main therapy for prostate cancer. GnRH agonists/antagonists monotherapy or combined androgen blockade (CAB) therapy with concurrent anti-androgenic agents is the main stream androgen deprivation drug therapy in Japan [Japanese Urological Association, 2012].

Castration-resistant prostate cancer (CRPC) is prostate cancer that progresses under endocrinotherapy with ADT. In an early ADT, serum prostate-specific antigen (PSA) level decreases and tumor partially regresses in most patients. Even during the resting period, tumor does not grow, and serum PSA remains low. However, some patients exhibit increased serum PSA and the course of radiographic disease progression in spite of the serum testosterone in the castration level. These patients are considered as castration-resistant. However, clinical researches and studies on the molecular profile of such progressive tumor demonstrate that the function of androgen receptor (AR) is maintained in CRPC, and tumor responds to treatment to lower the function of AR, such as blocking androgens and changing anti-androgenic agents. As a secondary endocrinotherapy, treatment can be selected from alternative antiandrogen therapy (AAT), estrogen therapy, corticosteroid therapy, and CYP17 inhibitors. Chemotherapy is selected for metastatic CRPC resistant to existing endocrinotherapy.

Enzalutamide is an anti-androgenic agent that inhibits AR signaling, and was jointly developed by Astellas Pharma Inc. and Medivation Inc. A clinical trial on enzalutamide targeting CRPC started in 2010 in Japan. In March 2014, marketing approval was obtained as the product name Xtandi® with an indication for castration-resistant prostate cancer.

In order to further investigate combination therapy of ADT and anti-androgenic agents for CRPC, a post-marketing clinical study is to be conducted to compare the efficacy and safety of enzalutamide + ADT and flutamide + ADT. The order of treatment in AAT will also be investigated by switching the drugs for 1st line treatment after progression of PSA.

1.2 Non-clinical and Clinical Data

1.2.1 Non-clinical Studies

In pharmacodynamic studies, enzalutamide exhibits inhibition of androgen binding to AR, inhibition of AR nuclear translocation, inhibition of AR binding to DNA, inhibition of AR-dependent transcription, inhibition of cancer cell proliferation, induction of cell death, and tumor regression. Although enzalutamide is an AR inhibitor, it affects multiple steps in the

AR signaling pathway in the setting of AR overexpression, and is different from other anti-androgenic agents.

A major human metabolite of enzalutamide, *N*-desmethyl enzalutamide, demonstrated pharmacological activity consistent with that demonstrated by enzalutamide. Enzalutamide and *N*-desmethyl enzalutamide bind to and antagonize the gamma amino butyric acid (GABA)-gated chloride channel. Enzalutamide given at high doses to mice induced dose-dependent convulsions, an observation that parallels the clinical data showing that dose appears to be an important predictor of the risk of seizure in subjects. As some molecules that antagonize the GABA-gated chloride channel are associated with convulsions, enzalutamide and *N*-desmethyl enzalutamide may both contribute to the convulsions that were observed in non-clinical studies. Safety pharmacology studies evaluating the central nervous, respiratory, and cardiovascular systems did not identify any additional acute effects at exposures relevant to the human clinical dose of 160 mg/day.

Following oral administration in animals, enzalutamide is eliminated slowly from plasma with a long terminal elimination half-life ($t_{1/2}$) across species. In vitro studies showed 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. In vitro, enzalutamide caused time-dependent inhibition of CYP1A2. Based on in vitro data, enzalutamide is an inducer of CYP3A4 but does not have a clinically problematic impact on CYP1A2.

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

Overall, enzalutamide was generally well tolerated in non-clinical species with the most prominent effects occurring in reproductive and hormone-sensitive organs. In studies in rats (4 and 26 weeks) and dogs (4, 13, and 39 weeks), changes in the reproductive organs associated with enzalutamide were decreases in the organ weight with atrophy of the prostate and epididymis. Additional changes related to reproductive and hormone-sensitive organs included hypertrophy/hyperplasia of the pituitary gland and atrophy in seminal vesicles in rats and testicular hypospermia, seminiferous tubule degeneration, and hypertrophy/hyperplasia of the Leydig cells in dogs. Sex differences were noted in rat mammary glands (i.e., male atrophy and female lobular hyperplasia). Changes in the reproductive organs in both species were consistent with the pharmacological activity of enzalutamide and reversed or partially resolved after an 8-week recovery period. There were no other important changes in clinical pathology or histopathology in any other organ system, including the liver in either species.

Electrocardiogram (ECG) and cardiovascular assessments in a toxicity study in dogs showed no enzalutamide-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 and non-clastogenic in mammalian cells.

Enzalutamide was non-genotoxic in vivo in mice. The 2 major human metabolites (*N*-desmethyl enzalutamide and an inactive carboxylic acid derivative) were negative for mutagenicity in the bacterial reverse mutation assay.

1.2.2 Clinical Data

1.2.2.1 Phase 1/2 Study in Japan [9785-CL-0111]

In phase 2 part, enzalutamide 160 mg/day was continuously administered to 38 patients with castration-resistant prostate cancer who had previously been treated with docetaxel. Radiographic response rate by Day 85, primary endpoint, was 5.3% (2/38 subjects, 90% CI: 0.9% to 15.7%), and the lower limit of 90% CI was lower than the threshold response rate (5%). PSA response rate (the proportion of patients whose lowest PSA decreased by at least 50% from baseline) was 28.9% (11/38 subjects, 90% CI: 17.2% to 43.3%).

In phase 2 part, adverse reactions were observed in 63.2% (24/38 subjects). Most commonly reported adverse reactions included constipation (15.8%), electrocardiogram QT prolonged and weight decreased (13.2% respectively), fatigue, decreased appetite, and hypertension (10.5% respectively). Fourteen serious adverse reactions were observed in 4 subjects (10.5%), including fall, gait disturbance, dehydration, hypotension, acute respiratory distress syndrome, pulmonary oedema, anaemia, disseminated intravascular coagulation, acute renal failure, cellulitis, tumour pain, haematuria, urinary retention, and bladder tamponade.

1.2.2.2 Overseas Phase 3 Study [CRPC2]

With placebo as control, enzalutamide 160 mg/day was continuously administered to 800 patients with castration-resistant prostate cancer who had previously been treated with docetaxel. For patients who had not undergone bilateral orchiectomy, concurrent castration treatment with GnRH agonists/antagonists was required.

In the result of interim analysis (at the time when 520 events occurred, of the targeted 650 events), the median overall survival (OS), which is the primary endpoint, was 18.4 months in enzalutamide group, and 13.6 months in placebo group. The OS of enzalutamide group was significantly longer than that of placebo group (hazard ratio: 0.631, 95% CI: 0.529 to 0.752, P value < 0.0001, stratified log-rank test).

Adverse reactions were observed in 69.3% (554/800 subjects) of enzalutamide group, and 66.7% (266/399 subjects) of placebo group. The most commonly reported adverse reactions in enzalutamide group included fatigue (21.5%), nausea (20.1%), and hot flush (15.0%).

Serious adverse events (SAEs) were observed in 268 subjects (33.5%) of enzalutamide group, and 154 subjects (38.6%) of placebo group. The most commonly reported SAEs in enzalutamide group included spinal cord compression (6.0%), anaemia (2.6%), and general physical health deterioration (2.1%). Seizure-related SAEs were observed in 6 subjects

(seizure in 2 subjects, partial seizures in 2 subjects, status epilepticus in 1 subject, syncope in 1 subject) in enzalutamide group, but were not observed in placebo group.

1.2.2.3 Global Phase 3 Study [9785-CL-0231]

With placebo as control, enzalutamide 160 mg/day was continuously administered to 871 patients with asymptomatic castration-resistant prostate cancer or castration-resistant prostate cancer with mild symptoms who are chemotherapy-naive (872 subjects including 28 Japanese were randomized). For patients who had not undergone bilateral orchiectomy, concurrent castration treatment with GnRH agonists/antagonists was required.

In the result of interim analysis (at the time when 540 events occurred, of the targeted 765 events), the median OS, one of 2 primary endpoints, was 32.4 months in enzalutamide group, and 30.2 months in placebo group. The OS in enzalutamide group was significantly longer than that in placebo group (hazard ratio: 0.706, 95% CI: 0.596 to 0.837, P value < 0.0001, non-stratified log-rank test). Radiographic progression-free survival (rPFS), the other primary endpoint, was defined as the period from randomization to the first radiographic evidence of disease progression, or to death within 168 days after treatment discontinuation irrespective of the cause, whichever occurred earlier. In 1633 subjects registered before the cut-off date, rPFS events judged by the central review facility as of the data cut-off were a total of 439 events: 118 events (14.2%) in enzalutamide group, and 321 events (40.1%) in placebo group. The risk of rPFS or death was statistically significantly lower in enzalutamide group than in placebo group (hazard ratio: 0.186, 95% CI: 0.149 to 0.231, P value < 0.0001, non-stratified log-rank test). The median duration of rPFS was 3.9 months in placebo group while the number of events was not enough to estimate the median in enzalutamide group.

The incidence of adverse reactions was higher in enzalutamide group at 65.0% than in placebo group at 49.9%. In enzalutamide group, adverse reactions with incidence ≥10% were nausea (13.3%), fatigue (25.3%), and hot flush (13.4%). The incidence of adverse reactions in Japanese patients was 46.4% in enzalutamide group, and 33.3% in placebo group. The incidence of adverse reactions in non-Japanese patients was 65.6% in enzalutamide group, and 50.6% in placebo group.

The incidence of SAEs was 32.0% (279/871 subjects) in enzalutamide group, and 26.8% (226/844 subjects) in placebo group. In enzalutamide group, SAEs with incidence ≥1% were anaemia (1.6%), general physical health deterioration (1.6%), pneumonia (1.1%), pathological fracture (1.1%), metastatic pain (2.0%), spinal cord compression (3.2%), and urinary retention (1.1%).

Seizure is the clinically most important adverse event (AE) reported on enzalutamide. In enzalutamide group in this study, seizure was observed in only 1 subject (0.1%) after data cut-off. In placebo group, seizure was observed in 1 subject (0.1%) before data cut-off.

1.3 Summary of Key Safety Information for Study Drugs

See package inserts of enzalutamide and flutamide.

1.4 Risk-Benefit Assessment

1.4.1 Risk Expected from Enzalutamide

The following information on adverse reactions is an excerpt from the package insert of Xtandi® Capsules 40 mg (version 6, revised in November 2015).

[Clinical study in Japan]

In the phase 1/2 study in Japan in patients with castration-resistant prostate cancer, adverse reactions were observed in 31 subjects (66.0%) of 47 subjects who received enzalutamide. Most commonly reported adverse reactions included hypertension (14.9%), constipation (14.9%), fatigue (12.8%), decreased appetite (12.8%), weight decreased (10.6%), and electrocardiogram QT prolonged (10.6%). (At approval: March 2014)

[Overseas clinical study]

In the overseas phase 3 study in patients with castration-resistant prostate cancer who had previously been treated with docetaxel, adverse reactions were observed in 554 subjects (69.3%) of 800 subjects who received enzalutamide. Most commonly reported adverse reactions included fatigue (21.5%), nausea (20.1%), hot flush (15.0%), decreased appetite (12.6%), and asthenia (10.0%). (At approval: March 2014)

[Global clinical study]

In the global phase 3 study in chemotherapy-naive patients with castration-resistant prostate cancer, adverse reactions were observed in 566 subjects (65.0%) of 871 subjects (including 28 Japanese subjects) who received enzalutamide. Most commonly reported adverse reactions included fatigue (25.3%), hot flush (13.4%), and nausea (13.3%). (At revision of Precautions for Indications: October 2014)

The incidence of the following adverse reactions are calculated based on the patients who received enzalutamide in the phase 1/2 study in Japan, overseas phase 3 study, and global phase 3 study.

(1) Significant adverse reactions

1) Seizure (0.2%): Seizure such as convulsion, status epilepticus may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

2) Platelets decreased (incidence unknown): Platelets decreased may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken.

(2) Other adverse reactions

	≥5%	1% to 5%	<1%	Incidence unknown
Blood		Anaemia	Haemoglobin decreased, leukopenia, neutropenia	
Heart			Electrocardiogram QT prolonged	
Kidney			Pollakiuria	
Ear			Vertigo	
Eye			Lacrimation increased	
Digestive organ	Nausea, diarrhoea, constipation	Vomiting, abdominal distension, abdominal pain upper, dyspepsia, flatulence	Dry mouth, abdominal pain, gastritis, stomatitis, abdominal discomfort, gastrooesophageal reflux disease	
General and administration site	Fatigue, asthenia	Oedema peripheral, weight decreased	Pain, chills, malaise, weight increased	
Liver				Hepatic function abnormal
Metabolism	Decreased appetite		Hypokalaemia, dehydration	
Musculoskeletal system		Arthralgia, myalgia, back pain, muscular weakness, pain in extremity	Musculoskeletal pain, muscle spasms, musculoskeletal stiffness	
Nervous system		Headache, dizziness, dysgeusia, paraesthesia, lethargy	Hypoaesthesia, memory impairment, somnolence, restless legs syndrome, neuropathy peripheral, cognitive disorder, disturbance in attention, syncope, amnesia	
Psychiatric		Insomnia	Anxiety, depression, confusional state, hallucination	

	≥5%	1% to 5%	<1%	Incidence unknown
Reproductive system and breast		Gynaecomastia		
Respiratory organ		Dyspnoea	Cough, epistaxis	
Skin		Dry skin, rash, hyperhidrosis	Pruritus, night sweats, alopecia, erythema, rash maculo-papular	
Blood vessel	Hot flush	Hypertension, flushing		
Other			Fall, spinal compression fracture, fracture (except for pathological fracture)	

The incidences of the adverse reactions above are calculated based on the updated data from the phase 1/2 study in Japan (47 subjects) and overseas phase 3 study (850 subjects), and the global phase 3 study (871 subjects).

1.4.2 Risks Expected from Flutamide

The following information on adverse reactions is an excerpt from the package insert of Odyne® Tab. 125 mg (version 16, revised in August 2014).

In the 6393 subjects in total (201 subjects at approval, 6192 subjects in post-marketing survey), the incidence of adverse reactions and abnormal laboratory test values was 29.0%. The most common adverse reactions included gynaecomastia (2.9%), inappetence (2.0%), diarrhoea (1.7%), nausea/vomiting (1.1%), AST increased (13.2%), ALT increased (13.2%), γ-GTP increased (5.9%), LDH increased (3.8%), ALP increased (3.1%), erythrocytes decreased (1.8%), haemoglobin decreased (1.5%), and haematocrit value decreased (1.5%). (At the end of re-examination)

(1) Significant adverse reactions

1) Serious liver disorder (0.5%): Hepatitis fulminant or other serious liver disorder (initial symptoms: inappetence, nausea/vomiting, general malaise, itching, rash, jaundice, etc.) may occur. Patients should be carefully monitored by regularly testing liver function (at least once a month). If any abnormalities are observed, administration should be discontinued and appropriate measures should be taken.

2) Interstitial pneumonia (<0.1%): Interstitial pneumonia associated with such as pyrexia, cough, dyspnoea, chest X-ray abnormal, and eosinophilia may occur. Patients should be carefully monitored, and if any abnormalities are observed, administration should

be discontinued and appropriate measures, such as administration of corticosteroid, should be taken.

3) Cardiac failure, myocardial infarction (incidence unknown): Cardiac failure and myocardial infarction may occur. Patients should be carefully monitored, and if any abnormalities are observed, appropriate measures, such as discontinuing administration, should be taken.

(2) Other adverse reactions

	≥1%	<1%
Liver	AST increased, ALT increased, γ-GTP increased, LDH increased, ALP increased	Bilirubin increased
Endocrine	Gynaecomastia	Sexual desire decreased
Digestive organ	Nausea/vomiting, inappetence, diarrhoea	Heartburn, gastralgia, stomach discomfort, thirst
Blood	anaemia	White blood cell decreased, platelets decreased
Kidney		Creatinine increased, BUN increased, urinary protein positive
Psychoneurotic system		Dizziness, wobble, dizziness on standing up, headache, feelings of weakness, somnolence, sleeplessness, bewilderment, depressed state, feeling anxious, nervousness
Hypersensitivity		Rash, photosensitivity
Skin		Itching
Other		Oedema, general malaise, pyrexia, flushing, sweaty, taste disturbance, sugar blood level increased, urine sugar positive, serum total protein decreased

1.4.3 Expected Benefit

Combination therapy of enzalutamide + ADT or combination therapy of flutamide + ADT may decrease PSA and improve symptoms.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

- To determine the benefit of enzalutamide + ADT therapy as compared to flutamide + ADT therapy as assessed by time to PSA progression with 1st line AAT (time to PSA progression 1 [TTPP1]).

