FIRST-IN-HUMAN DOSE-ESCALATION STUDY OF G1T48, AN ORAL SELECTIVE ESTROGEN RECEPTOR DEGRADER (SERD), IN POSTMENOPAUSAL WOMEN WITH ER+/HER2- LOCALLY ADVANCED OR METASTATIC BREAST CANCER (ABC)

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BACKGROUND

- Selective estrogen receptor degraders (SERDs) are competitive estrogen receptor (ER) antagonists that block signaling in ER-dependent tumors, including tumors resistant to other endocrine therapies[1,2]
- The SERD, fulvestrant, has demonstrated survival benefit in patients with advanced breast cancer (ABC), but intramuscular administration, poor solubility, and patient discomfort are all limiting factors[1]
- G1T48 is an oral SERD that has the potential to achieve higher exposure, improve clinical outcomes and patient experience, and allow more patients with ER-positive (ER+) ABC to be treated, including in the adjuvant setting
- Preclinical data have shown G1T48 to be highly potent with activity in both mutant and wild-type estrogen receptor 1 (ESR1) models of breast cancer[3]
- Based on these data, a first-in-human (FIH) study of G1T48 in patients with ER+/human epidermal growth factor receptor 2-negative (HER2-) ABC was initiated (NCT03455270; EudraCT number 2017-004502-17)
- This study consists of 2 parts: Part 1 is a dose-finding portion and Part 2 includes an expansion cohort of 2 doses of G1T48 to further characterize the safety and preliminary antitumor activity of G1T48
- Here, we describe preliminary results from the dose escalation part of the study (Part 1)

STUDY OBJECTIVES

- To determine the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) of oral G1T48 and to characterize the effect of food on the relative bioavailability of G1T48

METHODS

Study Design

- The G1T48 starting dose was 200 mg orally once daily (QD), and escalation proceeded according to a 3 + 3 design based on dose-limiting toxicities (DLTs): 1 cycle was defined as 28 days
- The projected dose levels were 200, 400, 600, 800, 1000, 1250, 1500, and 2000 mg QD
- Key eligibility criteria:
  - Postmenopausal women ≥ 18 years
  - Histologic/cytologic confirmation of ER+/HER2- ABC
  - ≤ 3 lines of prior chemotherapy in the metastatic setting
  - ≤ 3 prior endocrine therapies, including fulvestrant, aromatase inhibitors, and tamoxifen in the metastatic setting
  - Eastern Cooperative Oncology Group performance status: 0 or 1
- Primary objectives:
  - Safety, tolerability, DLTs
  - MTD, RP2D
- Secondary objectives:
  - PK profile
  - Antitumor activity (according to Response Evaluation Criteria in Solid Tumors [RECIST] v1.1)

Dose-Limiting Toxicities

- Defined to include any of the following treatment-emergent adverse events (TEAEs) considered related to study treatment (NCI-CTCAE v5.0) from cycle 1 day –3 through cycle 1 day 28:
  - 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 qualified as a DLT if the toxicity persisted 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 x ULN)
  - Any Grade ≥ 3 electrolyte abnormality lasting > 72 hours
  - Any Grade ≥ 3 electrolyte abnormality AND the patient is clinically symptomatic, regardless of duration
  - Any death not clearly due to the underlying disease or extraneous causes

Pharmacokinetics Analysis

- Blood samples were collected in a fasted state on cycle 1 day –3 (no G1T48 on days –2 and –1) and on cycle 2 day 1: pre-dose and at multiple time points for 72 hours post G1T48 administration during cycle 1; and pre-dose and at multiple time points for 24 hours post G1T48 administration during cycle 2
- Food effect was determined by administration of a high-fat meal 30 minutes before a single 200 mg dose of G1T48 on either cycle 1 day –10 or day –3 in a crossover fashion (either fed–fasted or fasted–fed). Blood samples were collected pre-dose and at multiple time points for 72 hours post G1T48 administration (no G1T48 from cycle 1 day –9 to cycle 1 day –4 as well as cycle 1 day –2 and –1; there was no day 0 in this study)
- PK parameters (including time to maximum concentration [T_{max}], maximum concentration [C_{max}], area under the curve over 24 hours [$AUC_{0\text{-}24h}$], and area under the curve from time 0 to time of last measurable concentration [AUC_{last}]) were determined by noncompartmental analysis (Phoenix® software)

Pharmacogenetic Analysis

- Whole-blood samples were collected at baseline for the assessment of UGT1A1 genetic polymorphisms; UGT1A1 may play a role in the clearance of G1T48

Pharmacodynamic Analysis

- ^{18}F-fluoroestradiol positron emission tomography (^{18}F-FES PET) imaging was performed at baseline and on cycle 2 day 2 (± 2 days) to determine the impact of G1T48 at steady state on ER occupancy/degradation in tumor lesions
- To evaluate mutational changes in cell-free DNA (cfDNA), peripheral blood samples were drawn at baseline, cycle 1 day 15, the end of every even-numbered cycle concurrent with tumor assessments, and treatment discontinuation. Samples were processed and analyzed at Guardant Health, Inc.

