A Phase 1, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics, and Preliminary Antitumor Activity of Ascending Doses of G1T48 Alone and in Combination with Palbociclib in Women with Estrogen Receptor Positive, HER2-Negative Advanced Breast Cancer

Published: 21-02-2018
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The primary objective of the study are to: 1) Determine the safety and tolerability of G1T48 alone (Parts 1 and 2) or in combination with palbociclib (Part 3), 2) Determine the MTD and RP2D of G1T48 alone (Parts 1 and 2) or in combination with...

Ethical review	Approved WMO
Status	Completed
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON50738

Source
ToetsingOnline

Brief title
G1T48-01 (3652/0007)

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Advanced Breast Cancer, Estrogen Receptor-Positive HER2-Negative Advanced Breast Cancer

Research involving
Human

Sponsors and support

Primary sponsor: G1 Therapeutics Inc.
Source(s) of monetary or material Support: The study sponsor as completed in section B7

Intervention

Keyword: Advanced breast cancer, G1T48, Phase 1

Outcome measures

Primary outcome

Primary:

1) AEs, SAEs, and other safety measures (ECGs, physical examinations, vital

signs, and laboratory parameters)

2) Safety, tolerability and DLTs

Secondary outcome

Secondary:

1) See Table 10.6 of the study protocol

2) See Section 10.7.1 of the study protocol (Part 3)

3) Cmax and AUC ratios

4) PFS, OS, ORR, BOR, and DoR according to RECIST, Version 1.1; CBR (including

CR, PR, and SD lasting >= 24 weeks)

Exploratory:

1) Correlation between response endpoints and the following cfDNA endpoints:

baseline ESR1 mutational status, quantity of cfDNA, mutational changes in cfDNA (including ESR1 and PI3K), and quantification of genetic changes in cfDNA

2) % change in SUV, parameters of kinetic modelling (ie, K1, VT)

3) Enumeration and proportion of ER positive CTCs

4) Evaluate estrogen receptors and downstream effectors

5) Correlation between PK endpoints and response endpoints, including RECIST assessment, FES PET (Parts 1 and 2 only) and fresh tumor tissue (Parts 2 and 3 only).

6) Biomarker status, including ESR1, Ki67, and others in archival tumor tissue, fresh tumor tissue (Parts 2 and 3 only) and correlations with response or resistance

Study description

Background summary

Approximately 80% of breast cancers express estrogen receptors (ERs), progesterone receptors, or both. The relapse rate after presentation with early-stage disease of these hormone receptor (HR)-positive cancers has been substantially reduced with the use of endocrine therapies, namely aromatase inhibitors (AIs) and tamoxifen. Despite the success of these therapies, relapse of disease often occurs either during or after completion of adjuvant endocrine therapy. The established standard of care following disease progression in the adjuvant setting is combination therapy with a cyclin-dependent kinase (CDK)4/6 inhibitor and an endocrine therapy, based on a significant improvement in progression-free survival (PFS) when compared to endocrine therapy alone. To date, 3 CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) have been approved for use in postmenopausal women with ER-positive, human epidermal growth factor receptor-2 (HER2)-negative advanced breast cancer. Palbociclib in combination with letrozole was approved as initial endocrine-based therapy in the United States (US) in February 2015, and use of palbociclib in combination with fulvestrant in patients with disease progression following endocrine therapy was approved in the US in February 2016. Palbociclib in combination with AI or fulvestrant was approved in the European Union (EU) in August 2017.

However, disease progression eventually ensues in the majority of patients and additional effective treatment options are limited. The standard of care in these patients is not yet established as CDK4/6 inhibitors are a relatively new addition to the treatment of HR positive breast cancer. Additionally, the mechanisms of resistance are for the most part unknown. Treatment options include a steroidal AI, tamoxifen, AI plus everolimus, fulvestrant (if not previously used), chemotherapy and other targeted agents where appropriate. While the efficacy of these agents in this setting is unknown, studies of these agents prior to the use of CDK4/6 inhibitors have shown only modest activity. Therefore, the development of effective therapies that can overcome resistance to previously administered endocrine therapies is of clinical importance.

