Supplementary Information

Lerociclib plus Fulvestrant in Patients with HR+/HER2- Locally Advanced or Metastatic Breast Cancer Who Have Progressed on Prior Endocrine Therapy: LEONARDA-1 A Phase III Randomized Trial

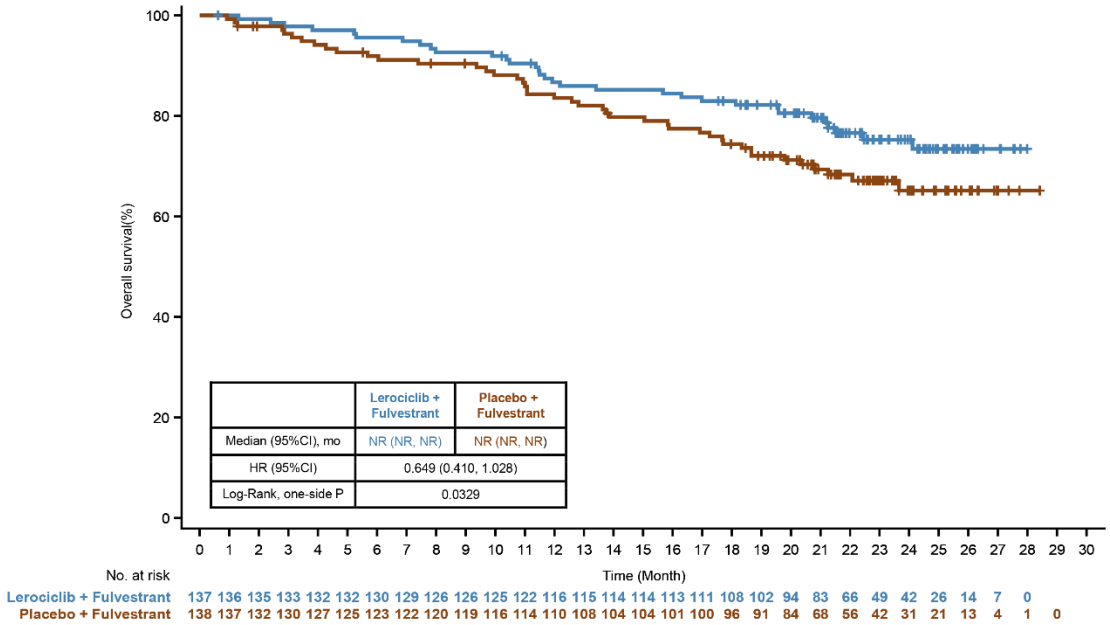
Table of content

Supplementary Table 1. Best overall response (BICR-assessed)

Best Overall Response*	Lerociclib+Fulvestrant n(%)	Placebo+Fulvestrant n(%)
ITT Population	N=137	N=138
CR	0	1 (0.7%)
PR	30 (21.9%)	13 (9.4%)
SD	87 (63.5%)	89 (64.5%)
SD≥6 months	37 (27.0%)	17 (12.3%)
PD	16 (11.7%)	30 (21.7%)
NE	2 (1.5%)	2 (1.4%)
NA	2 (1.5%)	3 (2.2%)
ORR(CR+PR)	30 (21.9%)	14 (10.1%)
95%CI	14.97%, 28.82%	5.11%, 15.18%
DCR(CR+PR+SD)	117 (85.4%)	103 (74.6%)
95%CI	79.49%, 91.31%	67.38%, 81.90%
CBR(CR+PR+SD≥6 months)	67 (48.9%)	31 (22.5%)
95%CI	40.53%, 57.28%	15.50%, 29.43%
Measurable disease at baseline	N=119	N=121
CR	0	1 (0.8%)
PR	30 (25.2%)	13 (10.7%)
SD	71 (59.7%)	74 (61.2%)
SD≥6 months	32 (26.9%)	15 (12.4%)
PD	15 (12.6%)	28 (23.1%)
NE	1 (0.8%)	2 (1.7%)
NA	2 (1.7%)	3 (2.5%)
ORR(CR+PR)	30 (25.2%)	14 (11.6%)
95%CI	17.41%, 33.01%	5.87%, 17.27%
CBR(CR+PR+SD≥6 months)	62 (52.1%)	29 (24.0%)
95%CI	43.13%, 61.08%	16.36%, 31.57%

Abbreviations: CBR, clinical benefit rate; CR, complete response; ITT, intent-to-treat; NA, not applicable; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease;

*Using RECIST version 1.1; CR/PR was estimated based on confirmed response.



Supplementary Fig. 1. Ad hoc Kaplan-Meier analyses of overall survival in the intent-to-treat population (DCO: March 30, 2024). Source data are provided as a Source Data file.

List of study sites

Study Center List	Priciple investigator
Cancer Hospital Chinese Academy of Medical Sciences	Binghe Xu
Harbin Medical University Cancer Hospital	Qingyuan Zhang
Cancer Hospital of China Medical University/Liaoning Cancer Hospital	Tao Sun
The First Hospital of Jilin University	Wei Li
First Affiliated Hospital of Nanjing Medical University	Yongmei Yin
Sun Yat-Sen University Cancer Center	Shusen Wang
Tianjin Medical University Cancer Institute and Hospital	Zhongsheng Tong
Affiliated Cancer Hospital of Chongqing University	Xiaohua Zeng
Beijing Chaoyang Hospital, Capital Medical University	Guangyu An
General Hospital of the People's Liberation Army (301 Hospital)	Weihong Zhao
Beijing Tiantan Hospital, Capital Medical University	Xiaoyan Li
Zhongshan Hospital Affiliated to Fudan University	Hongwei Zhang
Jilin Cancer Hospital	Ying Cheng
The Second Hospital of Jilin University	Jingwei Xu
West China Hospital, Sichuan University	Xi Yan
Cancer Hospital of the University of Chinese Academy of Sciences/Zhejiang Cancer Hospital	Xiaojia Wang
The Second Affiliated Hospital Zhejiang University School of Medicine	Fuming Qiu
Union Hospital, Tongji Medical College, Huazhong University of Science and Technology	Jing Cheng
Hubei Cancer Hospital	Xinhong Wu
Renmin Hospital of Wuhan University	Weiping Tao
Shandong Cancer Hospital	Lihua Song
The Affiliated Hospital of Jining Medical College, Jining	Changping Shan
Shandong Provincial Hospital	Weibo Wang
Jinan Central Hospital	Meili Sun
The Affiliated Hospital of Qingdao University	Wenfeng Li
Yantai Yuhuangding Hospital	Ping Sun
Shandong Qianfoshan Hospital	Jing Liang
Liaocheng People's Hospital	Yumin Yao
Tai'an Central Hospital	Zhaofeng Zhu
Guangdong Provincial Hospital of Traditional Chinese Medicine	Qianjun Chen
The First Affiliated Hospital of Sun Yat sen University	Ying Lin
The First People's Hospital of Foshan	Danmei Pang
Meizhou People's Hospital	Liang Li
Hainan Provincial People's Hospital	Haixia Wang
The Third People's Hospital of Hainan	Cuiying Wang

The First Hospital of Shanxi University	Hongyan Jia
The Second Hospital of Anhui Medical University	Zhendong Chen
Anhui Provincial Cancer Hospital	Changlu Hu
The First Affiliated Hospital of Bengbu Medical College	Yanjing Yao
The Affiliated Hospital of Hebei University	Aimin Zang
Henan Cancer Hospital	Hongqiang Guo
The First Affiliated Hospital of Zhengzhou University	Yuanting Gu
Jiangxi Provincial Cancer Hospital	Zhenggui Sun
The First Affiliated Hospital of Chongqing Medical University	Qiao Cheng
The Third Affiliated Hospital of Chongqing University (Chongqing Three Gorges Central Hospital)	Wenhua Liu
Fujian Medical University Union Hospital	Chunsen Xu
The First Affiliated Hospital of Xiamen University	Ru Zeng
General Hospital of Ningxia Medical University	Ranhua Cao
General Hospital of Ningxia Medical University	Xinlan Liu
Cancer Hospital of Xinjiang Medical University,	Bing Zhao
Yunnan Cancer Hospital (Third Affiliated Hospital of Kunming Medical University)	Jianyun Ni
Shengjing Hospital Affiliated to China Medical University	Caigang Liu

Supplementary Note 1 - Study protocol

The publicly posted protocol includes all the key sections that are relevant to evaluating the study, specifically those sections describing the study objectives and hypotheses, the patient inclusion and exclusion criteria, the study design and procedures, the efficacy and safety measures, and the statistical analysis plan.

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Clinical Trial of GB491 in Combination with Fulvestrant in Subjects with Hormone Receptor (HR) -positive, Human Epidermal Growth Factor Receptor 2 (HER2) -negative Locally Advanced or Metastatic Breast Cancer Who Have Progressed on Prior Endocrine Therapy

Phase of Trial:	Phase III
Protocol No.:	GB491-004
Protocol Version:	Version 6.0
Version Date:	Sept. 15, 2022

Study Site: Cancer Hospital, Chinese Academy of Medical Sciences

Principle Investigator: Binghe Xu

Sponsor: Genor Biopharma Co., Ltd.

contents

LIST OF TABLES

LIST OF FIGURES

1 Protocol Summary

Protocol No.	GB491-004
Protocol Name	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Clinical Trial of GB491 in Combination with Fulvestrant in Subjects with Hormone Receptor (HR) -positive, Human Epidermal Growth Factor Receptor 2 (HER2) -negative Locally Advanced or Metastatic Breast Cancer Who Have Progressed on Prior Endocrine Therapy
Version No./Date	V6.0, Sept. 15, 2022
Sponsor	Genor Biopharma Co., Ltd.
Clinical Trial Phase	Phase III
Proposed Indication	It is indicated to be used in combination with fulvestrant for the treatment of hormone receptor (HR) -positive and human epidermal growth factor receptor 2 (HER2) -negative (HR+/HER2-) locally advanced or metastatic breast cancer that has progressed following prior endocrine therapy
Objectives of the Trial	<u>Primary objective</u> To evaluate the progression-free survival (PFS, as assessed by the Investigator) of GB491 plus fulvestrant versus placebo plus fulvestrant in HR+/HER2- locally advanced or metastatic breast cancer with progressive disease following prior endocrine therapy. <u>Secondary objectives</u> To evaluate the progression-free survival (PFS, as assessed by the BICR); overall survival (OS); objective response rate (ORR), duration of response (DOR), disease control rate (DCR), clinical benefit rate (CBR); safety and tolerability; and pharmacokinetic (PK) profile of combination therapy.

Study Endpoints	<u>Primary endpoint</u> • PFS assessed by the Investigator based on RECIST v1.1. <u>Secondary endpoints</u> • PFS as assessed by the BICR based on RECIST v1.1. • Overall survival; • ORR, DOR, DCR, CBR based on RECIST v1.1; • Incidence of AEs/SAEs evaluated according to NCI-CTCAE version 5.0 criteria; laboratory abnormalities; changes in laboratory assessments, electrocardiograms, physical examinations; • PK parameters assessed by population pharmacokinetic analysis based on plasma concentrations of GB491 and its metabolite G1T30.
Study Design	This study is a multicenter, randomized double-blind, placebo-controlled, phase III clinical trial of GB491 plus fulvestrant versus placebo plus fulvestrant in patients with HR+/HER2- locally advanced or metastatic breast cancer who have progressed on prior endocrine therapy. Approximately 270 patients who met the eligibilty criteria were planned to be enrolled into the study. Patients will undergo a screening period of up to 28 days. Patients who met the eligibility criteria were assigned in a 1:1 ratio to GB491 plus fulvestrant or placebo plus fulvestrant based on a web interactive response system (IWRS). And the nature of disease (visceral metastasis vs bone only metastasis vs others), different menopausal status (male or premenopausal or perimenopausal vs postmenopausal), and number of prior lines of endocrine therapy failure (first-line vs second-line) were used as randomization stratification factors. Patients who were randomized received GB491 150 mg or placebo orally twice daily (taken with food, approximately 12 hours apart is

	recommended) according to different assigned groups. Fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1 (every 28-day a cycle) and 500 mg intramuscularly on Day 1 of each subsequent cycle. For premenopausal and perimenopausal female patients and male patients (unless there is a clear history of bilateral orchiectomy) requiring the use of LHRH analogues (e.g., goserelin), patients must start treatment with LHRH analogues (e.g., goserelin) at least 21 days before randomization, followed by subcutaneous injection of goserelin extended-release implants 3.6 mg every 28 days (or following other LRHR analogue treatment specifications). Patients will receive GB491 in combination with fulvestrant or placebo in combination with fulvestrant until disease progression, intolerable toxicity, criteria for discontinuation are met, withdrawal of consent or is lost to follow-up, or the sponsor terminates the trial. Each patient will be followed for 28 days as a treatment cycle after the start of trial treatment for efficacy assessments according to RECIST v1.1 criteria and safety assessments according to CTCAE v5.0. Pharmacokinetic (PK) sampling and population pharmacokinetic analysis will be performed from Cycle 1 to Cycle 4 of the study. This study includes screening period, treatment period and follow-up period (including efficacy follow-up, safety follow-up and survival follow-up). Following completion of the study screening, follow-up will occur on Cycle 1 Days 1 and 15 (C1D1 and C1D15). Follow-up will be performed on Day 1 (CnD1) of each subsequent cycle (28-day/cycle) and study procedures are detailed in **Appendix 3**. <u>Efficacy evaluation</u> All patients will undergo baseline tumor assessments within 28 days prior to randomization, including: • CT/MRI scans of chest, abdomen, pelvis and other sites of tumor involvement • For patients with inoperable locally advanced breast cancer, breast MRI scans will be performed at baseline (if applicable)

	• Radionuclide bone scan, lesions identified on bone scan must be confirmed by CT (bone window) or MRI Tumor assessments during the treatment period must consistently use the same assessment methods and techniques used at baseline, including all sites of disease (including but not limited to the chest, abdomen, and pelvis), and the cycle of tumor assessments must be fixed (fixed cycles set based on the date of randomization). All patients will undergo CT/MRI evaluation every 8 weeks (±7 days) during Year 1, every 12 weeks (±7 days) after Year 1, and bone scan every 24 weeks (±7 days) until disease progression. For patients who discontinue treatment prior to confirmed disease progression, CT/MRI imaging assessments should be performed according to the previous visit assessment schedule until: 1) objective disease progression; 2) death; 3) withdrawal of consent or loss to follow-up; 4) receiving new antineoplastic therapy; 5) end of study. Imaging assessments must be performed within 2 weeks if clinical progression is suspected. Patients with confirmed CR will undergo bone scan to confirm absence of bone metastases. At the investigator's discretion, additional bone scans may be performed and lesions confirmed by CT (bone window) or MRI if the patient has clinical symptoms and signs of worsening bone metastases. Note: Enhanced CT should be the first choice for imaging assessment. For patients with known hypersensitivity to CT contrast agents, plain chest CT + abdominal/pelvic contrast-enhanced MRI assessment is optional. <u>Safety evaluation</u> Safety evaluations include monitoring of adverse events, vital signs, physical examinations, electrocardiograms (ECGs), and clinical laboratory tests. All adverse events are collected from the time of the first dose of the blinded study drug through 30 days after the last dose of the blinded study drug (or until receiving subsequent new anticancer therapy). Only serious adverse events (SAEs) related to the study drug are collected beyond 30 days after the last dose of the blinded study drug until receiving subsequent new antineoplastic therapy or the end of the study. At the same time, only serious adverse events resulting

	from protocol-specified procedures (e.g., serious adverse events related to invasive procedures [e.g., biopsies]) are collected from the time of informed consent through the first dose. Pharmacokinetic evaluation Venous blood samples are collected at the visits indicated in the pharmacokinetic sampling schedule to determine plasma concentrations of GB491 and its metabolite G1T30 as detailed in **Appendix 3**
Total Number of Subjects	Approximately 270 subjects
Investigational Site	40-60 sites
Duration of Study	Estimated ~ 22 months
Inclusion/Exclusion Criteria	**Inclusion criteria:** Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study: 1. Female or male, 18 years of age or older and under 75 years of age at study screening; 2. Histologically or cytologically confirmed locally advanced or metastatic breast cancer that is not amenable to surgical resection or radiation therapy with curative intent; 3. Patients had a confirmed diagnosis of ER-positive breast cancer by local laboratory testing (based on the most recent tumor sample prior to randomization). ER positivity is defined as ≥ 10% staining positive cells regardless of PgR status. Refer to ASCO/CAP Version 2020 ER/PgR Testing Guidelines (Allison et al. 2020) for test methods and result determination;

	4. Patient who were diagnosed with HER2-negative breast cancer based on the most recent tumor sample prior to randomization by local laboratory testing. HER2 negativity is defined as having an IHC score of 0 or 1 +, or negative in situ hybridization. Testing methods and interpretation are described in the ASCO/CAP 2018 HER2 Testing Guidelines (Wolff et al. 2018); 5. Patients with any menopausal status (including premenopausal, perimenopausal, postmenopausal) Premenopausal and perimenopausal patients taking LHRH analogues such as goserelin who started treatment with LHRH analogues ≥ 21 days prior to randomization and who were willing to continue their use during the study were permitted; Note: Male patients who are willing to undergo treatment with an LHRH analogue such as goserelin (unless there is a clear history of bilateral orchiectomy) during the study may also be enrolled; Postmenopausal status is defined as meeting at least 1 of the following conditions: • Patients aged ≥ 60 years at screening for this study; • Patients < 60 years of age at screening for this study. Concurrently, amenorrhea for more than 1 year in the absence of other pathological or physiological causes (e.g., no chemotherapy, tamoxifen, toremifene, or ovarian suppression); and serum estradiol and FSH levels within the laboratory reference range for postmenopausal women; • Patients < 60 years of age who were taking tamoxifen or toremifene before enter screening for this study, with FSH and E2 levels in the postmenopausal range; • Bilateral oophorectomy has been performed; 6. Prior endocrine therapy and chemotherapy, the following are permitted: a) Prior endocrine adjuvant therapy:

	• Radiologic evidence of progressive disease (PD) during or within 12 months following (neo)adjuvant therapy with an aromatase inhibitor (AI) or an anti-estrogen such as tamoxifen, and no subsequent endocrine therapy for locally advanced or metastatic breast cancer; • Radiologic evidence of progressive disease (PD) during or within 12 months following (neo)adjuvant therapy with an aromatase inhibitor (AI) or an anti-estrogen such as tamoxifen, after receiving the first-line endocrine therapy for locally advanced or metastatic breast cancer, and who developed radiologically documented PD after receiving therapy for ≥ 6 months; • Radiologically documented progressive disease (PD) more than 12 months following the end of adjuvant therapy with aromatase inhibitors (AIs) or anti-estrogens such as tamoxifen, followed by radiographic progression following first-line therapy with aromatase inhibitors (AIs) or anti-estrogens for locally advanced or metastatic breast cancer; b) Progression with radiographic evidence of disease following prior first-line endocrine therapy for locally advanced or metastatic breast cancer in subjects who have not received prior (neo) adjuvant therapy; c) Prior chemotherapy: In addition to endocrine therapy, subjects are eligible if they received a maximum of 1 prior line of chemotherapy for locally advanced or metastatic breast cancer and discontinued treatment for at least 28 days prior to randomization; 7. Patients must meet one of the following conditions: • Measurable lesions, e.g., patients with at least one measurable lesion according to RECIST v1.1 criteria; • If there is no measurable lesion, at least one osteolytic lesion is predominant (if the patient has no measurable lesion and

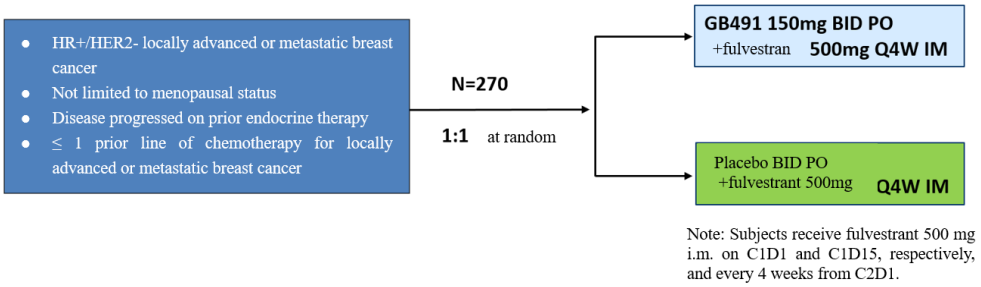
	only one irradiated osteolytic lesion is predominant, the patient can be enrolled if there is documented disease progression after radiotherapy); 8. ECOG performance status of 0 or 1; 9. The following laboratory parameters must be met to ensure that the patient has adequate bone marrow function prior to dosing (no blood transfusion, no component transfusion, no infusion of growth factors, etc. within 2 weeks before randomization): • Hemoglobin ≥ 90 g/L; • Absolute neutrophil count ≥ 1.5 × 10^9/L; • Platelet count ≥ 100 × 10^9/L; • Creatinine clearance or estimated glomerular filtration rate (GFR) > 50 ml/min (Cockcroft-Gault equation or ^{51} CR-EDTA); • Total bilirubin ≤ 1.5 × ULN; in case of Gilbert's disease, total bilirubin ≤ 3 × ULN is allowed; • Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤ 3× ULN; if liver metastasis is present, AST and/or ALT ≤ 5 × ULN may be accepted; • Alkaline phosphatase (ALP) ≤ 2.5 × ULN, ALP ≤ 5 × ULN if bone metastasis or liver metastasis is present; 10. Female patients of childbearing potential must have a serum pregnancy test (β-hCG) within 7 days prior to randomization and be non-pregnant and willing to use at least one medically recognized highly effective contraception (e.g., intrauterine device, contraceptive, or condom) during the study and for 6 months after the last dose of the study drug; female partners (partners) of male patients should use at least one medically recognized highly effective contraception (e.g., condom) during the study and for 6 months after the last dose of the study drug if there is potential for conception. Male patients should also refrain

	from participating in sperm donation during the study and for 6 months following the last dose of the study drug. 11. The patients agree and have signed an informed consent form and are willing and able to comply with scheduled visits, study treatment plan, laboratory tests, and other trial procedures. **Exclusion criteria:** 1. Subjects will not be eligible to participate in this study if they meet any of the following criteria Prior systemic therapy with fulvestrant, everolimus, or any other CDK4/CDK6 inhibitors; 2. Subjects with known hypersensitivity to GB491 or any component of fulvestrant; 3. Known active, uncontrolled, or symptomatic CNS metastases, meningeal metastases, clinical symptoms suggestive of leptomeningeal disease, cerebral edema, spinal cord compression, and/or progressive tumor growth. Patients with a history of central nervous system metastases, meningeal metastases, spinal cord compression, etc. could be enrolled if they were clearly treated and had stable clinical manifestations. Patients are eligible if they were treated with anticonvulsants and steroids for at least 2 months prior to randomization and were clinically stable; 4. Visceral crisis. Visceral crisis refers to multiple organ dysfunction confirmed by symptoms, signs, laboratory tests, rapid disease progression. Visceral crisis does not simply refer to the presence of visceral metastasis, but refers to critical visceral conditions requiring rapid and effective treatment to control disease progression (including uncontrollable pleural effusion, pericardial effusion, abdominal effusion, pulmonary lymphangitis carcinomatosa, diffuse liver metastasis, bone marrow metastasis, etc.), especially refers to conditions that fail to respond to other treatments after progression;

	5. Patients with skin lesions only at baseline and non-measurable imaging; 6. Patients with persistent unresolved toxicity of CTCAE > grade 2 caused by previous anti-tumor treatment; patients with irreversible toxicity (such as hearing loss) caused by previous treatment who are judged by the investigator and the sponsor not to be further aggravated by this study intervention can be enrolled; 7. Major surgery (or anticipated need for major surgery during the study), chemotherapy, radiotherapy, any investigational agent, or other anticancer therapy within 4 weeks prior to randomization; 8. Patients receiving bisphosphonates or denosumab at a stable dose for < 7 days prior to randomization; 9. Patients who received palliative radiotherapy to limited areas within 2 weeks prior to randomization, extensive palliative radiotherapy to extensive areas or radiotherapy to ≥ 30% of bone marrow areas within 4 weeks prior to randomization; 10. Taking drugs or fruits containing potent inducers or inhibitors of CYP3A4/5 or drugs with narrow therapeutic window mainly metabolized by CYP3A4/5 such as astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, pimozide, quinidine, tacrolimus and sirolimus within 2 weeks before randomization; 11. Patients receiving long-term systemic corticosteroids (excluding topical, inhaled sprays, eye drops or topical injections for the treatment of allergies or prevention of asthma relapse, and patients receiving hormone replacement therapy); 12. Any severe and/or uncontrolled medical condition such as: unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction within 6 months prior to randomization, severe uncontrolled arrhythmia; active or uncontrolled serious

	infection; history of stroke or cerebrovascular accident, pulmonary embolism or deep venous thrombosis within 6 months prior to randomization; active upper gastrointestinal ulcer; 13. Patients had significant lung function impairment (i.e., lung function showed FEV1 and DLCO < 60% of predicted value). History of pneumonitis, drug-induced interstitial lung disease, radiation pneumonitis, or any evidence of clinically active interstitial lung disease; 14. Known history of HIV infection or history of HIV seropositivity (including positive HIV antibody at screening); 15. Prolonged QTc interval on screening ECG (Fridericia method > 480 msec) or documented history of prolonged QT interval; 16. Patient has severe liver disease such as cirrhosis, decompensated liver disease, acute or active hepatitis. Patients may be enrolled if serum HBsAg is positive or HCV-Ab is positive, but the corresponding serum HBV-DNA or serum HCV-RNA is below the lower limit of quantification of the local assay; 17. Abnormal coagulation profile, such as active bleeding, bleeding diatheses, or ongoing anticoagulant therapy (enrollment permitted if INR ≤ 2 for patients taking low-dose warfarin, LMWH (low molecular weight heparin), and aspirin or equivalents); 18. Patients unable to swallow the study drug, intractable nausea, vomiting, other diseases or clinical conditions that may significantly affect the absorption, distribution, metabolism and excretion of the study drug as judged by the investigator; 19. Previous autologous or allogeneic stem cell transplantation; 20. Inflammatory breast cancer; 21. Subjects with a history of other primary malignancies, except for subjects with non-melanoma skin cancer and cervical carcinoma in situ who have been disease-free for ≥ 3 years;

	22. Breastfeeding women (such subjects may be enrolled in the study if breastfeeding is interrupted due to disease treatment); 23. Subjects with poor compliance in previous studies or judged as having poor compliance by the investigator. Subjects unwilling or unable to comply with the study protocol; 24. Subjects who are judged by the investigator to have participation in the trial that increases the safety risk or impacts the interpretation of the study results.
Investigational Drug	GB491: 150 mg orally twice daily (taken with food, approximately 12 hours apart is recommended).
Other Drugs	Fulvestrant: 500 mg intramuscularly (on Days 1 and 15 of Cycle 1, Day 1 of Cycle 2, and every 4 weeks thereafter); Goserelin and other LHRH analogues: For premenopausal and perimenopausal female patients, as well as male patients (unless there is a clear history of bilateral orchiectomy), LHRH analogues (e.g. goserelin) 3.6 mg subcutaneously every 28 days are required. Goserelin analogues are also permitted and used according to the NMPA approved Package Insert.
Control Drug and the Use	Placebo: taken orally twice daily (with food, recommended approximately 12 hours apart).
Antitumor Efficacy Evaluation	Investigator assessed PFS, BICR assessed PFS; OS; ORR, DOR, DCR, CBR.
Safety Evaluation	Safety will be evaluated according to CTCAE Version 5.0 and will include monitoring of adverse events, vital signs, physical examinations, electrocardiograms (ECGs), and clinical laboratory tests.
Pharmacokinetic	Blood sampling point design:

(PK) Evaluation	See **Appendix 3** Pharmacokinetic Blood Sampling Schedule Pharmacokinetic parameters Observed plasma concentrations of GB491 and its metabolite G1T30 are included in the population pharmacokinetic analysis, including evaluation of plasma PK parameters.
Procedures of the Trial	 Note: Subjects receive fulvestrant 500 mg i.m. on C1D1 and C1D15, respectively, and every 4 weeks from C2D1.
Statistical Analysis	**Sample size calculation** A total of 270 subjects are planned for enrollment, with 135 in each of the treatment group and the control group. Assuming a median PFS of 9 months in the control group, a hazard ratio (HR) of 0.55 for the treatment group relative to the control group, an enrollment period of 12 months and an overall dropout rate of 25%, this sample size will provide an overall power of 90% at one-sided α level of 0.025 with a total of approximately 119 PFS events. **Analysis nodes** Primary analysis nodes: Data cleaning and locking are performed when the number of events preset in the protocol (approximately 119) is all reached, and then the corresponding analysis is performed. Overall study analysis nodes: Data cleaning and locking and corresponding analysis are performed after the end of the study. **Analysis Set** • Full Analysis Set (FAS): includes all randomized subjects who receive at least one dose of the study drug. Analyses based on the FAS will be performed according to the treatment group to

	which the subject was randomized. • Per Protocol Set (PPS): A subset of the FAS excluding subjects whose efficacy was severely affected in the FAS. For example, some subjects seriously violating the trial protocol, subjects not achieving the minimum exposure dose, and subjects without data after randomization. Grouping was based on the first actual treatment received at the time of the PPS analysis. PPS needs to be determined prior to unblinding of the locked database. • Safety Analysis Set (SAS): includes all randomized subjects who receive at least one dose of the investigational drug. Grouping according to the first actual treatment received will be performed based on SAS analysis. • Pharmacokinetics consentration set (PKCS): includes all subjects who take the study drug at least once and have one valid plasma concentration measurement. **Analytical procedure** Unless otherwise specified, the following descriptive statistics are used for summaries by treatment group. For continuous endpoints, the number of non-missing observations, mean, standard deviation, median, minimum, and maximum will be summarized. The number of decimal places for the minimum and maximum values will be consistent with the raw data recorded in the database. Means and medians will be presented to one more decimal place than the raw data recorded in the database, and standard deviations will be presented to two more decimal places than the raw data recorded in the database, but no more than four decimal places. For categorical endpoints, frequency and percentage will be summarized and presented for each category. Unless otherwise specified, percentages will be calculated based on all subjects in the respective analysis population. Percentages will be presented to one decimal place. Percentages of 100% will be reported as 100% and frequencies of 0 will not be

	reported as percentages. For time-to-event endpoints, the Kaplan-Meier method will be used to estimate the survival function and estimate the median survival time and its 95% confidence interval, and survival curves will be plotted. <u>Efficacy analysis</u> Efficacy analyses will be based on the Full Analysis Set (FAS). The primary endpoint of this study is investigator-assessed PFS, defined as the time from randomization to disease progression or death for any cause, whichever comes first. Disease progression will be evaluated according to RECIST 1.1. The null hypothesis of this study is that PFS in the treatment group is not superior to that in the control group and the alternative hypothesis is that PFS in the treatment group is superior to that in the control group. $H_0: S_t(t) \leq S_c(t)$ vs. $H_a: S_t(t) > S_c(t)$; Where the survival probability $S(t) = P(T>t)$ refers to the probability that the time T of the event of interest is not less than the given time t. $S_t(t)$ represents the survival probability of subjects below the investigational product group and $S_c(t)$ represents the survival probability of subjects below the comparator group. When approximately 119 PFS events occur between the treatment group and the control group, a superiority test will be performed, and if the one-sided p-value is less than 0.025, the PFS of the treatment group will be considered superior to that of the control group, and the study meets the primary endpoint. Comparisons between groups are performed using stratified log rank tests with randomization stratification factors as stratification variables. Cox proportional hazards models including treatment group and randomization stratification factors are used to estimate the hazard ratio (HR) of PFS and its 95% confidence interval between the treatment and control groups. These analyses are repeated on the per protocol set (PPS).