RESULTS

Patient Demographics, Baseline Characteristics and Disposition

- A total of 26 patients were enrolled and treated in Part 1 as of data cutoff on August 12, 2019
- Patients in the food effect cohort were assigned to a G1T48 daily dose of either 600 mg (n = 4) or 800 mg (n = 4) following completion of the PK assessment period
- The 400 mg cohort was backfilled with an additional 3 patients to obtain supplementary safety data
- Baseline characteristics and patient disposition are summarized in **Table 1** and **Table 2**

Table 1. Baseline Characteristics

	200 mg (n = 3)	400 mg (n = 6)	600 mg (n = 7)	800 mg (n = 7)	1000 mg (n = 3)	Total (n = 26)
Median (range) age, years	59 (51–69)	61 (56–72)	65 (55–69)	66 (43–75)	54 (50–71)	61 (43–75)
ECOG PS, n (%)						
0	2 (66.7)	2 (33.3)	4 (57.1)	4 (57.1)	2 (66.7)	14 (53.8)
1	1 (33.3)	4 (66.7)	3 (42.9)	3 (42.9)	1 (33.3)	12 (46.2)
Race, n (%)						
White	3 (100)	6 (100)	6 (85.7)	7 (100)	3 (100)	25 (96.2)
Black/African American	0	0	1 (14.3)	0	0	1 (3.8)
Median (range) number of prior lines of therapy for advanced disease	2 (1–3)	2 (1–4)	4 (1–4)	4 (2–4)	4 (1–4)	3 (1–4)
Type of prior treatment in advanced setting, n (%)[a]	3 (100)	6 (100)	7 (100)	7 (100)	3 (100)	26 (100)
Cytotoxic chemotherapy	0	2 (33.3)	5 (71.4)	5 (71.4)	1 (33.3)	13 (50.0)
Endocrine therapy	3 (100)	6 (100)	7 (100)	7 (100)	3 (100)	26 (100)
Nonsteroidal AI	1 (33.3)	4 (66.7)	4 (57.1)	6 (85.7)	1 (33.3)	16 (61.5)
Steroidal AI	0	2 (33.3)	3 (42.9)	2 (28.6)	1 (33.3)	8 (30.8)
Fulvestrant	3 (100)	4 (66.7)	7 (100)	6 (85.7)	2 (66.7)	22 (84.6)
Tamoxifen	1 (33.3)	2 (33.3)	3 (42.9)	3 (42.9)	1 (33.3)	10 (38.5)
Targeted therapy	3 (100)	4 (66.7)	7 (100)	6 (85.7)	3 (100)	23 (88.5)
CDK4/6 inhibitor	3 (100)	3 (50.0)	5 (71.4)	6 (85.7)	3 (100)	20 (76.9)
mTOR inhibitor	0	1 (16.7)	3 (42.9)	2 (28.6)	2 (66.7)	8 (30.8)
PARP inhibitor	0	0	0	1 (14.3)	0	1 (3.8)
Bone-only disease, n (%)	0	1 (16.7)	2 (28.6)	1 (14.3)	1 (33.3)	5 (19.2)
Visceral disease, n (%)	1 (33.3)	4 (66.7)	3 (42.9)	6 (85.7)	2 (66.7)	16 (61.5)
Number of organs involved in visceral disease, n (%)						
1	1 (33.3)	3 (50.0)	3 (42.9)	4 (57.1)	2 (66.7)	13 (50.0)
2	0	1 (16.7)	0	0	0	1 (3.8)
≥ 3	0	0	0	2 (28.6)	0	2 (7.7)

[a] A patient can be counted in multiple categories.
AI, aromatase inhibitor; CDK, cyclin-dependent kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; mTOR, mammalian target of rapamycin; PARP, poly (ADP ribose) polymerase.