2.1.2 Secondary Objectives

- To determine the order of AAT treatment as assessed by time to PSA progression with 1st line AAT + 2nd line AAT (time to PSA progression 2 [TTPP2]).
- To determine the benefit of enzalutamide + ADT therapy as compared to flutamide + ADT therapy as assessed by PSA response rate to 1st line AAT (proportion of subjects with a decrease by at least 50% or 90% from baseline irrespective of the timing).
- To determine the benefit of enzalutamide + ADT therapy as compared to flutamide + ADT therapy as assessed by PSA response rate to 1st line AAT at Week 13 (proportion of subjects with a decrease by at least 50% or 90% from baseline).
- To determine the benefit of enzalutamide + ADT therapy as compared to flutamide + ADT therapy as assessed by time to PSA decrease by 50% from baseline with 1st line AAT.
- To determine the benefit of enzalutamide + ADT therapy as compared to flutamide + ADT therapy as assessed by time to treatment failure of 1st line AAT (time to treatment failure 1 [TTF1]).
- To determine the order of AAT treatment as assessed by time to treatment failure of 2nd line AAT (time to treatment failure 2 [TTF2]).
- To determine the benefit of enzalutamide + ADT therapy as compared to flutamide + ADT therapy as assessed by rPFS.

2.1.3 Safety Objective

- To determine the safety of enzalutamide + ADT therapy as compared to flutamide + ADT therapy.

2.1.4 Exploratory Objectives

- To evaluate time to PSA progression with 2nd line AAT (2nd time to PSA progression [2nd TTPP]).
- To evaluate PSA response rate to 2nd line AAT.
- To determine the benefit of enzalutamide + ADT therapy as compared to flutamide + ADT therapy as assessed by metastasis-free survival (MFS).

- To evaluate Quality of Life (QOL) on 1st line AAT and 2nd line AAT using Functional Assessment of Cancer Therapy–Prostate (FACT–P) and European Quality of Life 5-Dimension-5 Level instruments (EQ-5D-5L).
- To evaluate Brief Pain Inventory-Short Form (BPI-SF) with 1st line AAT and 2nd line AAT.
- To evaluate Brief Fatigue Inventory (BFI) with 1st line AAT and 2nd line AAT.
- To determine the benefit of enzalutamide + ADT therapy as compared to flutamide + ADT therapy as assessed by objective response rate (ORR) in soft tissue with 1st line AAT based on the best overall response in RECIST guidelines.
- To evaluate the efficacy in subgroups according to disease-related patient demographics.

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This is a randomized, open-label, comparative study on enzalutamide and flutamide.

Patients with M0 or M1 castration-resistant prostatic neoplasm that relapsed during CAB therapy with bicalutamide will be randomized to Group A or B. Dynamic allocation will be performed with minimization with biased coin technique. The following stages (M0/N0, M0/N1, or M1) will be used as allocation factors.

- M0/N0: No distant metastasis, and no lymph node metastasis
- M0/N1: Without distant metastasis, but with metastasis in lymph nodes distal to the aortic bifurcation
- M1: With distant metastasis (including metastasis in lymph nodes proximal to the aortic bifurcation)

For subjects in Group A, enzalutamide is administered as the 1st line AAT. After the confirmation of PSA progression, medication is changed from enzalutamide to flutamide as the 2nd line AAT. For subjects in Group B, flutamide is administered as the 1st line AAT. After the confirmation of PSA progression, medication is changed from flutamide to enzalutamide as the 2nd line AAT. The treatment period with each drug should not be more than 2 years from the enrollment of the last subjects.

PSA progression will be defined according to the consensus guidelines of PCWG2. For patients with PSA declines at Week 13, the PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained 3 or more weeks later. For patients with no PSA decline at Week 13, the PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the baseline is documented.

Data for the analysis of primary endpoint TTPP1 will be cut-off if not less than 135 events of PSA progression occurred in association with the 1st line AAT.

After the discontinuation of the 1st line AAT due to PSA progression or other reasons, the 2nd line AAT will be started. Subjects who discontinued the 1st line AAT due to PSA

progression will start the 2nd line AAT within 6 weeks after the date of examination that identified PSA progression. Subjects who discontinued the 1st line AAT due to other reasons will start the 2nd line AAT within 6 weeks from the day when the investigator or sub-investigator decided the discontinuation.

A safety follow-up visit should be performed wherever possible in 28 days from the final study treatment, or before starting other study drugs, or before starting other treatment for prostate cancer, whichever comes first. If subjects do not show up on the safety follow-up visit, confirm AEs by the telephone wherever possible.

2.2.2 Dose Rationale

This study targets adult patients with castration-resistant prostate cancer. As instructed on the package insert, enzalutamide 160 mg is to be administered orally once daily, and flutamide 125 mg is to be administered orally thrice daily after meals.

2.3 Endpoints

2.3.1 Primary Endpoint

- Time to PSA progression with 1st line AAT (TTPP1)

2.3.2 Secondary Endpoints

- Time to PSA progression with 1st line AAT + 2nd line AAT (TTPP2)
- PSA response rate to 1st line AAT (decrease by at least 50% or 90% from baseline)
- PSA response rate to 1st line AAT at Week 13 (decrease by at least 50% or 90% from baseline)
- Time to PSA decrease by 50% from baseline with 1st line AAT
- Time to treatment failure of 1st line AAT (TTF1)
- Time to treatment failure of 2nd line AAT (TTF2)
- rPFS

2.3.3 Safety Endpoints

- Characteristics, frequency, and severity of AEs
- Safety-related laboratory tests (biochemistry and hematology)
- Vital signs (blood pressure and pulse rate)
- ECOG Performance Status

2.3.4 Exploratory Endpoints

- Time to PSA progression with 2nd line AAT (2nd TTPP)
- PSA response rate to 2nd line AAT (decrease by at least 50% or 90% from baseline)

- MFS
- QOL assessment with 1st line AAT and 2nd line AAT by FACT–P) and EQ-5D-5L
- BPI-SF with 1st line AAT and 2nd line AAT
- BFI with 1st line AAT and 2nd line AAT
- ORR in best overall soft tissue response of RECIST guidelines with 1st line AAT
- Efficacy assessment by subgroups according to disease-related patient demographics

3 STUDY POPULATION

3.1 Selection of Study Population

Patients with castration-resistant prostate cancer that relapsed during CAB therapy with bicalutamide.

3.2 Inclusion Criteria

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

1. Subject must have submitted an informed consent form approved by the institutional review board (IRB) established at each study center prior to the study.
2. Age ≥20 years at the time of signing the informed consent form.
3. Subject is diagnosed with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small-cell histology.
4. Subject on continuous ADT with GnRH agonist/antagonist or bilateral orchiectomy (surgical or chemical castration).
5. Subject for whom treatment with effective GnRH agonist/antagonist is to be continued during the study period if bilateral orchiectomy is not performed.
6. Serum testosterone level ≤1.73 nmol/L (50 ng/dL or 0.5 ng/mL) at screening visit.
7. Subject with no change in the dose of bisphosphonate preparation or denosumab for at least 4 weeks if these drugs are used.
8. Subject with asymptomatic or mildly symptomatic prostate cancer (BFI-SF score is <4 to Question 3 “the worst pain within 24 hours”).
9. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
10. Subject has an estimated life expectancy of ≥12 months.
11. Subject is able to swallow the study drug and, comply with procedures required by the study.
12. Subject has progression of the disease that falls under at least one of the following 3 criteria during CAB therapy in combination of bicalutamide and ADT.
    - PSA increase should be confirmed at least 2 timepoints with an interval of ≥1 week. In at least 6 weeks after the last dose of bicalutamide, PSA should be confirmed higher than the highest PSA measured after the nadir was confirmed during administration of bicalutamide. PSA at screening visit should be ≥2 ng/mL (2 μg/L).

- Soft tissue disease progression defined by RECIST guidelines (version 1.1).
- Progression of ≥2 bone lesions defined as new lesions in bone scintigraphy by PCWG2.

13. A sexually active male subject and his female partner who is of childbearing potential must use 2 acceptable birth control methods shown below (1 of which must include a condom as a barrier method of contraception) from screening to 3 months after the last dose of the study drug.
    - A male or female condom as a barrier method of contraception;
    - Consistent and correct usage of established, proper use of oral contraceptives;
    - Established intrauterine device or intrauterine system by the female partner;
    - Tubal ligation in the female partner performed at least 6 months prior to subject's screening visit;
    - Vasectomy or other procedure resulting in infertility (e.g., bilateral orchiectomy) performed at least 6 months prior to screening;
    - Calendar-based contraceptive methods (Knaus-Ogino or rhythm method).
14. Subject must use a condom throughout the study if engaging in sexual intercourse with a pregnant woman.
15. Subject must agree not to donate sperm from screening to 3 months after the last dose of the study drug.
16. 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 the study if any of the following apply:

1. Subject with severe concurrent diseases, infections, or complications, which are considered inappropriate for enrollment by the investigator or sub-investigator.
2. Subject with confirmed or suspected brain metastasis or active leptomeningeal metastasis.
3. Subject with a history of malignant tumor other than prostate cancer in the past 5 years (except for non-melanoma skin cancer cured with radical therapy).
4. Subject hypersensitive to the ingredients of enzalutamide capsules or flutamide tablets.
5. Subject with a history of seizure, or any condition that may predispose to seizure.
6. Subject with liver disorder such as viral hepatitis and hepatic cirrhosis, or subject with AST and ALT at screening visit higher than the upper limit of normal.
7. Subject on warfarin.
8. Subject received treatment for prostate cancer with cytocidal chemotherapy that includes anti-androgenic agents other than bicalutamide (e.g., enzalutamide, flutamide), abiraterone, or estramustine.
9. Subject participated in a clinical trial on a drug other than GnRH agonist/antagonist in prostate cancer.

10. Subject received treatment with herbal medications that may have hormonal anti-prostate cancer activity or herbal medications (saw palmetto) that may decrease PSA levels; subject received treatment for prostate cancer with systemic corticosteroids, or treatment for other diseases with systemic corticosteroids greater than the equivalent of 10 mg per day of prednisone (Decadron 1 mg/day) within 4 weeks prior to enrollment (Day 1).
11. Subject received treatment with bicalutamide within 6 weeks prior to enrollment (Day 1).
12. Subject received treatment with 5-α reductase inhibitors (finasteride, dutasteride), estrogens, or drugs with anti-tumor action other than GnRH agonists/antagonists within 4 weeks prior to enrollment (Day 1).
13. Subject received treatment with opioid analgesic for pains associated with prostate cancer within 4 weeks prior to enrollment (Day 1).
14. Subject participated or is currently participating in a clinical trial or a post-marketing clinical study on other ethical drugs (excluding GnRH agonist/antagonist) or medical devices within 12 weeks or 5 half lives (in case of ethical drugs), whichever is longer, prior to screening.
15. Subject received treatment for primary or metastatic lesion with surgery or radiation therapy within 4 weeks prior to enrollment (Day 1).
16. Subject with unstable psychiatric disease (e.g., schizophrenia, dementia, uncontrollable depression/bipolar disorder).
17. Subject with a disease or reason unsuitable for participation in the study, which is considered by the investigator or sub-investigator to cause excessive risk to the subject or make the interpretation of safety data difficult.

Waivers to the exclusion criteria will NOT be allowed.

3.4 Criteria to Shift from 1st Line AAT to 2nd Line AAT

If any of the following is satisfied, the study drug will be shifted to the 2nd line AAT after the discontinuation of the 1st line AAT:

1. PSA progression
2. In case where the 1st line AAT is to be discontinued due to AEs, but the investigator or sub-investigator considers that there is no problem in the subject tolerance to transition to the 2nd line AAT
3. In case where the 1st line AAT is to be discontinued due to progression of disease other than PSA progression, but the investigator or sub-investigator considers that there is no problem in the subject tolerance to transition to the 2nd line AAT.

In any of the following cases, study treatment will be discontinued without shifting to the 2nd line AAT:

1. In case of enzalutamide as 2nd line AAT, subjects with seizure as an AE

2. In case of flutamide as 2nd line AAT, subjects with the latest AST or ALT exceeding the upper limit of normal
3. Other cases that the investigator or sub-investigator considers unsuitable for study continuation

4 TREATMENT(S)

4.1 Identification of Investigational Product(s)

4.1.1 Test Drug(s)

The investigational product (enzalutamide capsule 40 mg) is shown as follows.

Generic name	Enzalutamide
Chemical name	4-{3-[4 - Cyano - 3- (trifluoromethyl)phenyl]- 5,5 -dimethyl- 4- oxo- 2-sulfanylideneimidazolidin- 1- yl}-2-fluoro -*N* -methylbenzamide
Molecular formula and molecular weight	$C_{21}H_{16}F_4N_4O_2S$ (molecular weight : 464.44)
Content and dosage form	Enzalutamide capsule 40 mg: One capsule contains 40 mg of enzalutamide. This drug is a white to pale yellowish white, oval capsule.
Size	Longer diameter: Approx. 21 mm; shorter diameter: Approx. 10 mm
Lot No.	Specified by the Procedure for handling study drugs
Storage	At room temperature
Manufacturer	Astellas Pharma Inc.

4.1.2 Comparative Drug(s)

The comparative drug (flutamide tablets 125 mg) is as follows.

Generic name	Flutamide
Chemical name	2-Methyl-*N*-[4-nitro-3- (trifluoromethyl)phenyl] propanamide
Molecular formula and molecular weight	$C_{11}H_{11}F_3N_2O_3$ (molecular weight : 276.21)
Content and dosage form	Flutamide tablets 125 mg: One tablet contains 125 mg of flutamide. This drug is a round, pale yellow tablet.
Size	Diameter: Approx. 8.5 mm; thickness: Approx. 4.0 mm
Lot No.	Specified by the Procedure for handling study drugs
Storage	Shielded from light at room temperature
Manufacturer	Nippon Kayaku Co., Ltd.

4.2 Packaging and Labeling

All medication used in this study will be prepared, packaged, and labeled under the responsibility of qualified staff at API or Sponsor's designee in accordance with API or

Sponsor's designee Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH GCP guidelines, and applicable local laws/regulations.

(1) Packaging

1) Enzalutamide capsule 40 mg

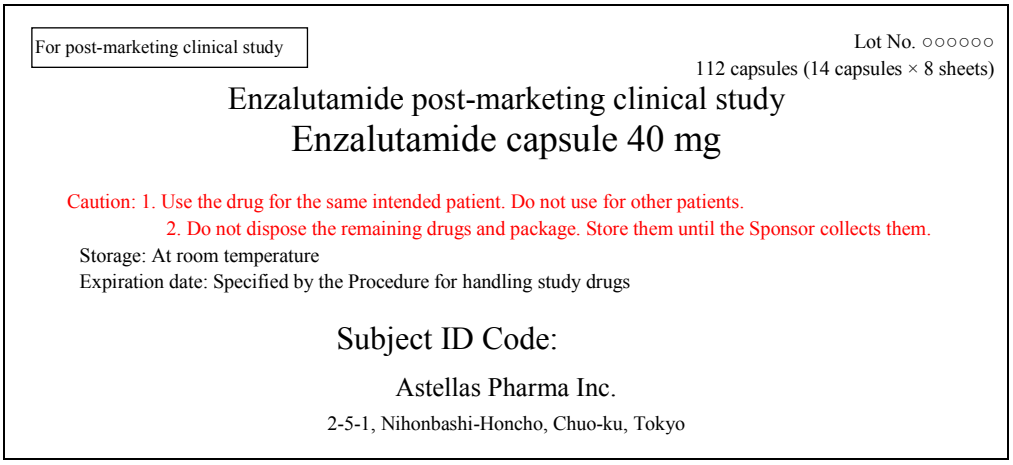
A PTP sheet contains 14 capsules of enzalutamide capsule 40 mg. An aluminum pillow contains 2 PTP sheets, and 4 aluminum pillows are packed in a small box.