	Time-event secondary endpoints, including OS, PFS as assessed by BICR, DOR, will be analyzed in the same manner as the primary analysis. For each type of the secondary endpoints (ORR, DCR, and CBR), two-sided 95% confidence intervals are estimated for each group using a normal approximation, and differences between groups and their 95% confidence intervals are estimated using a normal approximation. <u>Safety analysis</u> Safety analyses will be based on the Safety Analysis Set (SAS). All AEs are listed by subject. The number and percentage of subjects with treatment-emergent adverse events (TEAEs) and treatment-emergent drug-related adverse events (TRAEs) will be calculated by system organ class, preferred term, and group. SAEs including deaths and TEAEs leading to study discontinuation are summarized. Laboratory tests, vital signs, physical examinations, 12-lead ECG tests, and changes from baseline (if applicable) are analyzed descriptively by treatment group. Other safety measures will be described in a similar manner and listed by subject. <u>Pharmacokinetic (PK) analysis</u> Plasma concentrations are analyzed based on the PK concentration set. Each plasma concentration of GB491 and its metabolite G1T30 was tabulated and summarized. Additional summaries and analyses of the concentration data may be performed if the interpretation of the data is appropriate and useful. Population pharmacokinetic analyses were performed using actual sampling times relative to dosing times. Nonlinear mixed effects modeling was used to construct the pharmacokinetic model.
Blinded	A BICR will be established for this study to centrally review the imaging

Independent Central Review (BICR)	data of the enrolled subjects as an independent third party. BICR will review the study data prior to the pre-specified efficacy analysis and details of its membership and process will be provided in the BICR charter.
Independent Data Monitoring Committee (IDMC)	An Independent Data Monitoring Committee (IDMC) will be established for this study and the IDMC will conduct periodic or ad hoc risk-benefit assessments to advise the sponsor in an unblinded fashion using efficacy and safety data collected during the course of the clinical trial in accordance with a pre-specified protocol. Details of IDMC responsibilities and meetings are provided in the IDMC charter.

2 Abbreviations and Definitions of Terms

List of Abbreviations and Terms

AE	Adverse event
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Glutamic oxaloacetic transaminase
AUC_{0-inf}	Area under the plasma concentration-time curve from time 0 to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time 0 to time t
BCRP	Breast cancer resistance protein
β-HCG	β-human chorionic gonadotropin
BICR	Blinded Independent Central Review
BIL	Urine bilirubin
BLD	Urine red blood cell
BMI	Body mass index
BOR	Best overall response rate
BUN	Urea nitrogen
CTCAE	Common Terminology Criteria for Adverse Events
CBC	Complete blood count
CBR	Clinical benefit rate
CDK4/6	Cyclin-dependent kinase 4/6
CFDA	China Food and Drug Administration
CHO	Chinese hamster ovary
CI	Confidence interval
CK	Creatine kinase
Cl	Chloride ion
CL	Denotes apparent clearance as the product of Vd and Ke
CL/F	Apparent oral clearance
C_{max}	Maximum observed plasma concentration after dosing
CNS	Central nervous system
CRP	C-reactive protein
Cr	Creatinine
CR	Complete response rate
CRF	Case Report Form
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	Cytochrome P450 enzymes
DBIL	Direct bilirubin
DDI	Drug-drug interactions
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
EC/IRB	Ethics Committee

ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECRF	Electronic Case Report Form
ER	Estrogen receptor
ESR	Erythrocyte sedimentation rate
FAS	Full analysis set
FDA	Food and Drug Administration
FDG-PET	Fluorine-2-deoxy-D-glucose positron emission tomography
FSH	Follicle-stimulating hormone
G1	G1 phase of cell cycle
GCP	Good Clinical Practice
GEMM	Genetically engineered mouse model
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl Enzyme
GI	Gastrointestinal tract
GLB	Globulin
GLP	Good Laboratory Practice
GLU	Urine glucose
GnRH	Gonadotropin-releasing hormone
HACA	Human anti-chimeric antibody
Hb	Hemoglobin
HCV-Ab	Hepatitis C virus antibody
HBsAg	Hepatitis B surface antigen
HER2	Human epidermal growth factor 2
HR	Hormone receptor
HIV	Human immunodeficiency virus antibody
IB	Investigator’s Brochure
IC50	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational product
IV	Intravenous use
IWRS	Web-based Interactive Response System
K	Potassium ion
Ke	Elimination rate constant
KET	Urine ketone body
Lck	Lymphocyte-specific protein tyrosine kinase
LD	Long diameter
LDH	Lactate dehydrogenase
LHRH	Luteinizing hormone-releasing hormone
LEU	Urine leukocyte
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Adjusted intention-to-treat analysis
MTD	Maximum tolerated dose

Na	Sodium ion
NCI	National Cancer Institute
NE	Not evaluated
NIT	Urine nitrite
NMPA	National Medical Products Administration
NOAEL	No observed adverse effect level
ORR	Objective response rate
PD	Disease progression
PET	Positron emission tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
PH	PH value
PI3K	Phosphatidylinositol Kinase
PK	Pharmacokinetics
PLT	Platelets
PP	Per-Protocol Set
PR	Partial response
PRO	Subject Reported Outcomes
RA	Rheumatoid arthritis
Rb	Retinoblastoma tumor suppressor protein
RBC	Red blood cell
RECIST	Response Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
S	Synthetic phase of DNA replication cell cycle
SAE	Serious adverse event
SAS	Statistical analysis software
SAP	Statistical analysis plan
SD	Stable disease
SG	Urine specific gravity
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
$t_{l/2}$	Time required for plasma drug concentration to decrease by half after drug disposition has reached equilibrium in the body
TBIL	Total bilirubin
TEAE	Treatment-emergent adverse event
T_{max}	Refers to the time required for the peak plasma concentration to occur after administration
TNF-a/TNF-alpha	Tumor necrosis factor-a
TP	Total protein
T-SPOT	Tuberculosis infected T-cell spot test
Ua	Uric acid
UBG	Urobilinogen
ULN	Upper limit of normal
Urea	Urea

Vd	Apparent volume of distribution
V_{ss}	Volume of distribution at steady state
V_z/F	Apparent volume of distribution during the elimination phase
WBC	Leucocyte
WHO	World Health Organization
WinNolin	A pharmacokinetic analysis software

3 Introduction

3.1 Background

Breast cancer is a highly prevalent cancer in women worldwide. Data from Global Cancer Statistics 2020 suggest that breast cancer is the leading cause of morbidity and the fifth leading cause of mortality among all tumors[1]. In China, according to the 2015 Chinese Cancer Statistics, the annual incidence rate is 272.4/100,000 and the mortality rate is 69.5/100,000. Even with early treatment, nearly one-third of subjects experience relapse, including tumor metastasis[2], and metastatic breast cancer (mBC) is incurable, with a 5-year survival rate of nearly 25% (American Cancer Society 2017) and a mean overall survival (OS) of only 2-3 years[3, 4].

The 5-year survival rate of breast cancer in Chinese women has been reported to be 73.1% compared with 55.9% in rural areas[5]. For the age of onset, the median age of onset in the US is 61 years, as suggested by the 2017 SEER database[6]. According to the study report by Chen Wanqing et al[4] in 2016, Chinese women had a younger age of onset, and half were premenopausal. At the same time, there was a lower proportion of cancers in the early stages and a lower proportion of breast-conserving surgeries.

According to the molecular phenotypes such as estrogen receptor (ER), progesterone receptor (PR) and HER2 overexpression, breast cancer can be divided into different histopathological subtypes. Hormone receptor (HR: ER+PR) -positive cancers account for the majority of breast cancer cases, approximately 60-65%[7]. ER positivity in the Chinese breast cancer subjects has been reported to be 56.7% [5].

HR signaling pathways play an important role in the pathogenesis of breast cancer. Therefore, it has also emerged as an important target for the treatment of HR-positive breast cancer. Subjects with HR-positive breast cancer (including premenopausal, perimenopausal, and postmenopausal subjects) have hormone-specific treatment options. Because the main source of estrogen in postmenopausal subjects is androgen conversion by aromatase, there are a variety of hormone-specific treatment options, including aromatase inhibitors, tamoxifen, fulvestrant and so on. Aromatase inhibitors include nonsteroidal

agents such as letrozole, anastrozole, and steroidal agents such as exemestane. Tamoxifen is a selective estrogen receptor modulator. Fulvestrant is an effective antiestrogen that binds and degrades ERs. Goserelin is a gonadotropin-releasing hormone (GnRH; also called luteinizing hormone-releasing hormone [LHRH]) agonist approved for the palliative treatment of advanced breast cancer in premenopausal and perimenopausal women. Pharmacologic (or surgical) ovarian ablation yielded comparable results to tamoxifen monotherapy, supporting the combination of goserelin and fulvestrant in the treatment of premenopausal and perimenopausal women with metastatic breast cancer[8]. Although endocrine therapy is an effective treatment for breast cancer, most subjects with advanced disease will eventually demonstrate resistance to individual endocrine therapy. Other agents implicated in this therapeutic indication include mTOR inhibitors, PI3K inhibitors, and chemotherapeutic agents.

In cancers, the cyclin D/cyclin-dependent kinase 4/6 (CDK4/6)/p16INK4a/retinoblastoma protein (Rb) pathway is frequently disrupted. Most human tumors maintain functional Rb, but mutations that increase CDK4/6 activity promote inactivation of Rb function and allow cell proliferation[9,10]. Thus, CDK4/6 appears to be a critical enzyme essential for the proliferation of human cancers with functional Rb. Cancers with functional Rb may inhibit Rb function by increasing CDK4/6 activity in multiple ways. One of the most common events is inactivation of p16INK4a, a tumor suppressor that inhibits CDK4/6 activity.

Although endocrine therapy is often administered to women who have had a hormone receptor-positive (HR+) BC diagnosis, *de novo* initiation or acquisition of resistance is a common clinical concern in this population. Clinical studies have shown that cyclinD is overexpressed in more than 50% of breast cancers, most of which are also estrogen receptor-positive (ER+). CyclinD interacts directly with cyclin-dependent kinases 4 and 6 (CDK4 and CDK6) in active protein complexes. Thus, CDK4 and CDK6 represent potentially important targets to meet the unmet needs of BC subjects, particularly those with HR+ diseases.

So far, 3 CDK 4/6 inhibitors have been investigated for the treatment of HR-

positive breast cancer, including palbociclib (PD 0332991), ribociclib (LEE011), and abemaciclib (LY2835219). Phase 3 clinical trials of CDK4/6 inhibitors in combination with endocrine therapy are summarized inTable 1.

Although palbociclib and ribociclib are effective, daily treatment results in severe neutropenia, which requires a 7-day drug withdrawal period every 28-day course in order to restore neutrophil counts. Palbociclib/ribociclib induced neutropenia may lead to an increased risk of febrile neutropenia, and drug withdrawal period may lead to tumor regeneration and emergence of resistance. The potential cardiovascular risk of ribociclib, diarrhea caused by abemaciclib, and the potential risk of venous thromboembolism (VTE) also limit their clinical use. Therefore, it may be valuable to develop improved CDK4/6 inhibitors.

G1 Therapeutics and Genor Biopharma are developing GB491 as an oral, small molecule, effective, and selective inhibitor of the CDK4/6-cyclin D complex for the treatment of subjects with CDK4/6-dependent tumors. Nonclinical data suggests that GB491 effectively inhibits tumor growth without causing severe neutropenia. GB491 has been shown to effectively inhibit the growth of HR-positive breast cancer cells *in vitro* and in murine xenograft models. Therefore, GB491 may be the best therapeutic agent and can be used daily as an oral antineoplastic agent, which has a larger therapeutic window than palbociclib. The primary objective of this study is to evaluate the efficacy, safety and tolerability of GB491 plus fulvestrant versus placebo plus fulvestrant in the treatment of HR+/HER2- locally advanced or metastatic breast cancer that has progressed following prior endocrine therapy.

Table 1 Summary of Phase 3 Clinical Trials of CDK4/6 Inhibitors in Combination with Endocrine Therapy in Advanced Breast Cancer

Clinical Trial Title	CDK4/6 inhibitors	Inclusion Criteria	Number of Lines Treated	Sample Size (case)	Median PFS (months)
Combined with Nonsteroidal AI					
PALOMA-2[11]	Palbociclib	HR+/HER2- postmenopausal women with advanced breast cancer not treated systemically; (neo) adjuvant endocrine therapy requires a disease-free interval > 12 months from completion of treatment	First-line	666	27.6 vs. 14.5
MONALEESA-2[12]	Ribociclib		First-line	668	25.3 vs. 16.0
MONARCH-3[13]	Abemaciclib		First-line	493	28.2 vs.14.8
Combined with Fulvestrant					
MONALEESA-3[14]	Ribociclib	Postmenopausal subjects with HR+/HER2- advanced breast cancer, either untreated or progressing on first-line endocrine therapy	Progression on first line and prior endocrine therapy	726	20.5 vs.12.8
MONARCH-2[15]	Abemaciclib	Female subjects with HR+/HER2- metastatic breast cancer who progressed on prior endocrine therapy, regardless of menopausal status, are allowed to undergo first-line endocrine therapy without chemotherapy	Progression of prior endocrine therapy	669	16.9 vs. 9.3
PALOMA-3[16, 17]	Palbociclib	HR+/HER2- female subjects with advanced breast cancer who have relapsed or progressed on prior endocrine therapy, regardless of menopausal status, are permitted to undergo first-line chemotherapy	Progression of prior endocrine therapy and	521	9.5 vs. 4.6

			multiple lines		
Combined tamoxifen or nonsteroidal AIs and goserelin					
MONALEESA-7[18]	Ribociclib	Premenopausal or perimenopausal female subjects with HR+/HER2- breast cancer, not treated with endocrine therapy, allowed first line chemotherapy	First-line	672	23.8 vs.13.0
Combined with Nonsteroidal AI/Fulvestrant					
MOMARCH-PLUS	Abemaciclib	Postmenopausal HR-positive, HER2-negative postmenopausal subjects with advanced breast cancer not treated systemically	First-line	306	NR vs 14.7
		Postmenopausal subjects with HR-positive, HER2-negative locally advanced or metastatic breast cancer who have progressed on prior endocrine therapy	2nd line	157	11.5 vs 5.6

3.2 Summary of nonclinical data

A summary of the nonclinical data is presented in the following sections. Details are provided in the Investigator's Brochure (IB) of GB491.

3.2.1 Nonclinical pharmacology

GB491 represents a novel class of orally bioavailable CDK4/6 competitive inhibitors. These inhibitors prevented phosphorylation of Rb by the CDK4/6-cyclin D complex, thereby preventing G1 to S cell cycle transition.

Primary pharmacological studies confirmed that GB491 produced precise and reversible GI phase arrest in CDK4/6-dependent cells over a concentration range of 3 orders of magnitude *in vitro*. GB491 inhibited Rb phosphorylation at CDK4/6-specific sites with a mean half-maximal inhibitory concentration (IC50) of 30 nM only 16 hours after treatment. GB491 significantly inhibited cell proliferation in multiple CDK4/6-dependent tumorigenic cell lines including breast, melanoma, esophageal, prostate, leukemia, and lymphoma cells at concentrations as low as 12 nM. GB491 was inactive in CDK4/6-independent cell lines at concentrations < 2.6 μM. These data suggest that functional Rb is required for the effectiveness of GB491 and may affect multiple tumor types.

In vivo tumor models further strengthen the potential of GB491 as a highly potent antitumor agent in many CDK4/6-dependent tumor types. In the genetically engineered mouse model (GEMM) mammary tumors, GB491 administered orally at 100 mg/kg for 28 days resulted in significant tumor regression (38% regression) by day 21. In addition, GB491 administered orally once daily showed efficacy comparable to standard of care in nude mice bearing various human CDK4/6-dependent subcutaneous tumor xenografts, including ER-positive breast cancer and castration-resistant prostate cancer.

GB491 also showed dose-dependent target inhibition in tumors. Specifically, a single dose of 100 mg/kg GB491 administered to mice resulted in 98% reduction in Rb phosphorylation at 24 hours post-treatment. Interestingly, GB491 treatment did not cause clinically meaningful decreases in complete blood counts (CBCs) up to 5 mg/kg/day in rats or 1 mg/kg/day in dogs after 28 days of daily dosing. GB491 administered once daily, up to 15 mg/kg/day in rats and up to 5 mg/kg/day in dogs, did not cause severe neutropenia; this finding is particularly important as neutropenia is a dose-limiting toxicity (DLT) of treatment with palbociclib. These data suggest that GB491 treatment could be used as an orally bioavailable CDK4/6-targeted antineoplastic agent in subjects with CDK4/6-dependent tumors, including breast cancer and NSCLC.

GB491 (10 µM) was tested *in vitro* against a panel of 38 receptors, ion channels, and transporters. It was also tested in the panel whether GB491 could affect the activity of six human enzymes (cyclooxygenase 1, cyclooxygenase 2, phosphodiesterase 3A, phosphodiesterase 4D2, lymphocyte-specific protein tyrosine kinase [Lck], and acetylcholinesterase). GB491 inhibited acetylcholinesterase activity by 93% and Lck kinase activity by 70% at a concentration of 10 µM. At very high concentrations (> 4700 ng/mL), GB491 inhibited acetylcholinesterase *in vitro* and showed affinity for binding to various acetylcholine receptors (muscarinic or nicotinic), dopamine D2S receptor or transporter, and α1A adrenergic receptor. Safety pharmacology or toxicology studies with GB491 did not identify any adverse events associated with such interactions, most likely because peak plasma concentrations never reached 4700 ng/mL at the highest tolerated dose in animals. Peak plasma concentrations in human subjects are also not expected to reach 4700 ng/mL. In addition, GB491 enhanced serotonin binding to the serotonin 1b receptor at 4746 ng/mL.

None of the animal studies showed evidence that GB491 impacts neurological or cardiovascular function. GB491 inhibited potassium currents mediated by the human ether-à-go-go (hERG) -related gene channel in a concentration-related manner *in vitro*, with an IC_{50} estimated to be approximately 7800 ng/mL. However, this concentration greatly exceeded the maximum concentration (C_{max}) value at the maximum tolerated dose (MTD) level in rats (1770 ng/mL) or dogs (92 ng/mL). GB491 is unlikely to be better tolerated by human subjects (healthy volunteers or cancer subjects) than animals; however, peak plasma concentrations in human subjects are highly unlikely to reach 7800 ng/mL.

3.2.2 Nonclinical pharmacokinetics

GB491 showed high bioavailability following a single oral gavage dose to animals. Bioavailability was approximately 60% to 90% at doses of 50 to 100 mg/kg in mice, 10 to 90 mg/kg in rats, and 10 to 30 mg/kg in dogs. Systemic GB491 exposure did not differ between males and females after repeated oral doses for 7 or 28 days in rats and dogs, showed little accumulation, and generally showed a slightly greater than dose-proportional increase. GB491 is moderately to highly bound to proteins in rat, dog, and human plasma and tends to associate with red blood cells (RBCs) in blood of dogs. Volume of distribution values of GB491 suggests that the drug is widely distributed outside the systemic circulation. The drug penetrates the blood-brain barrier minimally, but GB491 is widely distributed into MCF7 xenograft tissue. The rate and extent of *in vitro*

metabolism of GB491 in liver microsomes and hepatocytes were low. However, GB491 has a high systemic clearance (CL) *in vivo*, suggesting that additional routes of excretion (e.g., kidney, bile) may play a role in its elimination.

GB491's major metabolite G1T30 is formed by biological oxidative transformation and G1T30 is an N-dealkylation product and a major metabolite. Overall, the *in vitro* metabolite profiles in rats, dogs and humans were qualitatively similar. Cytochrome P450 (CYP) 3A4 and CYP2C8 mediate oxidative metabolism. GB491 irreversibly inhibited CYP3A4/5, but not other major drug-metabolizing CYP isoforms, and did not significantly induce mRNA expression of CYP1A2, CYP2B6, or CYP3A4. GB491 is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) and inhibits P-gp, BCRP, organic cation transporter 1 (OCT1), organic cation transporter 2 (OCT2), multidrug and toxin extrusion protein 1 (MATE1), and multidrug and toxin extrusion protein 2-K (MATE2-K) in cell models.

3.2.3 Nonclinical toxicology

The toxicity of GB491 was evaluated in repeat-dose studies in rats and dogs as well as in a battery of *in vitro* genotoxicity studies. Please refer to the IB of GB491 for more information.

3.3 Summary of clinical data

G1 Therapeutics has conducted 5 clinical studies with this product, including 3 completed studies (G1T38-103, G1T38-01, and G1T38-06) and 2 ongoing studies (G1T38-02 and G1T38-03). G1T38-01 was a Phase 1 safety, tolerability, and pharmacokinetics study in healthy volunteers; G1T38-06 was a bioavailability study evaluating GB491 tablets versus a GB491 capsule formulation; G1T38-103 was a drug-drug interaction study in healthy subjects; G1T38-02 (NCT02983071) was a Phase 1/2 study to evaluate the safety, pharmacokinetics, and antitumor activity of G1T38 in combination with fulvestrant in subjects with metastatic breast cancer with HR+/HER2- locally advanced or after endocrine failure; G1T38-03 was a Phase 1b/2 study to evaluate the safety, pharmacokinetics, and efficacy of G1T38 in combination with osimertinib in EGFR tyrosine kinase inhibitor (TKI) -failing EGFR T790M mutation-positive NSLC subjects.

3.3.1 Clinical safety, tolerability and efficacy

The G1T38-01 study was a double-blind, placebo-controlled, single-center, single ascending dose (SAD) Phase 1 study in healthy subjects. This study was also designed as an open-label, crossover, two-period, single-dose, food-effect cohort, and twice-daily

(BID) dosing cohort (i.e., a single dose divided into 2 equal doses administered 12 hours apart) and assessed the effect of the formulation on GB491 PK parameters. GB491 administered orally as single or twice daily doses over the dose range of 3 to 600 mg was safe and well to moderately tolerated. Gastrointestinal adverse events were the most frequent moderate TEAEs in most subjects with moderate tolerability. Administration under fed conditions appears to improve gastrointestinal tolerability. No effects on hematology parameters were observed due to the limited duration of dosing.

No deaths, other SAEs, or AEs leading to study withdrawal occurred, and no subjects experienced severe or life-threatening TEAEs. Of the GB491-treated subjects in Study G1T38-01, 37 (65%) subjects reported a total of 121 GB491-related TEAEs. The most frequently reported GB491-related TEAEs (≥ 20% of subjects) by System Organ Class (SOC) as per Medical Dictionary for Regulatory Activities (MedDRA) were gastrointestinal disorders (60% vs 17% of GB491-treated subjects vs placebo-treated subjects) and nervous system disorders (33% vs 33%). The most frequently reported GB491-related TEAEs (≥ 10% of all subjects) by preferred terms were diarrhea (46% vs 6%), nausea (33% vs 6%), headache (18% vs 22%), and fatigue (12% vs 6%).

Sixteen of 57 subjects (28%) administered GB491 experienced at least 1 moderate (Grade 2) GB491-related TEAE. The most frequent moderate GB491-related TEAEs were diarrhea (6 subjects, 11%), nausea (5 subjects, 9%), headache (5 subjects, 9%), and somnolence (2 subjects, 4%). In the placebo group, 1 (6%) subject was reported with a moderate headache related event.

Coadministration with a high-fat meal improves gastrointestinal tolerability of GB491. Gastrointestinal TEAEs occurred in 4 of 8 (50%) fed subjects and 8 of 8 (100%) fasted subjects, respectively.

The G1T38-02 study was an open-label, multicenter, Phase 1/2 study in subjects with HR+/HER2- locally advanced or metastatic breast cancer who had failed endocrine therapy and was designed to evaluate the safety, PK, and antitumor activity of GB491 when administered continuously in combination with fulvestrant. Goserelin was coadministered in premenopausal or perimenopausal women. The study was divided into dose escalation and dose expansion phases. The dose escalation phase started with 200 mg QD and 100 mg BID in combination with 500 mg fulvestrant.

As of 17 April 2020, 98.2% (108/110) of the subjects experienced at least 1 TEAE. Grade 3 or higher TEAEs occurred in 62.7% of the subjects (69/110). Drug-related AEs occurred

in 101 subjects (91.8%): 59 subjects (53.6%) experienced drug-related AEs of Grade 3 or higher. Fifteen subjects (13.6%) experienced SAEs. In the GB491 150 mg BID group, 7 subjects (35%) experienced GB491-related AEs and 1 subject (5%) experienced SAEs. In the GB491 150 mg BID group, 7 subjects (35%) experienced GB491-related AEs and 3 subjects (15%) experienced letrozole related AEs.

Overall, the most common (> 40%) GB491-related TEAEs were neutropenia (terms of neutropenia and decreased neutrophil count were combined; 83 patients, 77.5%), nausea (60 patients, 54.5%), leukopenia (terms of leukopenia and decreased white blood cell count were combined; 56 patients, 50.9%), and diarrhea (53 patients, 48.2%).

In the GB491 BID dose groups, the most frequent (> 25%) GB491-related TEAEs in the 100 mg, 150 mg, and 200 mg groups were neutropenia (terms neutropenia and decreased neutrophil count were combined), leukopenia (terms leukopenia and decreased white blood cell count), nausea, diarrhea, vomiting, and anemia. The incidence of these GB491-related common AEs was generally similar across the 3 BID dose groups (100 mg, 150 mg, and 200 mg). The 150 mg BID dose was numerically better than both the 100 mg BID and 200 mg BID for most categories.

In the dose escalation and dose expansion phases, a total of 105 subjects were evaluable for efficacy (measurable lesions and ≥ 1 post-treatment scan or measurable lesions and clinical progression), of whom 31 (29.5%) had a confirmed partial response and 60 (57.1%) had stable disease for at least 50 days, yielding a clinical benefit rate (complete response + partial response + stable disease for ≥ 162 days) of 70.5% (74/105 subjects). In the 150 mg BID dose group of GB491, among 19 evaluable subjects, a total of 6 subjects (31.6%) achieved a confirmed partial response and 1 subject (5.3%) had an unconfirmed partial response. Nine subjects (47.4%) had stable disease for at least 50 days, resulting in a clinical benefit rate of 73.3% (14 of 19 subjects). Among the 31 subjects who achieved an objective response combined in Parts 1 and 2 of the study, the median duration of objective response was 13.4 months and the median time to first objective response was 3.5 months. In the150 mg BID dose group of GB491, the median duration of objective response was not yet reached and the median time to first objective response was 2.8 months. It is worth mentioning that the objective response rate was 37.5% and the clinical benefit rate was 75% in a population with advanced/metastatic breast cancer previously treated with first-line endocrine therapy. This population is the target population of the proposed GB491-004 study;

Study G1T38-03 is an ongoing, open-label Phase 1b/2 study to evaluate the safety, PK,

and efficacy of continuous GB491 administration in combination with osimertinib in subjects with EGFR-mutated NSCLC. The study consists of two parts. Part 1 evaluated the effect of osimertinib on GB491 PK parameters, and the safety and tolerability of GB491 (dose escalation) in combination with osimertinib to determine the recommended Phase 2 dose (RP2D). Part 1 of the study was designed to explore the dose of GB491 200 mg to 650 mg QD and to evaluate the selected dose of GB491 BID in combination with 80 mg osimertinib. Part 2 is a randomized evaluation of the safety, tolerability, and efficacy of osimertinib alone versus GB491 (RP2D determined in Part 1) plus osimertinib. Prior to the data cutoff date of 17 Apr 2020, 30 subjects had been enrolled in Part 1 of the study and received the study drug. Twenty-two subjects (73.3%) discontinued the study drug in Part 1 due to disease progression (19 subjects), investigator decision (1 subject), death (1 subject), and AE (1 subject). During the survival follow-up period, a total of 12 subjects (40.0%) withdrew from the study due to death; deaths were mostly attributed to disease progression; and 1 subject each was reported with unknown or unobtainable information. There were no deaths due to AEs.

In Part 1 of the study, a total of 27 subjects were evaluable for efficacy (measurable disease and ≥ 1 scan post-treatment). Of these, 7 (25.9%) had confirmed partial responses and 10 (37%) had stable disease lasting at least 50 days, for a disease control rate of 63% (17 of 27 subjects), Table 5-8. Of the 7 subjects with confirmed partial responses, the median duration of response was 12 months (range: 1.8 to 16.5 months) and the median time to response was 1.9 months (range: 1.64 to 7.29 months). Median progression-free survival (PFS) was 5.8 months (95% CI: 3.6 to 9.7).

Overall, GB491 demonstrated good safety and tolerability as part of its administration as a single agent or in combination in both healthy subjects, patients with advanced breast cancer, and patients with non-small cell lung cancer. In terms of efficacy, GB491 also showed good efficacy in combination with fulvestrant in patients with advanced breast cancer who had progressed after previous endocrine therapy.

3.3.2 Clinical pharmacokinetics

Single dose capsule

Following oral administration under fasted conditions, the first quantifiable timepoint of the GB491 concentration in plasma was 0.25 h or 0.5 h for doses of 48 mg and above, and median T_{max} increased with dose from 2 to 6 h post-dose. Following peak concentrations, multiphasic decreases in plasma concentrations were observed. The

geometric mean terminal elimination half-life ($t_{1/2}$) of GB491 ranged from 13.8 to 17.2 h.