Table 2. Patient Disposition and Reasons for Study Drug Discontinuation

Patients, n (%)	200 mg (n = 3)	400 mg (n = 6)	600 mg (n = 7)	800 mg (n = 7)	1000 mg (n = 3)	Total (n = 26)
Currently on treatment	1 (33.3)	0	3 (42.9)	2 (28.6)	1 (33.3)	7 (26.9)
Treatment discontinued	2 (66.7)	6 (100)	4 (57.1)	5 (71.4)	2 (66.7)	19 (73.1)
Reasons for discontinuation						
Progressive disease	2 (66.7)	5 (83.3)	4 (57.1)	5 (71.4)	2 (66.7)	18 (69.2)
Toxicity	0	1* (16.7)	0	0	0	1 (3.8)

* One patient discontinued treatment due to Grade 2 gastrointestinal symptoms.

Pharmacokinetics

- PK analyses were conducted for a total of 18 patients in fasted conditions during cycles 1 and 2
- Less than dose-proportional increases in G1T48 exposure were observed at doses above 400 mg
- Absorption was rapid (median T_{max} ~2 hours; **Table 3**), and the apparent mean terminal half-life estimated on day 1 was ~16 hours
- PK profiles showed multiple peaks post T_{max}, presumably due to enterohepatic recirculation
- Following a high-fat meal, $AUC_{0\text{-}24h}$ increased by ~21%, and T_{max} was delayed by 1 hour relative to fasted conditions; food appeared to increase exposure in patients with relatively low exposure in the fasted state
- Food intake resulted in less variability in C_{max} (fed: 46.3% vs fasted: 63%) and AUC_{last} (fed: 34.7% vs fasted: 46.1%)
- Patients with the *UGT1A1*28* genetic variant had increased mean AUC during the dosing interval at steady state (AUC_{tau}) by approximately 50% compared with those patients with wild-type *UGT1A1*1*

Table 3. Key Preliminary PK Parameters for Plasma G1T48 by Dose Group (Fasted)

		Day 1				Day 29			Racc AUC D29/D1
Dose, mg QD	n	T_{max}, h (min, max)	C_{max}, ng/mL (CV%)	$AUC_{0\text{-}24}$, ng*h/mL (CV%)	AUC_{last}, ng*h/mL (CV%)	T_{max}, h (min, max)	C_{max}, ng/mL (CV%)	$AUC_{0\text{-}24}$, ng*h/mL (CV%)	
200	2*	1.75 (1.5, 2.0)	138 (19.0)	423 (6.3)	526 (2.7)	1.25 (1.0, 1.5)	186 (16.0)	925 (16.0)	2.2
400	6	2.0 (1.5, 4.0)	404 (103)	1190 (75.5)	1460 (72.6)	1.75 (0.5, 3.0)	390 (79.4)	1940 (78.1)	1.8
600	3	2.0 (1.5, 4.0)	339 (61.3)	1250 (105)	1810 (81.1)	1.5 (1.0, 2.0)	231 (73.1)	2090 (112)	1.5
800	3	2.0 (2.0, 2.0)	579 (47.9)	1290 (35.7)	1700 (25.4)	2.5 (2.0, 3.0)	352 (29.2)	1230 (NA)[b]	1.0[c]
1000	3	1.5 (1.0, 3.0)	753 (103)	2030 (17.9)	2870 (14.2)	1.0 (0.5, 2.0)	472 (33.7)	2690 (33.3)	1.4

* One outlier was removed from the calculation; [a] n = 1, CV% for AUC_{inf}, could not be calculated; [b] Calculated from n = 1.
$AUC_{0\text{-}24h}$, area under the curve over 24 hours; AUC_{inf}, area under the curve during a dosage interval (τ); AUC_{last}, area under the curve from time zero to time of last measurable concentration; C_{max}, maximum concentration; CV, coefficient of variation; D, day; max, maximum; min, minimum; NA, not applicable; PK, pharmacokinetics; QD, once daily; Racc AUC, accumulation ratio calculated from AUC_{tau} steady state divided by $AUC_{0\text{-}24h}$ after single dosing; T_{max}, time to maximum concentration (median and range).