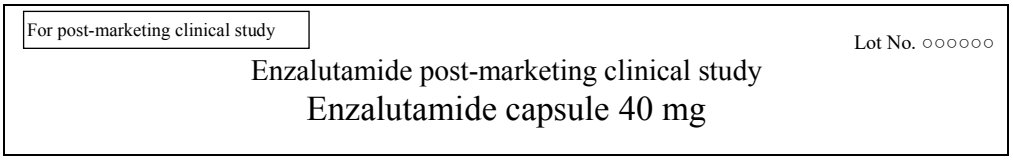
2) Flutamide tablets 125 mg

A PTP sheet contains 21 tablets of flutamide tablets 125 mg. An aluminum pillow contains PTP sheets, and is packed in a small box.

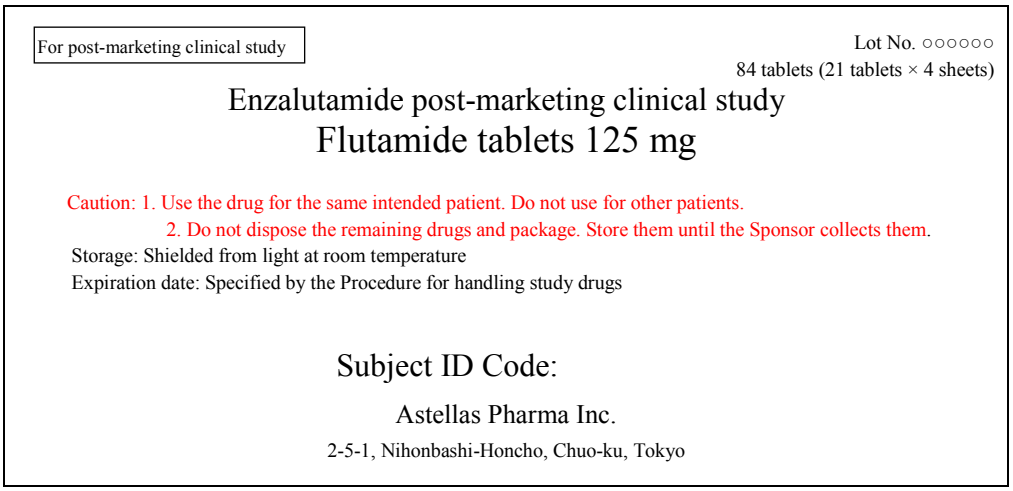
(2) Labeling

1) Enzalutamide capsule 40 mg

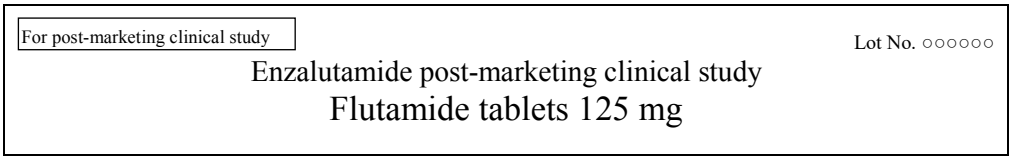




2) Flutamide tablets 125 mg



3)



4.3 Study Drug Handling

The head of the study site or the study drug storage manager should take accountability of the study drugs as following issues.

- The study drug storage manager should store and take accountability of the study drugs in conforming to the procedures for handling the study drugs written by the Sponsor.
- The study drug storage manager should prepare and retain records of the study drug's receipt, the inventory at the study site, the use by each subject, and the return to the Sponsor or alternative disposal of unused study drugs. These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the study drugs and subjects.
- The study drug storage manager should prepare and retain records that document adequately that the subjects were provided the doses specified by the protocol, and reconcile all the study drugs supplied from the Sponsor.

4.4 Blinding

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

4.5 Assignment and Allocation

The subject registration center will perform dynamic allocation with minimization with biased coin technique according to the subject registration procedure in the ratio of 1:1 to the

initial enzalutamide 160 mg/day group or the initial flutamide 125 mg/day group. The facilities and the following stages (M0/N0, M0/N1, or M1) will be used as allocation factors.

- M0/N0: No distant metastasis, and no lymph node metastasis
- M0/N1: Without distant metastasis, but with metastasis in lymph nodes distal to the aortic bifurcation
- M1: With distant metastasis (including metastasis in lymph nodes proximal to the aortic bifurcation)

After the investigator or sub-investigator confirmed the eligibility of the subject on Day 1, the staff in charge at the study site will register the subject via the Subject Registration System, and confirm the study drugs that are randomly allocated.

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

Enzalutamide capsule 40 mg:
Orally administer 160 mg (4 capsules) of enzalutamide once daily at the same time every day wherever possible.

Flutamide tablets 125 mg:
Orally administer 125 mg (1 tablet) of flutamide after each meal thrice a day.

If the subject fails to take the drug, or vomit it immediately after taking it, do not take another dose. Restart a dose the following day.

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

If an adverse reaction that falls under Grade 3 or higher according to the National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 occurred in association with the study drug during the study period, and is not improved by a proper medical intervention, stop the treatment for a week or until the severity of the adverse reaction improves to Grade 2 or lower. After the improvement, the study drug may be restarted at the original or reduced dose at the discretion of the investigator or sub-investigator.

If a strong CYP2C8 inhibitor (e.g., gemfibrozil) should be used concurrently with the study drug enzalutamide, reduce the dose of enzalutamide to 80 mg once daily. When the CYP2C8 inhibitor is discontinued, return the dose of enzalutamide to the original dose.

The study drug cannot be increased.

5.1.3 Previous and Concomitant Treatment (Medication and Non-Medication Therapy)

5.1.3.1 Previous Treatment

Enter in the electronic Case Report Form (eCRF) medication (previous medication) and non-medication therapy (prior therapy) that were used until the day before initiating the study drug as follows.

Previous treatment	Survey period	Information to be entered in eCRF
Previous medication	4 weeks (28 days) before Day 1 to the day before initial study treatment	Medication name, treatment period, reason for use
Prior therapy		Therapy name, treatment period, reason for treatment
Radiation therapy for prostate cancer	From diagnosis of prostate cancer to the day before initial study treatment	Irradiation site, irradiation dose, treatment period, reason for treatment
Other prior therapies that include surgical treatment for prostate cancer		Therapy name, treatment period
Bicalutamide		Treatment period
GnRH agonists/antagonists		Medication name, treatment period
Other previous medication for prostate cancer		Medication name, treatment period

5.1.3.2 Concomitant Treatment

Enter in the eCRF medication (concomitant medication) and non-medication therapy (combination therapy) that were used since initiation of the study drug until safety follow-up visit as follows.

Previous treatment	**Survey period**	**Information to be entered in eCRF**
Concomitant medication	From initial study treatment to safety follow-up visit	Medication name, treatment period, reason for use
Combination therapy		Therapy name, treatment period, reason for treatment

5.1.3.3 Required Concomitant Medications

All subjects must undergo continuous ADT with GnRH agonist/antagonist or bilateral orchiectomy during the study period. GnRH agonist/antagonist will be prepared and administered by the study site. Do not change the medications in principle.

5.1.3.4 Prohibited Concomitant Treatment (Medication and Non-Medication Therapy)

The use of the following drugs and therapies are prohibited during the study treatment and in the period from the end of the 1st line AAT to the start of the 2nd line AAT:

- Anti-androgenic agents (steroid or non-steroid) other than study drugs such as chlormadinone and bicalutamide
- CYP17 inhibitor (abiraterone)
- Cytocidal chemotherapy that includes estramustine
- Systemic corticosteroids for prostate cancer or systemic corticosteroids greater than the equivalent of 10 mg per day of prednisone (Decadron 1 mg/day) for other diseases
- 5-α reductase inhibitors (finasteride, dutasteride)
- Estrogen or progesterone agents such as medroxyprogesterone and diethylstilbestrol (DES)
- Biological agents or other drugs with anticancer activity to prostate cancer
- Herbal medicines that may exhibit hormonal anti-prostate cancer activity or herbal medicines that decrease serum PSA (saw palmetto)
- Androgen (e.g., testosterone, dehydroepiandrosterone [DHEA])
- Study drugs for prostate cancer
- Surgery or radiation therapy for primary lesion
- Warfarin

5.1.3.5 Precautions for Concomitant Medication with Enzalutamide (Drug Interactions)

Enzalutamide may affect the exposure to other medications. Other medications also may affect the exposure to enzalutamide.

- Concomitant use with strong CYP2C8 inhibitors (e.g., gemfibrozil) may elevate the plasma concentration of enzalutamide. Therefore, it is desirable to avoid the concomitant use. If the subject needs a strong CYP2C8 inhibitor, reduce the dose of enzalutamide to 80 mg once daily. Return the dose of enzalutamide to the level that is the same as before the initiation of strong CYP2C8 inhibitors when the concomitant use is discontinued.
- Concomitant use with strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, and rifampicin) or moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin, and hypericum erectum) may decrease the plasma concentration of enzalutamide. Therefore, it is desirable to avoid the concomitant use where possible. It is recommended to select a drug that is less likely to induce CYP3A4, or minimize the induction.
- Enzalutamide is a strong inducer of CYP3A4, and moderate inducer of CYP2C9 and CYP2C19. Enzalutamide decreases the exposure to drugs of CYP3A4 substrate with a small therapeutic range (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus), drugs of CYP2C9 substrate

with a small therapeutic range (e.g., phenytoin and warfarin), drugs of CYP2C19 substrate with a small therapeutic range, and drugs of UGT1A1 substrate with a small therapeutic range (e.g., S-mephenytoin). Therefore, it is desirable to avoid the concomitant use where possible.

- Enzalutamide is an inhibitor of human P-gp and may increase the exposure to drugs of P-gp substrate. Precaution is required for the combination use of drugs of P-gp substrate with a small therapeutic range (e.g., digoxin, colchicine, and dabigatran etexilate) with enzalutamide.

5.1.4 Treatment Compliance

Study subjects should be counseled on the need to meet 100% compliance with the study drug with an exception of drug discontinuation due to adverse reactions. Investigator or designee should ensure that study subjects meet this goal throughout the study period. At each visit, compliance will be verified based on the information from subjects, the amount of study drug prescribed, the amount unused and lost, etc. and recorded in the medical record or other source materials. The amount of study drug prescribed, the amount returned and lost will be entered in the eCRF. The consistency with the study drug control table will be confirmed where necessary.

The investigator or designee will, if there is a problem in the drug compliance, investigate the reason, and instruct the subject to improve the compliance. The investigator or designee will also carefully monitor the treatment compliance, and report deviation, if any, to the Sponsor.

5.1.5 Restrictions During the Study

The investigator or site designee will take heed of the following, in particular, before prescribing the study drug, and explain the subjects how to take the study drug.

- Take the study drug with water.
- Take the study drug from the day after the initial prescription of each study drug. Take the study drug from the day of prescription thereafter.
- Bring the unused study drug at the subsequent visit. Report the compliance to the investigator or site designee.
- If treatment is stopped at the discretion of the subject, visit the hospital as soon as possible for medical consultation with the investigator or sub-investigator.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

When obtaining written informed consent and at screening visit, the date of birth, sex, height, and body weight will be checked, and entered in the medical record or other source materials, and in the eCRF.

5.2.2 Medical History

(1) Medical history

Medical history includes diseases that were cured before the start of the study drug. Medical history within 1 year before the start of the study drug will be surveyed. Diagnosis, time of onset, and time of cure will be entered in the medical record or other source materials, and in the eCRF. Transient diseases (e.g., cold), otorhinolaryngologic diseases, dental diseases, skin diseases, and ophthalmologic diseases will not be entered in principle.

(2) Complications

Diseases that have not been cured at the start of the study drug will be handled as complications, surveyed, and confirmed. Diagnosis and time of onset will be entered in the medical record or other source materials, and in the eCRF.

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

At screening visit, the date of prostate cancer diagnosed, and PSA, TNM classification, and Gleason score on the day of diagnosis will be confirmed. The date of metastasis diagnosed and metastatic site will also be checked and entered in the eCRF.

5.3 Efficacy Assessment

5.3.1 PSA

In the screening period, at study visit at Week 1 (Day 1), Week 13, Week 17, and every subsequent 4 weeks of 1st line AAT and 2nd line AAT, at completion or discontinuation, and at safety follow-up visit, blood sample for PSA will be collected, and PSA will be measured by the central laboratory designated by the Sponsor. The PSA measured on Week 1 (Day 1) of 1st line AAT and 2nd line AAT will be handled as baseline. The following items will be calculated based on the measured PSA for evaluation.

5.3.1.1 Time to PSA Progression with 1st Line AAT (TTPP1)

PSA progression will be defined according to the consensus guidelines of PCWG2. For patients with PSA declines at Week 13, the PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second consecutive value obtained 3 or more weeks later. For patients with no PSA decline at Week 13, the PSA progression date is defined as the date that a ≥ 25% increase and an absolute increase of ≥ 2 ng/mL above the baseline is documented.

TTPP1 is defined as the period from the date of randomization to the date of PSA progression in the 1st line AAT period.

5.3.1.2 Time to PSA Progression with 1st Line AAT + 2nd Line AAT (TTPP2)

Time to PSA progression with 2nd line AAT is defined as the period from Day 1 of 2nd line AAT to the date of PSA progression with 2nd line AAT. TTPP2 will be the total of time to PSA progression with 1st line AAT and time to PSA progression with 2nd line AAT.

5.3.1.3 PSA Response Rate to 1st Line AAT (Decrease by at Least 50% or 90% from Baseline)

PSA response will be defined as PSA decreased by at least 50% or 90% from baseline when at least 3 weeks passed after the lowest PSA decreased by at least 50% or 90% from baseline in the 1st line AAT period after baseline. The proportion of the subjects who achieved PSA response will be evaluated.

5.3.1.4 PSA Response Rate to 1st Line AAT at Week 13 (Decrease by at Least 50% or 90% from Baseline)

PSA response will be defined as the lowest PSA at Week 13 decreased by at least 50% or 90% from baseline in the 1st line AAT period. The proportion of the subjects who achieved PSA response will be evaluated.

5.3.1.5 Time to PSA Decrease by 50% from Baseline with 1st Line AAT

Time to PSA decrease by 50% with 1st line AAT is defined as the period from the date of randomization to the day when the decrease of PSA from baseline by 50% is first identified.

5.3.1.6 Time to PSA Progression with 2nd Line AAT (2nd TTPP)

2nd TTPP is defined as the period from the start date of 2nd line AAT (Day 1) to the date of PSA progression.

5.3.1.7 PSA Response Rate to 2nd Line AAT (Decrease by at Least 50% or 90% from Baseline)

PSA response will be defined as PSA decreased by at least 50% or 90% from baseline when at least 3 weeks passed after the lowest PSA decreased by at least 50% or 90% from baseline in the 2nd line AAT period after baseline. The proportion of the subjects who achieved PSA response will be evaluated.

5.3.2 CT/MRI and Bone Scintigraphy

Imaging examination will be performed with chest CT, abdominopelvic CT or MRI, and bone scintigraphy in the screening period, at study visit every 12 weeks after Week 1 (Day 1) of 1st line AAT irrespective of switching the drugs, and at completion or discontinuation (chest CT will not be necessary at study visits after the screening period if chest metastasis is not observed in the image taken during the screening period). During the study period, imaging examination will be performed under the same condition for the same subject, and the image should be interpreted by the same reader at each study site wherever possible. Images taken within 42 days before randomization as part of daily consultation before informed consent may be used as data in the screening period. In case of disease progression suspected, imaging examination may be performed for confirmation at any time other than the scheduled examination.

The following will be evaluated with the images in the screening period as baseline.

5.3.2.1 Radiographic Progression-Free Survival (rPFS)

rPFS is defined as the period from randomization to the time when radiographic disease progression is observed or death of any cause during the study period, whichever occurs earlier. With regard to radiographic disease progression, soft tissue lesion will be defined by RECIST guidelines version 1.1 (RECIST 1.1), bone lesion will be defined as the occurrence of at least 2 new bone lesions confirmed by bone scintigraphy in line with PCWG2 recommendation. Evaluation will be made in subjects with distant metastasis at baseline.

The following are procedures necessary for confirmation of radiographic disease progression.