Food Effects

Median T_{max} following the 300 mg dose was 6 hours postdose under fasted or fed conditions. Geometric mean C_{max} was slightly higher in the fed (high-fat meal) state compared to the fasted state. Exploratory statistical analysis showed that food had a minimal effect on C_{max} (13%) and no effect on AUC_{0-t} and $AUC_{0-\infty}$.

BID dosing

When the GB491 daily dose was divided into two equal doses, the median T_{max} was 4-6 h after each dose. In most subjects, the highest peak GB491 plasma concentrations were observed after the morning dose. Geometric mean total C_{max} following the twice daily dosing was lower than following a single dose of the same total dose. The GB491 daily dose administered in two divided doses resulted in similar or slightly lower GB491 total plasma exposures (AUC_{0-t} and $AUC_{0-\infty}$) compared to the same total daily dose administered as a single dose.

Dose proportionality

Based on dose-normalized PK parameter profiles, both C_{max} and AUC increased with increasing dose in a greater than dose-proportional manner at lower doses (48 to 200 mg) and with increasing dose in an approximately dose-proportional (AUC) or less than dose-proportional (C_{max}) manner from 200 to 400 mg. See the IB for details.

3.4 Study principles and rationale for dose selection

3.4.1 Study principles

Hormone receptor (HR) -positive breast cancer represents the vast majority of breast cancers worldwide. Antiestrogens and aromatase inhibitors were identified as the first-line agents for adjuvant endocrine therapy in HR-positive breast cancer. Fulvestrant is an effective antiestrogen that binds and degrades ERs. Fulvestrant is currently indicated for the treatment of HR-positive metastatic breast cancer in postmenopausal women who have progressed on antiestrogen therapy (Fulvestrant Package Insert 2017). Goserelin is a gonadotropin-releasing hormone (GnRH; also known as luteinizing hormone-releasing hormone [LHRH]) agonist approved for the palliative treatment of advanced breast cancer in premenopausal and perimenopausal women (Goserelin Package Insert 2018). Pharmacologic (or surgical) ovarian ablation yielded comparable results to tamoxifen monotherapy, supporting the combination of goserelin and fulvestrant in the

treatment of premenopausal and perimenopausal women with metastatic breast cancer[8]. Although adjuvant endocrine therapy is an effective treatment for breast cancer, most subjects with advanced disease will eventually exhibit resistance to individual endocrine therapy.

The FDA-approved cyclin-dependent kinase 4/6 inhibitors palbociclib (also approved in China), ribociclib, and abemaciclib in combination with endocrine therapy for first-line and second-line HR-positive breast cancer have shown promising efficacy and acceptable safety. And it has been recommended for use in mainstream medical guidelines (ASCO, NCCN, CSCO). See background for details.

GB491 is a potent and selective CDK4/6 inhibitor that has been shown to effectively inhibit the growth of HR-positive breast cancer *in vitro* and *in vivo* in nonclinical models. Similar to other CDK4/6 inhibitors, GB491 showed synergy with endocrine therapy in nonclinical models. Based on the clinical benefit observed with the combination of palbociclib, ribociclib, and abemaciclib with fulvestrant or aromatase inhibitors, as well as the preliminary safety, PK, and antitumor activity observed with the combination of GB491 and fulvestrant conducted overseas. The pivotal registration study GB491-004, which is planned to be submitted this time, will be used for future NDA submission.

3.4.2 Rationale for dose selection

This study is a multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of GB491 combined with fulvestrant in the treatment of HR+/HER2- locally advanced or metastatic breast cancer subjects who have progressed after prior endocrine therapy. The starting dose was 150 mg BID orally. This dosing schedule was based on the RP2D determined by a combination of nonclinical and G1T38-01 and G1T38-02 studies.

Based on nonclinical animal xenograft models, the AUC_{0-24}, a potential therapeutic target of GB491, at steady state in cancer subjects ranged from 600 to 1200 ng•h/mL.

In a GLP toxicology study in beagle dogs receiving repeated doses of GB491 for 28 days, the highest non-severely toxic dose (HNSTD) was considered to be 5 mg/kg, corresponding to a steady-state AUC_{0-24} of 923 ng•h/mL.

The toxicity profile of GB491 under the canine HNSTD is generally reasonable, predictable, and easily monitored, with neutropenia being the most frequently occurring adverse event. Following an initial decrease in neutrophil counts, they were relatively stable from Day 14. As shown in **Figure 1**, this was observed at all dose levels tested.

Neutropenia was expected to occur less frequently in this study than observed in dogs based on predicted AUC_{0-24} at steady state. Neutropenia did not occur following a single dose in Study G1T38-01 and is not expected. Neutropenia is a class effect associated with chronic administration of CDK4/6 inhibitors (e.g., palbociclib) and rapid reversibility has been shown in humans following discontinuation or drug withdrawals. This reversibility of GB491 was also observed in nonclinical studies. These data support evaluation of continuous administration in humans through close clinical and laboratory monitoring.

Continuous dosing of 100 mg twice daily in healthy subjects with G1T38-01 is expected to result in a steady-state AUC_{0-24} of 159 ng·h/mL, which is only slightly higher than the no-observed-adverse-effect level (NOAEL) and nearly one-sixth of the HNSTD. The AUC_{0-24} for the 200 mg every 12 hours regimen was 263 ng·h/mL, while the simulated steady-state AUC_{0-24} was nearly 420 ng·h/mL, less than ½ of the HNSTD. For PK data from Study G1T38-02, steady-state AUC_{0-24} at the highest dose of 250 mg BID in the BID dose group: 710 (355*2) ng·h/mL, 77% of the HNSTD. In the G1T38-02 study, the dose of GB491 500 mg QD or 250 mg BID was identified as the maximum tolerated dose (MTD) based on the occurrence of DLT events.

The 150 mg BID dosing regimen had an objective response rate of 31.6% and a clinical benefit rate of 73.7% based on the evaluable population. Grade 3/4 neutropenia was 35%, grade 3/4 leukopenia was 15%, and grade 3/4 thrombocytopenia was 5%. No grade 3/4 lymphopenia, diarrhea, vomiting, nausea, or ALT/AST increase. The overall benefit-risk profile supports the 150 mg BID oral regimen as the ideal dosing regimen. Preliminary efficacy, safety (including absence of DLT events), and tolerability results in the G1T38-02 study suggest that 150 mg twice daily is an ideal and tolerable dose as shown in **Table 2** and **Table 3**. GB491 has little potential for ethnic sensitivity based on ICH E5 bridging assessments, as shown in **Table 4**.

Potential drug interactions

The Applicant considers that the potential for a clinically significant drug-drug interaction (DDI) between GB491 and fulvestrant is very low. The route of elimination of fulvestrant includes many combinations of possible biotransformation pathways similar to endogenous steroids, including oxidation, aromatic hydroxylation, conjugates with glucuronic acid, and/or sulfate. There are no known DDIs for fulvestrant. *In vitro*, fulvestrant dose not significantly inhibit any of the major CYP isozymes (CYPs 1A2, 2C9, 2C19, 2D6, and 3A4). Although fulvestrant is partially metabolized by CYP3A4, clinical

studies of fulvestrant coadministered with rifampin (a potent inducer of CYP3A4) or ketoconazole (a potent inhibitor of CYP3A4) showed no effect on the PK of fulvestrant. No dose adjustment of fulvestrant is required for subjects taking concomitant prescribed CYP3A4 inhibitors or inducers (Fulvestrant Package Insert 2017). Therefore, it is highly unlikely that fulvestrant alters the PK of GB491, nor is GB491 likely to affect the PK of fulvestrant.

Because GB491 is not expected to affect the PK of fulvestrant, based on the results of the CONFIRM study[19], this study will use the same dosing regimen as fulvestrant (i.e., 500 mg administered intramuscularly every 14 days for the first 3 injections to achieve steady-state concentrations and then every 28 days) (Fulvestrant Package Insert 2017).

The applicant also considers that the likelihood of a clinically significant DDI between GB491 and goserelin is very low. The main route of elimination of goserelin, a synthetic decapeptide analogue of GnRH, is C-terminal amino acid cleavage followed by renal excretion. No formal DDI studies have been conducted with goserelin and no interactions between goserelin and other drugs have been reported. There was no significant evidence of drug accumulation following monthly administration of goserelin 3.6 mg subcutaneous depot formulations (Goserelin Package Insert 2018).

Therefore, based on a combination of nonclinical, clinical assessments, and drug interactions, the starting dose for this study was 150 mg BID orally.

3.5 Risk/benefit assessment

Nonclinical studies and early clinical studies of GB491 support the continuation of the trial in the Chinese population and identified myelosuppression, gastrointestinal tolerability, and interstitial pneumonia/pneumonia as the main potential toxicities of concern. In this study, hematological parameters, gastrointestinal symptoms, respiratory symptoms and imaging tests will be closely monitored.

Patients with HR+/HER2- locally advanced or metastatic breast cancer who have progressed on prior endocrine therapy will be enrolled in this study, and there remains an unmet clinical need in this population. Although the clinical benefit of GB491 in patients at the proposed dose cannot be established, the aforementioned biological hypotheses, nonclinical data, and preliminary clinical data, as well as those described in the IB, support its potential benefit in the proposed study population. The PALOMA-3 study of palbociclib + fulvestrant, MONALEESA-3 study of riibocilib + fulvestrant, MONARCH 2 study of Abemacilib + fulvestrant, and MONARCH -Plus study may also serve as a strong rationale

to explore the combination therapy with GB491 + fulvestrant in the Chinese locally advanced or metastatic breast cancer patients with HR+/HER2- who have progressed on prior endocrine therapy.

In patients with ER-positive/HER2-negative breast cancer, the results of GB491 nonclinical studies and early clinical studies support the continuation of the trial in the Chinese population. The study design of this Phase 3 randomized clinical trial is intended to minimize potential risks in several ways. First, appropriate inclusion and exclusion criteria were included in the study protocol to protect patient safety and to include patients most likely to benefit from this treatment. Second, this protocol includes safety monitoring beyond the standard of care to protect patients participating in the study. In this study, hematological parameters, gastrointestinal symptoms, respiratory symptoms and imaging tests will be closely monitored. In addition, dose modification strategies to manage toxicities and monitoring were developed for myelosuppression, gastrointestinal tolerability, and interstitial pneumonitis/pneumonia as the main potential toxicities of concern.

Based on these considerations, GB491 may provide clinical benefit and in view of the measures taken to circumvent the risk, the benefit-risk assessment supports this proposed Phase 3 clinical study.

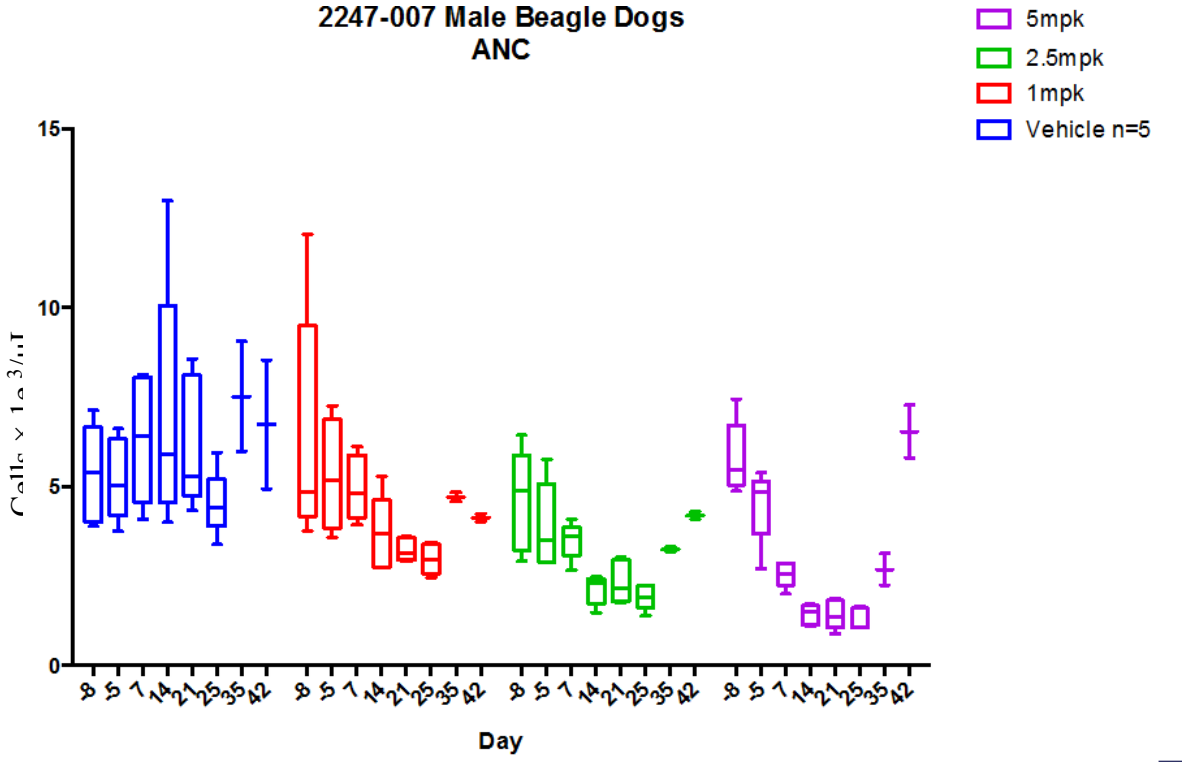


Figure 1 Absolute Neutrophil Counts Over Time in the 28-Day Repeated Dose Toxicology Study in Dogs

Table 2 Efficacy by Dose Group in G1T38-02 Study

Efficacy	200 mg QD N = 6 n (%)	300 mg QD N = 3 n (%)	400 mg QD N = 13 n (%)	500 mg QD N = 30 n (%)	650 mg QD N = 6 n (%)	100 mg BID N = 5 n (%)	150 mg BID N = 19 n (%)	200 mg BID N = 20 n (%)	250 mg BID N = 3 n (%)	Overall N = 105 n (%)
Confirmed CR	0	0	0	0	0	0	0	0	0	0
Confirmed PR	1 (16.7)	1 (33.3)	6 (46.2)	10 (33.3)	0	1 (20.0)	6 (31.6)	6 (30)	0	31 (29.5)
Stable Disease for 24 Weeks	(66.7)	1 (33.3)	7 (53.8)	18 (60)	5 (83.3)	2 (40.0)	9 (47.4)	12 (60)	(66.7)	60 (57.1)
Objective Response	1 (16.7)	1 (33.3)	6 (46.2)	10 (33.3)	0	1 (20.0)	6 (31.6)	6 (30)	0	31 (29.5)
Clinical Benefit at Week 24	4 (80)	(66.7)	10 (76.9)	22 (73.3)	2 (33.3)	3 (60.0)	14 (73.7)	14 (70)	(66.7)	74 (70.5)

Table 3 Summary of the Safety of BID Dosing Regimen

Preferred Terms (AE ≥ Grade 3)	GB491 100mg BID (N=6)	GB491 150mg BID (N=20)	GB491 200mg BID (N=21)	GB491 250mg BID (N=3)
Any GB491-relared TEAEs	1 (16.7)	7（35）	9 (42.9)	2 (66.7)
Neutropenia	1 (16.7)	7（35）	9 (42.9)	2 (66.7)
Leukopenia	0	3（15）	7 (33.3)	1 (33.3)
Lymphopenia	0	0	3 (14.3)	0
Diarrhea	0	0	1 (4.8)	0
Nausea	0	0	0	0
Vomiting	0	0	0	0
Fatigue	0	0	0	0
Thrombocytopenia	0	1 (5)	1 (4.8)	0
Anemia	1 (16.7)	1 (5)	0	0
Elevated ALT	0	0	0	0
Elevated GOT	0	0	0	0
DLT Event	0	0	1	0 (MTD)

Table 4 Ethnic Sensitivity Evaluation of GB491

Considerations	Conclusion
Exposure-response analysis across recommended doses and regimens	Population PK has not identified endogenous factors that contribute to clinically meaningful changes in GB491 exposure; subgroup analyses of treatments with marketed CDK4/6 in the same population have not identified ethnic factors that contribute to response differences.
Linear pharmacokinetics (PK)	Geometric mean AUC_{0-t} and $AUC_{0-\infty}$ values of GB491 increased with increasing dose in a greater than dose-proportional manner from 48 to 200 mg and in an approximately dose-proportional manner from 200 mg to 400 mg. GB491 exposure was comparable in cancer subjects and healthy subjects.
Safety window	Continuous dosing of 100 mg twice daily in healthy subjects is expected to result in a steady-state AUC_{0-24} of 159 ng·h/mL, which is only slightly higher than the no-observed-adverse-effect level (NOAEL) and nearly 1/6 of the HNSTD. In the breast cancer study, the highest dose of 250 mg BID in the BID dosing group had a steady-state AUC_{0-24} of 710 (355*2) ng·h/mL, which was 77% of the HNSTD. So GB491 is not a narrow safety window drug.
Drug metabolism pathway	*In vitro* studies have shown that CYP3A4 is the main metabolizing enzyme of GB491 and whether CYP3A is ethnically dependent, although there are some different views, most consensus suggests that drugs metabolized mainly by CYP3A do not have ethnically dependent PK effects.
Protein binding ratio	GB491 is not expected to cause drug-drug interactions due to plasma protein binding
Drug-food and drug-drug interactions	After administration of a high-fat meal, $AUC_{0-\infty}$ and C_{max} of GB491 increased by 29% and 39%, respectively, and were administered with food in relevant studies; although CYP3A4 inhibitors increased GB491 exposure, they did not exceed the exposure at the MTD dose and no dose adjustment was required for coadministration; CYP3A4 inducers significantly decreased the GB491 exposure and coadministration should be avoided.

External factors influencing ethnic sensitivity such as epidemiology, medical practice	Compared with foreign subjects, there are differences in early years such as age of onset, number of births. In recent years, with changes in lifestyle, the incidence in China, especially in large cities, has approached that of the European and American countries. It is also close to Europe and the United States in terms of treatment practice.

4 Study Objectives and Endpoint Measures

4.1 Study objectives

Primary objective: To evaluate progression free survival (PFS, as assessed by the investigator) of GB491 plus fulvestrant versus placebo plus fulvestrant for HR+/HER2- locally advanced or metastatic breast cancer with progressive disease following prior endocrine therapy.

Secondary objectives: To evaluate the combination in terms of progression-free survival (PFS, as assessed by the BICR); overall survival (OS); objective response rate (ORR), duration of response (DOR), disease control rate (DCR), clinical benefit rate (CBR); safety and tolerability; and pharmacokinetic (PK) profile.

4.2 Study endpoint measures

Primary endpoint

- PFS assessed by investigator based on RECIST v1.1;

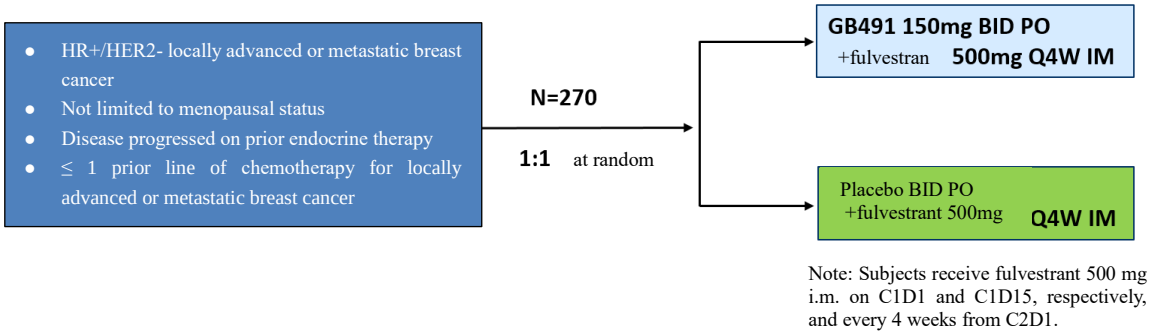
Secondary endpoints:

- PFS assessed by BICR based on RECIST v1.1;
- Overall survival;
- ORR, DOR, DCR, CBR based on RECIST v1.1;
- Incidence of AEs/SAEs evaluated according to NCI-CTCAE version 5.0 criteria; laboratory abnormalities; changes in laboratory assessments, electrocardiograms, physical examinations;
- PK parameters assessed by population pharmacokinetic analysis based on plasma concentrations of GB491 and its metabolite G1T30.

5 Study Plan

5.1 Overview of overall study design

This study is a multicenter, randomized double-blind, placebo-controlled, Phase III clinical trial of GB491 plus fulvestrant versus placebo plus fulvestrant in patients with HR+/HER2- locally advanced or metastatic breast cancer who have progressed on prior endocrine therapy.



HR+, hormone receptor positive; HER2-, human epidermal growth factor receptor 2 negative; N, number; BID, twice daily; IM, intramuscular; Q4W, every 4 weeks.

Figure 2 Study design diagram

Approximately 270 patients who met the eligibility criteria were planned to be enrolled into the study. Patients will undergo a screening period of up to 28 days. Patients who met the inclusion criteria were assigned in a 1:1 ratio to GB491 plus fulvestrant or placebo plus fulvestrant based on an Interactive Web Response System (IWRS). And the nature of baseline disease (visceral metastasis vs bone only metastasis vs others), different menopausal status (male or premenopausal or perimenopausal vs postmenopausal), and number of prior lines of endocrine therapy failure (first-line vs second-line) were used as randomization stratification factors.

- Treatment group: Patients received GB491 150 mg orally twice daily (taken with food, recommended approximately 12 hours apart) for 28 consecutive days as a cycle. At the same time, randomized patients will receive one fulvestrant 500 mg intramuscular injection on Day 1 and Day 15 of the first cycle (28-day/cycle), and one fulvestrant 500 mg intramuscular injection on Day 1 of each subsequent cycle.
- Control group: Placebo was administered orally twice daily (taken with food, recommended approximately 12 hours apart) for 28 consecutive days as a cycle. At the same time, randomized patients will receive one fulvestrant 500 mg intramuscular injection on Day 1 and Day 15 of the first cycle (28-day/cycle), and

one fulvestrant 500 mg intramuscular injection on Day 1 of each subsequent cycle.

For premenopausal and perimenopausal female patients and male patients (unless there is a clear history of bilateral orchiectomy) requiring the use of LHRH analogues (e.g., goserelin), they must start treatment with LHRH analogues (e.g., goserelin) at least 21 days before randomization, followed by subcutaneous injection of 3.6 mg goserelin extended-release implants every 28 days (or following other LHRH analogue treatment specifications).

Following completion of the study screening, follow-up will occur on Days 1 and 15 (C1D1 and C1D15) of Cycle 1 and on Day 1 of each subsequent cycle (28-day/cycle).

Subjects will be stratified by the nature of disease (visceral metastases vs bone only metastases vs others), menopausal status (male or premenopausal or perimenopausal vs postmenopausal), and number of prior lines of endocrine failure (first-line vs second-line). Visceral metastasis refers to visceral soft organ involvement at randomization, including but not limited to lung, liver, brain (CNS), reproductive system, pleural and/or peritoneum involvement (based on NCI dictionary). Menopausal status was defined as the subject's menopausal status at randomization. Endocrine treatment failure was defined as the development of endocrine resistance in adjuvant endocrine therapy or endocrine therapy for locally advanced or metastatic breast cancer. That is, relapse during or after discontinuation of adjuvant endocrine therapy within 1 year, or disease progression after endocrine therapy for locally advanced or metastatic breast cancer. (Refer to Guidelines and Specifications for Diagnosis and Treatment of Breast Cancer of Chinese Anti-Cancer Association (2021 Edition))

Switch Treatment Group is not allowed in this study.

Database lock for the final analysis based on the PFS endpoint will occur when a total of approximately 119 PFS events have occurred. All subjects will be followed until disease progression and survival information will be collected until death or the end of the study, whichever comes first. See Sections 12.1 and 12.2 for sample size and analysis.

Terms regarding the study period are defined as follows:

- Baseline period: Starting from the signing of the informed consent form and ending at the randomization (or at discontinuation, if not treated).

- Study period:
  - ✧ Study treatment period: Randomization was the starting point and the last dose of the blinded study drug was the end point. The date of last dose will be recorded in the eCRF and will serve as the date of end of study treatment.
  - ✧ Follow-up period after the end of treatment: Including the end-of-treatment follow-up period, safety follow-up period and survival follow-up period:
    - ◆ End of treatment follow-up (EOT): Conducted at the time of the last dose of the blinded study drug or early termination of the study (up to a 7-day window allowed).
    - ◆ Safety follow-up period: Conducted 30 days (± 7-day window) following the last dose of the blinded study drug.
    - ◆ Survival follow-up period (long-term follow-up): The end of safety follow-up will be used as the starting point until subject death or the end of the study as a whole.

5.1.1 Evaluation of antitumor efficacy

All patients will undergo baseline tumor assessments within 28 days prior to randomization, including:

- CT/MRI scans of chest, abdomen, pelvis and other sites of tumor involvement
- For patients with inoperable locally advanced breast cancer, breast MRI scans will be performed at the baseline (if applicable)
- Radionuclide bone scan, lesions identified on bone scan must be confirmed by CT (bone window) or MRI

Tumor assessments during the treatment period must consistently use the assessment methods and techniques used at baseline, including all sites of disease (including but not limited to the chest, abdomen, and pelvis), and the cycle of tumor assessments must be fixed (fixed cycles set based on the date of randomization). All patients will undergo CT/MRI evaluation every 8 weeks (± 7 days) during the first year and every 12 weeks (± 7 days) after 1 year, and bone scans will be performed every 24 weeks (± 7 days) until disease progression using the randomization day as the benchmark. For patients who discontinue treatment prior to confirmed disease progression, CT/MRI imaging assessments should be performed according to the previous visit assessment schedule until: 1) objective disease progression; 2) death; 3) withdrawal of consent or loss to

follow-up; 4) receiving new antineoplastic therapy; 5) end of study. Imaging assessments must be performed within 2 weeks if clinical progression is suspected. Patients with confirmed CR will undergo bone scan to confirm absence of bone metastases. At the investigator's discretion, additional bone scans may be performed and lesions confirmed by CT (bone window) or MRI if the patient has clinical symptoms and signs of worsening bone metastases. Note: Enhanced CT should be the first choice for imaging assessment. For patients with known hypersensitivity to CT contrast agents, plain chest CT + abdominal/pelvic contrast-enhanced MRI assessment is optional.

5.1.2 Safety evaluation

Safety evaluations included monitoring of adverse events, vital signs, physical examinations, electrocardiograms (ECGs), and clinical laboratory tests. All adverse events were collected from the first dose of the blinded study drug through 30 days after the last dose of the blinded study drug (or until initiation of the subsequent new anti-tumor therapy, whichever came first). Following the safety follow-up period, if the investigator became aware of any serious adverse events, only the study drug-related serious adverse events (SAEs) were to be reported until receiving subsequent new anticancer therapy or the end of the study. At the same time, only serious adverse events due to protocol-specified related procedures (e.g., serious adverse events related to invasive procedures [e.g., biopsies]) were collected from the time of informed consent through the first dose.

Treatment-emergent adverse events (TEAEs) were defined as adverse events that started with the first dose through 30 days after the last dose of the blinded study drug (or until receiving a new anticancer treatment, whichever came first).

5.1.3 Pharmacokinetic evaluation

Venous blood samples were collected at the visits indicated in the pharmacokinetic sampling schedule (**Appendix 3**) to determine the plasma concentrations of GB491 and its metabolite G1T30 and were included in the population pharmacokinetic analysis.

5.1.4 Study completion and end of study

Study completion is defined as completion of the primary endpoint (PFS) analysis as determined by the sponsor. The end of the study is defined as the last subject completing the last protocol-specified follow-up visit or the last study procedure, or death is observed in at least 50% of the subjects, or the sponsor decides to end the study. The investigator will continue to follow the procedures established for the study until the sponsor notifies

the end of the study. Inclusion of new data in the clinical database will stop after the end of the study.

Because the endpoint of this study is event-driven, the increase in the number of predetermined events included in the study endpoint will determine the duration of the study data collection phase. Data collection nodes (Data Cut-Off, DCO) for this study are as follows:

Study completion DCO:

- The final analysis based on the PFS endpoint was performed when approximately 119 PFS events had occurred;

End of study DCO:

- The last subject completes the last follow-up visit or study procedures specified in the protocol;
- Or the final DCO for overall survival (OS) will occur when at least 50% of deaths are observed;
- Or the sponsor decides to end the study.

5.2 Discussion of study design

This study used a randomized controlled design. Randomization minimizes systematic bias in selecting and assigning patients to study treatment and provides a basis for inferential statistical methods using data from this study. The use of an appropriate concurrent control group provides a direct estimate of the benefit-risk of the study treatment and minimizes errors in the assessment and interpretation of the observed treatment effect. Differences that may be expected to be associated with the patient's clinical outcomes will be stratified to reduce possible errors and increase power of the analysis. The use of double-blind and placebo controls further reduces bias. Treatment administration for this study was double-blind; i.e., patients, study personnel, and the sponsor’s study team did not have direct access to any patient's treatment assignment. This design feature minimizes the potential errors in assessing study endpoints.

6 Study Population

6.1 Target population and number of subjects

The target population for this study was HR+/HER2- locally advanced or metastatic breast cancer patients who had progressed on prior endocrine therapy, and approximately 270 patients who met the eligibility criteria were planned to enroll in this study.

Subjects who initially fail the screening may be rescreened after re-signing the informed consent. All screening steps will need to be repeated for re-screening. The subjects must meet all the inclusion criteria and none of the exclusion criteria at re-screening to be enrolled in the study. At re-screening, there is no minimum time limit for subjects to wait. If a subject has completed a tumor assessment (CT scan/MRI) at the initial screening but more than 35 days have passed since the rescreening visit, the tumor assessment should be repeated. The site may contact the sponsor as appropriate to confirm whether the subject can be rescreened.