Fulvestrant is a clinically effective selective estrogen receptor degrader (SERD), and a standard of care medicine in HR-positive advanced breast cancer. However, intramuscular injection of fulvestrant may be painful to the patient and also limits the maximum dose to 500 mg. Acquired mutations in the ligand-binding domain (LBD) of ESR1 (the gene encoding ER alpha) in patients with advanced breast cancer can cause the ER to remain constitutively active without estrogen; a major mechanism of resistance to AIs. Although some evidence suggests that cancers with ESR1 mutations may retain relative sensitivity to fulvestrant, higher relative doses and systemic exposures of ER degraders or novel therapies could improve efficacy. Therefore, developing an agent that has a more favorable route of administration (ie, oral), with the potential to achieve higher plasma concentrations than fulvestrant, and thus potentially improved ER degradation in patients with and without ESR1 mutations, is desirable.

G1T48 is an oral SERD that may be administered at doses with the potential to achieve higher relative exposure, enhanced target engagement, without painful injections, and potentially superior clinical benefit in the management of patients with ER-positive advanced breast cancer. Oral administration could provide a more convenient and effective solution for patients over injectable drug formulations.

Parts 1 and 2 of this study will characterize the safety, tolerability, and preliminary antitumor activity of G1T48 monotherapy in patients with ER-positive, HER2-negative advanced breast cancer. Furthermore, as the combination of CDK4/6 inhibitor with endocrine therapy has emerged as the current standard of care, Part 3 will evaluate the safety, tolerability, and preliminary antitumor activity of G1T48 in combination with palbociclib.

Study objective

The primary objective of the study are to: 1) Determine the safety and tolerability of G1T48 alone (Parts 1 and 2) or in combination with palbociclib (Part 3), 2) Determine the MTD and RP2D of G1T48 alone (Parts 1 and 2) or in combination with palbociclib (Part 3)

The secondary objectives of the study are to: 1) Characterize single and multiple dose PK parameters of G1T48 and metabolite(s), including PopPK, 2) Characterize PK parameters of palbociclib (Part 3), 3) Characterize the effect of food on the relative bioavailability of G1T48 and 4) Assess antitumor activity

The exploratory objectives of the study are to: 1) Assess correlation between cfDNA and response endpoints, 2) Assess changes in FES PET, 3) Assess CTCs, 4) Assess pharmacodynamic changes in fresh tumor tissue, 5) Assess PK/ pharmacodynamic relationships and 6) Assess biomarkers as predictors of response or resistance.

Study design

This is a Phase 1, open-label, first-in-human (FIH) study of G1T48 alone and in combination with palbociclib administered orally in patients with advanced ER-positive, HER2 negative breast cancer. This open-label study consists of 3 parts: Part 1 will evaluate the safety, tolerability, PK, including the effect of a high-fat meal on bioavailability, MTD, and RP2D of escalating doses of G1T48 monotherapy; Part 2 will include an expansion cohort at the RP2D to further characterize the safety and preliminary antitumor activity of G1T48 monotherapy; and Part 3 will evaluate the safety, tolerability, PK, and preliminary antitumor activity of G1T48 in combination with palbociclib.

Part 1
Part 1 Dose-Escalation Cohorts
This study will employ a standard 3 + 3 dose escalation design in Part 1. Patients will receive a single oral dose of G1T48 on Cycle 1 Day 3 followed by blood sampling over the next 72-hour period for PK analysis. Continuous oral daily dosing of G1T48 will then commence on Cycle 1 Day 1. Each cycle will be 28 days in duration.
FES PET will be acquired prior to G1T48 administration (during screening), at Cycle 2 Day 2, and at the time of treatment discontinuation to determine 18F estradiol tracer uptake.
All dose escalation/de-escalation decisions will be made by the safety monitoring committee (SMC) based on safety and available PK data from Cycle 1 Day -3 through Cycle 1 Day 28 of the current cohort (DLT period of the current cohort), as well as available FES PET data and cumulative safety data from all cohorts. The SMC will make the final dose determination for each subsequent cohort (projected dose levels are presented in Table 6 1). The maximum G1T48 dose in this study will not exceed 2000 mg/day.

Food Effect Cohort(s)
An additional G1T48 cohort of 8 patients may be enrolled during Part 1 to assess the effect of a high-fat meal on the rate and extent of the absorption of G1T48. At the discretion of the Sponsor and/or SMC additional food effect cohort(s) may be explored.