Study visit where disease progression is observed	Criteria for disease progression	Criteria for confirmation of disease progression (necessity for imaging for confirmation and time of confirmation)	Criteria for imaging for confirmation of disease progression
Visits up to Week 13 of 1st line AAT	Bone lesion: ≥2 new bone lesions in comparison with baseline bone scintigraphy by PCWG2	Timing: ≥6 weeks after disease progression confirmed or at Week 25 Visit	≥2 new bone lesions in comparison with bone scintigraphy at Week 13 of 1st line AAT
	Soft tissue lesion: Disease progression detected by CT or MRI, and defined by RECIST 1.1	No need of imaging for confirmation	N/A
Visits after Week 13 of 1st line AAT	Bone lesion: ≥2 new bone lesions in comparison with bone scintigraphy at Week 13* of 1st line AAT	No need of imaging for confirmation	N/A
	Soft tissue lesion: Disease progression detected by CT or MRI, and defined by RECIST 1.1	No need of imaging for confirmation	N/A

*: Compare with baseline bone scintigraphy if data from Week 13 are missing.

5.3.2.2 Metastasis-Free Survival (MFS)

MFS is defined as the period from randomization to new radiographic metastatic lesion or death of any cause during the study period, whichever occurs earlier. Evaluation will be made in subjects in whom distant metastasis is not confirmed at baseline.

5.3.2.3 Objective Response Rate (ORR) in Best Overall Soft Tissue Response of RECIST Guidelines with 1st Line AAT

According to RECIST 1.1, the investigator or sub-investigator will evaluate the overall response in target, non-target, and new lesions in soft tissue at each time point. At the end of the 1st line AAT period, the best overall response will be assessed. Of subjects with measurable soft tissue lesion (at least 1 target lesion according to RECIST 1.1) in baseline imaging, the proportion of subjects with objective response (complete or partial response) will be evaluated.

5.3.3 Time to Treatment Failure

Time to treatment failure is defined as the period to study drug discontinuation for any reason that includes disease progression, onset of AEs, subjects' request, or death. The following will be evaluated.

5.3.3.1 Time to Treatment Failure of 1st Line AAT (TTF1)

The period from randomization to discontinuation of 1st line AAT will be evaluated.

5.3.3.2 Time to Treatment Failure of 2nd Line AAT (TTF2)

The period from randomization to discontinuation of 2nd line AAT will be evaluated.

5.3.4 Subject Reported Outcome

The investigator or sub-investigator will instruct the subjects to record the following subject reported outcome, and evaluate the efficacy with Week 1 (Day 1) of 1st line AAT and 2nd line AAT as baseline based on the information recorded in subject reported outcome.

5.3.4.1 Functional Assessment of Cancer Therapy–Prostate (FACT–P)

The assessment will be conducted at study visit at Week 1 (Day 1), Week 13, and every subsequent 12 weeks of 1st line AAT and 2nd line AAT, and at completion or discontinuation.

FACT–P is a multi-faceted QOL scale of self-assessment for patients with prostate cancer. FACT–P includes 27 major items to evaluate subjects' functions in 4 areas; that is, physical health, social/family, emotional, and functional well-being. Site-specific 12 items are added for assessment of prostate-related symptoms. Each item will be assessed with a 5-grade Likert scale. The subtotal in each area is a low rank score. The total of all items is the overall QOL score. The higher the QOL score, the higher is the QOL.

5.3.4.2 European Quality of Life 5-Dimension-5 Level Instruments (EQ-5D-5L)

EQ-5D-5L will be performed at study visit at Week 1 (Day 1), Week 13, and every subsequent 12 weeks of 1st line AAT and 2nd line AAT, and at completion or discontinuation.

EQ-5D-5L is a QOL scale for self-assessment that consists of 5 items related to health, such as mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Each item will be evaluated in 5 levels from "no problem" to "extreme problem." The last question is a visual analog scale to evaluate the present health status in the range from "best imaginable health status" to "worst imaginable health status."

5.3.4.3 Brief Pain Inventory-Short Form (BPI-SF)

BPI-SF will be performed in the screening period, at study visit at Week 1 (Day 1), Week 13, and every subsequent 12 weeks of 1st line AAT and 2nd line AAT, and at completion or discontinuation.

BPI is a questionnaire slip verified as a self-assessment scale for subjects about the level of pain, effect of the pain on activities of daily living, and analgesic use. BPI used in this study is an abbreviated version (short form) that consists of questions in 9 items for which simple numerical evaluation scales from 0 to 10 are used. In order to evaluate prostate cancer-related pain in this study, the investigator or sub-investigator will instruct the subjects to describe prostate cancer-related pains.

5.3.4.4 Brief Fatigue Inventory (BFI)

BFI will be performed in the screening period, at study visit at Week 1 (Day 1), Week 13, and every subsequent 12 weeks of 1st line AAT and 2nd line AAT, and at completion or discontinuation.

BFI is a simple questionnaire slip that consists of questions in 10 items to evaluate the malaise (subjective symptoms characterized as debility that includes physical and mental wasting) of cancer patients.

5.4 Safety Assessment

5.4.1 Vital Signs (Blood Pressure and Pulse Rate)

Resting blood pressure in sitting position and pulse rate will be measured in the screening period, at each visit in 1st line AAT and 2nd line AAT, at completion or discontinuation, and at safety follow-up visit. The date and result of measurement will be entered in the medical record or other source materials, and in the eCRF.

5.4.2 ECOG Performance Status

In the screening period, at each visit in 1st line AAT and 2nd line AAT, at completion or discontinuation, and at safety follow-up visit, the investigator or sub-investigator will evaluate the general condition of subjects in line with the ECOG Performance Status, and enter it in the medical record or other source materials, and in the eCRF.

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. Subjects with AE's of hepatic origin accompanied by LFT abnormalities should be carefully monitored.

5.4.4 Laboratory Assessments

Below is a table of the laboratory tests that will be performed during the conduct of the study. Specimen will be collected at scheduled and unscheduled visits where necessary (see V. FLOW CHART AND SCHEDULE OF ASSESSMENTS). All specimen will be collected and measured by the central laboratory designated by the Sponsor.

Visits		Item	Collection Tube
Screening, Each visit in 1st line AAT, Each visit in 2nd line AAT, At completion or discontinuation, Safety follow-up	Hematology	RBC count WBC count Differential WBC count Hemoglobin Hematocrit Platelet count	2 mL
	Biochemistry	Albumin AST ALT γ-GTP LDH ALP Total bilirubin Total protein BUN Calcium Phosphatase Potassium Sodium Creatinine Testosterone	9 mL
	Blood glucose test	Glucose	2 mL
	Urinalysis	Specific gravity pH Protein Glucose Ketone Bilirubin Blood Nitrite Leucocyte Urobilinogen	10 mL
Screening, Week 1 (Day 1), Week 13, Week 17, every subsequent 4 weeks of 1st line AAT and 2nd line AAT, At completion or discontinuation, Safety follow-up	Biochemistry	PSA	Use the same specimen collected for other biochemistry tests

Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator/sub-investigator who is a qualified physician.

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.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, 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.

Clinical signs or clinical symptoms associated with disease progression should be reported as AEs, but should not be reported in the event name, “disease progression.” Disease progression leading to death will be reported in the event name, “disease progression.”

5.5.2 Definition of Serious Adverse Events (SAEs)

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 assume that if the event had occurred in a more severe form, it 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 in case the study drug administered to the subject that may require expedited reporting and/or safety evaluation include, but are not limited to cases as follows:

- Overdose
- Suspected abuse/misuse
- Inadvertent or accidental exposure to the study drug
- Medication error involving the study drug

All of the events of interest noted above should be recorded on the eCRF. Any situation involving these events of interest that also meets the criteria for an SAE should be recorded on the AE page of the eCRF and marked 'serious' and on the SAE worksheet/report.

In addition, if an AE indicated in "Appendix 12.3 Always Serious Events" occurs, it must be reported as SAE whether or not it meets the conditions above.

5.5.3 Criteria for Causal Relationship to the Study Drug

AEs that fall under either "Possible," "Probable," or "Not assessable" 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).
Not assessable	A report suggesting an adverse reaction which cannot be judged because Information is insufficient or contradictory, and which cannot be supplemented or verified.

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 guidelines (version 4.0). The items that are not stipulated in the NCI-CTCAE version 4.0 will be assessed according to the criteria below and entered into the eCRF:

Grade	Assessment Standard
1-Mild	Asymptomatic, or mild symptoms, clinical or diagnostic observations noted; intervention not indicated.
2-Moderate	Local or noninvasive intervention indicated.
3-Severe	Medically significant but not immediately life threatening, hospitalization or prolonged hospitalization.
4-Life Threatening	Life threatening consequences, urgent intervention indicated
5-Death	Death related to AE

5.5.5 Reporting of Serious Adverse Events (SAEs)

In the case of an SAE, the investigator or sub-investigator must report to the head of the study site and must contact delegated CRO by telephone/fax or email immediately (within 24 hours of awareness).

The investigator should complete and submit JUTOKUNA YUUGAIJISHOU HOUKOKUSHO containing all information that is required by the Regulatory Authorities to delegated CRO by fax or email immediately (within 24 hours of awareness) and to the head of the hospital. If the faxing or emailing of JUTOKUNA YUUGAIJISHOU HOUKOKUSHO is not possible or is not possible within 24 hours, delegated CRO should be informed by phone.

For contact details, see Section II.CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL. Please fax JUTOKUNA YUUGAIJISHOU HOUKOKUSHO to the following address, or report by email to an address arranged in advance.

Contract Research Organization (CRO)
[redacted]
Fax: [redacted]

5.5.6 Follow-up of Adverse Events

All AEs occurring during or after the subject has discontinued the study 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 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.

Even if the subject does not return to normal or baseline level, and the investigator or sub-investigator judged follow-up survey is not necessary or will be completed, the reason for the judgment should be recorded in the source materials.

Please refer to Appendix 12.2 Liver Safety Monitoring and Assessment for detailed instructions on drug-induced liver injury (DILI).

5.5.7 Procedure in Case of Pregnancy

If a female subject or partner of a male subject becomes pregnant during the study dosing period or within 3 months from the discontinuation of dosing, the investigator should report the information to the Sponsor or delegated CRO 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.

When the outcome of the pregnancy falls under the criteria for SAEs [spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus)], the investigator should respond in accordance with the report procedure for SAEs. 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

5.5.8 Emergency Procedures and Management of Overdose

1. Enzalutamide

Seizure, rash, confusional state, severe fatigue, etc. may be caused by overdose. In the overseas phase 1 study, with doses that exceed the maximum tolerable dose of enzalutamide 240 mg/day, seizure (1 event each with 360 mg/day, 480 mg/day, and 600 mg/day), rash (1 event with 600 mg/day), and confusional state (1 event with 600 mg/day) were reported. In the study, enzalutamide was reduced due to fatigue in some subjects, indicating dose-dependently increasing incidence with doses that exceed 240 mg. In the overseas phase 3

study, some subjects mistakenly took 640 mg/day for 8 days, and reported fatigue and asthenia as AEs whose causal relationship with enzalutamide cannot be ruled out.

There is no detoxicant specific to overdosed enzalutamide. Enzalutamide has a large distribution volume, and high protein bonding rate. Thus, intermittent hemodialysis and continuous ambulatory peritoneal dialysis are not an effective means to eliminate enzalutamide from body. For suspected overdose, stop the administration, and take appropriate measures according to the symptoms.

2. Flutamide

In the clinical study, flutamide up to 1500 mg per day was administered to a maximum of 36 weeks. No significant adverse reactions were reported. It has not been clear whether a single administration of flutamide will usually cause symptoms of overdose or life-threatening symptoms.

Most of flutamide is bonded with protein, and dialysis is not useful to treat an overdose. Similar to means taken against an overdose of any drug, we should note that multiple drugs may have been taken. If voluntary vomiting does not occur, vomiting should be induced for conscious patients. Vital signs should be frequently checked, and general supportive care that includes thorough observation will be conducted.

5.5.9 Supply of New Information Affecting the Conduct of the Study

1. When information is obtained regarding serious and unexpected adverse drug reactions (or other) that are specified in Article 273 of the Enforcement Regulations of the Pharmaceutical Affairs Law, in compliance with Article 80-2 Paragraph 6 of the Pharmaceutical Affairs Law, the Sponsor should inform all the investigators involved in the clinical study, the head of the study site, and the regulatory authorities of such information. The head of the study site who receives such information will decide whether the clinical study should be continued after hearing the opinions of the IRB. The investigator will supply the new information to the subjects, in compliance with Section 8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information.
2. In addition to the above item (1), when the head of the study site receives the revisions of the protocol or written information, information on the matters covering the quality of the study drug, efficacy and safety, information necessary for conducting the clinical study properly, or documents to be examined by the IRB should be sent to the IRB.

5.5.10 Deviations from the Protocol and Other Actions Taken to Avoid Life-Threatening Risks to Subjects

The investigator must not deviate from or amend the protocol, excluding an emergency case for avoiding risks to the subjects. When the investigator does not follow the protocol in order to avoid urgent risks for subjects, the investigator should take the following actions.

1. Describe the contents of the deviation or amendment and the reasons for it in a written notice, and immediately send the document stating the deviation or amendment and the reasons to the Sponsor and the head of the study site. Keep a copy of the notice.
2. Consult with the Sponsor at the earliest possibility for cases in which it is necessary to amend the protocol. Obtain approval for a draft of the amended protocol from the IRB and the head of the study site as well as written approval from the Sponsor.

5.6 Test Drug Concentration

Not applicable.

5.7 Other Measurements, Assessments or Methods

Not applicable.

5.8 Total Amount of Blood

The total amount of blood collected from a subject differs according to the course of the disease and study drug treatment period. The total amount of blood collected at each visit will be 13 mL (hematology: 2 mL, biochemistry: 9 mL, blood glucose test: 2 mL).

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 prematurely 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:

1. AEs (excluding events in the discontinuation criteria 2 and 3) that are intolerable for the subject, and are not improved by proper medical intervention or reduction of the study drug; or AEs, which the investigator or sub-investigator considers that continuation of the study drug may cause an excessive risk to subjects.
2. Seizure during the treatment period of enzalutamide (subjects who had seizure on the1st line AAT may be shifted to the 2nd line AAT.)
3. Liver disorder (abnormal AST or ALT that exceed 3 fold of the upper limit of normal) or interstitial pneumonia (subjects who had a case on the 1st line AAT may be shifted to the 2nd line AAT.) during the treatment period with flutamide
4. With or without PSA progression, the investigator or sub-investigator considers that the study should be discontinued due to the progression of the disease
5. Subject withdraws the informed consent.
6. Observation cannot be continued (e.g., subject stops study visit; subjects lose contact)
7. The Sponsor, investigator, or sub-investigator considers that the study should be discontinued due to deviation from the protocol (excluding the discontinuation criterion 8).
8. It turns out after the enrollment that the subject did not satisfy the inclusion criteria or met the exclusion criteria at the time of registration, and the continuation of the study is judged inappropriate.
9. Other
   For reasons other than those mentioned above, the investigator or sub-investigator considers that the study should be discontinued.

For discontinuation after the start of the study drug, a discontinuation examination/observation will be conducted wherever possible after the decision of discontinuation.

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the Sponsor and the head of the study site.

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 CRO to whom the Sponsor delegates the operation. 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 finalized before the database hard-lock at the latest. Any changes from the analyses planned in SAP will be justified in the Clinical Study Report (CSR).

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

7.1 Sample Size

The number of evaluable subjects will be approximately 200 subjects (1st line AAT enzalutamide group: 100, 1st line AAT flutamide group: 100).

The sample size to evaluate the time to PSA progression with 1st line AAT (TTPP1), which is the primary endpoint of the study, was calculated in consideration of the following points:

- Median TTPP1 with enzalutamide: 10.5 months.
  [redacted]
- Median TTPP1 with flutamide: 6 months.
  Values reported in the literature: 5 months according to [Okihara et al., 2007], 6.25 months according to [Narimoto et al., 2010].
- The ratio of randomization of 1st line AAT enzalutamide and flutamide groups is 1:1.
- Subject enrollment period is 12 months, and the observation period is 24 months from the enrollment of the last subject.
- Type I error of the two-sided test is 0.05, and power is 90%.
- A log-rank test with the TTPP1 parameters shown above requires 135 events. The necessary number of subjects calculated based on the required number of events is 74 subjects per group.
  Required number of events and necessary number of subjects above are calculated with the formulas below based on [Schoenfeld, 1983]. The codes in the formulas are defined as follows.
  M_t: Median TTPP1 in enzalutamide group
  M_c: Median TTPP1 in flutamide group
  t_a: Enrollment period
  t_f: Observation period from the last subject enrollment
  $Z_{1-\alpha}$: 1-α% point of standard normal distribution
  $Z_{1-\beta}$: 1-β% point of standard normal distribution

Hazard in enzalutamide group $(H_t) = \frac{\log_e 2}{M_t}$

Hazard in flutamide group $(H_c) = \frac{\log_e 2}{M_c}$

Hazard ratio for enzalutamide group/flutamide group $(HR) = \frac{H_t}{H_c}$

Required number of events $(N_d) = \frac{4\times (Z_{1-\alpha}+Z_{1-\beta})^2}{(\log_e HR)^2}$ *The number after the decimal point will be rounded up to the nearest integer.