6.2 Inclusion criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's research team prior to enrollment in the study. Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Female or male, 18 years of age or older and less than 75 years of age at study screening;
2. Histologically or cytologically confirmed locally advanced or metastatic breast cancer that is not amenable to surgical resection or radiation therapy with curative intent;
3. Patients had a confirmed diagnosis of ER-positive breast cancer by local laboratory testing (based on the most recent tumor sample prior to randomization). ER positivity is defined as ≥ 10% staining positive cells regardless of PgR status. Refer to ASCO/CAP 2020 ER/PgR Testing Guidelines (Allison et al. 2020) for test methods and result determination;
4. Patient who were diagnosed with HER2-negative breast cancer based on the most recent tumor sample prior to randomization by local laboratory testing. HER2 negativity is defined as having an IHC score of 0 or 1 +, or negative in situ hybridization. Testing methods and interpretation are described in the ASCO/CAP 2018 HER2 Testing Guidelines (Wolff et al. 2018);

5. Patients with any menopausal status (including premenopausal, perimenopausal, postmenopausal);

   Premenopausal and perimenopausal patients taking LHRH analogues such as goserelin who started treatment with LHRH analogues ≥ 21 days prior to randomization and who were willing to continue their use during the study were permitted;

   Note: Male patients who are willing to undergo treatment with an LHRH analogue such as goserelin (unless there is a clear history of bilateral orchiectomy) during the study may also be enrolled;

   Postmenopausal status is defined as meeting at least 1 of the following conditions:

   - Patients aged ≥ 60 years at screening for this study;
   - Patients < 60 years of age at screening for this study. Concurrently, amenorrhea for more than 1 year in the absence of other pathological or physiological causes (e.g., no chemotherapy, tamoxifen, toremifene, or ovarian suppression); and serum estradiol and FSH levels within the laboratory reference range for postmenopausal women;
   - Patients < 60 years of age who were taking tamoxifen or toremifene before enter screening for this study, with FSH and E2 levels in the postmenopausal range;
   - Bilateral oophorectomy has been performed;

6. Prior endocrine therapy and chemotherapy, the following are permitted:

   a) Prior endocrine adjuvant therapy:

   - Radiologic evidence of progressive disease (PD) during or within 12 months following (neo)adjuvant therapy with an aromatase inhibitor (AI) or an anti-estrogen such as tamoxifen, and no subsequent endocrine therapy for locally advanced or metastatic breast cancer;
   - Radiologic evidence of progressive disease (PD) during or within 12 months following (neo)adjuvant therapy with an aromatase inhibitor (AI) or an anti-estrogen such as tamoxifen, after receiving the first-line endocrine therapy for locally advanced or metastatic breast cancer, and who developed radiologically documented PD after receiving therapy for ≥ 6 months;

- Radiologically documented progressive disease (PD) more than 12 months following the end of adjuvant therapy with aromatase inhibitors (AIs) or anti-estrogens such as tamoxifen, followed by radiographic progression following first-line therapy with aromatase inhibitors (AIs) or anti-estrogens for locally advanced or metastatic breast cancer;

b) Progression with radiographic evidence of disease following prior first-line endocrine therapy for locally advanced or metastatic breast cancer in subjects who have not received prior (neo) adjuvant therapy;

c) Prior chemotherapy: In addition to endocrine therapy, subjects are eligible if they received a maximum of 1 prior line of chemotherapy for locally advanced or metastatic breast cancer and discontinued treatment for at least 28 days prior to randomization;

7. Patients must meet one of the following conditions:

- Measurable lesions, e.g., patients with at least one measurable lesion according to RECIST v1.1 criteria;
- If there is no measurable lesion, at least one osteolytic lesion is predominant (if the patient has no measurable lesion and only one irradiated osteolytic lesion is predominant, the patient can be enrolled if there is documented disease progression after radiotherapy);

8. ECOG performance status of 0 or 1;

9. The following laboratory parameters must be met to ensure that the patient has adequate bone marrow function prior to dosing (no blood transfusion, no component transfusion, no infusion of growth factors, etc., within 2 weeks prior to randomization):

- Hemoglobin ≥ 90 g/L;
- Absolute neutrophil count ≥ 1.5 × 10^9/L;
- Platelet count ≥ 100 × 10^9/L;
- Creatinine clearance or estimated glomerular filtration rate (GFR) > 50 ml/min (Cockcroft-Gault equation or[51] CR-EDTA);
- Total bilirubin ≤ 1. ×ULN; in case of Gilbert's disease, total bilirubin ≤ 3×ULN is allowed;

- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤ 3 × ULN; if liver metastasis is present, AST and/or ALT ≤ 5 ×ULN may be accepted;
- Alkaline phosphatase (ALP) ≤ 2.5× ULN, ALP ≤ 5×ULN if bone metastasis or liver metastasis is present;

10. Female patients of childbearing potential must have a serum pregnancy test (β-hCG) within 7 days prior to randomization and be non-pregnant and willing to use at least one medically recognized highly effective contraception (e.g., intrauterine device, contraceptive, or condom) during the study and for 6 months after the last dose of the study drug; female partners (partners) of male patients should use at least one medically recognized highly effective contraception (e.g., condom) during the study and for 6 months after the last dose of the study drug if there is potential for conception. Male patients should also refrain from participating in sperm donation during the study and for 6 months following the last dose of the study drug.
11. The patients agree and have signed an informed consent form and are willing and able to comply with scheduled visits, study treatment plan, laboratory tests, and other trial procedures.

6.3 Exclusion criteria

Subjects will not be eligible to participate in this study if they meet any of the following criteria:

1. Prior systemic therapy with fulvestrant, everolimus, or any other CDK4/CDK6 inhibitors;
2. Subjects with known hypersensitivity to GB491 or any component of fulvestrant;
3. Known active, uncontrolled, or symptomatic CNS metastases, meningeal metastases, clinical symptoms suggestive of leptomeningeal disease, cerebral edema, spinal cord compression, and/or progressive tumor growth. Patients with a history of central nervous system metastases, meningeal metastases, spinal cord compression, etc. could be enrolled if they were clearly treated and had stable clinical manifestations. Patients are eligible if they were treated with anticonvulsants and steroids for at least 2 months prior to randomization and were clinically stable;

4. Visceral crisis. Visceral crisis refers to multiple organ dysfunction confirmed by symptoms, signs, laboratory tests, rapid disease progression. Visceral crisis does not simply refer to the presence of visceral metastasis, but refers to critical visceral conditions requiring rapid and effective treatment to control disease progression (including uncontrollable pleural effusion, pericardial effusion, abdominal effusion, pulmonary lymphangitis carcinomatosa, diffuse liver metastasis, bone marrow metastasis, etc.), especially refers to conditions that fail to respond to other treatments after progression;
5. Patients with skin lesions only at baseline and non-measurable imaging;
6. Patients with persistent unresolved toxicity of CTCAE > grade 2 caused by previous anti-tumor treatment; patients with irreversible toxicity (such as hearing loss) caused by previous treatment who are judged by the investigator and the sponsor not to be further aggravated by this study intervention can be enrolled;
7. Major surgery (or anticipated need for major surgery during the study), chemotherapy, radiotherapy, any investigational agent, or other anticancer therapy within 4 weeks prior to randomization;
8. Patients receiving bisphosphonates or denosumab at a stable dose for < 7 days prior to randomization;
9. Patients who received palliative radiotherapy to limited areas within 2 weeks prior to randomization, extensive palliative radiotherapy to extensive areas or radiotherapy to ≥ 30% of bone marrow areas within 4 weeks prior to randomization;
10. Taking drugs or fruits containing potent inducers or inhibitors of CYP3A4/5 or drugs with narrow therapeutic window mainly metabolized by CYP3A4/5 such as astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, pimozide, quinidine, tacrolimus and sirolimus within 2 weeks before randomization;
11. Patients receiving long-term systemic corticosteroids (excluding topical, inhaled sprays, eye drops or topical injections for the treatment of allergies or prevention of asthma relapse, and patients receiving hormone replacement therapy;
12. Any severe and/or uncontrolled medical condition such as: unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction within 6 months prior to randomization, severe uncontrolled arrhythmia; active or uncontrolled serious infection; history of stroke or cerebrovascular accident,

pulmonary embolism or deep venous thrombosis within 6 months prior to randomization; active upper gastrointestinal ulcer;

13. Patients had significant lung function impairment (i.e., lung function showed FEV1 and DLCO < 60% of predicted value). History of pneumonitis, drug-induced interstitial lung disease, radiation pneumonitis, or any evidence of clinically active interstitial lung disease;
14. Known history of HIV infection or history of HIV seropositivity (including positive HIV antibody at screening);
15. Prolonged QTc interval on screening ECG (Fridericia method > 480 msec) or documented history of prolonged QT interval;
16. Patient has severe liver disease such as cirrhosis, decompensated liver disease, acute or active hepatitis. Patients may be enrolled if serum HBsAg is positive or HCV-Ab is positive, but the corresponding serum HBV-DNA or serum HCV-RNA is below the lower limit of quantification of the local assay;
17. Abnormal coagulation profile, such as active bleeding, bleeding diatheses, or ongoing anticoagulant therapy (enrollment permitted if INR ≤ 2 for patients taking low-dose warfarin, LMWH (low molecular weight heparin), and aspirin or equivalents);
18. Patients unable to swallow the study drug, intractable nausea, vomiting, other diseases or clinical conditions that may significantly affect the absorption, distribution, metabolism and excretion of the study drug as judged by the investigator;
19. Previous autologous or allogeneic stem cell transplantation;
20. Inflammatory breast cancer;
21. Subjects with a history of other primary malignancies, except for subjects with non-melanoma skin cancer and cervical carcinoma in situ who have been disease-free for ≥ 3 years;
22. Breastfeeding women (such subjects may be enrolled in the study if breastfeeding is interrupted due to disease treatment);
23. Subjects with poor compliance in previous studies or judged as having poor compliance by the investigator. Subjects unwilling or unable to comply with the study protocol;

24. Subjects who are judged by the investigator to have participation in the trial that increases the safety risk or impacts the interpretation of the study results.

7 Study Treatment

Blinded study drug for this study is defined as: GB491 or placebo. Study treatment is defined as the combination of blinded study drug, fulvestrant, LHRH analogues such as goserelin (for premenopausal and perimenopausal female patients only and male patients unless there is a clear history of bilateral orchiectomy).

The following treatments will be administered in this study:

- Treatment group: 150 mg GB491 administered orally twice daily taken with food (recommended approximately 12 hours apart) on Days 1 through 28 of a 28-day cycle. Fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, then 500 mg intramuscularly on Day 1 of Cycle 2 and each subsequent cycle.
- Control group: Placebo administered orally twice daily (taken with food) on Days 1 through 28 of a 28-day cycle (recommended approximately 12 hours apart). Fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, then 500 mg intramuscularly on Day 1 of Cycle 2 and each subsequent cycle.

  For premenopausal and perimenopausal female patients and male patients (unless there is a clear history of bilateral orchiectomy) requiring the use of LHRH analogues (e.g., goserelin), LHRH analogues (e.g., goserelin) must be started at least 21 days before randomization, followed by subcutaneous goserelin delayed-release implants 3.6 mg every 28 days (or following other LHRH analogue treatment specifications).

The investigator or his/her designee is responsible for the following:

- Explain to the subjects/site personnel/legal representatives the correct use of the medication and the planned duration of each person's medication;
- Verify that instructions are followed correctly;
- Accurate recording of the study drug dispensing and collection;
- All unused drugs are returned to the sponsor or its designee at the end of the study.

7.1 Materials and supplies

7.1.1 Investigational medicinal products (IMPs)

Both GB491 (Lerociclib) and placebo will be supplied as white to off-white round film-coated tablets. GB491 tablets contain 50 mg equivalent of GB491 free base and excipients used in the formulation include: microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate, and coating premixes. Placebo tablets do not contain GB491 free base.

7.1.1.1 Packaging and labeling

GB491 tablets and placebo tablets are individually packaged in high-density polyethylene (HDPE) bottles and sealed with child-resistant closures. Bottles of GB491 tablets and placebo tablets will be labeled and provided to the pharmacist/designee who will count the contents and make records according to drug accountability requirements.

7.1.1.2 Storage

GB491 50 mg tablets and placebo tablets will be individually packaged in HDPE bottles with child-resistant closures and stored at 15℃ to 30℃.

The blinded study drug will be stored in a locked cabinet/secure area under the applicable storage conditions at the site and only the pharmacist/designee and designee will have access to the study drug.

7.1.2 Other medicinal products

7.1.2.1 Fulvestrant

Descriptions of the formulation, packaging, and labeling and storage conditions for fulvestrant are provided in the respective current dosage/dosage form information (see Appendix 2).

7.1.2.2 Goserelin or other LHRH analogues

For premenopausal and perimenopausal female patients and male patients (unless there is a clear history of bilateral orchiectomy), LHRH analogues (e.g. goserelin) are required. Goserelin or its analogues are administered according to the local standard of care and are not the study drugs. Goserelin or its analogues are described in their current dosage/dosage form information (see Appendix 2) in terms of formulation, packaging and labeling and storage conditions.

7.1.3 Distribution procedure

Dispensing instructions will be provided in the Pharmacy Manual and maintained in the pharmacy records.

7.1.4 Investigational product accountability

The pharmacist/designee will check the completeness of the clinical trial supplies (storage conditions, correct quantity received, shipment conditions, kit numbers, etc.) according to the site's Standard Operating Procedures (SOPs).

At least, the following data will be tracked on the pharmacy records at the site:

- Date received
- Batch No.

The study drug (used, missing, destroyed, and the returned containers, individual bottles) will be documented at each visit in drug accountability and dispensing. Drug accountability and reconciliation will be checked and reconciled by the pharmacy team and the site monitor during the study and at study completion. Unused and unopened study drugs will be returned to the sponsor by the site monitor.

7.2 Method of assigning treatments

Once the informed consent is obtained, the EDC system will assign a patient number. Patients who meet all the inclusion criteria will be randomly assigned to receive GB491 plus fulvestrant or placebo plus fulvestrant. Treatment group assignment will be determined by a random sequence generated by an Interactive Web Response System (IWRS). Premenopausal and perimenopausal female patients and male patients (unless there is a clear history of bilateral orchiectomy) need to use LHRH analogues (e.g. goserelin).

Randomization will be stratified according to the nature of the disease (visceral metastases vs bone only metastases vs others), menopausal status (male or premenopausal or perimenopausal vs postmenopausal), and number of prior lines of endocrine failure (first-line vs second-line).

7.3 Selection and timing of dosing

The study is designed to administer blinded study drug orally twice daily (approximately 12 hours apart is recommended) in 28-day cycles. Patients were to take blinded study medication with food and at approximately the same time each day. If a patient vomits

after taking the drug or misses a dose for any reason, no additional doses of the study drug are required. Fulvestrant should be administered at approximately the same time as the blinded study drug. Fulvestrant will be given intramuscularly on Days 1 and 15 of Cycle 1, then on Day 1 of Cycle 2 and each subsequent cycle. For Cycle 4 and beyond, the time interval between the blinded study drug and fulvestrant may be adjusted at the investigator's discretion. Adjustments to the PK sampling schedule may be required if dosing with the blinded study drug is withheld prior to the start of a cycle due to toxicity. The sponsor should be notified of these exceptions.

7.4 Dosage, regimen and route

7.4.1 Blinded study drug (GB491/Placebo)

GB491 is administered at 150 mg twice daily with food approximately 12-hour apart and at approximately the same time each day; placebo will be administered twice daily with food approximately 12-hour apart and at approximately the same time each day.

7.4.2 Fulvestrant

Fulvestrant 500 mg is administered intramuscularly on Days 1 and 15 of Cycle 1 and 500 mg intramuscularly on Day 1 of Cycle 2 and each subsequent cycle. Fulvestrant 500 mg should be injected intramuscularly and slowly (1-2 minutes per injection), 250 mg on each side.

7.4.3 LHRH analogues (e.g., goserelin)

For premenopausal and perimenopausal female patients and male patients (unless there is a clear history of bilateral orchiectomy) requiring the use of LHRH analogues (e.g., goserelin), LHRH analogues (e.g., goserelin) must be started at least 21 days before randomization, followed by subcutaneous goserelin delayed-release implants 3.6 mg every 28 days (or following other LHRH analogue treatment specifications).

7.5 Special considerations for treatment

7.5.1 Dose modifications and delays

Toxicities will be graded using NCI CTCAE version 5.0 and blinded dose modifications of the study medication will be made according to the toxicity grade. Study drug dose modifications are allowed within and between the cycles. Dose modifications for the study drug are shown in**Table 5**. Patients requiring dose reductions are allowed to return to the previous dose level only after consultation with the sponsor. If a patient has

already had a dose reduction to 50 mg twice daily due to drug toxicity and further dose reduction is still required, the patient must discontinue the use of GB491.

Table 5 Blinded drug modifications

Dose Level	Oral Dose
Starting Dose	Starting dose level (150 mg in the morning, 150 mg in the evening)
First Dose Reduction	Dose reduced by 1 dose level (100 mg in the morning, 100 mg in the evening)
Second Dose Reduction	Dose reduced by 1 additional dose level (50 mg in the morning, 50 mg in the evening)

If the investigator considers the potential benefit of continued therapy outweighs the potential risk, a withdrawal period of more than 14 days is permitted, but these must be discussed with the medical monitor.

Fulvestrant: The dose of fulvestrant should not be adjusted during the study (patients may still need to continue taking blinded study drug during periods of dose interruption due to fulvestrant).

Goserelin or other LHRH analogues: No dose adjustment of goserelin or other LHRH analogues is allowed during the study.

7.5.2 Dose modifications due to hematologic toxicity and non-hematologic toxicity

Study medication modifications in Table 6 are based on hematologic adverse reactions (except lymphopenia) unless accompanied by a clinical event such as opportunistic infection.

Table 6 Toxicity dose modifications and delays for GB491 in Study GB491-004

Toxicity Type	**Toxicity Profile and Severity**	**Dose Withhold**	**Dose Reduction**
Hematologic toxicity	Grade 3 (**except for** Grade 3 neutropenia with fever)	Dosing **must** be withheld until the toxicityresolves to at leastGrade 2.	Dose remains **unchanged**.
Hematologic toxicity	Recurrent Grade 3	Dosing **must** be withheld until the toxicity resolves to at least Grade 2.	Dose **must** be reduced by 1 dose level.

Toxicity Type	Toxicity Profile and Severity	Dose Withhold	Dose Reduction
Hematologic toxicity	Grade 4 or Grade 3 neutropenia with fever	Dosing **must** be withheld until the toxicity resolves to at least Grade 2.	Dose **must** be reduced by 1 dose level.
Hematologic toxicity: Subject requires blood cell growth factor	Regardless of the severity (Growth factors are used according to the American Society of Clinical Oncology (ASCO) Guidelines)	Following the last administration of blood cell growth factor, dosing **must** be withheld for at least 48 hours until the toxicity resolves to at leastGrade 2.	Dose modifications are determined according to the respective hematologic toxicity dose modification rules.
Non-hematological toxicity	Persistent or recurrent Grade 2 that does not resolve to baseline or Grade 1 with best supportive care within 7 days	Dosing **may** be withheld until the toxicity has resolved to baseline or Grade 1. - at the discretion of the investigator.	Dose may be reduced by 1 dose level – at the discretion of the investigator. *
Non-hematological toxicity	Grade 3 or 4	Dosing **must** be withheld until the toxicity has resolved to baseline or Grade 1 or to ≤ Grade 2 at the discretion of the investigator without apparent safety risk to the patient	Dose **must** be reduced by 1 dose level.

Abbreviation: ASCO = American Society of Clinical Oncology

* In case of Grade 2 non-hematological toxicity, if dose reduction is considered after recovery of toxicity, please contact the sponsor first and consider dose reduction after confirmation;

Note: May = according to the investigator's clinical judgment; must = mandatory

7.5.3 Dose withhold

Dose hold is allowed for up to 14 days to allow sufficient time for recovery from toxicities that could be related to the study drug. Patients had to meet all of the following criteria before resuming treatment after treatment due to toxicity interruption: absolute neutrophil count ≥ 1×10^9/L, platelet count ≥ 50×10^9/L, and any nonhematologic, drug-

related toxicities recovered to ≤ Grade 1 or baseline (or recovered to ≤ Grade 2 as judged by the investigator without significant safety risk to the patient). Fulvestrant may be administered as scheduled on Cycle 1 Day 15 if there is a study drug dose hold during Cycle 1. If toxicity that could be related to the study drug occurs prior to initiating the next cycle, fulvestrant may be administered and the study drug may be held until recovery from toxicity. If fulvestrant is taken, but the study drug is held , then the date of fulvestrant administration remains on Day 1 of the next cycle.

7.5.4 Hematologic toxicities

If a subject experiences Grade 4 hematologic toxicity or neutropenia Grade 3 with fever, dosing must be held until the toxicity has decreased to at least Grade 2, and the dose of the study drug must be reduced by 1 dose level.

If a subject experiences Grade 3 hematologic toxicity (except neutropenia Grade 3 with fever), dosing must be held (until toxicity has decreased to at least Grade 2) and the dose of the study drug remains unchanged. If a subject experiences repeated episodes of Grade 3 hematologic toxicity, dosing must be withheld (until toxicity reaches Grade ≤ 2) and the dose investigated must be reduced by 1 dose level.

If a subject requires blood cell growth factor, the study drug must be withheld for at least 48 hours after the last dose of blood cell growth factor until the toxicity resolves to at least Grade 2 with appropriate dose modifications for hematologic toxicities.

Hematologic toxicities must be resolves to at least Grade 2 prior to restarting the study drug.

7.5.5 Non-hematologic toxicities

If a subject experiences a ≥ Grade 3 nonhematologic toxicity, dosing must be interrupted (until the toxicity has decreased to baseline or ≤ Grade 1 or the investigator judges that recovery to ≤ Grade 2 poses no apparent safety risk to the patient) and the dose of the study drug must be reduced by 1 dose level.

If a subject had persistent or recurrent Grade 2 non-hematologic toxicity that did not resolve to baseline or Grade 1 by maximum supportive measures within 7 days, the study drug could be withheld (until the toxicity resolves to baseline or ≤ Grade 1) and the dose of the study drug could be reduced by 1 dose level at the discretion of the investigator. If Grade 2 non-hematologic toxicities occur, consider dose reduction after recovery from toxicity, contact the sponsor first and consider dose reduction after confirmation

Non-hematologic toxicities (except alopecia and fatigue) must have resolved to Grade 1 or baseline (or to Grade ≤ 2, at the discretion of the investigator, with no apparent safety risk to the patient) prior to restarting the study drug.

7.5.6 Diarrhoea

Diarrhoea is a common gastrointestinal adverse reaction with CDK 4/6 inhibitors, Because diarrhoea may lead to dehydration and electrolyte loss, patients who develop diarrhoea should be closely monitored. Generally, the incidence and severity of CDK4/6-related diarrhea will lessen with prolonged treatment. At the beginning of the symptoms, if infection is ruled out, aggressive symptomatic support including diet modification, increased fluid intake, and antidiarrheal therapy (e.g., loperamide, etc.) should be performed, and patients should seek prompt medical attention if symptoms are severe. Diarrhea-related adverse events are handled in the same way as described in Section 7.5.5 “Non-hematological Toxicities”.

7.6 Prior and concomitant medications and concomitant therapies

All concomitant therapies administered within 28 days prior to randomization, during study treatment, and 30 days after the last dose of the blinded study medication, including prescription medications, over-the-counter medications, growth factors, blood products, and parenteral nutrition, will be recorded. Documentation will include information on start and stop dates, dose, and reason for medication.

Other concomitant non-protocol anti-cancer therapies, including Chinese herbal medicine/Chinese patent medicine with anti-tumor indications, may not be administered prior to disease progression during this study.

No other concomitant trial drug may be administered during this study for any indication.

Subjects may be pretreated with a 5-HT3 antagonist prior to randomization to improve gastrointestinal tolerability. Continue 5-HT3 antagonists as needed. If necessary, diarrhea should be treated symptomatically with loperamide and other drugs according to diarrhea treatment guidelines and local clinical practice in a timely manner. Sites should ensure that subjects are fully informed about the correct use of medications for diarrhea.

7.6.1 CYP3A4 substrates

The results of clinical studies showed that GB491 had a minor effect on the PK of CYP3A4 substrates. Concomitant use of CYP3A4 substrates with GB491 is permitted

unless the CYP3A4 substrates are administered orally and the therapeutic index is narrow.

For CYP3A4 substrates administered orally with a narrow therapeutic index, caution is required during participation in this study (from 14 days before randomization to 14 days after the last dose of the study medication). Such agents include, but are not limited to:

- Midazolam, alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus.
- Doses of CYP3A4 substrates with a narrow therapeutic index should be reduced if necessary.

When such drugs are administered by routes other than oral (e.g., intravenous [IV], transdermal, inhalation, etc), their potential for clinically significant drug interactions with GB491 is low.

7.6.2 CYP3A4 inhibitors and inducers

In vitro studies suggest that CYP3A4 and CYP2C8 are primarily responsible for the oxidative metabolism of GB491. In human liver microsomes, CYP3A4/5 and CYP2C8 enzymes contribute approximately 70% and < 10% to GB491 metabolism, respectively.

Because GB491 is a substrate of CYP3A4, concomitant use with strong CYP3A 4 inhibitors or inducers or consumption of fruits containing CYP3A4 inhibitors or inducers may alter GB491 exposure.

- Caution should be exercised when coadministered with strong CYP3A inhibitors, including, but not limited to, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole.
- Concomitant use with strong CYP3A inducers (including, but not limited to, carbamazepine, enzalutamide, phenytoin, rifampin, and St. John's Wort (Hypericum perforatum)) is prohibited.
- Use of moderate CPY3A inducers (including but not limited to ziprasidone, cilostazol, ticagrelor, aprepitant, netupitant, ondansetron, domperidone) should be avoided or replaced.
- Fruits or juices containing inhibitors or inducers of CYP3A4 (grapefruit, grapefruit-related citrus fruits [e.g., Seville oranges, pomelos], etc) should be avoided.

7.6.3 CYP2C8 inhibitors and inducers

Because GB491 is a CYP2C8 substrate, concomitant use with strong CYP2C8 inhibitors or inducers may alter GB491 exposure.

- Caution should be exercised when coadministered with strong inhibitors of CYP2C8 (e.g., gemfibrozil, quercetin, sulfinpyrazone, trimethoprim, nicardipine).
- Caution should be exercised when coadministered with strong or moderate CYP2C8 inducers such as rifampin, phenobarbital, and carbamazepine.

7.6.4 Bisphosphonates and denosumab

Bisphosphonates and denosumab may be continued for osteoporosis or to manage pre-existing bone metastases in subjects receiving stable doses of the drug for at least 7 days prior to randomization. However, subjects who do not start bisphosphonates or denosumab for osteoporosis or bone metastases within 7 days prior to randomization will be excluded. Treatment should not be changed while receiving the study treatment. However, in exceptional cases where there is no evidence of disease progression, replacement may be considered after consultation with the sponsor. These exceptional circumstances did not lead to protocol deviations.

7.6.5 Growth factors

Growth factors are not permitted in an attempt to meet the inclusion criteria for the subjects in the study.

Growth factors may be used according to the American Society of Clinical Oncology (ASCO) guidelines (Smith et al. 2015). If administration of growth factors is required, the study drug must be held and the administration may not be restarted within 48 hours of the last dose of growth factor until the toxicity is ≤ Grade 2. Following administration of the growth factors, appropriate dose modifications were decided according to the corresponding hematological toxicity dose modification regulations.

7.6.6 Drugs not recommended

Long-term immunosuppressive therapy, including systemic corticosteroids, should be avoided. Steroids for physiological replacement, as antiemetics, or administered by inhalation, and short-term oral/topical steroids for allergic reactions or asthma attacks are permitted. Any use of systemic corticosteroids should be discussed with the medical monitor before use for reasons other than those listed above.

7.6.7 Additional precautions

GB491 inhibits P-gp, BCRP, MATE1, MATE2-K, and OCT1 and 2 membrane transporters, therefore, caution should be exercised when the co-administered drugs are the substrates of these transporters (Section 3.2.2). MATE2-K is associated with tubular creatinine secretion, and inhibition of MATE2-K by GB491 may result in increased serum creatinine levels independent of true alterations in renal function.

GB491 is a substrate and inhibitor of P-gp and BCRP efflux transporters. Concomitant use with strong P-gp or BCRP inhibitors or inducers may alter the GB491 exposure.

7.7 Concomitant radiotherapy or surgery

Subjects with locally advanced breast cancer may undergo surgery ± radiotherapy if the tumor is surgically amenable to the study treatment. However, such subjects should not receive the study treatment for a period of time (at least 7 days before surgery and until at least 14 days after completion of surgery ± radiotherapy) in order to achieve tissue healing and recovery. After this period, study treatment and study procedures may be resumed based on the most recent cycle completed prior to the surgery ± radiotherapy or the subject discontinued the study treatment. Importantly, subjects receiving surgery ± radiotherapy for locally advanced breast cancer will not be considered non-compliant with the study and will not result in protocol deviations. Documentation is required to include information on date, indication, procedure description, and any clinical or pathological findings.

Radiotherapy is not permitted in this study except for subjects with locally advanced breast cancer who may undergo surgery ± radiotherapy following the study treatment. All other subjects requiring radiotherapy should have the study treatment permanently suspended and their lesions assessed for tumor prior to receiving radiotherapy. Palliative radiotherapy is permitted for painful bony lesions provided lesions are known to be present when the subjects entering the study and the investigator clearly documents the necessity of palliative radiotherapy and clearly excludes disease progression.

7.8 Supportive therapy

Subjects should receive comprehensive supportive care to maximize quality of life. If it is unclear whether treatment should be considered supportive care, the investigator should consult with the sponsor. Any use of supportive care should be reported in the eCRF.

7.9 Treatment compliance

As described in this protocol, the investigator or designee will dispense the study drug for use only by subjects enrolled in this study. The study drug should not be used for reasons other than those described in the protocol. The investigator or other study staff will oversee the first dose of the study medication; thereafter, compliance will be evaluated by calculating the planned dose and actual dose. The clinical study site will maintain records of the receipt, preparation, and dispensing of the study drug, including the applicable lot numbers, bottle numbers, and counts of the tablets returned from study medication bottles at clinic visits.

7.10 Blinding

To maintain the study blind, ensure that a minimum number of staff are exposed to the randomization table and treatment assignment prior to study completion. Access to unblinded data/files will be controlled by restricting access to data/files in the sponsor's corporate data and statistical databases. Any changes to this unblinding plan may be described in a protocol amendment, statistical analysis plan, and/or separate unblinding plan documents.

Efficacy information will not be shared with the sites until the study is completed. After the overall study is completed, study personnel may unblind the subjects to the study treatment assignment.

7.10.1 Emergency unblinding

In case of an emergency, it is the sole responsibility of the investigator to determine whether it is necessary to unblind the subject's treatment assignment. Subject safety must always be the first consideration when making such a decision. If the investigator considers unblinding necessary, he/she should make every effort to reach out to the sponsor before unblinding the subject's treatment assignment unless this could delay the subject's emergency care.

Emergency unblinding due to an adverse event must be handled through an Interactive Web Response System (IWRS). This option may only be used if the subject's acute health condition requires knowledge of the subject's treatment assignment, or if the subject discontinues treatment due to disease progression according to RECIST v1.1 and the subject's treatment assignment is deemed critical to selecting their next regimen. In case of disease progression, the investigator has to consult the sponsor before unblinding.