Safety and Tolerability

- No DLTs were observed and the MTD was not determined
- No patient experienced a serious adverse event (SAE) considered related to study treatment
- 19 of 26 (73.1%) patients experienced at least 1 G1T48-related AE (TRAE); the majority were Grade 1 (**Table 4**)
- The most common Grade 1/2 TRAEs were fatigue (26.9%), hot flush (26.9%), diarrhea (26.9%), headache (15.4%), and nausea (15.4%); no dose relationship was observed
- A single Grade 3 TRAE (fatigue) and no Grade 4 TRAEs were observed
- G1T48 dose reduction occurred in 1 patient (400 mg dose level) due to Grade 3 fatigue

Table 4. G1T48-Related AEs Occurring in ≥ 3 Patients

Patients, n (%)	200 mg (n = 3)			400 mg (n = 6)			600 mg (n = 7)			800 mg (n = 7)			1000 mg (n = 3)			Total TRAEs (n = 26)			All TEAEs (n = 26)		
Grade	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Any AEs	2 (66.7)	1 (33.3)	0	1 (16.7)	2 (33.3)	1 (16.7)	3 (42.9)	2 (28.6)	0	4 (57.1)	0	0	1 (33.3)	2 (66.7)	0	11 (42.3)	7 (26.9)	1 (3.8)	8 (30.8)	11 (42.3)	4 (15.4)
Fatigue	1 (33.3)	0	0	2 (33.3)	0	1 (16.7)	0	0	0	2 (28.6)	0	0	1 (33.3)	1 (33.3)	0	6 (23.1)	1 (3.8)	1 (3.8)	9 (34.6)	1 (3.8)	1 (3.8)
Hot flush	0	1 (33.3)	0	1 (16.7)	0	0	1 (14.3)	1 (14.3)	0	3 (42.9)	0	0	0	0	0	5 (19.2)	2 (7.7)	0	6 (23.1)	2 (7.7)	0
Diarrhea	1 (33.3)	0	0	0	1 (16.7)	0	2 (28.6)	0	0	1 (14.3)	0	0	2 (66.7)	0	0	6 (23.1)	1 (3.8)	0	7 (26.9)	1 (3.8)	0
Headache	2 (66.7)	0	0	0	0	0	2 (28.6)	0	0	0	0	0	0	0	0	4 (15.4)	0	0	5 (19.2)	0	0
Nausea	2 (66.7)	0	0	1 (16.7)	0	0	0	0	0	0	0	0	1 (33.3)	0	0	4 (15.4)	0	0	5 (19.2)	0	0
Muscle spasms	1 (33.3)	0	0	0	0	0	0	0	0	0	0	0	1 (33.3)	1 (33.3)	0	2 (7.7)	1 (3.8)	0	4 (15.4)	1 (3.8)	0
Myalgia	1 (33.3)	0	0	1 (16.7)	0	0	0	0	0	1 (14.3)	0	0	0	0	0	3 (11.5)	0	0	3 (11.5)	0	0

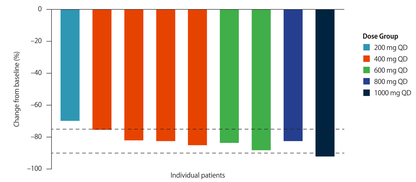
No Grade 4/5 TRAEs or TEAEs were reported.
AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Pharmacodynamics

^{18}F-FES PET

- Data were available at baseline and cycle 2 day 2 for 9 patients
- Median ^{18}F-FES PET maximum standardized uptake values decreased (ranging from 70% [200 mg] to 92% [1000 mg]) after 4 weeks of G1T48 treatment (**Figure 1**)

Figure 1. G1T48 Occupancy of ER by Dose Level (^{18}F-FES PET Results)

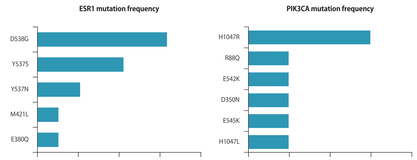


ER, estrogen receptor; QD, once daily.

cfDNA at Baseline

- 100% (22/22) of patients evaluated had detectable cfDNA at baseline; 50% (11/22) had detectable ESR1 mutations and 36% (8/22) had detectable PIK3CA mutations
- The most common ESR1 mutations were D538G and Y537S; the most common PIK3CA mutation was H1047R (**Figure 2**)
- 1 patient had an ESR1 amplification and 1 other patient had a PIK3CA amplification

Figure 2. ESR1 and PIK3CA Mutation Frequency at Baseline



ESR1, estrogen receptor 1; PIK3CA, phosphatidylinositol 4,5-biphosphate 3-kinase catalytic subunit alpha.