Incidence of events of enzalutamide group

$$(P_t) = 1 - \frac{1}{6}\left(\exp(-H_t \times t_f) + 4 \times \exp\left(-H_t \times (t_f + \frac{1}{2} \times t_a)\right) + \exp(-H_t \times (t_f + t_a))\right)$$

Incidence of events of flutamide group

$$(P_c) = 1 - \frac{1}{6}\left(\exp(-H_c \times t_f) + 4 \times \exp\left(-H_c \times (t_f + \frac{1}{2} \times t_a)\right) + \exp(-H_c \times (t_f + t_a))\right)$$

Incidence of events of both groups $(P) = \frac{1}{2} \times (P_t + P_c)$

Necessary number of subjects per group $(N) = \frac{1}{2} \times \frac{N_d}{P}$ * The number after the decimal point will be rounded up to the nearest integer.

- Considering the dropout rate of approximately 25%, 100 subjects are to be enrolled in each group.

	[redacted]	[redacted]
Number of subjects	[redacted]	[redacted]
With PSA progression	[redacted]	[redacted]
Censored	[redacted]	[redacted]
25%	[redacted]	[redacted]
50%	[redacted]	[redacted]
75%	[redacted]	[redacted]

7.2 Analysis Set

7.2.1 Intent-to-Treat (ITT)

Intent-to-Treat (ITT) population is defined as all subjects randomized in this study. The ITT population will be analyzed by randomized treatment group (treatment group based on randomization). Efficacy analyses will be done in the ITT population.

7.2.2 Safety Analysis Set (SAF)

For the statistical summary of the safety data, the safety analysis set (SAF) will be used. The SAF consists of all subjects who took at least one dose of study medication, and will be used for safety analyses.

7.2.3 Pharmacokinetic Analysis Set (PKAS)

The pharmacokinetic analysis set (PKAS) will not be established for this study.

7.2.4 Pharmacodynamic Analysis Set (PDAS)

The pharmacodynamic analysis set (PDAS) will not be established for this study.

7.3 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized by treatment group for the SAF and ITT. 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

Efficacy analysis will be conducted on the ITT. The interpretation of results from statistical tests will be based on the ITT.

7.4.1 Analysis of Primary Endpoint

7.4.1.1 Primary Analysis

TTPP1 is the period from randomization to the first day when PSA progression is objectively identified. Convention of censoring is specified in Section 7.10.

The benefit of enzalutamide as compared to flutamide will be assessed with the stratified log-rank test as the primary efficacy analysis. The stratification factor will be the disease stages (M0/N0, M0/N1, or M1) used as stratification factor for allocation.

The hypothesis for comparisons is as follows:

H0: The survival time distribution of enzalutamide group is the same as that with flutamide group.

H1: The survival time distribution of enzalutamide group is not the same as that with flutamide group.

The significance level is 0.05 (two-sided). ITT is used for the primary analysis.

7.4.1.2 Secondary Analysis

As the secondary analysis of the primary endpoint, TTPP1, the benefit of enzalutamide as compared to flutamide will be also assessed with the hazard ratio and its 95% CI based on the Cox proportional hazards model. Disease stages (M0/N0, M0/N1, or M1) will be used as a covariate for adjustment. Furthermore, the distribution of time to PSA progression will be

estimated using the Kaplan–Meier method. The median time to PSA progression will be estimated using the 50 percentile value of the Kaplan–Meier curve. The two-sided 95% CI will be calculated based on the estimation. The significance level is 0.05 (two-sided). ITT is used for the primary analysis.

7.4.1.3 Subgroup Analysis

For the primary and secondary analyses on the primary endpoint, TTPP1, subgroup analyses will be performed. Subgroup setting is specified by the SAP.

7.4.2 Analysis of Secondary Endpoints

7.4.2.1 Time to PSA Progression with 1st Line AAT + 2nd Line AAT (TTPP2)

TTPP2 is defined as the period from Day 1 of 2nd line AAT to the date of PSA progression with 2nd line AAT. The total of time to PSA progression with 1st line AAT and time to PSA progression with 2nd line AAT will be evaluated. Convention of censoring is specified in Section 7.10.

The distribution of the TTPP2 will be estimated using the Kaplan–Meier method. The median TTPP2 will be estimated using the 50 percentile value of the Kaplan–Meier curve. The two-sided 95% CI will be calculated based on the estimation. The benefit of enzalutamide as compared to flutamide will be descriptively assessed.

7.4.2.2 PSA Response Rate to 1st Line AAT (Decrease by at Least 50% or 90% from Baseline)

The PSA response rate decreasing by at least 50% will be calculated by treatment groups of subjects with baseline PSA value and PSA measured at least once after baseline. For the comparison of the response rate between the enzalutamide and flutamide groups, the stratified Cochran–Mantel–Haenszel test will be used. The stratification factor will be the disease stages (M0/N0, M0/N1, or M1) used as stratification factor for allocation.

PSA decrease by at least 90% will also be compared at the 0.05 significance level (two-sided) between the enzalutamide and flutamide groups using the stratified Cochran–Mantel–Haenszel test.

7.4.2.3 PSA Response Rate to 1st Line AAT at Week 13 (Decrease by at Least 50% or 90% from Baseline)

The PSA response rate decreasing by at least 50% (or by at least 90%) will be calculated by treatment groups of subjects with baseline PSA value with 1st line AAT and PSA measured at Week 13.

The response rate between the enzalutamide and flutamide groups will be compared using the stratified Cochran–Mantel–Haenszel test. The stratification factor will be the disease stages (M0/N0, M0/N1, or M1) used as stratification factor for allocation.

7.4.2.4 Time to PSA Decrease by 50% from Baseline with 1st Line AAT

The time to PSA decrease by 50% with 1st line AAT is defined as the period from randomization to the day when the decrease of PSA from baseline by 50% is first identified. Convention of censoring is specified in Section 7.10.

The benefit of enzalutamide as compared to flutamide will be assessed by the stratified log-rank test. The significance level is 0.05 (two-sided). The stratification factor will be the disease stages (M0/N0, M0/N1, or M1) used as stratification factor for allocation.

The distribution of the period when PSA decreases by 50% will be estimated using the Kaplan–Meier method. The median period when PSA decreases by 50% will be estimated using the 50 percentile value of the Kaplan–Meier curve. The two-sided 95% CI will be calculated based on the estimation.

7.4.2.5 Time to Treatment Failure of 1st Line AAT (TTF1)

TTF1 is defined as the period from randomization to the date of discontinuation of 1st line AAT. Convention of censoring is specified in Section 7.10.

The benefit of enzalutamide as compared to flutamide will be assessed with the stratified log-rank test. The significance level is 0.05 (two-sided). The stratification factor will be the disease stages (M0/N0, M0/N1, or M1) used as stratification factor for allocation.

The distribution of the TTF1 will be estimated using the Kaplan–Meier method. The median TTF1 will be estimated using the 50 percentile value of the Kaplan–Meier curve. The two-sided 95% CI will be calculated based on the estimation.

7.4.2.6 Time to Treatment Failure of 2nd Line AAT (TTF2)

TTF2 is defined as the period from randomization to the date of discontinuation of 2nd line AAT. Convention of censoring is specified in Section 7.10.

The distribution of the TTF2 will be estimated using the Kaplan–Meier method. The median TTF2 will be estimated using the 50 percentile value of the Kaplan–Meier curve. The two-sided 95% CI will be calculated based on the estimation. The benefit of enzalutamide as compared to flutamide will be descriptively assessed.

7.4.2.7 Radiographic Progression-Free Survival (rPFS)

rPFS will be assessed using the same method as that with TTPP1 in subjects with distant metastasis confirmed at baseline.

7.4.3 Analysis of Exploratory Endpoints

7.4.3.1 Time to PSA Progression with 2nd Line AAT (2nd TTPP)

2nd TTPP is defined as the period from the start of 2nd line AAT to the first day when PSA progression is objectively identified. Convention of censoring is specified in Section 7.10.

The distribution of the 2nd TTPP will be estimated using the Kaplan–Meier method. The median 2nd TTPP will be estimated using the 50 percentile of the Kaplan–Meier curve. The two-sided 95% CI will be calculated based on the estimation. The benefit of enzalutamide as compared to flutamide will be descriptively evaluated.

7.4.3.2 PSA Response Rate to 2nd line AAT

The PSA response rate to 2nd line AAT will be assessed by the same method as that with the PSA response rate to 1st line AAT.

7.4.3.3 Metastasis-Free Survival (MFS)

MFS will be assessed using the same method as that with 2nd TTPP in subjects without distant metastasis at baseline.

7.4.3.4 FACT–P and EQ-5D-5L with 1st Line AAT and 2nd Line AAT

For FACT–P and EQ-5D-5L, summary statistics will be calculated at each assessment.

7.4.3.5 Brief Fatigue Inventory (BFI) with 1st Line AAT and 2nd Line AAT

For BFI, summary statistics will be calculated at each assessment.

7.4.3.6 Objective Response Rate (ORR) in best Overall Soft Tissue Response of RECIST Guidelines with 1st Line AAT

ORR will be assessed using the same method as that with the PSA response rate.

7.5 Analysis of Safety

The safety analysis will be performed in the safety analysis set, and summarized by the time of assessment and by the treatment group that actually received the study drugs. The period of onset in the treatment period with the study drug is defined up to 28 days after the final treatment with the study drug, start date of cytocidal chemotherapy, or start date of new treatment for prostate cancer, whichever occurs first. Safety will be assessed by AEs, frequency of treatment discontinuation associated with AEs, and laboratory test value summary statistics. Descriptive statistics, and not inferential statistics, will be used.

7.5.1 Adverse Events

The severity of all AEs will be evaluated by the investigator or sub-investigator based on NCI-CTCAE version 4.0. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of AEs, SAEs, AEs leading to discontinuation, and AEs related to study drug will be summarized by system organ class, preferred term and treatment group. The number and percentage of AEs by severity will also be summarized. All AEs will be listed.

7.5.2 Laboratory Assessments

For quantitative laboratory measurements descriptive statistics will be used to summarize results and change from baseline by treatment group and time point. Shifts relative to normal ranges from baseline to each time point during treatment period in lab tests will also be tabulated. Laboratory data will be displayed in listings.

7.5.3 Vital Signs

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

7.5.4 ECOG Performance Status

For actual measurement of ECOG Performance Status, frequency distribution will be calculated by time point. ECOG Performance Status data will be displayed in listings.

7.5.5 Physical Examination

Physical examination will not be performed in this study.

7.5.6 ECGs

ECGs will not be performed in this study.

7.5.7 Imaging

A list of data on disease progression collected from imaging examinations, which includes abdominopelvic CT/MRI, bone scintigraphy, and chest CT (by treatment group and time point), will be prepared.

7.6 Analysis of Pharmacokinetics

Pharmacokinetics will not be analyzed in this study.

7.6.1 Estimation of Pharmacokinetic Parameters

Pharmacokinetic parameters will not be estimated in this study.

7.6.2 Statistical Analysis

A statistical analysis will not be performed in this study.

7.6.3 Concentration-Response Relationship Analysis

A concentration-response relationship analysis will not be performed in this study.

7.7 Analysis of Pharmacodynamics

An analysis of pharmacodynamics will not be performed in this study.

7.8 Protocol Deviations and Other Analyses

Protocol deviations and other analyses that are not included in the preceding sections, if performed, will be specified by the statistical analysis plan.

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

No formal interim analysis is planned.

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 group, 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. Subjects who do not receive the study drug to which they have been randomized will be analyzed as treated.

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

Sites that do not enroll at least 10 subjects will be pooled for analyses by site. The pooling decisions will be made and documented prior to study database hard-lock. The handling of outlier is specified by the SAP. The acceptable time range for study visit is specified by “VI. ACCEPTABLE RANGE OF SCHEDULE OF ASSESSMENTS.” Values that fall out of the range will be excluded. Convention of censoring for each endpoint are defined in the table below.

	TTPP1	TTPP2	2nd TTPP	Time to PSA 50%/90% decline	TTF1	TTF2	rPFS	MFS
Subjects without PSA value at baseline or in observation period	Considered as censoring at randomization	Considered as censoring at randomization	Excluded from analysis	Considered as censoring at randomization	Not considered as censoring *To be judged based on continuation of study treatment	Not considered as censoring *To be judged based on continuation of study treatment	Not considered as censoring *To be judged based on result of radiographic assessment	Not considered as censoring *To be judged based on result of radiographic assessment
Subjects without the result of radiographic assessment at baseline or in observation period	Not considered as censoring *To be judged based on result of PSA measurement	Not considered as censoring *To be judged based on result of PSA measurement	Not considered as censoring *To be judged based on result of PSA measurement	Not considered as censoring *To be judged based on result of PSA measurement	Not considered as censoring *To be judged based on continuation of study treatment	Not considered as censoring *To be judged based on continuation of study treatment	Considered as censoring at randomization	Considered as censoring at randomization
Subjects without PSA progression at final data cut-off (Including cases inconsistent with PSA progression defined by the protocol)	Subjects who continue the first study drug are considered as censoring at final PSA measurement	Considered as censoring at final PSA measurement	Subjects who continue the first study drug are excluded from analysis Subjects who have shifted to the second study drug are considered as censoring at final PSA measurement	Considered as censoring at final PSA measurement	Not considered as censoring *To be judged based on continuation of study treatment	Not considered as censoring *To be judged based on continuation of study treatment	Not considered as censoring *To be judged based on result of radiographic assessment	Not considered as censoring *To be judged based on result of radiographic assessment
Subjects without radiographic progression at final data cut-off (Including cases inconsistent with progression defined by the protocol)	Not considered as censoring *To be judged based on result of PSA measurement	Not considered as censoring *To be judged based on result of PSA measurement	Not considered as censoring *To be judged based on result of PSA measurement	Not considered as censoring *To be judged based on result of PSA measurement	Not considered as censoring *To be judged based on continuation of study treatment	Not considered as censoring *To be judged based on continuation of study treatment	Considered as censoring at final radiographic assessment	Considered as censoring at final radiographic assessment

	TTPP1	TTPP2	2nd TTPP	Time to PSA 50%/90% decline	TTF1	TTF2	rPFS	MFS
Death during the study	Subjects who died during treatment with the first study drug are considered as censoring at final PSA measurement before death	Considered as censoring at final PSA measurement before death	Subjects who died during treatment with the first study drug are excluded from analysis Subjects who died during treatment with the second study drug are considered as censoring at final PSA measurement before death	Considered as censoring at final PSA measurement before death	The event is considered to occur at the time of death	The event is considered to occur at the time of death	The event is considered to occur at the time of death	The event is considered to occur at the time of death
Subjects who discontinued treatment during the study	Subjects who discontinue the first study drug are considered as censoring at final PSA measurement before discontinuation	Considered as censoring at final PSA measurement before discontinuation	Subjects who discontinue the first study drug are excluded from analysis Subjects who discontinue the second study drug are considered as censoring at final PSA measurement before discontinuation	Considered as censoring at final PSA measurement before discontinuation	The event is considered to occur at the time of discontinuation	The event is considered to occur at the time of discontinuation	Considered as censoring at final radiographic assessment before discontinuation	Considered as censoring at final radiographic assessment before discontinuation

	TTPP1	TTPP2	2nd TTPP	Time to PSA 50%/90% decline	TTF1	TTF2	rPFS	MFS
Subjects who used prohibited concomitant medication or therapy during the study	Subjects who use one with the first study drug are considered as censoring at final PSA measurement before use	Considered as censoring at final PSA measurement before use	Subjects who use one with the first study drug are excluded from analysis Subjects who use one with the second study drug are considered as censoring at final PSA measurement before use	Considered as censoring at final PSA measurement before use	Not considered as censoring *To be judged based on continuation of study treatment	Not considered as censoring *To be judged based on continuation of study treatment	Considered as censoring at final radiographic assessment before use	Considered as censoring at final radiographic assessment before use
Subjects who miss PSA data at least twice consecutively at scheduled PSA measurement points	Considered as censoring at final PSA measurement before missing data occur	Considered as censoring at final PSA measurement before missing data occur	Subjects who continue the first study drug are excluded from analysis Subjects who have shifted to the second study drug are considered as censoring at final PSA measurement before missing data occur	Considered as censoring at final PSA measurement before missing data occur	Not considered as censoring *To be judged based on continuation of study treatment	Not considered as censoring *To be judged based on continuation of study treatment	Not considered as censoring *To be judged based on result of radiographic assessment	Not considered as censoring *To be judged based on result of radiographic assessment
Subjects who miss radiographic assessment at least twice consecutively at scheduled radiographic assessment points	Not considered as censoring *To be judged based on result of PSA measurement	Not considered as censoring *To be judged based on result of PSA measurement	Not considered as censoring *To be judged based on result of PSA measurement	Not considered as censoring *To be judged based on result of PSA measurement	Not considered as censoring *To be judged based on continuation of study treatment	Not considered as censoring *To be judged based on continuation of study treatment	Considered as censoring at final radiographic assessment before missing data occur	Considered as censoring at final radiographic assessment before missing data occur

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

8.1.1.1 Case Report Forms

The investigator or site designee will enter data collected using an Electronic Data Capture (EDC) system. In the interest of collecting data in the most efficient manner, the investigator or site designee should enter data (including laboratory values, if applicable) in the eCRF within 5 days after the subject visit wherever possible. For subjects who dropped out before randomization and after obtaining written informed consent, the minimum demographic data (subject No., sex, date of birth, date of informed consent) and the reason for dropout will be collected in screen failure log (SFL).