The Interactive Web Response System (IWRS) records and reports all events leading to unblinding. If the study personnel or the subject are unblinded, the subject is to undergo a visit after discontinuation of dosing.

7.10.2 Accidental unblinding

Every effort will be made to blind the subject and study personnel to the treatment status, but inadvertent unblinding of the subject may occur. Double-blind study designs are also notoriously imperfect because there is a possibility of individual unblinding for signs and symptoms associated with treatment. If the investigator, site personnel performing assessments, or the subject is unblinded, the unblinding itself is not sufficient to suspend the subject from receiving the study treatment or to exclude the subject from any safety or efficacy analyses.

In addition, there may be ethical reasons for the subject to continue receiving study treatment. In order for a subject to continue making the study treatment unblinded, the investigator must obtain specific approval from the sponsor for the subject to continue the study.

8 Schedule of Study Procedures

Study procedures are summarized in the Schedule of Assessments (**Appendix 3**).

8.1 Screening

Patients should be screened within 28 days prior to randomization. Written informed consent has to be obtained from each subject before any screening procedures are started. Eligibility criteria will be determined by review of the inclusion/exclusion criteria and completion of **Appendix 3** and all screening procedures listed below after the subject has signed the informed consent.

Patients who have not had ER and HER2 status testing at the screening may have samples collected at this visit for HR and HER2 status testing. In patients with previous test results no re-sampling is required.

- Informed consent
- Collection of demographic data
- Collection of medical and medication history

  Note: Medication history will record medications taken within 28 days prior to randomization. Past medical history: Significant clinical history findings (e.g., previous diagnosis, disease, or surgery) considered relevant to the patient's eligibility prior to signing the ICF will be collected and documented in the electronic case report form, including the severity at baseline, and if the condition persists, it needs to be recorded in the eCRF. Clinically meaningful refers to any event, diagnosis, or laboratory value that requires treatment, follow-up, or the development of symptoms or signs that require medical intervention. Accompanying medical symptoms and signs must be documented to determine baseline severity.

- ECOG score

  0 Fully active, able to carry on all pre-disease performance without restriction

  1 Ambulatory and able to carry on light physical activity, including light housework or office work, but unable to carry on heavy physical activity

  2 Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours

  3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

  4 Bedridden and unable to carry on any self-care

  5 Death

- Physical examination

Note: A complete physical examination included the following: 1) general appearance; 2) head, eyes, ears, nose, and throat; 3) neck; 4) heart; 5) chest (including lungs); 6) abdomen; 7) extremities; 8) skin; 9) lymph nodes; 10) cardiovascular; and 11) neurological status. A complete physical examination is required only at baseline and at the EOT visit. Limited, symptom-based physical examinations will be performed at other visits (or as clinically indicated).

- Height, weight, and vital sign measurements
- Blood biochemistry, hematology and urinalysis
- Blood HBsAg, blood HCV-Ab, if HBsAg or HCV-Ab is positive, additional measurement of blood HBV DNA or blood HCV RNA is required, respectively; HIV antibody (confirmation is not required when HIV antibody is positive at screening);
- Electrocardiogram (single): ECG examination is performed at rest and can be performed at any time in the screening window.
- Pregnancy test (serum β-hCG)
- Radionuclide bone scan (if performed within 45 days prior to randomization, scans obtained prior to signing the informed consent will not be repeated; lesions identified on bone scan must be confirmed by x-ray, CT (bone window), or MRI)
- CT/MRI imaging assessments (see Section **9.1** for details). CT or MRI scans obtained prior to signing the informed consent will not need to be repeated if performed within 28 days prior to randomization.

Other necessary examinations, including brain CT/MRI, serum FSH, estradiol, pulmonary function, blood gas analysis, coagulation function, etc. may be additionally performed at the subject's screening at the investigator's discretion.

Hormone receptor status (estrogen receptor, progesterone receptor, or both) and HER2 status will be based on the prior diagnosis and testing from the local labs. Assay and result interpretation should be consistent with ASCO/CAP version 2020 ER/PgR tesing guidelines (Allison et al. 2020 and ASCO/CAP version 2018 HER2 testing guidelines (Wolff et al. 2018);

Serious adverse events (SAEs) that occur from informed consent to before the first dose and are associated with protocol-specified procedures should also be recorded in the EDC.

Eligibility will be determined prior to enrollment and initiation of the study treatment. Eligible patients will be instructed about all protocol requirements, including any restrictions on concomitant medication use.

8.2 Cycle 1

Cycle 1 Day 1 (C1D1)

The following procedures will be performed at this visit:

- Subject dosing diary
- Adverse event/concomitant medication
- ECOG score
- Physical examination
- Body weight and vital signs measurements: Vital signs include body temperature, blood pressure, pulse rate, and respiratory rate and are performed prior to dosing.
- Blood chemistry, hematology, urinalysis results can be obtained within 7 days prior to the first dose. Blood chemistry and hematology results should be reviewed prior to dosing. If the above tests were performed within 7 days before the first dose of the study drug, they did not need to be repeated on Cycle 1 Day 1.
- Electrocardiogram (single): ECG is performed at rest and before the study drug administration.
- Blinded study drug and fulvestrant administration
- For premenopausal/perimenopausal female and male patients (unless there is a clear history of bilateral orchiectomy), goserelin or other LHRH analogues should be administered according to their preplanned schedule.

C1D15

On Cycle 1 Day 15, the following procedures will be performed:

- Physical examination
- ECOG score
- Body weight and vital signs measurements
- Blood biochemistry, hematology and urinalysis

- GB491 PK trough samples (see "Pharmacokinetics (PK)" blood sampling schedule for specific blood sampling points)
- Electrocardiogram (single): ECG examination is performed at rest and before dosing.
- Adverse event/concomitant medication
- Subject dosing diary
- Blinded study drug and fulvestrant administration
- For premenopausal/perimenopausal female and male patients (unless there is a clear history of bilateral orchiectomy), goserelin or other LHRH analogues should be administered according to their preplanned schedule.

8.3 Beginning of Cycle 2 and subsequent cycles (Day 1 of each cycle)

- ECOG score
- Physical examination
- Body weight and vital signs measurements
- Blood biochemistry, hematology and urinalysis
- Electrocardiogram (single): ECG examination is performed at rest and before dosing.
- GB491 PK blood sampling (see "Pharmacokinetics (PK)" blood sampling schedule for specific blood sampling points)
- Adverse event/concomitant medication
- Subject dosing diary
- Blinded study drug and fulvestrant administration
- For premenopausal/perimenopausal female and male patients (unless there is a clear history of bilateral orchiectomy), goserelin or other LHRH analogues should be administered according to their preplanned schedule.
- Tumor evaluation is performed by CT or MRI or appropriate scan every 8 weeks (± 7 days) for 1 year and every 12 weeks (± 7 days) for 1 year from the date of randomization. The evaluation period is set as a fixed period based on random days.

- Radionuclide bone scans are performed at fixed cycles every 24 weeks (± 7 days) from the date of randomization and new lesions identified on bone scans are confirmed by CT/MRI. Note: Subjects who have a confirmed CR by CT/MRI will have a bone scan to confirm absence of bone metastases. Additional bone scans may be performed as clinically indicated at the investigator's discretion.

8.4 End of treatment visit

At the time of the last dose of the blinded study medication or early termination (+ 7 days), patients will return to the site for an end-of-treatment visit. The following procedures will be performed at this visit:

- ECOG score
- Physical examination
- Body weight and vital signs measurements
- Blood biochemistry, hematology and urinalysis
- Electrocardiogram (single)
- Adverse event/concomitant medication
- Tumor evaluation by CT or MRI or appropriate scanning

Note: Patients who discontinued study treatment without PD are assessed according to the original tumor assessment plan until objective disease progression, death, withdrawal of consent or loss to follow-up, receiving new antineoplastic therapy, or end of study. If possible, the EOT visit should occur as early as possible within 7 days after the last dose of the study drug.

Following completion of the end-of-treatment visit, subjects will enter the safety visit period.

8.5 Safety visit

Subjects will return to the study site 30 days (± 7 days) after the last dose of the blinded study drug for safety follow-up to undergo the required safety assessments. If new anticancer therapy is started prior to this safety follow-up visit, the safety follow-up visit should be performed as scheduled as early as possible, preferably before the start of other anticancer therapy. Patients who are unwilling or unable to return to the clinic for safety follow-up should be contacted by telephone regarding adverse events. The following procedures will be performed at this visit:

- ECOG score
- Physical examination
- Body weight and vital signs measurements
- Blood biochemistry, hematology
- Adverse event/concomitant medication

Following completion of the safety visits, subjects will enter the survival follow-up.

8.6 Survival follow-ups

For patients in the survival follow-ups, follow-ups should be performed and recorded at least every 12 weeks (± 14 days) from the day following completion of the safety visit. Follow-ups may be conducted by telephone, clinic visit, email, or by receiving information from the subject's family or care provider. Subjects will be followed for survival at a minimum until all subjects have died or to the end of study.

The following information will be collected for all subjects:

- Survival status
- Details of any anticancer therapy

For subjects who have not progressed at the time of discontinuation of the blinded study drug, efficacy assessments should be performed according to the original tumor assessment schedule until objective disease progression, death, withdrawal of consent or loss to follow-up, receiving new antineoplastic therapy, or the end of the study.

8.7 Unscheduled visits

Additional visits may be performed at the discretion of the investigator.

9 Study Evaluations

9.1 Efficacy evaluation

9.1.1 Efficacy assessments at baseline and during study treatment

All subjects will undergo baseline tumor assessments within 28 days prior to randomization, including:

- CT/MRI scans of chest, abdomen, pelvis and other sites of tumor involvement
- For subjects with inoperable locally advanced breast cancer, a breast MRI scan will be performed at baseline (if applicable)

- Bone scan, lesions identified on bone scan must be confirmed by CT (bone window) or MRI

Tumor assessments during the treatment period must consistently use the baseline assessment method and technique, including all lesion sites (including but not limited to the chest, abdomen, and pelvis), and the cycle of tumor assessments must be fixed (fixed cycles set based on the date of randomization). All patients will undergo CT/MRI evaluation every 8 weeks (± 7 days) during Year 1 and every 12 weeks (± 7 days) after Year 1. A fixed cycle will be set based on a random day, with bone scans performed every 24 weeks (± 7 days) until disease progression occurs. For patients who discontinue treatment prior to confirmed disease progression, CT/MRI imaging assessments should be performed according to the previous visit assessment schedule until 1) objective disease progression; 2) death; 3) withdrawal of consent or loss to follow-up; 4) receiving new antineoplastic therapy; and 5) end of study. Imaging assessments must be performed within 2 weeks if clinical progression is suspected. Patients with confirmed CR will undergo bone scan to confirm absence of bone metastases. At the investigator's discretion, additional bone scans may be performed and lesions confirmed by CT (bone window) or MRI if the patient has clinical symptoms and signs of worsening bone metastases.

Note: Enhanced CT should be the first choice for imaging assessment. For patients with known hypersensitivity to CT contrast agents, plain chest CT + enhanced abdominal/pelvic MRI assessment is optional.

Patients who undergo surgery for locally advanced disease during the course of the trial are considered to have objective disease progression if there is no evidence of residual disease following surgery and at least one of the following criteria is met:

- Local recurrence, or
- Advances in metastatic disease.

9.1.2 Efficacy assessments during post-discontinuation visits

For subjects who discontinued the study treatment for reasons other than progressive disease, tumor response is assessed at regular intervals approximately every 8 weeks during the first year after randomization and approximately every 12 weeks thereafter by the same method used at baseline and throughout the study until the subject experienced 1) objective disease progression; 2) death; 3) withdrawal of informed consent or loss to follow-up; 4) receiving new antineoplastic therapy; 5) end of study or until the primary

endpoint (PFS) analysis node. Following objective disease progression, imaging studies are no longer required and subjects will be followed approximately every 12 weeks (± 14 days) for survival until death or completion of the overall study.

9.1.3 Antitumor efficacy measurements

The primary efficacy endpoint of this study is PFS assessed by the investigator. The sponsor or its designee will collect and store all tumor imaging data of the enrolled patients throughout the study for evaluation.

The following efficacy measurements will be collected according to the study schedule in **Appendix 3**.

Table 7 Efficacy endpoints measures

Endpoint	Definition
Progression Free Survival (PFS)	Time from randomization to the date of objective progression or death for any cause, whichever occurs first
Objective Response Rate (ORR)	Proportion of subjects achieving a complete response or partial response according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
Disease Control Rate (DCR)	Proportion of subjects achieving complete response, partial response or stable disease according to the Response Evaluation Criteria in Solid Tumors version 1.1
Duration of Response (DOR)	Time from the date of the first evidence of confirmed complete response or partial response until the early objective progression or death for any cause
Clinical Benefit Rate (CBR)	Proportion of subjects achieving complete response, partial response, or stable disease ≥ 6 months based on the Response Evaluation Criteria in Solid Tumors version 1.1

Abbreviations: CR = complete response; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

Progression Free Survival (PFS): Time to progression free survival as defined by RECIST v1.1 (Eisenhauer et al. 2009) is calculated from the date of randomization to the date of objective progression or death for any cause, whichever comes first. Progression free survival periods will be censored in the methods specified in the SAP for subjects who are not known to have disease progression at the time of data cut-off for inclusion in each specific analysis.

Objective Response Rate (ORR): Objective response rate is the percentage of subjects achieving a best response (complete or partial response).

Disease Control Rate (DCR): Disease control rate is the percentage of subjects achieving a best response (complete or partial response) and stable disease.

Duration of Response (DOR): Duration of response is defined only for responders (subjects with confirmed complete response or partial response). Defined as calculated from the date of the first evidence of complete response or partial response until the date of objective progression or death for any cause, whichever comes first. For clarity, the start date should be determined by the initial assessment of complete response or partial response and not by the date of confirmation of complete response or partial response. If at the time of evaluation for the included data cut-off, it is not known whether a responder has died or has had an objective progression, then censoring will be performed using the method specified in the SAP.

Clinical Benefit Rate (CBR): The clinical benefit rate is the percentage of subjects who have had a best response (complete or partial response) and stable disease for at least 6 months.

9.1.4 Tumor lesions: identification and follow-up

Measurable lesions:

Measurable tumor lesions are defined as tumor lesions having the longest diameter (measured in at least one dimension) of the following smallest dimensions[20]:

- 10 mm by CT or MRI (slice thickness no greater than 5 mm)

Measurable lymph nodes must have short axis ≥ 15 mm by CT or MRI (slice thickness no greater than 5 mm); only the short axis must be measured at baseline and follow-ups.

Lytic bone lesions or mixed lytic-blastic lesions with soft tissue components meeting the definition of measurability described above may be considered measurable lesions. Cystic lesions that meet the definition of measurability described above and represent cystic metastases may be considered measurable. If cystic lesions are present, non-cystic lesions should be selected as target lesions for this study.

Target lesions:

At baseline, up to 5 measurable tumor lesions/lymph nodes (up to 2 lesions per organ) should be identified as target lesions and will be followed to quantify disease status during the study. Target lesions should be those of the longest diameter that represent all involved organs and can be measured reproducibly. Lesions that have been irradiated can be selected as target lesions if they meet the criteria for repeated measurement and

are the only available lesions. Lesions biopsied at screening should not be selected as target lesions (unless the biopsied lesion has healed for at least two weeks before baseline imaging).

At baseline and at each follow-up time point, each target lesion should be measured and the overall tumor burden will be calculated as the sum of the diameters of target lesions (longest diameter [LD] of tumor lesions and short axis of lymph nodes) and recorded in the electronic case report form (eCRF). If the target lesion is divided into multiple smaller lesions, the LD of all the divided parts is added to the sum of the diameters. If multiple lesions coalesce, LD of the confluent lesion will be included in the sum of diameters.

Non-measurable lesions:

Nonmeasurable lesions include tumor lesions < 10 mm in the longest diameter, lymph nodes ≥ 10 to < 15 mm in the short axis, or nonmeasurable lesions such as leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of the skin or lung, or abdominal masses/abdominal organomegaly identified by physical examination that could not be measured by CT scan or MRI [20].

Non-target lesions:

All other lesions (or sites of disease) identified at baseline should be identified as non-target lesions and documented in the electronic case report form (eCRF). Measurements of these lesions are not required, but the presence, absence, or unequivocal progression of each non-target lesion should be recorded in the eCRF at each follow-up time point. Multiple non-target lesions in the same organ may be recorded under a single item in the eCRF.

New lesions:

Any new lesions should be identified and documented at each follow-up evaluation as these are markers of disease progression. According to the RECIST v1.1 guidelines[20], new lesions include the following:

- Lesions in anatomical locations not scanned at baseline
- Suspected small new lesions, progression on continued treatment and follow-ups, representing new disease (progression should be considered as having started on the date of the initial scan)

- Negative 2-deoxy-2- [fluoro-18] fluoro-D-glucose positron emission tomography (FDG-PET) at baseline, but positive FDG-PET at follow-ups
- No FDG-PET was performed at baseline, but the FDG-PET result was positive at follow-ups, corresponding to a new lesion site that needs to be confirmed by CT (the date of disease progression should be the date of the initial abnormal FDG-PET scan)

Note: Findings attributable to differences in scanning technique or changes in imaging type (CT vs MRI) and findings representing lesions other than tumor (e.g., healing or recurrence of existing bone lesions, necrosis of liver lesions) should not be considered as new lesions.

9.1.5 Definitions of tumor response and disease progression

Tumor response and progression will be determined according to the RECIST v1.1 criteria[20]. Tumor response is defined according to the RECIST v1.1 as follows:

9.1.5.1 Target lesion response evaluation

- **Complete response (CR)**: disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- **Partial Response (PR)**: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD)**: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to a relative increase of 20%, the sum of diameters must also show an absolute increase of at least 5 mm. The appearance of 1 or more new lesions is also considered progression.
- **Stable disease (SD)**: neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD using the sum of the smallest diameters during the study as a reference.

If there was insufficient information to classify response status, the non-evaluable (NE) response category was used.

9.1.5.2 Evaluation of Non-Target Lesions

- **Complete Response (CR)**: disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must have the short axis < 10 mm.
- **Non-CR/Non-PD**: Persistent presence of 1 or more non-target lesions and/or maintenance of tumor marker level above the normal range.
- **Progressive Disease (PD)**: Unequivocal progression of existing non-target lesions or appearance of at least 1 new lesion.

9.1.5.3 Overall response evaluation

Subjects who have undergone at least one post administration tumor assessment (CT scan or MRI) will be considered evaluable for tumor response.

Table 8 describes the overall response evaluation at each time point based on target and non-target lesion response at each time point, as well as the appearance of new lesions. Best overall response (BOR) is the best response recorded from the start of treatment until disease progression or receiving new antineoplastic therapy, whichever occurs earlier.

9.1.5.4 Evaluation of bone lesions

For those subjects with unmeasurable pure bone lesions, objective progression will be established if at least one of the following criteria is met:

- Appearance of one or more new lesions (intraosseous or extraosseous), or
- Definite progression of existing bone lesions.

Pathologic fractures, new compression fractures, or bone metastasis complications will not be considered as evidence of disease progression unless at least one of the above criteria is met.

Table 8 Evaluation of overall response at each time point

Target Lesion	Non-Target Lesion	New Lesion	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/Not evaluated	No	PR

SD	Non-PD/Not evaluated	No	SD
NE	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = source not evaluable [20].

9.2 Pharmacokinetic evaluation

Venous blood samples will be collected to determine plasma concentrations of GB491 and its metabolite G1T30 at the visits and times specified in the Pharmacokinetic Blood Sampling Schedule in **Appendix 3** for inclusion in the population pharmacokinetic analysis.

Before the study is unblinded, drug concentration information that may cause the study to be unblinded will not be reported to the site or the blinding individuals.

Sample processing and other information are detailed in the sample management manual.

9.3 Safety evaluation

All adverse events are collected from the time of the first dose of the blinded study drug through 30 days after the last dose of the blinded study drug (or until the start of a subsequent new anticancer therapy, whichever comes first). Following the safety follow-up period, if the investigator becomes aware of any serious adverse events, only the study drug-related serious adverse events (SAEs) are to be reported until receiving subsequent new anticancer therapy or the end of study. At the same time, only serious adverse events resulting from protocol-specified procedures (e.g., serious adverse events related to invasive procedures [e.g., biopsies]) are collected from the time of informed consent through the first dose.

Treatment-emergent adverse events (TEAEs) are defined as adverse events that started with the first dose until 30 days after the last dose of the blinded study medication (or until receiving a new antineoplastic treatment, whichever comes first).

The investigators will evaluate the safety tolerability of GB491 or placebo in combination with fulvestrant using the NCI CTCAE version 5.0.

9.3.1 Adverse events and serious adverse events

9.3.1.1 Definition of adverse events

An adverse event refers to any untoward medical occurrence in a clinical trial in a subject administered with a medicinal product, which does not necessarily have a causal relationship with the treatment. An adverse event may be any unfavorable and unintended symptom, sign, laboratory abnormality or disease, including the following:

- Worsening of preexisting (prior to entry into the clinical trial) medical conditions/diseases (including worsening of symptoms, signs, laboratory abnormalities; except for events clearly related to disease progression);
- Any new adverse event: any new untoward medical condition (including symptoms, signs, newly diagnosed disease)
- Abnormal clinically significant laboratory values or results that are not due to concomitant illness.

Adverse events do not include the following:

- Pre-existing conditions not worsening or conditions present or detected at the start of the study
- Symptoms and signs associated with the disease under investigation
- Circumstances in which an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience hospitalization). For patients with locally advanced breast cancer, surgery ± radiotherapy is allowed in this study in case the tumor can be operated upon by the study treatment, and if the subject is hospitalized only for receiving the relevant surgery ± radiotherapy, such case does not need to be recorded as an AE or expedited reporting as an SAE.
- Overdose of the study drug or concomitant medication without any signs or symptoms
- Disease progression
- Clinically insignificant laboratory abnormalities as determined by the investigator (only clinically significant laboratory abnormalities should be reported as adverse events in the eCRF)

An unexpected adverse event is any adverse event that is not identified in nature, severity, or frequency in the current Investigator’s Brochure or Product Information.

- An adverse drug reaction is defined as an adverse event caused by a drug (also called a drug-related adverse event). An unexpected adverse reaction is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product). All noxious and unintended responses to a medicinal product associated with any dose should be considered adverse reactions. The phrase "reaction to a medicinal product" refers to a causal relationship between a medicinal product and an adverse event that is at least a reasonable possibility, i.e., an association cannot be ruled out.

The investigator is responsible for recording all adverse events occurring during the study and every effort should be made to remain vigilant for possible adverse events. During the study, the investigator should collect the AEs by active inquiry and encourage the subjects to report AEs spontaneously. Adverse events should be reported in the appropriate pages of the eCRF.

In the event of an adverse event, the primary concern is subject safety. Appropriate medical intervention should be provided and investigational product discontinued if necessary.

9.3.1.2 Definition of serious adverse events

A serious adverse event (SAE) is defined as any adverse event that meets any of the following criteria:

- Causing death
- Life threatening

  Note: The term "life-threatening" in the definition of "serious adverse event" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires hospitalization or prolongation of the existing hospital stay
- Results in persistent or significant disability or incapacity
- Congenital anomaly/birth defect
- Other important medical events (defined as events that jeopardize the subject or require intervention to prevent any of the above)

9.3.1.3 Assessment of the severity of adverse Events

The severity of adverse events (toxicity grading) will be graded according to NCI CTCAE version 5.0.

To ensure there is no confusion or misinterpretation between the terms "serious" and "severe", the following clarifying note is provided:

The term severe is often used to describe the intensity (severity) of a specific event (e.g., mild, moderate, or severe myocardial infarction); however, the event itself may be of relatively minor medical significance (e.g., severe headache). This differs from "serious", which is based on the criteria for action taken with respect to the subject/event outcome or to an event that is typically associated with an event that jeopardizes the subject's life or function. Criteria for "seriousness" are specified in Section 9.3.1.2.

9.3.1.4 Assessment of the relationship between adverse events to study drug

The investigator is required to make an assessment of the causal relationship of the adverse event to the study drug. Investigators should use their knowledge of the subject, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered related to the study drug. The following guidelines should be considered when determining causality:

- Temporal relationship between the onset of an event and start of the study drug
- Consistency with known drug profile. Whether the AE is consistent with existing information on the suspected drug (pharmacology and toxicology) or drug of the same pharmacological class, or whether the occurrence of the AE can be predicted from the pharmacological properties
- Course of the event, particularly considering the effects of dose reduction, discontinuation of the study drug, or reintroduction of the study drug (if applicable)
- Known association with the study drug or similar therapy
- Known events related to the disease under study
- Presence of risk factors in the subject or concomitant medication known to increase the occurrence of the event
- Presence of non-treatment-related factors known to be associated with the occurrence of the event

Causal relationship to the study drug or study procedure should be assessed using the following terms:

- Related: Assessed as "Related" if following review of relevant data, there is factual evidence, support of drug mechanism of action, or relevant laboratory diagnostic criteria suggest a definite causal relationship.
- Unrelated: The available information should be causally assessed and judged and assessed as "unrelated" when there is insufficient evidence to establish a causal relationship or there is limited information in the medical record.

For subjects receiving combination therapy, causality will be evaluated separately for each protocol-specified treatment.

9.3.1.5 Assessment of outcome of adverse events

Action taken with the study drug (e.g., dose increased, dose not changed, dose decreased, dose interrupted, discontinued, not applicable, unknown) will be documented in the eCRF.

Other measures (e.g., no measures, administration of concomitant medications, new or prolonged hospitalization, surgical procedures) will also be recorded in the eCRF.

Outcomes will be assessed according to the following criteria:

- Fatal
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Recovering/Resolving
- Recovered/resolved
- Unknown

9.3.1.6 Methods, frequency, and time periods for detecting adverse events and serious adverse events

All adverse events are collected from the time of the first dose of the blinded study drug through 30 days after the last dose of the blinded study drug (or until the start of subsequent new anticancer therapy, whichever comes first). At the same time, only serious adverse events resulting from protocol-specified procedures (e.g., serious adverse events related to invasive procedures [e.g., biopsies]) are collected from the time of signing the informed consent through the first dose. Following the safety follow-up period, if the investigator becomes aware of any serious adverse events, only the study drug-related serious adverse events (SAEs) are to be reported until receiving subsequent new anticancer therapy or the end of study.

Treatment-emergent adverse events (TEAEs) are defined as AEs starting from the first dose until 30 days after the last dose of the blinded study drug (or until receiving a new anticancer therapy, whichever occurs first).

9.3.1.7 Recording of adverse events and serious adverse events

All adverse events will be recorded in the Adverse Events page of the eCRF. CTCAE Version 5.0 grading scale is used to aid in the classification and grading of adverse events. All serious adverse events will be additionally documented in the Serious Adverse Event Report Form.

The following will be recorded for each adverse event in the eCRF:

- Describe the adverse event in medical terms rather than subject-reported wording. Whenever possible, a diagnosis should be provided if certain signs and symptoms are due to a common cause (e.g., cough, runny nose, sneezing, sore throat, and dizziness should be reported as"upper respiratory tract infection").
- Onset date (Start date)
- Outcome

The following are general rating categories.

AE grading system, Grade 1-5 (semicolon indicates 'or' in the description of grade).

1. Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2. Moderate; minimal, local, or noninvasive intervention indicated; age-appropriate instrumental activities of daily living are limited *
3. Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living *
4. Life-threatening; urgent intervention indicated
5. Death related to AE

ADL = Activities of Daily Living Scale.

* Instrumental ADL refers to cooking, purchasing groceries or clothes, making phone calls, managing finances, etc.

* Self-care ADL refers to bathing, dressing and undressing, eating, using the toilet, taking medications, and not being bedridden.

9.3.1.8 Coding of adverse events

Adverse event verbatim terms provided by the investigator will be coded by the sponsor or its designee using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) as described in the Statistical Analysis Plan (SAP).

9.3.1.9 Reporting of serious adverse events

Reporting period for serious adverse events begins after signing of the informed consent and continues until 30 days after the last dose of the blinded study drug (or until the start of a new antineoplastic therapy, whichever occurs earlier) (Note: only serious adverse events resulting from protocol-specified procedures are collected from signing the informed consent until the first dose). Following the safety follow-up period, if the investigator becomes aware of any serious adverse events, only study drug-related serious adverse events (SAEs) are to be reported until receiving subsequent new anticancer therapy or the end of study. All serious adverse events or follow-up information will be reported to the sponsor's pharmacovigilance department or a designated third-party service provider **within 24 hours** of awareness. For reporting of death events, the investigator should provide the sponsor or designated third-party service provider and ethics committee with other required information, such as autopsy reports and final medical reports.

The investigator should complete the standard SAE Report Form provided by the sponsor according to the SAE Completion Guidelines and send it to the email address and/or fax number provided by the sponsor so that the sponsor can process the relevant SAEs in its safety database and submit the individual case report that meets the unexpected serious adverse reactions (SUSARs) in accordance with the local regulatory guidelines.

The sponsor or its designated third-party service provider shall report the suspected unexpected serious adverse reactions (SUSARs) to all participating investigators, clinical trial institutions and ethics committees within an expedited time limit according to the requirements of local regulatory guidelines.

The sponsor or its designated third-party service provider reports all SUSARs to the drug regulatory authority and health authorities within an expedited timeframe as required by local regulatory guidelines.

For SAEs, symptoms and signs, severity, onset time, relevant laboratory tests, concomitant therapy and drugs, intervention and treatment measures taken, outcome of the event, assessment of the relationship between the event and the investigational drug, and relevant supporting evidence should be recorded in detail.

For SAEs where the following important medical information is changed, the investigator should submit a follow-up report within 24 hours of awareness:

- New signs or symptoms or changes in diagnosis
- Important new diagnostic test results
- Change in causal relationship
- Change in event outcome.

If the investigator believes that a previously reported SAE has misreported information, corrections, withdrawals, or explanation for de-escalation may be made in the follow-up report and reported according to the SAE reporting procedure.

The investigator shall timely respond to and clarify the SAE-related queries raised by the sponsor.

9.3.1.10 Follow-up of adverse events

All adverse events (serious and non-serious) should be followed up by the investigator according to Good Clinical Practice until resolution, return to baseline, or considered unlikely to recover further. If at the time the subject completed the safety visit, he/she still had unresolved adverse events, the investigator was to follow these events until resolution, the patient was lost to follow-up, or the adverse event had an alternative explanation, or it was considered that further recovery was impossible. All actions required for adverse event management and the final outcome of the adverse event will be documented in the source documents and reported to the sponsor or designated third party service provider.