Definition of Dose-Limiting Toxicities
Dose-limiting toxicities are defined as follows:
- Grade 4 neutropenia
- >= Grade 3 neutropenic infection/febrile neutropenia
- Grade 4 thrombocytopenia
- >= Grade 3 thrombocytopenia with bleeding
- >= Grade 3 nonhematologic toxicity (the following Grade 3 toxicities only qualify as a DLT if the toxicity persists for >= 24 hours despite maximal medical management: nausea, vomiting, diarrhea; or >= 5 days with maximal medical management: fatigue)
- Liver function test abnormalities meeting Hy*s Law criteria (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] >= 3 × upper limit of normal [ULN] and total bilirubin >= 2 × ULN); G1T48 must be permanently discontinued in any patient meeting Hy*s Law criteria
- Any Grade 3 or greater electrolyte abnormality lasting >72 hours
- Any Grade 3 or greater electrolyte abnormality AND the patient is clinically symptomatic, regardless of duration
o NOTE: Grade 3 or greater amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis does not need to be reported as a DLT
- Any death not clearly due to the underlying disease or extraneous causes

Part 2
After the G1T48 RP2D has been determined, an open-label expansion cohort (Part 2) will be enrolled at the RP2D to further characterize the safety and preliminary antitumor activity of G1T48. Following screening, patients will begin continuous oral daily dosing of G1T48 on Cycle 1 Day 1. Pre- or perimenopausal patients will also receive luteinizing hormone-releasing hormone (LHRH) agonist for the duration of study treatment.
FES PET will be acquired prior to G1T48 administration (during screening), at Cycle 2 Day 2, and at the time of treatment discontinuation in approximately 50% of patients enrolled in Part 2 to determine 18F-estradiol tracer uptake as a measure of G1T48 pharmacodynamic action. Only postmenopausal women may provide FES PET scans in Part 2.

The SMC will review all cumulative safety data, as well as all available PK and FES PET data, approximately every 4 months during the Treatment Phase of Part 2.

Part 3
An open-label cohort will be enrolled to evaluate the safety and preliminary antitumor activity of G1T48 in combination with palbociclib. Based on similar safety profiles seen in the 600 mg and 1000 mg dose cohorts in Parts 1 and 2, patients enrolled in Part 3 will receive G1T48 at either dose (600 mg once daily or 1000 mg once daily). Additional dose levels may be explored at the discretion of the Sponsor and/or SMC based on emerging safety and efficacy data. Palbociclib 125 mg oral daily will be administered on Days 1 to 21 of each 28-day cycle, starting on Cycle 1 Day 1. Pre- or perimenopausal patients

will also receive LHRH agonist for the duration of study treatment.
The SMC will review all cumulative safety data, as well as all available PK and biomarker data, after the first 6 patients in Part 3 have completed 1 cycle of therapy, then approximately every 4 months during the Treatment Phase of Part 3.

Intervention

The starting dose is 200 mg G1T48, taken orally once daily. Subsequent dose levels will be determined by the SMC.

Study burden and risks

Please refer to appendix D of the subject information sheet for an overview of the side effects and possible risks of the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

For a patient to be eligible for participation in this study, all of the following criteria must apply. A full list of inclusion criteria are provided in Section 7.1.1 of the study protocol.
• Age 18 years or older females (postmenopausal only in Part 1 and any menopausal status in Parts 2 and 3; pre- and peri-menopausal women in Parts 2 and 3 must be chemically or surgically postmenopausal)
• Histological or cytological confirmation of adenocarcinoma of the breast with evidence of metastatic or locally advanced disease, which is not amenable to surgical resection ± radiation therapy with curative intent
• Documented ER-positive tumor, defined as >= 1% positive stained cells utilizing an assay consistent with local standards. The tumor may be progesterone receptor positive or negative.
• Documented HER2-negative tumor per 2017 College of American Pathologists (CAP) criteria
• Not eligible for standard therapy that would confer clinical benefit to the patient
• For Parts 1 and 2 of the study, objective evidence of either progression after an AI for metastatic/locally advanced disease OR recurrence while on or within 12 months of the end of adjuvant treatment with an AI
• For Part 3, patients must meet at least ONE of the following:
- Received >= 24 months of endocrine therapy in the adjuvant setting prior to recurrence or progression
- Received >= 6 months of endocrine therapy in the advanced/metastatic setting prior to progression
• Not eligible for standard therapy that would confer clinical benefit to the patient
• For Part 1 of the study, evaluable or measurable disease as defined by RECIST, Version 1.1
• For Parts 2 and 3 of the study, approximately 75% of enrolled patients must have measurable disease as defined by RECIST, Version 1.1
• Exposure to the following:
- Part 1: <= 3 lines of prior cytotoxic chemotherapy
- Part 2: <= 1 line of prior cytotoxic chemotherapy
- Part 1 and Part 2:
o <= 3 prior endocrine therapies in the metastatic setting
o Prior CDK4/6 inhibitor therapy and/or everolimus is allowed
- Part 3:
o <= 1 prior line of endocrine therapy in the metastatic setting
o <= 1 prior line of cytotoxic chemotherapy in the metastatic setting
o Prior CDK4/6 inhibitor therapy is not allowed
o Prior everolimus is allowed