The investigator or site designee is responsible to ensure that all data in the eCRFs 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 eCRFs with source documents and confirm that there are no inconsistencies between them. In case of correction to data, confirm that an appropriate record is retained.

8.1.1.2 Subject Reported Outcome

The investigator or site designee will confirm the subject reported outcome questionnaire slip (FACT–P, EQ-5D-5L, BPI-SF, BFI) entered by subjects, and enter in the eCRF. Subjects will confirm the content with the investigator or site designee at study visit, make addition and modification where necessary in case of unclear description, enter the date of correction to the place of addition/modification, and sign or affix the seal.

8.1.1.3 Examination Data

Laboratory tests are performed at central laboratory. Laboratory data will be electronically transferred at predefined intervals during the study to the Sponsor or CRO to whom the Sponsor delegates the operation. The laboratory will provide a complete and clean copy of the data for the Sponsor or CRO to whom the Sponsor delegates the operation.

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.

In this study, the following source materials and content entered in the eCRF (including the content of follow-up report if follow-up of AEs is conducted) will be verified.

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

- Demographic data (e.g., date of birth, sex, height, body weight, etc.)
- Inclusion and exclusion criteria
- Participation in study and original signed and dated informed consent forms
- Medical record and document attached to it
- Medical history and physical examination details
- Key efficacy and safety data (as specified in the protocol)
- Results of relevant examinations (e.g., image films, image photos, etc.)
- Laboratory printouts (including central measurement result slip)
- Subject reported outcome questionnaire slip
- Dispensing and return of study drug details (e.g., study drug control table) and the prescriptions etc. for concomitant medications.

If the following data are not entered in the medical record, the content of the eCRF (or follow-up report) will be handled as source materials. However, if the following data are entered in the medical record or records attached to or stored with the medical record, or the following data can be obtained from source materials, data entered in source materials will be handled as source data.

- Route of administration, reason for use, and treatment period of previous medication and concomitant medication
- Reason for treatment, and treatment period of prior therapy and combination therapy
- Detail of AEs (severity, seriousness, outcome, intervention, relationship with the study drug, and rationale for the judgment of relationship)
- Date of final observation, date of discontinuation, reason for discontinuation, background of discontinuation
- Comment in the eCRF (or follow-up report)

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/sub-investigator 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 CRO to whom the Sponsor delegates the operation in accordance with the standard operating procedures (SOPs) for data management. All study specific processes and definitions will be documented by Data Management. eCRF retrieval and correction process will be referenced in the CRF instructions. Coding of medical terms and medications will be performed using MedDRA and World Health Organization Drug Dictionary Enhanced (WHODDE) respectively.

8.1.6 End of Trial

The end of trial is defined as the last subject's last visit, decision on discontinuation of the study, or the last contact to the last subject, whichever occurs last.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board (IRB)

Prior to signing the contract agreement of this study, the IRB at each study site will review and approve the protocol, and other materials used to obtain informed consent from patients in order to ensure the protection of human right, safety, and welfare of the patients. Any agreement should not be signed without the approval of the IRB.

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, 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 or placed a personal seal on 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 or sealed 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.

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

1. 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.
2. The investigator must update their ICF and submit it for approval to the IRB. 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 or place a personal seal, and date the informed consent form. A copy of the signed or sealed 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.

All individuals and organizations involved in the study must pay very careful attention to protect subjects' privacy with appropriate measures, for example, by prohibiting the use of any private information that may identify a subject (e.g., name or address). These details shall be processed in accordance with the applicable local and regional laws.

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to subject's privacy due to direct access to source documents, or from other sources, they may not leak the content to third parties.

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, 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 for the collection of information on proper use of the study 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.

After agreement between investigator(s) and sponsor, the manuscript can be submitted for publication.

8.3.2 Documents and Records Related to the Clinical Study

The Sponsor will provide the investigator and/or institution with the following:

- Study protocol (and amendments, where applicable)
- eCRFs and their relevant documents, JUTOKUNA YUUGAIJISHOU HOUKOKUSHO, and follow-up report
- Study drug with all necessary documentation
- Study contract

In order to start the study, the investigator and study site is required to provide the following documentation to the Sponsor:

- Agreement with the investigator on this protocol
- Current Curricula Vitae of all investigators

- List of sub-investigators and collaborators
- IRB approval of the protocol, protocol amendments (if applicable) including a membership list with names and qualification (COPY)
- Instruction and decision of the head of the study site
- Study contract
- Laboratory normal reference ranges (including modified or revised versions)

At the end of the study, the sponsor is responsible for the collection of:

- Unused study documentation,
- Unused study drug

The investigator will archive all study data (e.g., Subject Identification Code List, source data, eCRFs, and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation.

The records to be retained at the study sites are the ones listed as essential documents in GCP. These records shall be retained by the head of the study site or the record keeper designated by the head until notice issued by the Sponsor on completion of the retention period is received. These documents are also subject to direct access and should be provided upon request from the Sponsor or regulatory authorities.

The head of the study site will retain the essential documents that should be stored at the study site in an appropriate manner according to the rules of the study site concerned until the date of the end of re-examination/re-evaluation of the test drug.

The following are the major documents to be retained at the study site.

1. Source documents (clinical data, documents, and records for preparing the CRF)
   Hospital records, medical records and record attached to the medical records, test records, memoranda, subject reported outcome questionnaire slip, prescription records, data recorded by automatic measuring instruments, reproductions or transcripts verified as precise copies, microfiche, negative films, microfilms/magnetic media, X-ray films, subject files and study-related records kept at either a pharmacy, a laboratory, or medical technical office, as well as subject registration forms, laboratory test slips including central measurement, worksheets specified by the Sponsor, records of clinical coordinators, and records related to the clinical study selected from those verified in other departments or hospitals.
2. Contracts, written informed consent forms, written information, and other documents or their copies prepared by the study personnel.
   A letter of request for clinical study (including a request for continuation/amendment), letter of request for review, notice of clinical study contract, clinical study contract, notification of discontinuation or completion of clinical study, written information for informed consent (including revisions), signed and dated written informed consent

(including revisions), CVs of investigators, list of sub-investigators, list of signatures and print of seals (copy), and electronic media that contain data of eCRFs, etc.

3. The protocol, documents obtained from the IRB related to the adequacy of conducting the clinical study by the head of the study sites (Article 32-1, MHW Ordinance No. 28), documents obtained from the IRB related to the adequacy of conducting a clinical study whose period exceeds one year or the adequacy of continuously conducting the clinical study from which information on adverse drug reactions is obtained, and other documents obtained.
   An agreed-upon protocol (including revisions), operational procedures for the investigator, materials and information supplied by the Sponsor (e.g., AE report), matters reported by the investigator (revisions of the protocol, AE reports, etc.), operational procedures for the IRB, the list of names of the IRB members, materials for IRB review (including continuous deliberation), IRB review records (including continuous deliberation), and the review result report of the IRB (including continuous deliberation), etc.
4. Records of control for study drugs and other duties related to the clinical study.
   Procedure for controlling the study drugs, drug accountability record, vouchers for the receipt and return of the study drugs, and the prescriptions for concomitant medications.

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 and/or revisions. Depending on the nature of the amendment, either IRB, Competent Authority approval or notification may be required. The changes will become effective only after the approval of the Sponsor, the investigator, and the IRB followed by the approval of the head of the study site.

8.3.4 Insurance of Subjects and Others

If a subject suffers any study-related injury, the Sponsor will compensate appropriately according to the severity and duration of the damage. However, if it was caused intentionally or was due to gross negligence by the study site, the Sponsor will consult with the study site about handling the injury, based on the agreed study contract. Compensation for the study-related injury is provided by the following procedures:

1. If a subject incurs an injury as a result of participation in the clinical study, the study site should provide medical treatment and other necessary measures. The Sponsor should be notified of the injury.
2. When the subject claims compensation from the study site for the above study-related injury, or such compensation may be claimed, the study site should immediately communicate the fact to the Sponsor. Both parties should work together towards compensation settlement.

3. The Sponsor shall pay compensation or indemnification and bear expenses necessary for the settlement as provided in the clinical contract.
4. The Sponsor shall make an arranging for insurance and take measures necessary to ensure the compensation or indemnification mentioned above.

8.3.5 Signatory Investigator for Clinical Study Report

Not applicable.

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, eCRFs, 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) | Monitoring Committee | Other Evaluation Committee(s)

Not applicable.

10.2 Other Study Organization

See Attachments 1 and 2.

10.3 Registration of Subjects

The investigator or sub-investigator will survey the background of prospective subjects, obtain written informed consent, and confirm inclusion/exclusion criteria during the screening period. The investigator or site designee will enter necessary information in a subject registration form on the web registration system at study visit at Week 1 (Day 1) of 1st line AAT, and transmit it to the registration center. The registration center will receive the content of subject registration, confirm inclusion/exclusion criteria, and allocate the study

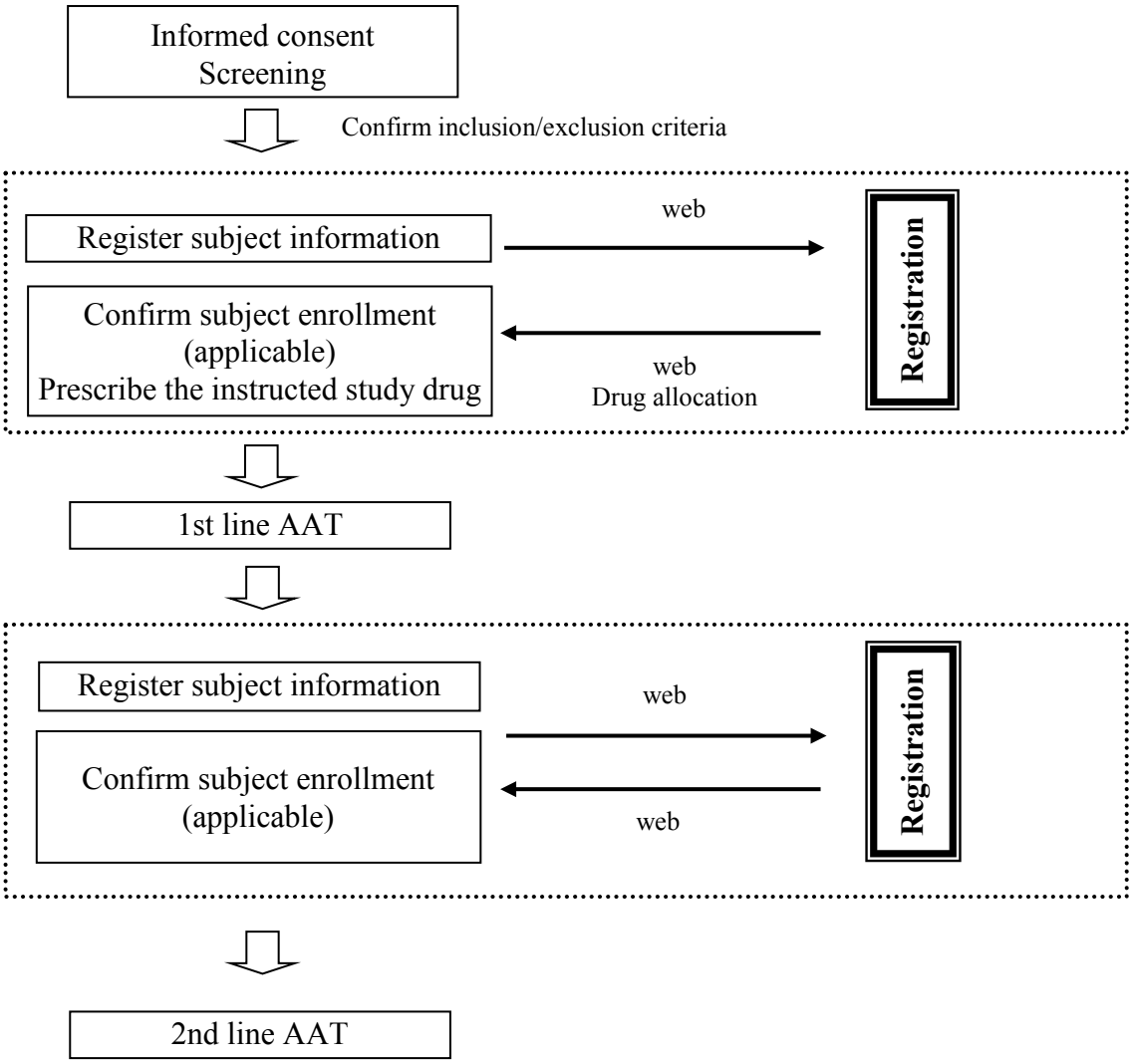
drug to qualified subjects. The registration center will notify the judgment of subject registration and allocated drug name to the study site via the web registration system.

The investigator or sub-investigator will confirm that the registration is appropriate, and prescribe the study drug instructed by the registration center as 1st line AAT. For patients who are judged unqualified for the registration, the study for those subjects will be discontinued at that time.

The investigator or sub-investigator will confirm the criteria for shifting from 1st line AAT to 2nd line AAT at study visit at Week 1 (Day 1) of 2nd line AAT. The investigator or site designee will enter necessary information in a subject registration form on the web registration system, and transmit it to the registration center. Thereafter, the investigator or sub-investigator will confirm that the registration is appropriate, and prescribe the drug of 2nd line AAT, which is different from the drug of 1st line AAT.

The investigator or site designee will, at completion or discontinuation of the study, enter necessary information in a subject registration form on the web registration system, and transmit it to the registration center.