9.3.1.11 Adverse events of special interest and risk management plan

The most important risks identified to date in relation to GB491 are:

Neutropenia:

- GB491 has direct pharmacological effects on bone marrow stem cells and progenitor cells and is the result of non-fatal cell cycle arrest that can be reversed by treatment interruption.
- Initial decreases in neutrophil counts leveled off during the first 4 to 5 weeks of

treatment and remained generally at the same toxicity grade thereafter.

- Complications of neutropenia (e.g., fever, infection) are uncommon.

Gastrointestinal tolerability:

- Subjects or healthy volunteers exposed to GB491 commonly presented with diarrhea and nausea; most were Grade 1 or 2.
- No adverse events of diarrhea or nausea were reported at the maximum toxicity grade 4 or higher.
- Most GB491-related gastrointestinal TEAEs were toxicity of Grade 1 or 2.

ILD/Pneumonia:

- FDA's Drug Safety Newsletter warned (September 13, 2019) that the use of the CDK 4/6 inhibitors Ibrance/palbociclib, Kisqali (ribociclib), and Verzenio (abemaciclib) for the treatment of some patients with advanced breast cancer will lead to rare but serious pulmonary inflammation, including life-threatening or fatal ILD and/or pneumonia.
- A total of 4 subjects (2.9%) from Studies G1T38-02 and G1T38-03 were diagnosed with suspected or confirmed ILD/pneumonia based on clinical history and diagnosis. Two subjects required hospitalization without intensive care. Two subjects presented concurrent conditions including worsening pleural effusion and viral infection with dyspnea. One subject received pembrolizumab 6 months prior to osimertinib, which may increase the risk of developing serious immune-related AEs. No fatal cases were reported. No ILD/pneumonitis was reported in healthy subjects (Studies G1T38-01, G1T38-06, and G1T38-103).

Table 9 Risk management plan

Safety of Concern	Associated Inclusion/Exclusion Criteria and Management	Management Measures and Monitoring Recommendations
Hematology-related adverse events (including neutropenia, leukopenia, anemia, thrombocytopenia, lymphopenia)	Inclusion criteria: • The following laboratory parameters must be met: a) Hemoglobin ≥ 90 g/L and no red blood cell transfusion within 14 days prior to the first dose;	• Hematology was performed at screening and baseline measurements were performed; • During the study treatment, hematology

	b) Absolute neutrophil count ≥ 1.5 x 10^9/L; c) Platelet count ≥ 100 × 10^9/L; Exclusion criteria: • Patients with persistent unresolved toxicity of CTCAE > 2 caused by previous anti-tumor treatment; for patients with irreversible toxicity caused by previous treatment (such as hearing loss), they can be enrolled if the investigator and the sponsor judged that the toxicity will not be further aggravated by this study intervention; • Abnormal coagulation function, such as active bleeding, bleeding diatheses, or ongoing anticoagulant therapy (for patients using low-dose warfarin, LMWH (low molecular weight heparin), and aspirin or equivalent, enrollment is allowed if INR ≤ 2);	tests were performed regularly for monitoring; • Methods for dose level adjustment of GB491 based on hematological toxicities were developed; • Subjects must meet all of the following criteria before resuming treatment after treatment due to toxicity interruption: absolute neutrophil count ≥ 1 × 10^9/L, platelet count ≥ 50 × 10^9/L, and any nonhematologic, drug-related toxicities must return to ≤ Grade 1 or baseline (or recover to ≤ Grade 2 as judged by the investigator without significant safety risk to the patient); • The sponsor conducts regular medical reviews of the safety data and communicates with the investigator at any time if necessary;
Gastrointestinal-related adverse events (including nausea, diarrhea, vomiting)	Exclusion criteria: • Patients unable to swallow the study drug, due to intractable nausea, vomiting, or other diseases and clinical conditions that may significantly affect the absorption, distribution, metabolism and excretion of the study drug as judged by the investigator;	• Closely monitor the gastrointestinal symptoms during the study • The sponsor conducts regular medical reviews of the safety data and communicates with the investigator at any time if necessary;
Interstitial lung disease and/or pneumonitis	Exclusion criteria: • Patients with persistent unresolved toxicity of CTCAE > 2 caused by previous anti-tumor treatment; for patients with irreversible toxicity caused by previous treatment (such	• Closely monitor the pulmonary symptoms and observe adverse events during the study; • Or suspected interstitial lung disease and/or non-infectious pneumonia;

	as hearing loss), they can be enrolled if the investigator and the sponsor judged that the toxicity will not be further aggravated by this study intervention; • Patients had significant lung function impairment (i.e., lung function showed FEV1 and DLCO < 60% of the predicted values). History of pneumonitis, drug-induced interstitial lung disease, radiation pneumonitis, or any evidence of clinically active interstitial lung disease;	after excluding infection, tumor and other causes, complete relevant examinations, including but not limited to chest X-ray, CT, etc.; • For subjects who developed new or worsening respiratory symptoms or suspected pneumonia, discontinue the dosing and conduct subject evaluation; • For all subjects with severe interstitial lung disease or non infectious pneumonia, GB491 will be permanently discontinued.
Combined with other risks identified for marketed CDK4/6 agents and the pre-clinical study data of GB491, the following risks are identified as potential risks to develop risk control measures		
Cardiac-related Risks	Exclusion criteria: • Any severe and/or uncontrollable medical condition such as: unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction within 6 months prior to enrollment, severe uncontrolled arrhythmia; active or uncontrolled serious infection; history of stroke or cerebrovascular accident within 6 months prior to enrollment; • Screening ECG demonstrating QTc prolongation (> 480 msec per Fridericia method) or a clear history of QT prolongation.	• All grades of cardiotoxicity require investigation and intervention; • Screening and baseline 12-lead ECGs were performed, and regular 12-lead ECGs were performed for monitoring during the study; • Subjects must meet all of the following criteria before resuming treatment after treatment due to toxicity interruption: absolute neutrophil count ≥ 1 × 10^9/L, platelet count ≥ 50 × 10^9/L, and any nonhematologic, drug-related toxicities must return to ≤ Grade 1 or baseline (or recover to ≤ Grade 2 as judged by the investigator without significant safety risk to the patient);

		• ECG, echocardiography and other examinations were performed according to the signs and symptoms (considering heart disease); • For admitted subjects, cardiology consultation was requested.
Liver-related Risks	Inclusion criteria: • The following laboratory parameters must be met: a) Total bilirubin ≤ 1.5 times the upper limit of normal (ULN); in case of Gilbert's disease, total bilirubin ≤ 3 times ULN is allowed; b) Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≤ 3 times ULN; if liver metastasis is present, AST and/or ALT ≤ 5 times ULN may be accepted. Exclusion criteria: • Administration of drugs or fruits containing potent inducers or inhibitors of CYP3A4/5 within 14 days prior to randomization, or administration of drugs with a narrow therapeutic window that are mainly metabolized by CYP3A4/5 such as astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, everolimus, pimozide, quinidine, tacrolimus, and sirolimus; • Patients with severe liver disease, such as cirrhosis, decompensated liver disease, acute or active hepatitis. Patients may be	• Laboratory tests (hematology, blood chemistry) were performed at screening and baseline, and liver function was closely monitored regularly during the study; • Subjects must meet all of the following criteria before resuming treatment after treatment due to toxicity interruption: absolute neutrophil count ≥ 1 × 10^9/L, platelet count ≥ 50 × 10^9/L, and any nonhematologic, drug-related toxicities must return to ≤ Grade 1 or baseline (or recover to ≤ Grade 2 as judged by the investigator without significant safety risk to the patient); • If liver injury is suspected, the investigators should ensure that etiologic evidence is conclusive or other causes can be ruled out; • The sponsor conducts regular medical reviews of the safety data and communicates with the investigator at any time if necessary.

	enrolled if serum HBsAg is positive or HCV-Ab is positive, but the corresponding serum HBV-DNA is below the local lower limit of quantification or serum HCV-RNA is below the local lower limit of quantification.	

9.3.1.12 Handling of overdose and toxicity

In clinical studies, an overdose is any dose that exceeds the daily dose defined in the clinical study protocol.

If an overdose of the study drug occurs during the course of the study, the investigator or other site personnel should promptly or **no later than 24 hours after awareness** report via mail to the appropriate sponsor representative. The sponsor's designated representatives will work with the Investigator to ensure that all relevant information is provided to the Sponsor or designee.

In case of GB491 overdose, if there are no symptoms of overdose, no specific treatment is needed, and in case of overdose and clinical symptoms, the physician should follow general supportive measures for symptomatic treatment. If an AE/SAE is due to an overdose, the AE/SAE will be recorded.

9.3.1.13 Pregnancy reporting

All pregnancy reports from the first dose to the safety follow-up period need to be reported.

Subjects who become pregnant (including ectopic pregnancy) during the clinical study and within 30 days of the last dose of the study drug will be excluded from the study, and the pregnancy will be reported to the sponsor within 24 hours of the investigator's awareness of the pregnancy, and the sponsor's relevant Pregnancy Report/Follow-up Form will be completed. If a male subject's partner experiences pregnancy during the study period and within 30 days after the last administration of the study drug, the same process needs to be followed to report to the sponsor.

The investigator needs to follow up the pregnancy outcome until two months after the delivery and report the outcome to the sponsor.

Pregnancy is not considered an adverse event unless there is reason to believe that the study drug may interfere with the effectiveness of the contraceptives. Uncomplicated elective abortions should not be classified as adverse events. Hospitalization of healthy newborns with normal delivery should not be considered a serious adverse event. If the

outcome of the pregnancy is fatal, spontaneous course, congenital anomaly/birth defect should be reported and handled as a serious adverse event.

It is recommended to avoid pregnancy or childbearing for 6 months following discontinuation of the study drug. No information is currently available on the effects of GB491 on fertility, pregnancy, or subsequent child development.

9.3.1.14 Disease progression

Disease progression refers to the deterioration of a patient's condition caused by the disease, which is being treated with the study drug. Disease progression may be an increase in the severity of the disease under study and/or an increase in the symptoms of the disease. New metastases or progression of existing metastases from the primary cancer investigated should be considered as disease progression and not an AE. Events clearly due to disease progression are not to be reported as AEs during the study.

9.3.1.15 Death

Death due to disease progression is an expected efficacy endpoint and does not need to be reported as an SAE, but needs to be documented in the death instructions page in EDC, and the description to the event of death including primary cause of death needs to be documented.

Unexplained deaths occurring during the study treatment period or during the safety follow-up period after the last dose should always be reported as SAEs.

The investigator should follow up to know and evaluate the cause of death as far as possible. Autopsy helps to assess the cause of death and if performed, autopsy reports should be sent to the sponsor.

9.3.1.16 Events of liver enzyme abnormalities

Abnormal elevations in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) and total bilirubin (TBL) that meet the following conditions and have no other cause of liver injury will be considered drug-induced liver injury. Cases of such liver enzyme abnormalities should be reported as SAEs and followed up, assessed, and reported as important medical events.

Baseline Period	Normal (AST/ALT and TBL)	Abnormal (above normal AST/ALT and TBL)
Treatment Period	ALT or AST ≥ 3 × ULN With total bilirubin ≥ 2 ×	1) AST or ALT ≥ 2 x baseline and ≥ 3 x ULN

	ULN And alkaline phosphatase ≤ 2 × ULN And no hemolysis	AST or ALT ≥ 8 × ULN Lower 2) with total bilirubin increase ≥ 1 × ULN or value ≥ 3 × ULN Lower And no hemolysis

9.3.2 Clinical laboratory assessments

Blood samples will be collected for clinical laboratory evaluations. The following clinical laboratory tests will be performed:

- Hematology (red blood cell count, white blood cell count, hemoglobin, platelet count, hematocrit, neutrophils (ANC), lymphocytes, monocytes, eosinophils, basophils)
- Blood chemistry (serum sodium, serum potassium, serum chloride, blood glucose, blood urea/urea nitrogen, serum creatinine, creatinine clearance, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, γ-glutamine transpeptidase, total protein, albumin, serum calcium, serum magnesium, serum phosphorus)
- Coagulation function (PT, APTT, INR) *
- Urine routine (including dry chemical analysis and formed element analysis)
- Others: Plasma drug concentration of GB491 and its metabolites; blood HBsAg, blood HCV-Ab; if HBsAg or HCV-Ab is positive, additional measurement of blood HBV DNA or blood HCV RNA; blood HIV antibody; and blood human chorionic gonadotropin (hCG) test is required#

* Coagulation tests (PT, APTT, INR) may be added when the investigator judges that the patient is at high risk of venous thromboembolism (VTE), develops clinically suspected VTE, or the investigator considers it necessary, in combination with imaging studies and other means for comprehensive assessment

Performed at Screening only. Pregnancy testing, including but not limited to serum hCG testing, may be added during the study if deemed necessary by the investigator.

If treatment is interrupted, the subject should still complete all clinical laboratory evaluations as planned and on the actual dosing day of restarting treatment.

Laboratory parameters will be analyzed by a locally certified laboratory and laboratory value reports will be sent to the site. The investigator will review the laboratory report

immediately upon receiving the results and indicate the clinical significance of any outliers, then sign the laboratory report and file it with the subject's original records/tables and figures. Laboratory parameters for which clinically significant values are observed will be remeasured at appropriate clinical follow-ups scheduled by the investigator. Values will be followed until stabilization or until laboratory values return to clinically acceptable ranges regardless of the relationship to the study drug. Any laboratory value that remains abnormal at the end of treatment and is considered clinically significant will be followed according to acceptable medical standards for a maximum of 30 days or until resolution of the abnormality or recovery is deemed unfeasible.

Abnormal laboratory findings (e.g., blood chemistry, hematology) or other abnormal assessments (ECG, vital signs) that are judged by the investigator to be clinically significant will be recorded as adverse events or serious adverse events. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. Significant clinical significance was defined as any abnormality that, in general, was judged by the investigator to be clinically significant, was accompanied by clinical signs or symptoms, required active medical intervention, or led to dose interruption or termination, or required close observation, or more frequent follow-up assessments, or further diagnostic tests.

Table 10 Laboratory tests

Blood Chemistry [c]	Blood Routine	Other
Blood sodium	Red blood cell count	Plasma concentrations of GB491 and its metabolites Blood anti-HIV Ab Blood HBsAg Blood HCV-Ab If HBsAg or HCV-Ab is positive, additional blood HBV DNA or blood HCV RNA blood human chorionic gonadotropin (hCG) test [d] is required
Blood potassium	White blood cell count	
Blood chloride	Hemoglobin	
Blood glucose	Platelet count	
Blood urea/urea nitrogen	Hematocrit	
Serum creatinine	Neutrophils	
Creatinine clearance [a]	Lymphocytes	
Glutamic oxaloacetic transaminase	Monocytes	
Alanine aminotransferase	Eosinophils	
Alkaline phosphatase	Basophils	
Total bilirubin [b]	Coagulation [e]	
Gamma-glutamyl transpeptidase	PT	
Total protein	APTT	

Albumin	INR	
Blood calcium	Urine routine	
Blood magnesium	Urine routine (including dry chemical analysis and formed element analysis)	
Blood phosphorus		

a. Actual body weight is used for Cockcroft-Gault: CrCL (mL/min) = (140-age (years)) * body weight (Kg)/(serum creatinine (mg/dL) 72); coefficient* 0.85 (females) *1 (males), performed at screening only

b. Including direct bilirubin and indirect bilirubin

c. Fasting blood chemistry is required for this study

d. Performed at screening only. Pregnancy testing, including but not limited to serum hCG testing, may be added during the course of the study if deemed necessary by the investigator.

e. Coagulation tests (PT, APTT, INR) may be added when the investigator judges that the patient is at high risk for venous thromboembolism (VTE), develops clinically suspected VTE, or the investigator considers it necessary, in combination with imaging studies and other means for comprehensive assessment

9.3.3 Demographics and vital signs

The following parameters will be collected:

- Height (cm)
- Weight (kg)
- Temperature (℃)
- Systolic and diastolic blood pressure, pulse rate, and respiratory rate will be measured. Blood pressure should be evaluated after 5 minutes of rest. If a patient with no history of hypertension presents with blood pressure > 150/100 mmHg or if a patient with a previous history of hypertension presents with an increase of > 20 mmHg (diastolic blood pressure) above the baseline measurement, the measurement should be repeated 10 minutes later for confirmation.

9.3.4 Physical examination

Complete physical examinations include the following: 1) general appearance; 2) head, eyes, ears, nose, and throat; 3) neck; 4) heart; 5) chest (including the lungs); 6) abdomen; 7) extremities; 8) skin; 9) lymph nodes; 10) cardiovascular; and 11) neurological status. A complete physical examination is required only at baseline and at the EOT visit. Limited, symptom-based physical examinations will be performed at other visits (or as clinically indicated).

Information regarding the physical examination must be documented in the source documents at the site. Clinically significant findings from the physical examination before the first IMP administration must be recorded as medical history in the eCRF. Clinically

significant physical examination findings that meet the definition of an adverse event obtained after the first IMP administration must be recorded as an adverse event in the eCRF.

9.3.5 Electrocardiographic evaluation

A standard 12-lead ECG will be performed as described in **Appendix 3**. Subjects should rest for 5 minutes before each ECG evaluation.

9.3.6 Concomitant medications

Concomitant medications will be reviewed at times described in **Appendix 3**. Further information on concomitant medications.

9.4 Suitability of measurement indicators

The measures of antitumor activity, PK, and safety evaluated in this study are based on the mechanism of action and activity of GB491 and the type of standard evaluations typically performed in subjects with breast cancer. Tumor response measurements based on RECIST v1.1 [20] are standard. The PK and safety measures included in this study are also standard.

10 Study Discontinuation

10.1 Discontinuation by subjects

In general, the study drug will be administered until disease progression, unacceptable toxicity, withdrawal of consent or loss to follow-up, discontinuation of treatment at the investigator's request, or at the end of study, whichever occurs first. A withdrawal period of up to 14 days is allowed to allow recovery from any toxicities to meet the criteria for continuation. A withdrawal period of more than 14 days is permitted if the investigator considers the potential benefit of continued therapy to outweigh the potential risk, but these circumstances have to be discussed with the sponsor.

Following discontinuation of the study drug, subjects should be strongly encouraged to complete all scheduled laboratory evaluations; return for a post-treatment visit; and complete safety and long-term follow-up for this study.

If the blinded study drug is discontinued, patients may continue receiving fulvestrant at the investigator's discretion until disease progression, unacceptable toxicity, withdrawal of consent or loss to follow-up, Investigator's request to terminate treatment, or end of study, whichever comes first; if fulvestrant is discontinued, at the investigator's discretion, patients may continue receiving the blinded study drug until disease progression,

intolerable toxicity, withdrawal of consent or loss to follow-up, Investigator's request to terminate treatment, or end of study, whichever comes first.

If the Investigator site determines that the subject does not meet the inclusion criteria but inadvertently enrolled, the sponsor must be notified. Discussions must be made between the sponsor and the investigator to determine whether the subject can continue participation in the trial, whether or not the study drug has been administered. When the sponsor agrees that the investigator considers the subject medically appropriate, inadvertently enrolled subjects may be retained in the study and treated with the study drug. If the sponsor did not agree with the investigator's medical judgment and considered the subject medically unsuitable for continuation of the treatment, the subject could not continue the trial with or without the study drug. The investigator must obtain written approval from the sponsor to allow the inadvertently enrolled subjects to continue the trial. In this case, the site is required to report the protocol violations.

In addition, subjects will stop taking the study medication and/or stopping the trial in the following situations:

- Progressive disease (PD) as defined by the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1);
- Subject experiences an adverse event that, in the opinion of the investigator or sponsor, makes further medication inappropriate.
- Subjects who, in the opinion of the investigator or sponsor, had serious compliance issues during the course of the study.
- Participation in any other clinical trial involving an investigational product, or participation in any other type of medical research, judged to be scientifically or medically incompatible with this study;
- Subject is pregnant or intends to become pregnant
- Lost to follow-up
- Investigator's decision;
    - The investigator decides that the subject should stop the trial or study drug;
    - If the subject requires the treatment with another medication for any reason that has been shown to be effective in treating the study indication,

the study medication is to be discontinued prior to introduction of the new medication.

- Subject’s decision
    - The subject or his/her designated person (e.g., parent or legal guardian) requested withdrawal from the trial or the study drug.
    - If a patient is only withdrawn from the study drug treatment, the patient should continue to attend the follow-up visit.
- Sponsor's decision
    - The sponsor stops the study or participation of the subject in the trial for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP).

If the study drug is discontinued, subjects should be strongly encouraged to complete all the scheduled evaluations, post-treatment visits, and the survival follow-up period of this study. For patients who discontinue treatment prior to confirmed disease progression, CT/MRI imaging assessments should be performed according to the previous visit assessment schedule until: 1) objective disease progression; 2) death; 3) withdrawal of consent or loss to follow-up; 4) receiving new antineoplastic therapy; 5) end of study.

The investigator will record the reason for the study drug discontinuation in the appropriate eCRF page.

When discontinued due to a serious adverse event or Grade 3 or 4 toxicity considered related to the study drug, the investigator follows the event until it is resolved, returned to baseline, or is considered unlikely to recover further.

If a subject was discontinued due to an adverse event or pregnancy, the investigator was to notify the sponsor's medical monitor or pharmacovigilance department by telephone within 24 hours.

Subjects who withdraw from study treatment cannot be re-enrolled. Subjects will discuss their subsequent treatment options with the study doctor, and further treatment will be at the discretion of the physician.

10.2 Discontinuation of the site

Participation at the study site may be discontinued if deemed necessary by the sponsor or site's study staff, ethical review board (ERB) for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice.

10.3 Discontinuation of the study

The trial will be stopped if deemed necessary by the sponsor for medical, safety, regulatory, ethical or other reasons in accordance with applicable laws, regulations, and Good Clinical Practice, such as:

- Occurrence of an adverse event unknown so far in nature, severity and duration, or unexpected occurrence of a known adverse event
- Medical or ethical reasons impacting study continuation
- Difficult to recruit subjects
- Cancel of drug development program
- Sponsor's decision for other reasons

11 Data Management

To ensure accurate, complete, and reliable data, the sponsor or his/her representative will take the following measures:

- Provide clarifying materials to sites as appropriate.
- Sponsor initiates training to instruct the study personnel and study coordinators. Guidance on the protocol, eCRF completion, and study procedures will be provided at this meeting.
- Visit the site regularly.
- Consultation is available and site personnel are contacted by mail, telephone, and/or fax.
- Electronic case report forms are regulaorly checked and assessed for data accurary and completeness , and standard computerized edits are utilized to identify errors in data collection.
- Performing quality review of the database.

Addtionally, the sponsor or its representative will periodically conduct on-site inspections to review the subject data samples in the source documents for verifications and compliance.

To ensure the safety of the study subjects and to ensure the accuracy, completeness, and reliability of data, the researchers will retain the laboratory tests, clinical records, and patient medical records in the subject files as the original source documents for the study.

11.1 Data acquisition system

An electronic data capture system will be used for this trial. The site retains a separate source for data entry into the electronic data capture system provided by the sponsor.

Case report form data will be coded and stored in the clinical trial database.

Any data provided by the subject that will serve as source documents will be identified by each site and documented in the site's study file.

12 Sample Size and Statistical Methods

Detailed summaries and statistical analysis methods of the data collected in this study will be documented in a Statistical Analysis Plan (SAP) and kept by the Sponsor/designated CRO. This document may revise the analysis plan in the protocol; however, any major revisions to the definition of the primary endpoint and/or its analysis method should be reflected in the protocol amendment.

12.1 Determination of sample size

A total of 270 subjects are planned for enrollment, with 135 in each of the treatment group and the control group. Assuming a median PFS of 9 months in the control group, a hazard ratio (HR) of 0.55 for the treatment group relative to the control group, an enrollment period of 12 months and an overall dropout rate of 25%, this sample size will provide an overall power of 90% at one-sided α level of 0.025 with a total of approximately 119 PFS events.

12.2 Analysis sets

- Full Analysis Set (FAS): Includes all randomized subjects who received at least one dose of the study drug.
- Per Protocol Set (PPS): A subset of FAS, excluding subjects whose efficacy is severely affected in FAS. For example, some subjects who seriously violated the protocol, those who did not reach the minimum exposure dose, and those who were randomized without data. PPS needs to be determined prior to unblinding of the locked database.
- Safety Analysis Set (SAS): Includes all subjects who have received at least one dose of the study drug and have had at least one post-dose safety assessment.
- Pharmacokinetics consentration set (PKCS): Includes all subjects who have taken the study drug at least once and have had one valid plasma concentration

measurement.

12.3 General principles

The statistical analysis plan must be finalized before database lock. Statistical programming and analysis (tables, listings and graphs) will be performed using SAS 9.4 or above.

Descriptive summary

Unless otherwise specified, the following descriptive statistics are used for summaries by treatment group. For continuous endpoints, the number of non-missing observations, mean, standard deviation, median, minimum, and maximum will be summarized. The number of decimal places for the minimum and maximum values will be consistent with the raw data recorded in the database. Means and medians will be presented to one more decimal place than the raw data recorded in the database, and standard deviations will be presented to two more decimal places than the raw data recorded in the database, but no more than four decimal places. For categorical endpoints, frequency and percentage will be summarized and presented for each category. Unless otherwise specified, percentages will be calculated based on all subjects in the respective analysis population. Percentages will be presented to one decimal place. Percentages of 100% will be reported as 100% and frequencies of 0 will not be reported as percentages. For the time-to-event endpoints, the Kaplan-Meier method will be used to estimate the survival function and estimate the median survival time and its 95% confidence interval, and survival curves will be plotted.

Analysis nodes

Primary analysis nodes: When the preset number of events (approximately 119) in the protocol is reached, data cleaning and locking are carried out, and corresponding analysis is then conducted.

Overall study analysis nodes: After the study is completed, data cleaning and locking will be carried out, and corresponding analysis will be conducted.

12.4 Efficacy analysis

Efficacy analyses will primamrly be conducted using the Full Analysis Set (FAS)..

12.4.1 Primary efficacy endpoints and analyses

The primary endpoint of this study is the investigator-assessed progression-free survival, defined as the time from randomization to disease progression or death for any cause, whichever comes first. Disease progression will be evaluated according to RECIST 1.1.

The null hypothesis of this study is that PFS in the treatment group is not superior to that in the control group and the alternative hypothesis is that PFS in the treatment group is superior to that in the control group.

$$H_0: S_t(t) \leq S_c(t) \text{ vs. } H_a: S_t(t) > S_c(t);$$

Where the survival probability S(t) = P (T > t) refers to the probability that the time T of the event of interest is not less than the given time t. $S_t(t)$ represents the survival probability of subjects in the investigational product group and $S_c(t)$ represents the survival probability of subjects in the comparator group. When approximately 119 PFS events occur in the treatment group and the control group, a superiority test will be performed, and if the one-sided p-value is less than 0.025, the PFS of the treatment group will be considered superior to that of the control group, and the study meets the primary endpoint.

The inter group comparison is conducted using a stratified log rank test by using random stratified factors as stratified variables. A Cox proportional risk model is used to estimate the hazard ratio (HR) and 95% confidence interval of PFS between the experimental group and the control group, including treatment group and randomized stratified factors.

These analyses will be repeated in the Per Protocol Set (PPS).

12.4.2 Secondary efficacy endpoints and analyses

Progression-free survival (PFS) by BICR: defined as the time from randomization to either disease progression or death for any cause, whichever occurs first. Disease progression will be evaluated according to RECIST 1.1.

Overall survival (OS): defined as the time from randomization to death from any cause.

Objective response rate (ORR): defined as the proportion of subjects achieving a best overall response (BOR) of complete response (CR) or partial response (PR) based on the RECIST v1.1 criteria during the study, with CR or PR at the first assessment requiring confirmation of response at least 4 weeks later. BOR is defined as the best overall response from the start of treatment until disease progression or the development of a

new antineoplastic therapy or, whichever occurs first, until the last evaluable assessment in the absence of RECIST progression.

Disease control rate (DCR): defined as the proportion of subjects achieving a best overall response (BOR) of complete response (CR) or partial response (PR) or stable disease (SD) during the study.

Clinical benefit rate (CBR): the proportion of subjects achieving complete response, partial response, or stable disease for ≥ 6 months based on RECIST 1.1.

Duration of response (DOR): calculated based solely on the subjects with BOR as confirmed complete response or partial response, defined as the time from the first occurrence of CR or PR in tumor assessment to progressive disease (PD) or death for any cause, whichever occurs first.

For the time-to-event secondary endpoints (OS, PFS assessed by BICR, DOR), the same approach as for the primary analysis will be applied. For each type of the secondary endpoints (ORR, DCR, and CBR), two-sided 95% confidence intervals are estimated for each group using a normal approximation, and differences between groups and their 95% confidence intervals are estimated using a normal approximation.

12.5 Pharmacokinetic and pharmacodynamic Analyses

Plasma concentrations are analyzed based on the PK concentration set.

Mean population pharmacokinetic parameters (clearance, exposure, volume of distribution, and half-life) and inter-individual pharmacokinetic variability of GB491 and its metabolites in plasma will be calculated by nonlinear mixed effects modeling implemented in NONMEM. The influence of covariates such as age, body weight, sex, baseline creatinine clearance and plasma protein level on the pharmacokinetic parameters of GB491 in plasma will also be investigated.

Finally, the response data collected in this study (such as neutrophils, lymphocytes, or platelet counts in the blood) are analyzed using NONMEM and included in a population pharmacokinetic model to analyze the exposure/response relationship.

Details of the analyses will be provided in a separate population modeling analysis plan. The results of these modeling analyses may be reported separately from the clinical study report.

12.6 Safety analysis

Safety analyses will be based on the Safety Analysis Set (SAS).

All AEs are listed by subject. The number and percentage of subjects with treatment-emergent adverse events (TEAEs) and treatment-emergent drug-related adverse events (TRAEs) will be calculated by system organ class, preferred term, and group. SAEs including deaths and TEAEs leading to study discontinuation are summarized. Laboratory tests, vital signs, physical examinations, 12-lead ECG tests, and changes from baseline (if applicable) are analyzed descriptively by treatment group.

Other safety measures will be described in a similar manner and listed by subject.

12.7 IDMC

An Independent Data Monitoring Committee (IDMC) will be established for this study and the IDMC will conduct periodic or ad hoc risk-benefit assessments to advise the sponsor in an unblinded fashion using the efficacy and safety data collected during the course of the clinical trial in accordance with a pre-specified protocol. The responsibilities of IDMC and the details of the meetings can be found in the IDMC charter.