Efficacy

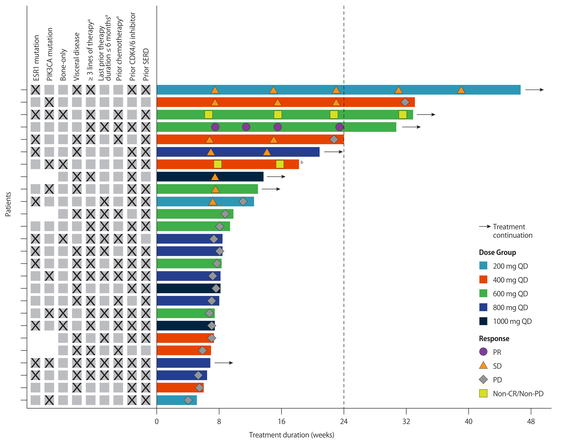
- Best overall responses in patients with measurable disease (n = 19) are shown in **Table 5**
- Treatment duration and response by dose in all patients (n = 26) are shown in **Figure 3**
- Patient characteristics associated with early progression were ≥ 3 lines of prior therapy in the advanced setting, any prior chemotherapy in the advanced setting, ≤ 6 months on most recent prior therapy, and visceral disease

Table 5. Best Overall Response (Confirmed) in Patients with Measurable Disease

Patients, n (%)	200 mg (n = 2)	400 mg (n = 4)	600 mg (n = 6)	800 mg (n = 5)	1000 mg (n = 2)	Total (n = 19)
Best overall response						
CR	0	0	0	0	0	0
PR	0	0	1 (16.7)	0	0	1 (5.3)
SD	2 (100)	2 (50.0)	1 (16.7)	1 (20.0)	1 (50.0)	7 (36.8)
Progressive disease	0	2 (50.0)	4 (66.7)	4 (80.0)	1 (50.0)	11 (57.9)
Objective response (CR + PR)	0	0	1 (16.7)	0	0	1 (5.3)
Clinical benefit (CR + PR + SD lasting ≥ 24 weeks)	1 (50.0)	1 (25.0)	1 (16.7)	0	0	3 (15.8)

CR, complete response; PR, partial response; SD, stable disease.

Figure 3. Treatment Duration and Response by Dose (All Patients)



Includes all patients (measurable and non-measurable disease). No grey box indicates samples were not collected.
* In advanced/metastatic setting. † One patient discontinued treatment due to Grade 2 gastrointestinal symptoms.
CDK, cyclin-dependent kinase; CR, complete response; ESR1, estrogen receptor 1; PD, progressive disease; PIK3CA, phosphatidylinositol 4,5-biphosphate 3-kinase catalytic subunit alpha; PR, partial response; QD, once daily; SD, stable disease; SERD, selective estrogen receptor degrader.

CONCLUSIONS

- G1T48 is an orally active SERD with a favorable safety profile and preliminary evidence of antitumor activity in heavily treated patients with ER+/HER2- ABC
- The majority of TRAEs were Grade 1, with a single Grade 3 TRAE observed
- No DLTs were observed at any dose level
- Food increased exposure to G1T48 by 21% and decreased variability
- Substantial decreases in ^{18}F-FES uptake during G1T48 treatment (70–92% decrease) indicate target engagement with the ER for all doses tested
- In the absence of MTD, considering the safety, PK, pharmacodynamics, and preliminary antitumor activity, 600 and 1000 mg QD with food were selected for Part 2, and patients are being enrolled

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CONFLICTS OF INTEREST
ECD: institutional financial support from Pfizer, Merck, H3 Biosciences, G1 Therapeutics, Lilly, Cerulean, Meryx, and Novartis. **PA:** consultation fees from Boehringer Ingelheim, Macrogenics, Roche, Novartis, and Amcure; honoraria from Synthon, Amgen, and Novartis; travel grants from Amgen, MSD, Pfizer, and Roche; and institutional research grants from AstraZeneca, Lilly, MSD, Novartis, Pfizer, Roche-Genentech, Synthon, Radius, and Servier. **CVWVdHvO:** advisor to Novartis and G1 Therapeutics. **EdV:** institutional financial support for advisory roles for NSABP, Sanofi, Daiichi Sankyo, and Pfizer; and for clinical trials or contracted research from Amgen, Genentech, Roche, Chugai, CytomX Therapeutics, Nordic Nanovector, AstraZeneca, Bayer, and Synthon. **JX, CS, CL, SJ, JS, RM,** and **AB:** employees of G1 Therapeutics. **PN, MP, RI, JB, AG:** no conflicts of interest

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