Flow of subject enrollment:



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12 APPENDICES

12.1 List of Excluded Concomitant Medications

- Anti-androgenic agents (steroid or non-steroid) other than study drugs such as chlormadinone and bicalutamide
- CYP17 inhibitor (abiraterone)
- Cytocidal chemotherapy that includes estramustine
- Systemic corticosteroids for prostate cancer or systemic corticosteroids greater than the equivalent of 10 mg per day of prednisone (Decadron 1 mg/day) for other diseases
- 5-α reductase inhibitors (finasteride, dutasteride)
- Estrogen or progesterone agents such as medroxyprogesterone and diethylstilbestrol (DES)
- Biological agents or other drugs with anticancer activity to prostate cancer
- Herbal medications that may have hormonal anti-prostate cancer activity or herbal medications (saw palmetto) that may decrease serum PSA levels
- Androgen (e.g., testosterone, dehydroepiandrosterone [DHEA])
- Study drug for prostate cancer
- Warfarin

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 × ULN (to > 5 × ULN in subjects with liver metastases), or bilirubin > 2 × ULN, should undergo detailed testing for liver enzymes (including at least ALT, AST, ALP, and TBL). Testing should be repeated within 48 to 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 × ULN (in patients without liver metastases), >5 × ULN (in patients with liver metastases)	or	> 2 × ULN
Severe*	> 3 × ULN	and	> 2 × ULN

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

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks (in the absence of liver metastases)
- ALT or AST > 3 × ULN and INR > 1.5 (If INR testing is applicable/evaluated).
- ALT or AST > 3 × 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) or an 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 the eCRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Non-alcoholic 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 pre-dates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including non-prescription 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 eCRF. 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, pre-existing 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 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks (in subjects without liver metastases)
- ALT or AST > 3 × ULN and TBL > 2 × ULN or INR > 1.5 (If INR testing is applicable/evaluated)
- ALT or AST > 5 × ULN (TBL > 2 × ULN in patients with liver metastases)
- ALT or AST > 3 × 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 two "requirements" for Hy's Law are: 1. Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher 3 times the ULN ("2 × ULN elevations are too common in treated and untreated patients to be discriminating"). 2. Cases of increased bilirubin (at least 2 × ULN) with concurrent transaminase elevations at least 3 × 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 Always Serious Events

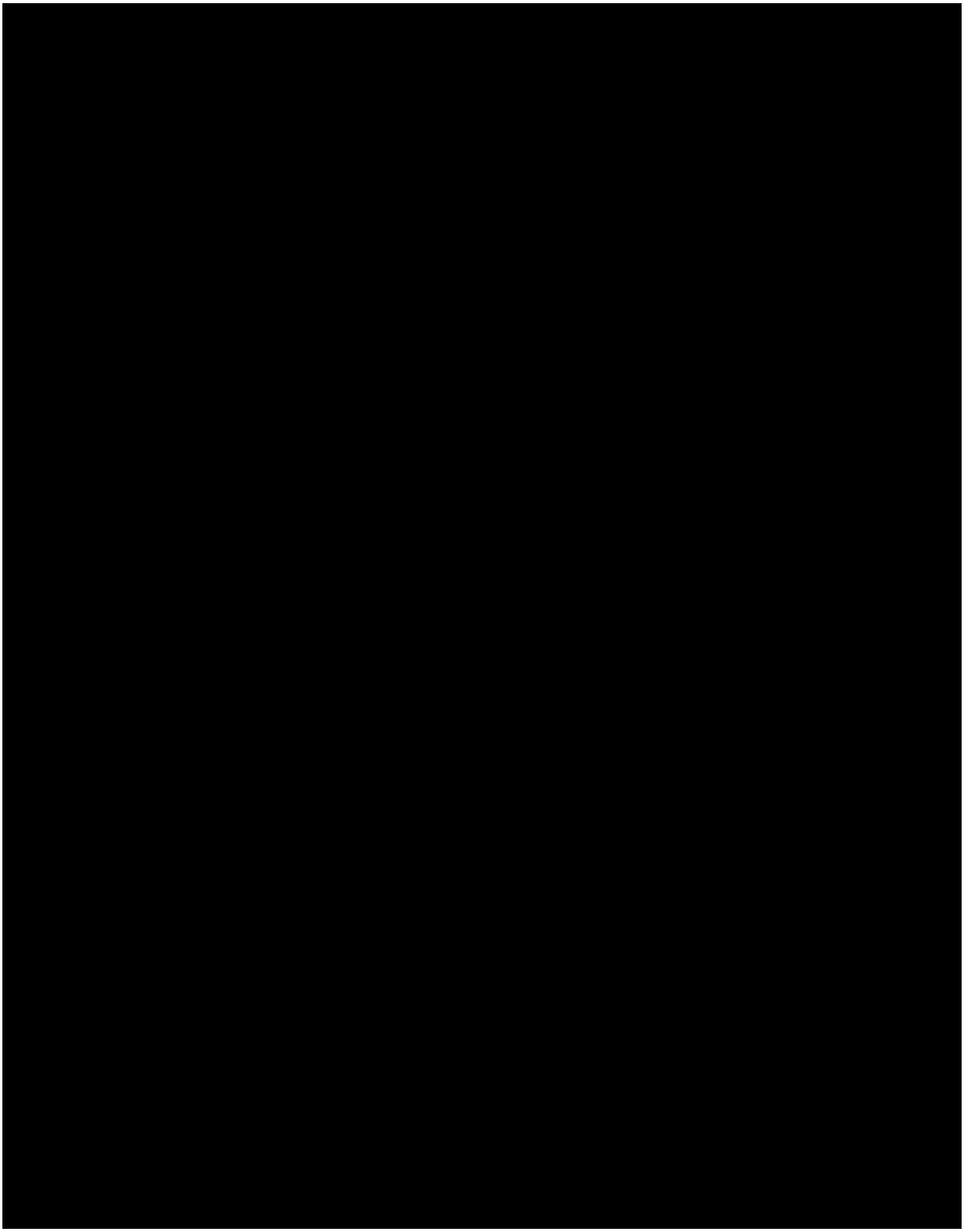
The following events must be reported as SAEs in accordance with Section 5.5.5 Reporting of Serious Adverse Events (SAEs).

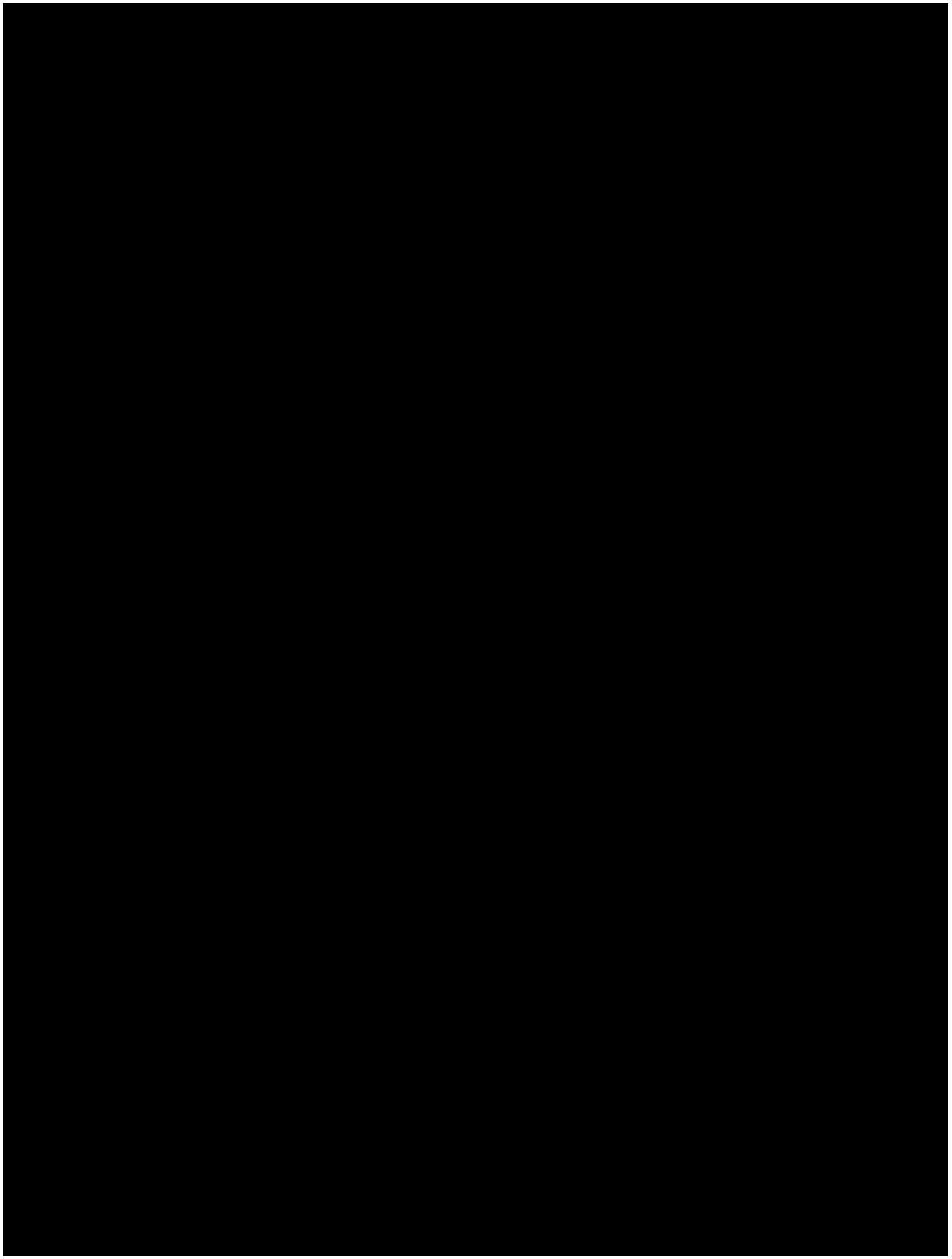
- Acute liver failure
- Acute renal failure
- Acute respiratory failure
- Agranulocytosis
- Anaphylaxis
- Any malignancy
- Aplastic anaemia
- Confirmed or suspected transmission of infectious agents by marketed product
- Congenital anomalies
- Hepatic necrosis
- Malignant hypertension
- Pulmonary hypertension
- Convulsion
- Torsades de pointe
- Toxic epidermal necrolysis
- Ventricular fibrillation
- Haemolytic anaemia
- Bone marrow failure
- Myocardial infarction
- Cardiac arrest
- Deafness
- Blindess
- Pancreatitis acute
- Acute graft versus host disease
- Septic shock
- Sepsis
- Rhabdomyolysis
- Respiratory failure
- Stevens-Johnson syndrome