13 Quality Control and Quality Assurance

An eCRF must be completed for each enrolled subject. The signature of the site principal investigator is required for each completed eCRF and for documentation of subjects who discontinued the study. If a subject withdraws from the study, the reason must be indicated in the eCRF, and if the subject withdraws from the study due to a treatment-limiting adverse event, every effort should be made to clearly document the outcome. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.

The investigator maintains a drug dispensing log to ensure the accuracy and reliability of data collection by verifying and cross-checking the eCRFs against the investigator's records (source document verification) by the study monitor.

A comprehensive validation check procedure will check the data and generate a corresponding discrepancy report for resolution by the investigator. When a subject completes the study (or withdrawal of concent) and his/her signed eCRF is available for review, a comparison check will be run to identify and resolve any discrepancies in the database.

14 Ethics and Protection of Human Subjects

14.1 Statement of ethical conduct

The investigator will ensure that the study is conducted in full compliance with the principles of the Declaration of Helsinki (as amended in Tokyo, Venice, Hong Kong, and South Africa) or the laws and regulations of the country in which the study is conducted, whichever affords greater protection to the subjects.

14.2 Independent Ethics Committee

The local IEC or central IEC at the site will review and approve the protocol and all relevant amendments, as well as the informed consent. Prior to the start of the study, the investigator was responsible for obtaining approval of the protocol and informed consent form, as well as any other study-related materials (e.g., advertisements or information leaflets), from his/her IEC. Written approval must be obtained by letter stating the protocol, date of IEC meeting, and date of approval. Any modifications to the protocol after receiving IEC approval must also be submitted by the investigator to the IEC in accordance with local procedures and regulatory requirements. Any updates to the protocol will obtain the IEC approval or favorable opinion prior to implementation and will be documented in a letter to the Investigator.

14.3 Informed consent

The investigator is responsible for obtaining written informed consent from each subject participating in this study after adequate explanation of the objectives, methods, potential benefits, and risks of this study. The investigator or designee must also explain that subjects are permitted to withdraw from the study at any time for any reason. All subjects will be provided with a copy of the informed consent form and any updates. The original signed informed consent will remain at the site and may be inspected at any time as appropriate.

14.4 Subject confidentiality

The investigator must ensure that the subjects' anonymity is maintained and that their identity is protected from unauthorized parties. Names of the subjects will not be provided to the sponsor, subject numbers will only be recorded in the eCRF, and findings stored in computers will be stored in accordance with local data protection laws. Representatives of the sponsor, IEC/IRB or the regulatory authorities may inspect the subjects' medical records to verify the information collected, and all personal information provided for the

inspection will be treated in strict confidence and will be informed in writing to the subjects in accordance with local data protection laws.

14.5 Protocol compliance

The study should be conducted as described in this protocol, except for appropriate emergency situations for subjects who require immediate additional intervention. The sponsor will provide this protocol to the IEC and appropriate local regulatory authorities for approval. Any protocol amendments will be made in accordance with the terms agreed in Section 15.6. Any study design deviations specified in this document will be documented as protocol deviations and will be explained in detail as they occur and/or are tested.

14.6 Protocol amendments

Protocol amendments must be prepared by the Sponsor’s representative and initially reviewed and approved by the Sponsor.

All protocol amendments (non-substantial and substantial amendments) must be submitted to the appropriate IEC and competent authority (as required) in accordance with local requirements. Approval for substantial amendments must be obtained prior to implementation (i.e., if the risk-benefit ratio is compromised and/or changes representing the definition of the underlying trial, such as objectives, design, sample size, and outcome measures), except for changes that may reduce the risk of the subjects.

14.7 Subject compliance

Subjects must attend all scheduled study visits. Reasons for any subject noncompliance will be documented.

14.8 Study termination

The sponsor and investigator reserve the right to terminate the study at any time in accordance with the terms set forth in the Study Contract. The investigator will notify the IEC in writing of the completion or early termination of the study. When terminating the study, the sponsor and investigator will ensure that adequate consideration is given to protecting the subjects' interests.

15 Data Handling and Record Keeping

15.1 Data collection and retrieval

An electronic data capture system that meets the national requirements will be used for this study. An eCRF will be used for data recording. All data required by the eCRF must be entered and any missing data must be explained.

The investigator maintains a drug dispensing log to ensure the accuracy and reliability of data collection by verifying and cross-checking the eCRFs against the investigator's records (source document verification) by the study monitor.

Prior to the start of the trial, at an initial site visit, or at an investigator meeting, a representative of the sponsor will review the trial protocol and eCRFs with the investigator and his/her staff. During the study, the CRA will visit the site regularly to check the completeness of subject records, accuracy of eCRF entry, compliance with the protocol and GCP, and enrollment progress. The monitor will ensure that the study drug is stored, dispensed, and accounted according to specifications during site visits. Critical study personnel must assist the monitor during these visits.

The investigator must allow the monitor access to relevant hospital or clinical records to confirm consistency with the eCRF entries. Information about the subjects' identity in these records will not be left at the site. The monitoring standards require adequate verification of the existence of informed consent, compliance with inclusion/exclusion criteria, documentation of serious adverse events, and documentation of major antitumor activity and safety variables. Additional checks for consistency between the source data and eCRFs will be performed according to the protocol-specified monitoring plan.

15.2 Investigator reporting requirements

Local regulations may require the investigator to provide regular safety updates regarding the conduct of the study and to notify the IEC of study closure. Such updates and notifications are the responsibility of the investigator.

15.3 Record retention

The investigator will maintain copies of all study records (i.e., Investigator files and Subject files) in a secure location following the end of the study. The investigator's study file will contain the protocol, protocol amendments, eCRFs and query forms, IEC and governmental correspondence approvals, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Subject’s clinical source documents may include (but are not limited to) subject’s hospital records, physician and nurse notes, original laboratory reports, ECGs, electroencephalograms (EEGs), X-rays, signed informed consent forms, counseling letters, and subject screening and enrollment logs.

These documents must be filed by the investigator for a period of 5 years from the date the marketing application is approved for the indication of the drug for which it is being investigated. If an application is not submitted or if the application is not approved for such indication, all records related to the conduct of the clinical investigation must be adequately maintained until 5 years after termination of the investigation and notification to the regulatory authorities. Afterwards, the documents may be destroyed in accordance with local regulations.

The investigator will not destroy any records associated with the study without approval from the sponsor. In the event of accidental loss or destruction of any study records, the investigator must notify the sponsor and shall notify the sponsor to reassign or transfer any study records to another location.

15.4 Study monitoring

Qualified sponsor’s representatives or designees (study monitors) will monitor the study according to a predetermined monitoring plan. The investigator must allow the study monitor to periodically review all eCRFs and source documents supporting the participation of each subject in the study. The investigator and site staff must promptly update the eCRFs and other documents supporting the study. At each monitoring visit, these study materials must be reviewed by the study monitor and/or other qualified representatives of the sponsor and subject confidentiality must be protected in accordance with local institutional and national requirements.

15.5 Audit and inspection

Qualified personnel of the Sponsor's Quality Assurance Group or their authorized representatives or representatives of the regulatory authorities may visit the investigator to inspect the study and the site at some point during or after the study is completed. During this audit, the investigator agrees to allow the auditors to directly access all relevant documents supporting the eCRFs and other study-related documents and to discuss any findings with the auditors. If the regulatory authority conducts an inspection, the investigator agrees that the monitor has direct access to all relevant documents and discusses any findings with the monitor.

16 References

1. Freddie Bray, Jacques Ferlay, Isabelle Soerjomataram et al. GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin.2018 Nov; 68 (6): 394-424.
2. Otto Metzger-Filho, Zhuoxin Sun, Giuseppe Viale et al. Patterns of Recurrence and outcome according to breast cancer subtypes in lymph node-negative disease: results from international breast cancer study group VIII and IX.J Clin Oncol. 2013 Sep 1; 31 (25): 3083-90.
3. F Cardoso, N Harbeck, L Fallowfield, et al. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2012 Oct; 23 Suppl 7: vii11-9.
4. Wanqing Chen, Rongshou Zheng, Peter D Baade et al. Cancer statistics in China, 2015. CA Cancer J Clin. Mar-Apr 2016; 66 (2): 115-32.
5. Chuang Chen, Si Sun, Jing-Ping Yuan et al. Characteristics of breast cancer in Central China, literature review and comparison with USA. Breast. 2016 Dec; 30:208-213.
6. SEER Cancer Statistics Database. 2017.
7. Intrinsic tumor subtypes, race, and long-term survival in the Carolina Breast Cancer Study. O'Brien, KM et al. 2010, Clin Breast Cancer Research, pp. 6100-6110.
8. Tatiana M Prowell, Nancy E Davidson. What is the role of ovarian ablation in the management of primary and metastatic breast cancer today? Oncologist. 2004; 9 (5): 507-17.
9. Sagrario Ortega, Marcos Malumbres, Mariano Barbacid. Cyclin D-dependent kinases, INK4 inhibitors and cancer. Biochim Biophys Acta. 2002 Mar 14; 1602 (1): 73-87.
10. Geoffrey I Shapiro. Cyclin-dependent kinase pathways as targets for cancer treatment. J Clin Oncol. 2006 Apr 10; 24 (11): 1770-83.
11. RugoHS, FinnRS, DiérasV, etal. Palbociclib plus letrozole as first-line follow-up therapy in estrogen receptor-positive/human epidermal growth factor receptor2-advanced breast cancer with extended negative [J].Breast Cancer Res Treat, 2019, 174 (3): 719-729.

12. Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative breast cancer [J]. Ann Oncol, 2018, 29 (7): 1541-1547.

13. Johnston S, Martin M, Di Leo A, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breastcancer [J]. NPJBreastCancer, 2019, 5:5.

14. Slamon DJ, Neven P, Chia S, et al. Phase III randomized study of ribociclib and fulvestrant in receptor-positive, human epidermal growth factor receptor 2-advanced breast cancer: MONALEESA-3 [J]. J ClinOncol, 2018, 36 (24): 2465-2472.

15. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who progressed while receiving endocrine therapy [J]. J Clincol, 2017, 35 (25): 2875-2884.

16. Verma S, Bartlett CH, Schnell P, et al. Palbociclib in combination with fulvestrant in women with hormone receptor-positive/HER2negative advanced metastatic breast cancer: detailed safety analysis from a multicenter, randomized, placebo-controlled, phase III study (PA LOMA-3) [J].Oncologist, 2016, 21 (10): 1165-1175.

17. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormonereceptor-positive, HER2-negativemetastaticcancerthaton endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised trial [J].LancetOncol, 2016, 17 (4): 425-439.

18. Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial [J]. Lancet Oncol, 2018, 19 (7): 904-915.

19. Angelo Di Leo, Guy Jerusalem, Lubos Petruzelka, et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive breast cancer. J Clin Oncol. 2010 Oct 20; 28 (30): 4594-600.

20. E A Eisenhauer, P Therasse, J Bogaerts, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan; 45 (2): 228-47.

21. Breast Cancer Professional Committee of Chinese Anti-Cancer Association. Expert consensus on clinical application of ovarian function suppression in early breast cancer in China (Version 2018). Chin J Cancer. 2018, 28(11): 871-880.

22. Xu Binghe, Ma Fei, etc. Consensus on the clinical application of CDK4/6 inhibitors in the treatment of hormone receptor positive and human epidermal growth factor receptor 2 negative advanced breast cancer. Chin J of Oncol. April 2021, 43(4): 405-413.

17 Appendices

Appendix 1: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 5.0)

https://evs.nci.nih.gov/ftp1/CTCAE/About.html

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/NCIt_CTCAE_5.0.xlsx

Appendix 2: Additional Drug Dose/Formulation Information

芙仕得®/FASLODEX® (Fulvestrant Injection): http://zy.yaozh.com/instruct/sms20190318/7.pdf

诺雷得®/Zoladex® (Goserelin Acetate Extended-release Implant): http://zy.yaozh.com/instruct/201604201/22.jpg

Appendix 3: Study Flow Chart

Procedures and evaluations to be performed during the study are listed in the Table below.

Test Flow Chart

Study Period	Screening Period	Cycle 1[17] (28 Days/Cycle)		Cycle 2-4[17] (28 Days/Cycle)	≥ Cycle 5[17] (28 Days/Cycle)	End of Treatment Follow-up	Safety Follow-Up	Survival Follow-up
Cycle Day	D-28	D1	D15	D1	D1	EOT[17]	30 days after last dose of blinded study drug	Every 12 weeks
Visit Window (Days)	-28 to -1	± 3	± 3	± 3	± 3	+ 7	± 7	± 14
Informed Consent	×							
Demographic Information	×							
Past Medical/Medication History[1]	×							
Inclusion/Exclusion Criteria	×							
Physical Examination[2]	×	×	×	×	×	×	×	
ECOG Score	×	×	×	×	×	×	×	

Study Period	Screening Period	Cycle 1[17] (28 Days/Cycle)		Cycle 2-4[17] (28 Days/Cycle)	≥ Cycle 5[17] (28 Days/Cycle)	End of Treatment Follow-up	Safety Follow-Up	Survival Follow-up
Cycle Day	D-28	D1	D15	D1	D1	EOT[17]	30 days after last dose of blinded study drug	Every 12 weeks
Visit Window (Days)	-28 to -1	± 3	± 3	± 3	± 3	+ 7	± 7	± 14
Vital Signs[3]	×	×	×	×	×	×	×	
12-lead ECG[4]	×	×	×	×	×	×		
Adverse Event[5]		×						
Concomitant Medication		×						
Blood Routine[6]	×	×	×	×	×	×	×	
Blood Chemistry[6]	×	×	×	×	×	×	×	
Urine Routine[6]	×	×	×	×	×	×		
Pregnancy Test[7]	×							
HBsAg and Blood HBV DNA[8]	×							
Blood HCV Ab and Blood H CV RNA[8]	×							

Study Period	Screening Period	Cycle 1[17] (28 Days/Cycle)		Cycle 2-4[17] (28 Days/Cycle)	≥ Cycle 5[17] (28 Days/Cycle)	End of Treatment Follow-up	Safety Follow-Up	Survival Follow-up
Cycle Day	D-28	D1	D15	D1	D1	EOT[17]	30 days after last dose of blinded study drug	Every 12 weeks
Visit Window (Days)	-28 to -1	± 3	± 3	± 3	± 3	+ 7	± 7	± 14
HIV Antibody[8]	×							
Collection of Tumor Samples	× (Only for patients without HR and HER2 status testing at screening)							
PK Sample Collection[9]			×	×				
CT or MRI[10, 11]	×	× (Imaging PD as defined by RECIST v 1.1 from date of randomization every 8 weeks (± 7 days) during the first year and every 12 weeks (± 7 days) after 1 year)						
Radionuclide Bone Scan[10, 11]	×	× (Imaging PD as defined by RECIST v 1.1 from date of randomization every 24 weeks)						
Tumor Evaluation[11]	×	× (Imaging PD as defined by RECIST v 1.1 from date of randomization every 8 weeks during the first year and every 12 weeks after 1 year)						
GB491/Placebo, Oral[12]		× (Twice daily taken orally with food, approximately 12 hours apart recommended)						

Study Period	Screening Period	Cycle 1[17] (28 Days/Cycle)		Cycle 2-4[17] (28 Days/Cycle)	≥ Cycle 5[17] (28 Days/Cycle)	End of Treatment Follow-up	Safety Follow-Up	Survival Follow-up
Cycle Day	D-28	D1	D15	D1	D1	EOT[17]	30 days after last dose of blinded study drug	Every 12 weeks
Visit Window (Days)	-28 to -1	± 3	± 3	± 3	± 3	+ 7	± 7	± 14
Fulvestrant, i.m.[13]		×	×	× (every 4 weeks i.m.)				
Goserelin or LHRH Analogue[13]		× (Only for subjects applicable to LHRH analogues such as goserelin, subcutaneous injection every 4 weeks, other LHRH analogues administered according to local standard of care)						
Survival Follow-up[14]								× (every 12 weeks)
Subject Dosing Diary[15]		×						
Other Necessary Examinations[16]	×							

1. Medications taken within 28 days prior to randomization will be recorded in the past medication history. Past medical history: Before signing the ICF, meaningful clinical medical history findings (such as previous diagnoses, illnesses, or surgeries) deemed relevant to the patient's eligibility will be collected and recorded in the electronic case report form, including baseline severity. If such findings continue to exist, they will need to be recorded in the eCRF. Clinically meaningful refers to any event, diagnosis, or laboratory values that require treatment, follow-up, or the development of symptoms or signs that require medical intervention. Accompanying medical symptoms and signs must be documented to determine the baseline severity.

2. A complete physical examination included the following: 1) general appearance; 2) head, eyes, ears, nose, and throat; 3) neck; 4) heart; 5) chest (including lungs); 6) abdomen; 7) extremities; 8) skin; 9) lymph nodes; 10) cardiovascular; and 11) neurological status. A complete physical examination is required only at baseline and at the EOT visit. Limited, symptom-based physical examinations will be performed at other visits (or as clinically indicated). Net body weight (without shoes) must be measured at the physical examination, while measurement of net body height (without shoes) is only required at the screening visit.

3. Vital signs during the treatment period are measured prior to the blinded study drug administration, and the remaining visits can be performed at any time.

4. 12-lead electrocardiograms (ECGs) are performed at rest and during the treatment period prior to the blinded study drug administration The remaining visits can be performed at any time. ECG should preferably be performed before any blood draw.

5. Adverse events will be evaluated according to NCI CTCAE 5.0. All adverse events are collected from the time of the first dose of the blinded study drug until 30 days after the last dose of the blinded study drug (or until initiation of subsequent new anticancer therapy, whichever comes first). Following the safety follow-up period, if the investigator became aware of any serious adverse events, only the study drug-related serious adverse events (SAEs) are to be reported until receiving subsequent new anticancer therapy or at the end of study. Only SAEs due to protocol-specified procedures (e.g., SAEs related to invasive procedures such as biopsies) will be collected from the time of signing the informed consent through the first dose.

6. C1D1 hematology, blood chemistry and urinalysis are performed within 7 days before randomization, and do not need to be repeated on Cycle 1 Day 1.

7. Female patients of childbearing potential shall has a serum pregnancy test completed within 7 days prior to randomization and the result should be nonpregnant; pregnancy testing can be added at any time during the study if necessary.

8. Blood HBsAg and HCV-Ab tests will be performed during the screening period, and if the result is positive, blood HBV DNA or blood HCV RNA will be added separately. When the result of blood anti-HIV screening is positive, no further confirmation is required.

9. See "Schedule for Pharmacokinetics (PK) Blood Sample Collection" for details.

10. All subjects will undergo baseline tumor assessments within 28 days prior to randomization: CT/MRI scans of the chest, abdomen, pelvis, and other sites of tumor involvement; breast MRI scans will be performed at baseline for subjects with inoperable locally advanced breast cancer (if applicable); bone scans, and lesions identified on bone scans must be confirmed by CT (bone window) or MRI. Note: Enhanced CT should be the first choice for imaging assessment. For patients with known hypersensitivity to CT contrast agents, plain chest CT with enhanced abdominal/pelvic MRI assessment is an option.

11. Tumor assessments during the treatment period must always use the assessment method and technique used at baseline, including all lesion sites (including but not limited to the chest, abdomen, and pelvis), and the cycle of tumor assessment must be fixed (fixed cycle is set based on the date of randomization). All patients will undergo CT/MRI evaluation every 8 weeks (± 7 days) during Year 1 and every 12 weeks (± 7 days) after Year 1. The fixed cycle will be set based on the date of randomization, and bone scan will performed every 24 weeks (± 7 days) until disease progression. For patients who discontinue treatment prior to confirmed disease progression, imaging assessments for CT/MRI should be performed according to the previous visit assessment schedule until 1) objective disease progression; 2) death; 3) withdrawal of consent or loss to follow-up; 4) receiving new antineoplastic therapy; 5) end of study. If clinical progression is suspected, radiographic assessments must be performed within 2 weeks. Patients with confirmed CR will undergo bone scan to confirm absence of bone metastases. At the investigator's discretion, additional bone scans may be performed and lesions confirmed by CT (bone window) or MRI if the patient has clinical symptoms and signs of worsening bone metastases. Following objective disease progression, tumor assessments are no longer required and patients will continue to be followed for end of treatment until patient death, withdrawal of consent or loss to follow-up, receiving new antineoplastic therapy, or end of study.

12. Blinded study drug (GB491 150 mg or placebo) will be administered orally twice daily (approximately 12 hours apart with food) starting on C1D1 at approximately the same time each day. If a subject misses a dose or vomits a dose, the dosing should be ignored.

13. Subjects will receive 500 mg of fulvestran intramuscularly on C1D1 and C1D15, respectively, then every 4 weeks from C2D1. For premenopausal and perimenopausal female patients and male patients (unless there is a clear history of bilateral orchiectomy) requiring LHRH analogues (e.g. g oserelin), patients must start LHRH analogues (e.g. goserelin) at least 21 days before randomization, followed by subcutaneous goserelin extend ed-
release implants 3.6 mg every 28 days (or following other LHRH analogue treatment specifications). When the study medication cycle is delayed, LHRH analogues should still be administered according to their preplanned schedule.

14. Survival follow-up: Calculated from the day following completion of the Safety Visit, patients are contacted every 12 weeks (by telephone or by accessible medical history) for survival status and subsequent antineoplastic therapy.
15. A dosing diary will be distributed to the patients to record the date and time of taking the blinded study drug and to assess patient compliance with the study medication.
16. At screening, other necessary examinations may be additionally performed at the investigator's discretion, including brain CT/MRI, serum FSH, estradiol, pulmonary function, blood gas analysis, coagulation, etc.
17. If the epidemic situation of COVID-19 leads to traffic restriction or restriction of clinical trial institutions, and practical difficulties such as sending of investigational drugs, inspection after medication, and follow-up occur, the study site should communicate with the sponsor in a timely manner to discuss feasible alternative methods as appropriate according to the Guidelines for the Management of Drug Clinical Trials during the epidemic period of COVID-19 issued by the Center for Drug Evaluation of NMPA under the premise of ensuring the safety and rights and interests of the subjects, ensuring the availability of study data, and ensuring their quality and traceability.

    Note: Assessments requested other than C T/MRI do not need to be repeated at the EOT Visit/Safety Visit if performed 4 days prior to the EOT Visit/Safety Visit.

    Visit window for each cycle during study drug treatment is ± 3 days; Visit assessments must be performed prior to the study drug administration for each cycle unless otherwise noted. Coagulation tests (PT, APTT, INR) may be added when the investigator judges that the patient is at high risk for venous thromboembolism (VTE), develops clinically suspected VTE, or the investigator considers it necessary, in combination with imaging studies and other means for comprehensive assessment.

    Following Cycle 1, the date of fulvestrant administration is defined as Day 1 of the next cycle regardless of whether or not the blinded study drug was delayed.

Pharmacokinetics (PK) Blood Sampling Schedule

Treatment Cycle	Date	Blood Sampling Time	Time Window	GB491[a,b]
Cycle 1	D15	Before blind drug dosing in	Within 30 min	X

		the morning		
Cycle 2	D1	Before blind drug dosing in the morning	Within 30 min	X
Cycle 3	D1	Before blind drug dosing in the morning	Within 30 min	X
Cycle 4	D1	Before blind drug dosing in the morning	Within 30 min	X

Remarks:

a, Active metabolite G1T30 will also be measured.

b. Plasma samples are collected after ECG examination; in other cycles, if ECG examination and plasma sample collection are required at the same time, the same procedure is followed, that is, ECG examination is performed first, followed by blood sampling.

c, Blood sampling for P K is recommended whenever possible prior to fulvestrant administration.

d, If the patient has suspended the blinded drug prior to the scheduled PK blood sample collection day, it is recommended that the PK blood samples be collected at least 4 days after the blinded drug is restarted.

Genor Biopharma Co., Ltd.

Protocol No.: GB491-004

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase III Clinical Trial of GB491 in Combination with Fulvestrant in Subjects with Hormone Receptor (HR) -positive, Human Epidermal Growth Factor Receptor 2 (HER2) -negative Locally Advanced or Metastatic Breast Cancer Who Have Progressed on Prior Endocrine Therapy

Statistical Analysis Plan

Version: 1.0

Date: February 11, 2023

Abbreviation

Abbreviation	Definition
AE	Adverse event
CR	Complete response
CBR	Clinical benefit rate
DCR	Disease control rate
DOR	Duration of response
FAS	Full Analysis Set
IDMC	Independent Data Monitoring Committee
BICR	Blinded Independent Central Review
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not assessed
NE	Not evaluated
ORR	Objective response rate
OS	Overall survival
PD	Disease progression
PFS	Progression-free survival
PPS	Per-Protocol Set
PN	Preferred name
PR	Partial response
PT	Preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
SOC	System Organ Class
SAS	Safety Analysis Set

WHODrug	World Health Organization Drug Dictionary

CONTENTS

Brief Introduction

This statistical analysis plan specifically describes the statistical analysis and reporting methods included in the study protocol GENOR GB491-004, Version 6.0, dated 15 September 2022. This statistical analysis plan may modify some of the analytical methods of the protocol, but the primary endpoint and primary analyses will be consistent with the protocol.

This statistical analysis plan includes the pharmacokinetic analysis part, but the population pharmacokinetic analysis in it will be described in a separate analysis plan.

The statistical analysis plan must be finalized before database lock.

Study Objectives and Study Design

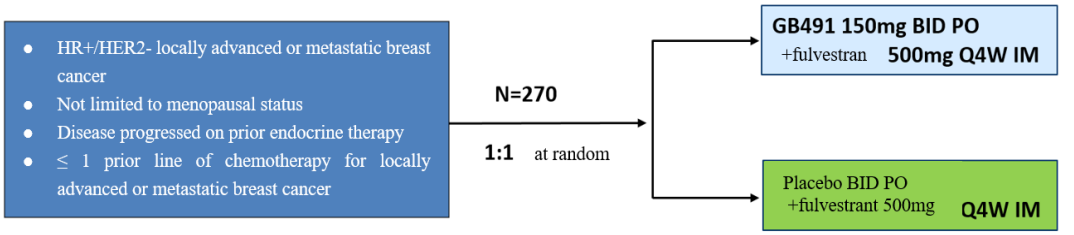
Study objectives

Primary objective: To evaluate the progression-free survival (PFS, as assessed by the Investigator) of GB491 plus fulvestrant versus placebo plus fulvestrant in HR+/HER2- locally advanced or metastatic breast cancer with progressive disease following prior endocrine therapy.

Secondary objectives: To evaluate the progression-free survival (PFS, assessed by the BICR); overall survival (OS); objective response rate (ORR), duration of response (DOR), disease control rate (DCR), clinical benefit rate (CBR); safety and tolerability; and pharmacokinetic (PK) profile of combination therapy.

Study design

This study is a multicenter, randomized, double-blind, placebo-controlled, Phase 3 clinical trial of GB491 plus fulvestrant versus placebo plus fulvestrant in patients with HR+/HER2 − locally advanced or metastatic breast cancer who have progressed on prior endocrine therapy.



Note: Subjects receive fulvestrant 500 mg i.m. on C1D1 and C1D15, respectively, and every 4 weeks from C2D1.

HR+, hormone receptor positive; HER2-, human epidermal growth factor receptor 2 negative; N, number; BID, twice daily; IM, intramuscular; Q4W, every 4 weeks.

Approximately 270 patients who met the eligibility criteria were planned to be enrolled into the study. Patients will undergo a screening period of up to 28 days. Patients who met the eligibility criteria were assigned in a 1:1 ratio to GB491 plus fulvestrant or placebo plus fulvestrant based on a web interactive response system (IWRS). The nature of baseline disease (visceral metastases vs bone only metastases vs others), different menopausal status (premenopausal or perimenopausal vs postmenopausal), and number of prior lines of endocrine therapy failure (first-line vs second-line) were used as randomization stratification factors.

- Treatment group: Patients received GB491 150 mg orally twice daily (taken with food, approximately 12 hours apart) for 28 consecutive days as a cycle. At the same time, randomized patients will receive one fulvestrant 500 mg intramuscular injection on Day 1 and Day 15 of the first cycle (28-day cycle), and one fulvestrant 500 mg intramuscular injection on Day 1 of each subsequent cycle.
- Control group: Placebo was administered orally twice daily (taken with food, approximately 12 hours apart) for 28 consecutive days as a cycle. At the same time, randomized patients will receive one fulvestrant 500 mg intramuscular injection on Day 1 and Day 15 of the first cycle (28-day cycle), and one fulvestrant 500 mg intramuscular injection on Day 1 of each subsequent cycle.

For premenopausal and perimenopausal female patients and male patients (unless there is a clear history of bilateral orchiectomy) requiring the use of LHRH analogues (e.g. goserelin), LHRH analogues (e.g. goserelin) must be started at least 21 days before randomization, followed by subcutaneous goserelin delayed-release implants 3.6 mg every 28 days (or following other LHRH analogue treatment specifications).

Following completion of study screening, follow-up will occur on Days 1 and 15 (C1D1 and C1D15) of Cycle 1. Follow-up will be performed on Day 1 of each subsequent cycle (28-day cycle).

Subjects will be stratified by the nature of disease (visceral metastases vs bone only metastases vs others), menopausal status (male or premenopausal or perimenopausal vs postmenopausal), and number of prior lines of endocrine therapy

failure (first vs second line). Visceral metastasis refers to involvement of visceral soft organs at randomization, including but not limited to lung, liver, brain (CNS), reproductive system, involvement of pleura and/or peritoneum (based on NCI dictionary). Menopausal status was defined as the subject's menopausal status at randomization. Endocrine treatment failure was defined as the development of endocrine resistance in adjuvant endocrine therapy or endocrine therapy for locally advanced or metastatic breast cancer. That is, relapse during or within 1 year of discontinuation of adjuvant endocrine therapy, or disease progression following endocrine therapy for locally advanced or metastatic breast cancer.

Switch Treatment Group is not allowed in this study.

Data cleaning and locking were performed when the number of events preset in the protocol (approximately 119) was all reached. All subjects will be followed until disease progression and survival information will be collected until death or the end of the study, whichever comes first.

Study Endpoints

Efficacy endpoints

Primary efficacy endpoint

The primary endpoint of this study is the investigator-assessed progression-free survival, defined as the time from randomization to disease progression or death for any cause, whichever comes first. Disease progression will be evaluated according to RECIST 1.1.

Secondary efficacy endpoints

Progression-free survival (PFS) by BICR: defined as the time from randomization to either disease progression or death for any cause, whichever occurs first. Disease progression will be evaluated according to RECIST 1.1.

Overall survival (OS): defined as the time from randomization to death from any cause.