• Required washout for FES PET (Parts 1 and 2 only), if applicable
- >= 5-week interval since the last use of tamoxifen (or other selective estrogen receptor modulators [SERMs]) or fulvestrant (or other SERDs)
• Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
• Life expectancy > 12 weeks
• Adequate bone marrow reserve and organ function as demonstrated by the following laboratory values:
- Hemoglobin >= 9 g/dL
- Absolute neutrophil count (ANC) >= 1.5 × 109/L
- Platelet count >= 100 × 109/L
- Estimated glomerular filtration rate >= 50 mL/minute/1.73 m2
- Total bilirubin <= 1.5 × ULN
- ALT and AST <= 3 × ULN; <= 5 × ULN in the presence of liver metastases

Exclusion criteria

A patient will not be eligible for participation in this study if any of the following criteria apply. A full list of exclusion criteria are provided in Section 7.1.2 of the study Protocol.
• Patients with immediately life-threatening or rapidly progressive disease or those who experience rapid visceral recurrence during adjuvant endocrine therapy
• Known active uncontrolled or symptomatic central nervous system (CNS) metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and or progressive growth. Patients with a history of CNS metastases or cord compression are eligible if they have been definitively treated (eg, radiotherapy, stereotactic surgery) and clinically stable (including patients with residual CNS symptoms/deficits) off enzyme-inducing anticonvulsants and steroids for at least 28 days prior to the first dose of study drug (patients may continue to receive non-enzyme-inducing anticonvulsants throughout the study if needed)
• Major surgery, chemotherapy, radiotherapy, or other anticancer therapy within 14 days of first dose of study drug
• Prior hematopoietic stem cell or bone marrow transplantation
• Blood transfusions or hematopoietic growth factor therapy within 14 days prior to the first dose of study drug
• Concurrent use of prohibited medications
• Any unresolved toxicities from prior surgeries or therapies > Grade 1 (Common Terminology Criteria for Adverse Events [CTCAE] Version 5.0) at the time of starting study drug with the exception of alopecia (any grade) and Grade 2 peripheral neuropathy
• Cardiac criteria as outlined in Section 7.1.2 of the study protocol
• Known clinically significant history of liver disease (excluding metastases to the liver)
• Unexplained symptomatic endometrial disorders
• Any evidence of severe or uncontrolled systemic diseases, which in the

investigator opinion makes it undesirable for the patient to participate in the study or that would jeopardize compliance with the protocol
• Known chronic, active infection
• Refractory nausea and vomiting, chronic gastrointestinal (GI) disease, GI ulcer, GI bleeding, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption of study drug
• History of other malignancies, except for the following: (1) adequately treated basal or squamous cell carcinoma of the skin; (2) curatively treated a) in situ carcinoma of the uterine cervix, b) superficial bladder cancer; or (3) other curatively treated solid tumor with no evidence of disease for >= 3 years
• For Part 3 of the study, prior CDK4/6 inhibitor therapy, oral SERDs, or selective estrogen receptor covalent antagonists (SERCAs) in any setting

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	02-10-2018
Enrollment:	45
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Not yet known
Generic name:	Not yet known

Ethics review

Approved WMO Date:	21-02-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-04-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-07-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-08-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-05-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
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Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	31-07-2019
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Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
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Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	15-06-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-06-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-08-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
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Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-07-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	19-10-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
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Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-03-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-004502-17-NL
CCMO	NL64591.042.18

Study results

Date completed:	29-04-2022
Results posted:	11-05-2023

First publication
21-02-2023