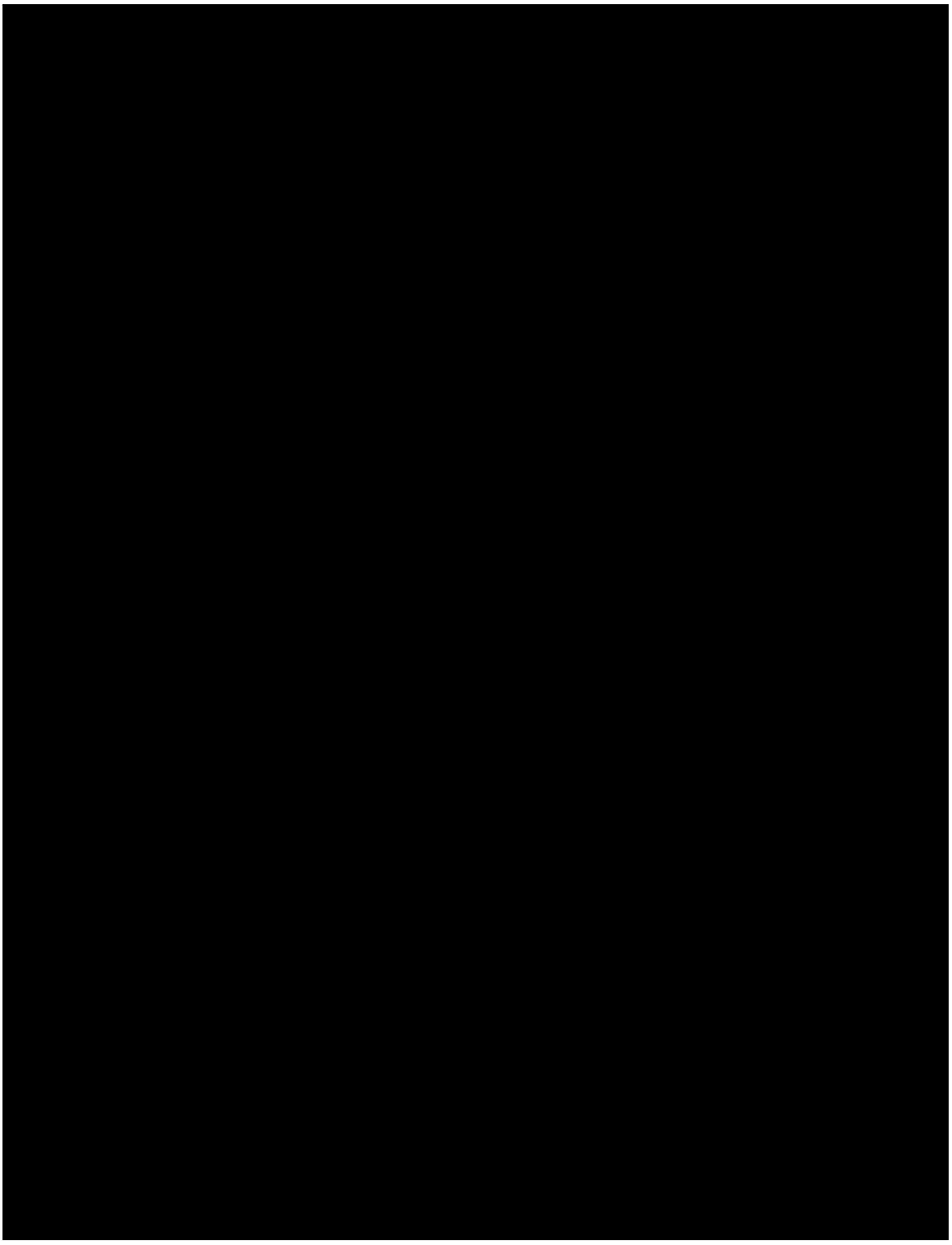
12.4 ECOG Performance Status

Performance Status Score

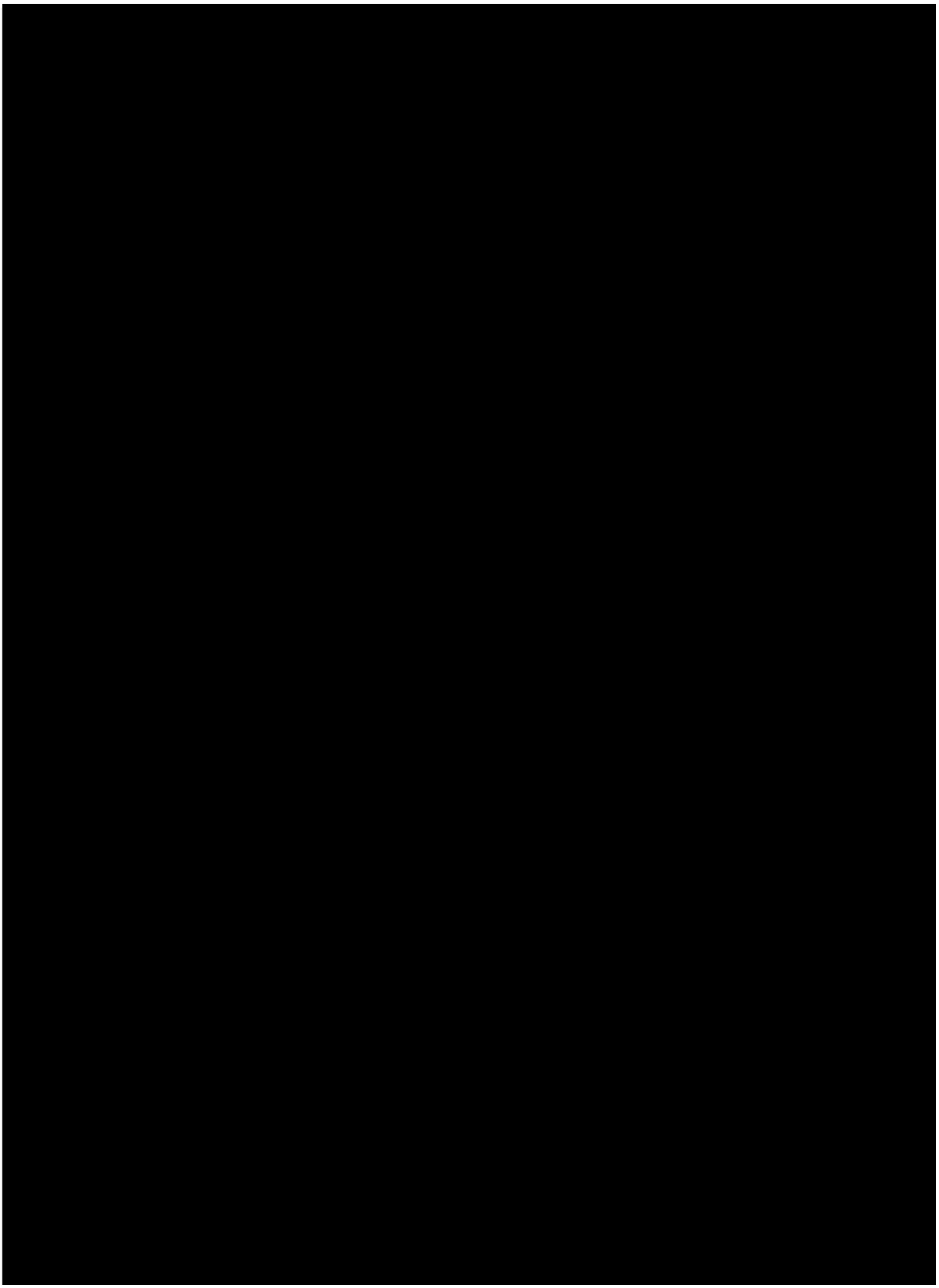
12.5 FACT–P

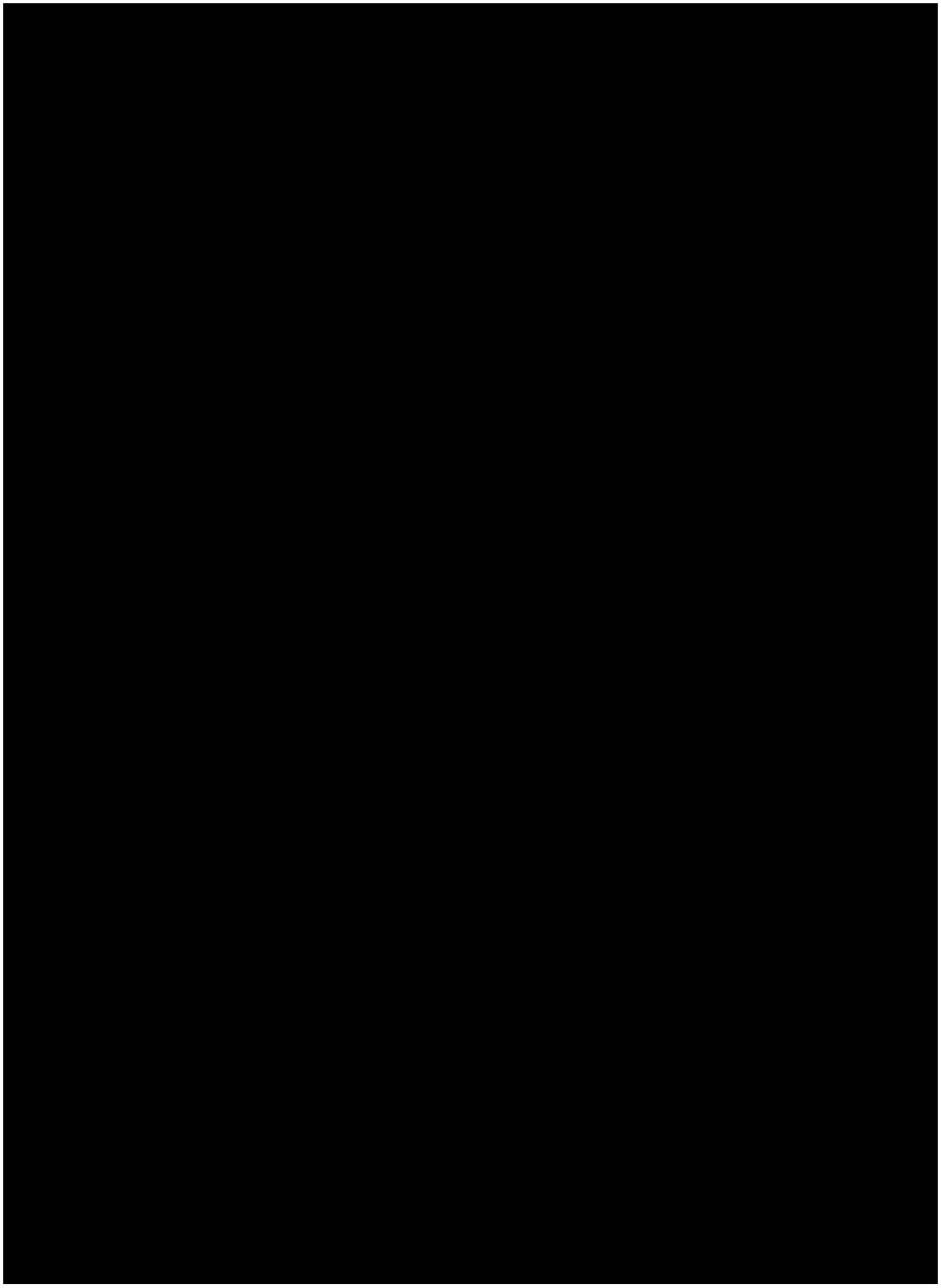




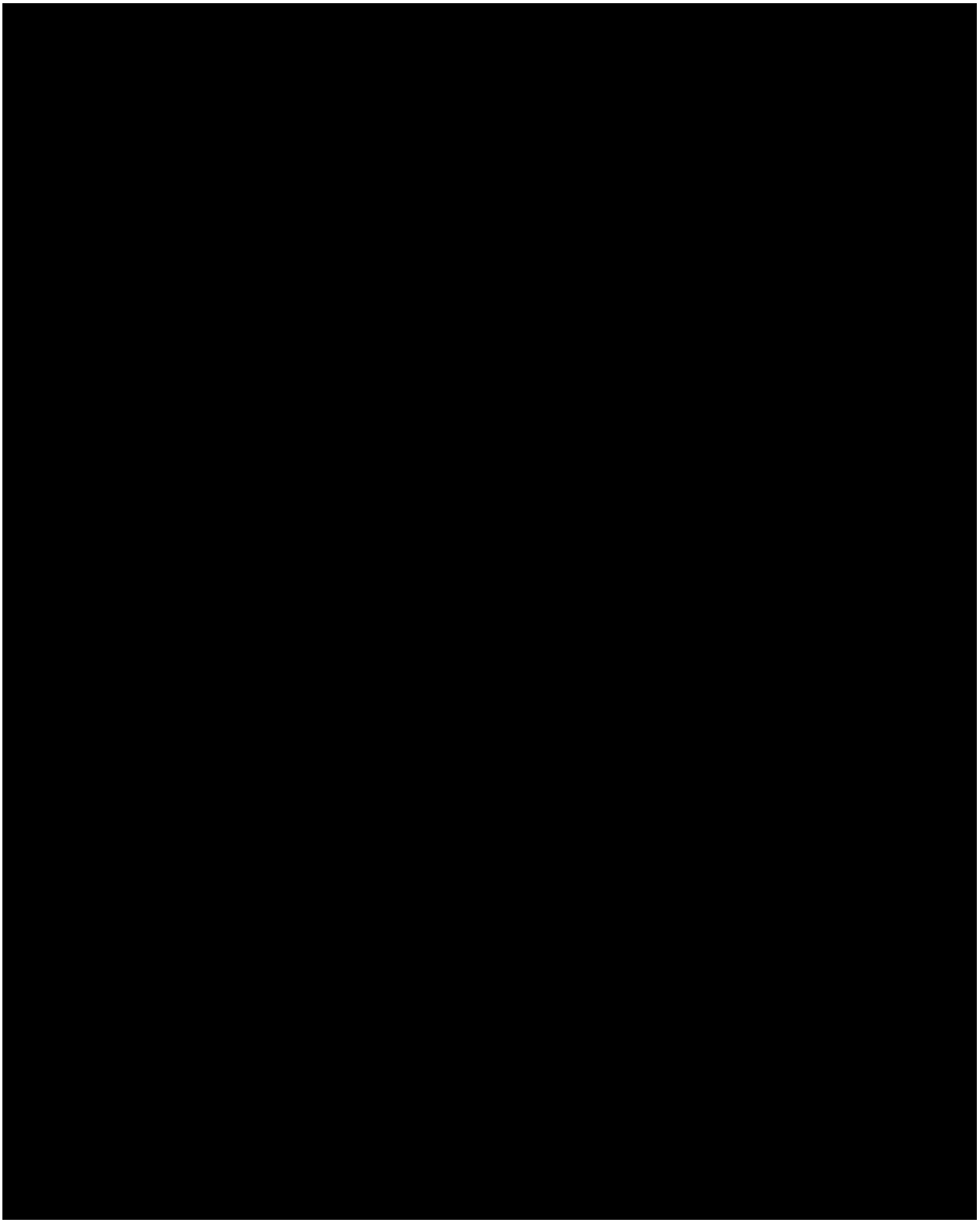


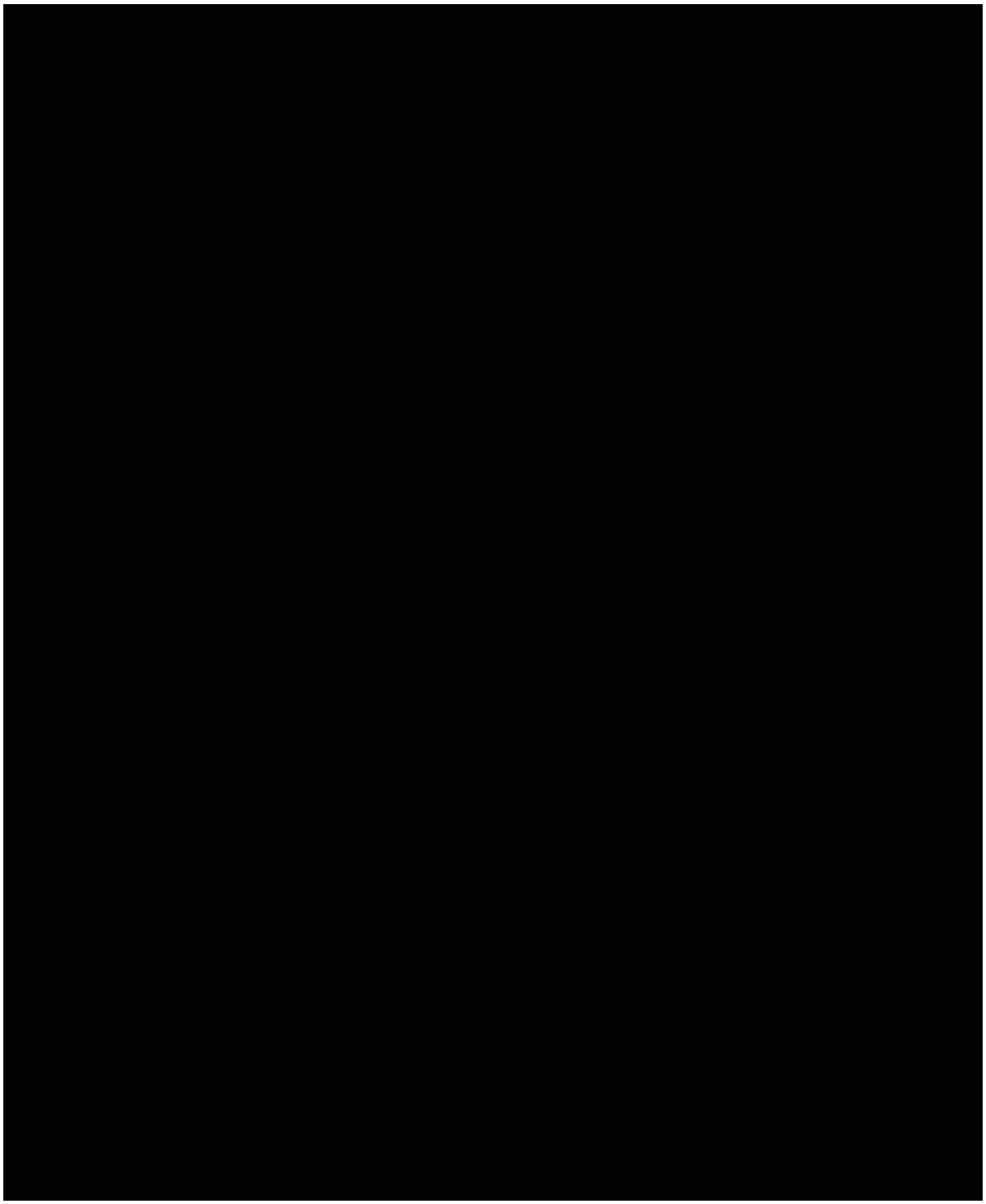
12.6 EQ-5D-5L



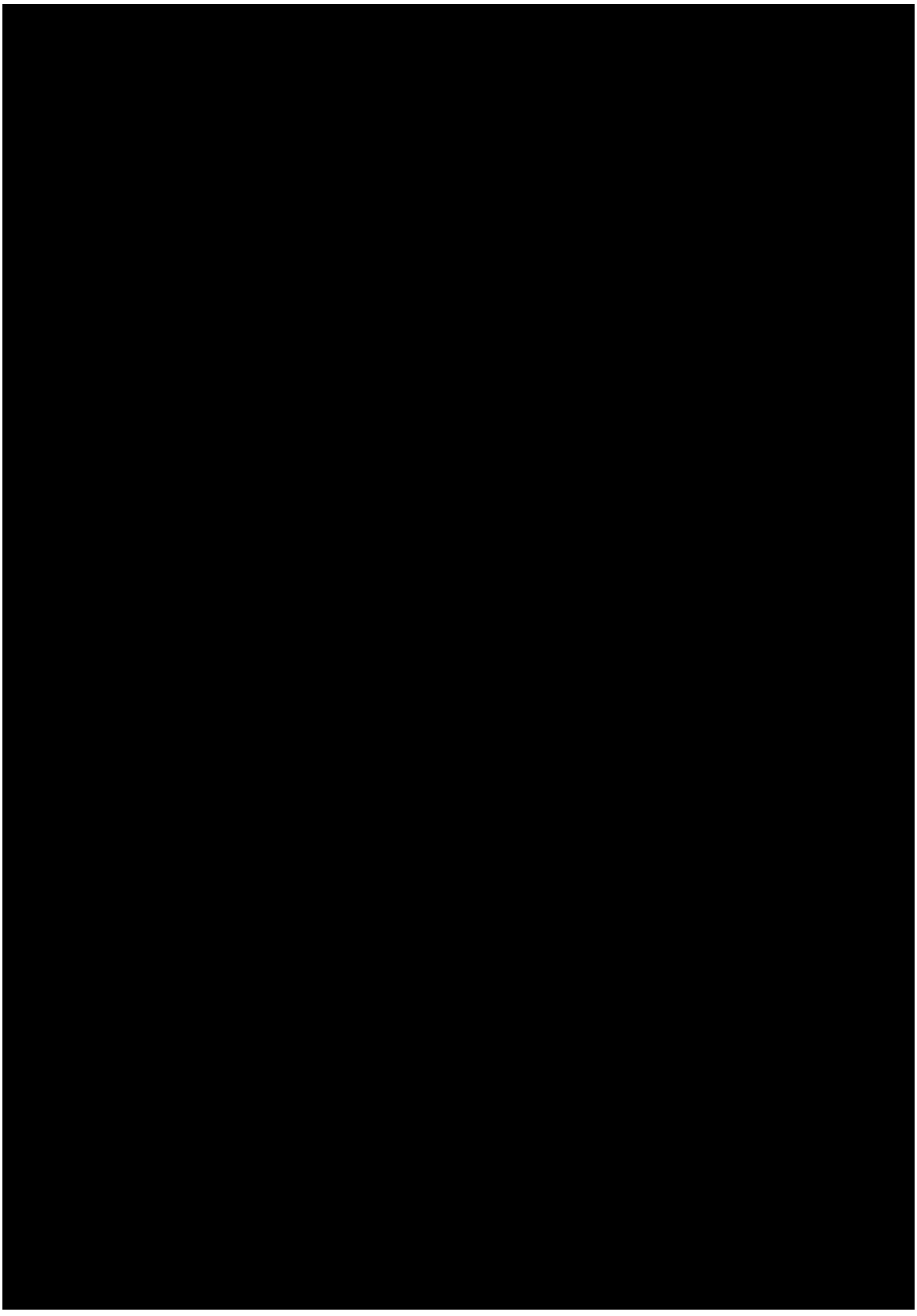


12.7 BPI-SF





12.8 BFI



(GPF 4.1J)