Objective response rate (ORR): defined as the proportion of subjects achieving a best overall response (BOR) of complete response (CR) or partial response (PR) based on RECIST v1.1 criteria during the study, with CR or PR at the first assessment requiring confirmation of response at least 4 weeks later. BOR is defined as the best overall

response from the start of treatment until disease progression or the development of new antineoplastic therapy or until the last evaluable assessment in the absence of RECIST progression, whichever occurs first.

Disease control rate (DCR): defined as the proportion of subjects achieving a best overall response (BOR) of complete response (CR) or partial response (PR) or stable disease (SD) during the study.

Clinical benefit rate (CBR): the proportion of subjects achieving complete response, partial response, or stable disease for ≥ 6 months based on RECIST 1.1.

Duration of response (DOR): calculated based solely on the subjects with BOR as confirmed complete response or partial response, defined as the time from the first occurrence of CR or PR in tumor assessment to progressive disease (PD) or death for any cause, whichever occurs first.

Safety endpoints

Adverse events

Treatment-emergent adverse events (TEAEs): AEs starting from the first dose until 30 days after the last dose of the blinded study drug (or until receipt of a new anticancer therapy, whichever comes first). An adverse event is classified as treatment-emergent if it could not be judged due to a total or partial missing of the time of onset of the adverse event and the end time of the adverse event is on-treatment or missing. All adverse events related to the study drug (GB491/placebo) are classified as treatment-emergent adverse events.

Treatment-emergent drug-related adverse events (TRAEs): TEAEs judged by the Investigator as "related" or missing relationship to study drug will be considered drug-related AEs.

Laboratory tests

Including blood routine, blood chemistry, urine routine and other examination results of the following indicators, as well as the corresponding clinical assessments (normal, abnormal not clinically significant, abnormal clinically significant).

- Hematology (red blood cell count, white blood cell count, hemoglobin, platelet count, hematocrit, neutrophils (ANC), lymphocytes, monocytes, eosinophils, basophils)
- Blood chemistry (serum sodium, serum potassium, serum chloride, blood glucose, blood urea/urea nitrogen, serum creatinine, creatinine clearance rate, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, γ-glutamine transpeptidase, total protein, albumin, serum calcium, serum magnesium, serum phosphorus)
- Coagulation (PT, APTT, INR)
- Urine routine (including dry chemical analysis and formed element analysis)

Others: Plasma drug concentration of GB491 and its metabolites; blood HBsAg, blood HCV-Ab; if HBsAg or HCV-Ab is positive, additional measurement of blood HBV DNA or blood HCV RNA is required; blood HIV antibody; blood human chorionic gonadotropin (hCG) test

Vital signs

Including the measurements of body temperature, blood pressure, pulse rate and respiratory rate of the subjects.

Electrocardiogram

Including electrocardiogram (ECG) test results (heart rate, RR interval, QT interval, QTcF interval, QRS interval,) and their clinical assessments (normal, abnormal not clinically significant, abnormal clinically significant).

Physical examination

Including a general appearance; head, eyes, ears, nose and throat; neck; heart; chest (including lung); abdomen; limbs; skin; lymph nodes; cardiovascular; neurological status and other physical examination results and their clinical assessments (normal, abnormal not clinically significant, abnormal clinically significant).

ECOG score

Subject's ECOG score.

Additional endpoints

Plasma PK parameters of GB491 and its metabolite G1T30.

Analysis Datasets

Full Analysis Set (FAS)

Full Analysis Set (FAS): includes all randomized subjects who receive at least one dose of the study drug. Analyses based on the FAS will be performed according to the treatment group to which the subject was randomized.

Per-Protocol Set (PPS)

Per Protocol Set (PPS): A subset of the FAS excluding subjects whose efficacy was severely affected in the FAS. For example, some subjects seriously violating the trial protocol, subjects not achieving the minimum exposure dose, and subjects without data after randomization. PPS needs to be determined prior to unblinding of the locked database.

Safety Analysis Set (SAS)

Safety Analysis Set (SAS): includes all subjects who receive at least one dose of the study drug and have at least one post-dose safety assessment.

Additional Analysis Sets

Pharmacokinetics consentration set (PKCS): includes all subjects who take the study drug at least once and have one valid plasma concentration measurement.

Hypothesis Test and Decision Rules

The null hypothesis of this study is that PFS in the treatment group is not superior to that in the control group and the alternative hypothesis is that PFS in the treatment group is superior to that in the control group.

H_0: $S_t(t) \leq S_c(t)$ vs. H_a: $S_t(t) > S_c(t)$;

Where the survival probability S(t) = P(T>t) refers to the probability that the time T of the event of interest is not less than the given time t. $S_t(t)$ represents the survival probability of subjects below the investigational product group and $S_c(t)$ represents the survival probability of subjects below the comparator group.

When approximately 119 PFS events have occurred in the treatment group and the control group, a superiority test will be performed, and if the one-sided p-value is less

than 0.025, the PFS of the treatment group will be considered superior to that of the control group, and the study meets the primary endpoint.

Sample Size Estimation

A total of 270 subjects are planned for enrollment, 135 in each of the treatment group and the control group. Assuming a median PFS of 9 months in the control group, a hazard ratio (HR) of 0.55 for the treatment group relative to the control group, an enrollment period of 12 months and an overall dropout rate of 25% for the overall study, a final analysis is performed when approximately 119 PFS events were reached to achieve 90% power of the statistical test.

Statistical Analysis Methods

General principles for statistical analysis

Statistical programming and analyses (tables, listings and graphs) will be performed using SAS 9.4 or above.

Descriptive summary

Unless otherwise specified, the following descriptive statistics are used for summaries by treatment group :

For continuous endpoints, the number of non-missing observations, mean, standard deviation, median, minimum and maximum will be summarized as applicable. The number of decimal places for the minimum and maximum values will be consistent with the raw data recorded in the database. Means and medians will be presented to one more decimal place than the raw data recorded in the database, and standard deviations will be presented to two more decimal places than the raw data recorded in the database, but no more than four decimal places.

For categorical endpoints, frequency and percentage will be summarized and presented for each category. Unless otherwise specified, percentages will be calculated based on all subjects in the respective analysis population. Percentages will be presented to one decimal place. Percentages of 100% will be reported as 100% and frequencies of 0 will not be reported as percentages.

For time-to-event endpoints, the Kaplan-Meier method will be used to estimate the survival function and estimate the median survival time and its 95% confidence interval, and survival curves will be plotted.

Statistical inference

General statistical tests are performed with two-sided tests, and one-sided tests need to be specified. A *p* value of less than or equal to 0.05 is used as a criterion to determine whether the difference is statistically significant. *P* values will be presented to 3 decimal places as "< 0.001" for *p* values less than 0.001 and as "> 0.999" for *p* values greater than 0.999.

The confidence interval adopts a 95% confidence level. The upper and lower limits of the 95% confidence intervals will be presented to one more decimal place than the raw data recorded in the database, but no more than four decimal places.

Confidence intervals will be two-sided 95% unless otherwise specified. Confidence interval values will be presented to one more decimal place than the original value, but no more than four decimal places.

Baseline definition

Baseline is defined as the last valid record prior to the first dose of the study drug.

Date decision rules

When the data supporting the efficacy judgment of the same visit were obtained at different dates, if PD occurred, the earliest date of occurrence of PD at the same visit was used, otherwise the latest date at the same visit was used.

Analysis nodes

When the preset number of events (approximately 119) in the protocol is reached, data cleaning and locking are carried out, and corresponding analysis is then conducted.

Censoring rules and handling of missing values

Missing values not mentioned in this section will not be handled and only observed values will be reported.

Handling of missing values for safety endpoints

For missing dates: refer to Appendix 10.1.

Handling of missing values for Best Overall Response (BOR)

Subjects with a BOR of unknown or none (ie, no valid documentation of post-treatment tumor assessment) will be considered NA.

Handling of missing values for ORR and DCR

Participants with a BOR of NA are considered non-responders and failed to achieve SD.

Censoring rules for PFS

Subjects who fail to observe an event will be censored. Censoring rules for PFS analysis are detailed in the table below:

Censoring Rules for PFS Analysis

No.	Situation	Censoring Rules/Date of Analysis
1	PD or death	Date of Event/PD or death
2	Remains in trial with no PD and no deaths	Date of censored/last tumor assessment
3	No baseline tumor assessment	Censored/randomization date
4	No post-baseline tumor assessments	Censored/randomization date
5	PD or death after missed ≥ 2 consecutive post-baseline tumor assessments	Date of last tumor assessment prior to censored/missed assessment
6	Initiation of new antineoplastic therapy	Date of last assessment prior to censored/new anticancer therapy
7	Lost to follow-up	Date of last tumor assessment before censoring/lost to follow-up

Note: If more than one condition exists, the earliest date will prevail.

Censoring rules for OS

Subjects who fail to observe an event will be censored. Censoring rules for OS analysis are detailed in the table below:

Censoring rules for OS analysis

No.	Situation	Censoring Rules/Date of Analysis
1	Death	Date of event/death
2	No death	Censored/last confirmed survival
3	Lost to follow-up	Censored/last confirmed survival

Censoring rules for DOR

Censoring rules for DOR analyses are the same as for PFS.

Study population

Subject disposition

Disposition of subjects who signed the informed consent was summarized. In case of screening failure, subjects will be summarized and tabulated by reason for screening failure.

Based on the FAS, the disposition of subjects in each group was summarized and described separately. According to the reasons for treatment termination, whether the trial was completed and the trial was still ongoing on the data cutoff date, and the reasons for not completing the trial were summarized.

Based on the FAS, subjects included in each analysis population and reasons not included in each analysis set were summarized according to the overall and randomization stratification factors, and the reasons for exclusion of subjects from each analysis set were listed in detail. Randomization information will also be listed for subjects randomized.

Protocol deviations

Subjects with important protocol deviations requiring exclusion from the analysis population will be identified prior to database lock.

Important protocol deviations for this study generally include:

1. Minimum exposure dose of study drug not reached;
2. The primary efficacy endpoint was not assessed;
3. Significant protocol deviations affecting efficacy (if inclusion and exclusion criteria are not met);
4. Criteria for study drug discontinuation were met, but the patient was not withdrawn from study treatment.

Based on the FAS, subjects with important protocol deviations in each arm during the treatment period were summarized according to the categories of protocol deviations, and all protocol deviations were listed.

Demographic and baseline characteristics

Demographic data (age, gender, ethnicity, height, weight, body mass index, baseline ECOG score, etc.) were summarized descriptively and tabulated based on the FAS.

Baseline disease characteristics (TNM stage at enrollment, histopathological grade at enrollment, clinical stage at enrollment, tumor lesion site at enrollment, ER result, PgR result, HER-2 IHC assay, HER-2 ISH assay, etc.) were summarized and tabulated.

Medical history

Medical history was coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25. 1.

Medical history will be summarized by system organ class (SOC) and preferred term (PT) for subjects in each group separately and listed in detail based on the FAS.

Prior and subsequent antineoplastic therapy

Antitumor drug therapy was coded using the World Health Organization Drug Dictionary (WHODrug) version September 2018 or the updated version.

Prior and subsequent surgeries, radiotherapy, and anticancer drug therapies were summarized and tabulated, respectively, based on the FAS. Prior and subsequent anticancer drug therapies were summarized by anatomic, therapeutic and chemical taxonomy (ATC) and preferred name (PN) of the drug.

Prior/concomitant nonantineoplastic medications and therapies

Prior non-antineoplastic medications and concomitant non-antineoplastic medications were coded using the World Health Organization Drug Dictionary (WHODrug). Prior

non-antineoplastic therapies, concomitant non-antineoplastic therapies were coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Prior non-antineoplastic medications and prior non-antineoplastic therapy

Prior medications or prior therapies are defined as non-study medications or therapies with a start date prior to the first study medication in the treatment period. If a non-study medication or treatment start date is missing or incomplete for comparison, the non-study medication or treatment will also be counted as prior medication or treatment unless clear evidence precludes this.

Prior medications were summarized according to Anatomical Therapeutic Chemical (ATC) Grade 4 and Preferred Name (PN) based on the FAS and tabulated in detail.

Prior therapies were summarized by SOC and PT for subjects based on the FAS and tabulated in detail.

Concomitant non-antineoplastic medications and concomitant non-antineoplastic therapy

Concomitant medications or treatments include over-the-counter medications, prescription medications, and therapeutic measures, and concomitant medications (including concomitant medications for adverse events) and any therapeutic measures should be recorded from 28 days before the first dose of study drug through the last safety follow-up.

Concomitant medications/concomitant therapies were defined in the analyses as non-study medications/therapies with a start date on or after the date of the first study medication and before the last visit, with no (ongoing) end date or a end date on or after the date of the first study medication. Non-study medication/therapy was also considered as concomitant medication/therapy if both start and end dates were on the day of the first study medication. Non-study medication/therapy with a start date prior to the first study medication, an end date on or after the first medication date, or a missing end date will also be considered concomitant medication/therapy. If a non-study medication/treatment start and/or end date is missing or incomplete for comparison, the non-study medication will also be counted as a concomitant medication/treatment unless there is clear evidence to exclude it.

Concomitant medications for subjects were summarized according to ATC4 and PN based on the FAS and tabulated in detail.

Subjects' concomitant therapies were summarized by SOC and PT and tabulated in detail based on the FAS.

Efficacy analysis

Primary efficacy endpoint analysis

The primary efficacy endpoint for this study was PFS as assessed by the investigator.

Primary analysis

Endpoint calculations: Statistical analyses of investigator-assessed PFS were performed based on the FAS.

Descriptive summary: Number of events, censored number and reasons for censoring in each group will be summarized. The 25th percentile, median, 75th percentile, and 95% confidence interval of the median for PFS were estimated for each group using the Kaplan-Meier method, and the PFS rate at specified times was estimated and corresponding Kaplan-Meier curves were plotted.

Hypothesis test: *p*-value will be calculated by stratified log-rank test with randomization stratification factors as stratification variables for comparison between groups. Superiority of the test treatment over the control treatment was considered established if the one-sided *p* value of the comparison between groups was < 0.0 25.

Estimation of difference between groups: Hazard Ratio (HR) and its 95% confidence interval (CI) of PFS in the treatment group and the control group were estimated using a Cox proportional hazards model including treatment group and randomization stratification factors.

Sensitivity analysis

Endpoint calculation: Statistical analysis based on PPS was performed on the investigator-assessed PFS.

Descriptive summary: same as the primary analysis.

Hypothesis test: As with the primary analysis, the results of hypothesis test are not used as criteria for the success of the study.

Estimation of difference between groups: same as the primary analysis.

Subgroup analysis

Hazard ratios and their 95% confidence intervals were estimated using a Cox proportional hazards model including treatment groups for each subgroup based on PFS from FAS and investigator assessment, and forest plots were prepared. Baseline characteristics of subgroups included:

- Nature of disease at baseline (visceral metastases vs bone only metastases vs others)
- Visceral metastasis (Yes versus No)
- Liver metastases (Yes versus No)
- Lung metastases (Yes versus No)
- Different menopausal status (male or premenopausal or perimenopausal versus postmenopausal)
- Prior endocrine therapy (adjuvant/neoadjuvant endocrine therapy versus recurrent/metastatic endocrine therapy)
- Number of lines of prior endocrine therapy failure (first line vs second line)
- Age (< 65 years vs ≥ 65 years)
- Number of visceral metastases (< 3 vs ≥ 3)
- ECOG score (0 vs 1)
- Prior 1st line chemotherapy (Yes versus No)
- Prior chemotherapy (Yes versus No)
- Primary versus secondary resistance
- Prior endocrine therapy (AI vs SERM vs AI and SERM vs others)
- Hormone receptors (ER+ and PR- vs ER- and PR+ vs ER+ and PR+)
- Measurable versus non-measurable lesions

Secondary efficacy endpoint analysis

PFS by BICR

Endpoint calculation: PFS assessed by BICR was statistically analyzed based on the FAS.

Descriptive summary: same as the primary analysis.

Hypothesis test: As with the primary analysis, the results of hypothesis test are not used as criteria for the success of the study.

Estimation of difference between groups: same as the primary analysis.

In addition, concordance analysis was performed between PFS assessed by BICR and PFS assessed by the investigator through a shift table. Each treatment group is tabulated below:

	Assessed as Event by BICR	Assessed as Censored by BICR	Total
Assessed as Event by Investigator	a	b	a + b
Assessed as Censored by Investigator	c	d	c + d
Total	a + c	b + d	n = a + b + c + d

Concordance ratio per group = (a + d)/n.

Overall survival (OS)

Endpoint calculation: Statistical analysis of OS was performed based on the FAS.

Descriptive summary: same as the primary analysis.

Hypothesis test: As with the primary analysis, the results of hypothesis test are not used as criteria for the success of the study.

Estimation of difference between groups: same as the primary analysis.

ORR

Endpoint calculation: The best overall response (BOR) and ORR were determined and calculated for each group based on the FAS, BICR assessment and Investigator assessment, respectively, taking into account the evaluation results at each visit.

Descriptive summaries: Number and percentage of subjects in each group confirmed by BOR for complete response (CR), confirmed partial response (PR), stable disease (SD), progressive disease (PD), not evaluable (NE), not assessed (NA). Two-sided 95% confidence intervals for ORR were estimated for each group using normal approximation.

Hypothesis test: None.

Estimation of difference between groups: The difference value of ORR between groups and its 95% confidence interval were estimated using normal approximation method.

DCR and CBR

Endpoint calculation: Based on the FAS, DCR and CBR were determined and calculated for each group by combining the evaluation results at each visit for the assessment of BICR and for the assessment of Investigator, respectively.

Descriptive summary: same as the ORR.

Hypothesis test: None.

Estimate of difference between groups: same as the ORR.

DOR

Endpoint calculation: Based on the FAS, DOR was calculated for subjects with BICR assessment and Investigator assessment, BOR confirmed CR or PR, respectively.

Descriptive summary: same as the primary analysis.

Hypothesis test: None.

Estimate for difference between groups: None.

Safety analysis

All safety analyses will be based on the Safety Analysis Set (SAS).

Adverse events

Adverse events were coded using MedDRA 25.1. Only treatment-emergent adverse events (TEAEs) were summarized, and adverse events (AEs) occurring before the first dose and 30 days after the last dose were presented in listings.

The incidence of adverse events was calculated based on the number of subjects who experienced adverse events rather than the number of adverse events at the time of adverse event summaries. In calculating the number and percentage of subjects with adverse events, multiple occurrences of the same adverse event in the same subject were counted only once; when the severity of an adverse event was counted, the most severe occurrence of multiple adverse events in the same subject under the same system organ class (SOC) and preferred term (PT) was counted once.

The following summaries and listings will be provided for adverse events:

- In summary tables, adverse events were summarized by treatment group for the following categories:
  - Treatment-emergent adverse events (TEAEs), treatment-emergent drug (GB491/placebo, fulvestrant, or LHRH) -related adverse events (TRAEs);
  - Serious adverse events (SAEs), drug-related serious adverse events;
  - Treatment-emergent adverse events with CTCAE Grade≥3, treatment-emergent drug-related adverse events with CTCAE Grade ≥ 3;
  - Treatment-emergent adverse events leading to study treatment discontinuation (GB491/placebo, fulvestrant, or LHRH), treatment-emergent drug-related adverse events leading to study treatment discontinuation;
  - Treatment-emergent adverse events leading to dose reduction of study treatment (GB491/placebo, fulvestrant, or LHRH), treatment-emergent drug-related adverse events leading to dose reduction of study treatment;
  - Treatment-emergent adverse events leading to discontinuation of study treatment (GB491/placebo, fulvestrant, or LHRH), treatment-emergent drug-related adverse events leading to discontinuation of study treatment;
  - Adverse events with fatal outcome, treatment-emergent drug-related adverse events with fatal outcome.
- Summaries by SOC and PT and highest CTCAE grade by treatment group:
  - Treatment-emergent adverse events (TEAEs), treatment-emergent drug-related adverse events;

- Treatment-emergent serious adverse events, drug-related serious adverse events;
- Treatment-emergent adverse events with CTCAE Grade 3 or higher, and treatment-emergent drug-related adverse events with CTCAE Grade 3 or higher.

- Summarized by PT and highest CTCAE grade by treatment group and sorted by decreasing frequency:
  - Treatment-emergent adverse events with incidence ≥5%, treatment-emergent drug-related adverse events with incidence ≥ 5%.
- Treatment-emergent adverse events of special interest (AESIs)

Treatment-emergent adverse events of special interest included neutrophil count decreased, diarrhoea, nausea, vomiting, interstitial lung disease/pneumonia. The search strategy was as follows:

- Neutrophil count decreased, PTs searched: neutropenia, neutrophil count decreased, neutrophil percentage decreased, pancytopenia, febrile neutropenia, cytopenia, agranulocytosis, myelosuppression, neutropenic infection, neutropenic colitis, and neutropenic sepsis;
- Diarrhoea: SMQ (narrow) searched: non-infectious diarrhoea;
- Nausea: PT searched: nausea;
- Vomiting: PT searched: vomiting;
- Interstitial lung disease/pneumonia: SMQ (narrow) searched: interstitial lung disease.

Adverse events of special interest were calculated according to the highest CTCAE number and percentage, median and minimum and maximum AE onset time (months), number and percentage leading to study treatment suspension, study treatment dose reduction, study treatment discontinuation, number and percentage of AE recovery, median and minimum and maximum AE recovery time (months).

- AE onset time is the time from the first dose of study drug to the first occurrence of the highest CTCAE grade of the AE;

- AE recovery time is the time from the first occurrence of the highest CTCAE grade of the AE to the end of the first outcome of "recovered";
- Grade ≥ 3 AE duration is the time from the first occurrence of the AE with the highest CTCAE Grade ≥ 3 to the start of the first resolution to Grade ≤ 2.

- In addition, the following summaries and listings were included:
  - Summary of causes of death;
  - Adverse event list (including whether related to the drug, whether SAE, CTCAE grading, and measures taken);
  - List of serious adverse events (SAEs);
  - List of adverse events leading to death;
  - List of adverse events in subjects with adverse events leading to suspension of treatment;
  - List of adverse events in subjects with adverse events leading to dose reduction;
  - List of adverse events in subjects with adverse events leading to discontinuation;
  - List of subjects who died.

Clinical laboratory tests

Hematology and chemistry results and urinalysis measured at each visit and corresponding changes from baseline will be summarized descriptively by treatment group. Frequency of subjects from baseline CTCAE grade (Grade 0 to 4, Grade 0 is normal) to worst postdose CTCAE grade will be summarized using a shift table by treatment group. For indicators without CTCAE grade, tables were transposed as lower than normal, normal, and higher than normal values.

The number and percentage of subjects with treatment-emergent elevations in ALT, AST, ALP, and total bilirubin will be summarized:

- ALT > 1 × ~ ≤ 3, > 3 × ~ ≤ 5 ×, > 5 × ~ ≤ 10 ×, > 10 × ~ ≤ 20 × and > 20 × ULN;

- AST > 1 × ~ ≤ 3, > 3 × ~ ≤ 5 ×, > 5 × ~ ≤ 10 ×, > 10 × ~ ≤ 20 × and > 20 × ULN;
- ALP > 1 × ~ ≤ 1.5, > 1.5 × ~ ≤ 2.5 ×, > 2.5 × ~ ≤ 5 ×, > 5 × ~ ≤ 20 × and > 20 × ULN;
- Total bilirubin > 1 × ~ ≤ 1.5, > 1.5 × ~ ≤ 2 ×, > 2 × ~ ≤ 3 ×, > 3 × ~ ≤ 10 × and > 10 × ULN;
- AST or ALT > 3 × ULN and total bilirubin > 1.5 × ULN, AST or ALT elevation must precede or coincide with the date of the total bilirubin elevation;
- AST or ALT > 3 × ULN and total bilirubin > 2 × ULN, AST or ALT elevation must precede or coincide with the date of the total bilirubin elevation.

All results of hematology, chemistry and urinalysis will be listed separately. Associated tests with CTCAE Grade ≥ 3 will also be listed for all laboratory tests.

Vital signs

Results for vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, body temperature) and corresponding changes from baseline were summarized descriptively by treatment group. Frequency of subjects from baseline category (below normal, normal, and above normal) to the category corresponding to the worst case post-treatment (below normal, normal, and above normal) will also be summarized using a shift table by treatment group according to the table below. Detailed listings of vital sign measurements were provided for the subjects.

Criteria for Above-normal and Below-normal Values for Vital Signs

	Above Normal	**Below Normal**
Systolic Blood Pressure (mmHg)	≥ 140	< 90
Diastolic Blood Pressure (mmHg)	≥ 90	< 60
Pulse (beats/min)	> 100	< 60

	Above Normal	Below Normal
Respiratory Rate (breaths/min)	> 20	< 12
Body Temperature (degrees Celsius)	≥ 37. 5	< 36

Electrocardiogram

Descriptive summaries will be provided for ECG indicators measured at each visit and corresponding changes from baseline, and summarized in the form of worst case shift table before and after treatment.

For QTc interval with normal baseline (≤ 450 ms), post-treatment abnormalities were categorized using the maximum post-treatment value and its change from baseline, and the maximum was divided into three categories (> 450 - ≤ 480 ms, > 480 - ≤ 500 ms, > 500 ms), and its changes were divided into three categories (≤ 30 ms, >30 - ≤ 60 ms, > 60 ms), and the number and percentage of subjects in each category were counted. The maximum post treatment value includes that of the unscheduled visits.

Change in QTc interval = QTc interval at the end of treatment - QTc interval at baseline.

Subjects' ECG results were listed in detail.

Physical examination

Physical examination results were listed by visit for subjects.

ECOG score

Subjects' ECOG scores were listed in detail by visit.

For laboratory tests, vital signs, electrocardiograms, physical examinations, and ECOG scores, data generated by subjects following subsequent antineoplastic therapy were not included in the statistical analysis but presented in listings.

Pharmacokinetic analysis

Observed plasma concentrations of GB491 and its metabolite G1T30 were summarized descriptively based on the PK concentration set separately: GB491 and G1T30 plasma concentrations were tabulated by statistical analysis summarized by

treatment cycle and date; and mean plasma concentrations over time curves were presented for GB491 and G1T30, respectively.

Other analyses

None.

Study drug exposure and compliance

Study drug exposure and compliance were analyzed using the Safety Analysis Set (SAS). Drug exposure was counted separately for "GB491/placebo" and "fulvestrant".

Drug exposure time (months) = (last study medication date – first study medication date + 1)/30.4375.

Actual cumulative dose (mg): the sum of the actual dose received from the first dose of study medication until treatment discontinuation, i.e. until the date of last dose;

Dose intensity (mg/day) = actual cumulative dose/drug exposure time (days).

Relative dose intensity = dose intensity/planned dose intensity * 100%, planned dose intensity is dose group intensity.

For Fulvestrant:

Drug exposure time (months) = (last study medication date – first study medication date + 28)/30.4375.

(%) Compliance = actual total dose/planned total dose × 100%.

Descriptive summaries were provided for the duration of drug exposure (months), compliance (%), actual cumulative dose, dose intensity, and relative dose intensity of the subjects by treatment group, and for the study treatment pauses and dose modifications of the subjects. Compliance was graded and summarized as < 8 0%, ≤ 80% ~ ≤ 100%, > 10 0% ~ ≤ 120%, > 120%. In addition, the drug exposure data of the subjects were tabulated in detail.

References

None.

Appendices

Appendix 1. Missing Date Imputation Guidelines

This appendix provides common imputation of dates for oncology projects.

1. Imputation of date of death

If the date of death is partially missing or completely missing, it is imputed based on the last confirmed alive date:

a) If only the day is missing, the imputed date of death = max (date last confirmed alive + 1, date (year of death, month of death, day of death = 01) ;

b) If both month and day are missing, the imputed date of death = max (date last confirmed alive + 1, date (year of death, month of death = 01, day of death = 01);

c) If completely missing, the imputed date of death = date last confirmed alive + 1.

2. Imputation for date of the last dose of the study drug

Date of the first study medication requires that the complete date must be collected without imputation.

Date of the last dose of the study medication if partially missing or completely missing:

a) The imputed date of the last dose of the study medication = designated data cut-off date if the subject is still on medication (subject's end of treatment (EOT) not yet collected);

b) If relevant information on treatment discontinuation or date of death has been collected:

i. If only the day is missing and the year = min (year of discontinuation, year of death) and the month < min (month of discontinuation, month of death), the imputed date of the last study medication = date (year, month, day = last day of the month);

ii. If both the month and day are missing and the year < min (year of discontinuation, year of death), the imputed date of the last study medication = date (year, month = 12, day = 31);

iii. In other cases, the imputed date of the last study medication = min (date of discontinuation, date of death).

3. Imputation of the start date of new anticancer therapy

If the new anti-tumor start date is partially missing or completely missing, the imputation rules will be based on the date of disease progression, date of the last study medication, and date of the end of new anticancer therapy, so that

The imputed date = min [max (date of disease progression + 1, date of the last dose of study medication + 1), end date of the new anticancer therapy].

a) If only the day is missing,

   i. If the year = year of imputed date and the month < month of imputed date, the imputed new anti-tumor start date = date (year, month, day = last day of the month);

   ii. If the year = year of the imputed date and the month = month of the imputed date, the imputed new anti-tumor start date = the imputed date;

   iii. If the year = year of the imputed date and the month > month of the imputed date, the imputed new anti-tumor start date = date (year, month, day = 01);

   iv. If the year < the imputed year, the imputed new anti-tumor start date = date (year, month, day = last day of the month);

   v. If the year > the imputed year, the imputed new anti-tumor start date = date (year, month, day = 01).

b) If both the month and day are missing,

   i. If the year < the imputed year, the imputed new anti-tumor start date = date (year, month = 12, day = 31);

   ii. If the year = the imputed year, the imputed new anti-tumor start date = the imputed date;

   iii. If the year > the imputed year, the imputed new anti-tumor start date = date (year, month = 01, day = 01).

c) The imputed new anti-tumor start date = the imputed date if completely missing.

4. Imputation for dates other than the above (e.g. start of AE, end date, start of concomitant medication, end date, etc.):

a) For the start date:

   i. The start date is imputed if only the day is missing = date (year, month, day = first day of the month);

   ii. The start date is imputed if the month and day are missing = date (year, month = 01, day = 01);

   iii. If completely missing, no imputation is needed.

b) For the end date:

   i. The end date is imputed = date (year, month, day = last day of month) if only the day is missing;

   ii. If both the month and day are missing, the imputed end date = date (year, month = 12, day = 31);

   iii. If completely missing, no imputation is needed.

c) If the imputation method leads to a start date earlier than the end date, the start date and end date in this case should be the same day and should be imputed as the imputation method for the start date.