LEROCICLIB (G1T38), A CONTINUOUSLY DOSED ORAL CDK4/6 INHIBITOR, WITH FULVESTRANT IN HR+/HER2- ADVANCED BREAST CANCER PATIENTS: UPDATED PHASE 2 RESULTS AND DOSE SELECTION

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BACKGROUND

- Endocrine therapy is an established treatment for patients with hormone receptor–positive (HR+) human epidermal growth factor receptor 2–negative (HER2-) advanced breast cancer (ABC); however, endocrine resistance remains a serious challenge in the clinic[1,2]
- Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in combination with endocrine therapy (fulvestrant) represent an established treatment for HR+/HER2- ABC, with significant improvements in progression-free survival (PFS) and overall survival (OS) compared with fulvestrant monotherapy[3–5]
  - Two marketed CDK4/6 inhibitors have dose-limiting neutropenia requiring a drug holiday, potentially limiting efficacy, with the third administered continuously but limited by gastrointestinal toxicity[6]
- Preliminary results of this study demonstrated continuous dosing of lerociclib with fulvestrant was generally well tolerated and showed early evidence of antitumor activity[7]
- Here, we present updated results and dose selection

STUDY OBJECTIVES

Primary Objectives:

- Evaluate the safety, tolerability, and dose-limiting toxicities of lerociclib administered with fulvestrant
- Determine the dose and schedule (once daily [QD] or twice daily [BID]) of lerociclib administered continuously with fulvestrant

Secondary Objectives:

- Determine the pharmacokinetic (PK) parameters of lerociclib when administered with fulvestrant (refer to Bulat et al for PK results)[7]
- Assess fulvestrant and goserelin day 15 plasma concentrations when administered with lerociclib
- Assess response rate, clinical benefit rate (CBR), PFS, and OS

Key Exploratory Objectives:

- Assess correlation between changes in cell-free DNA (cfDNA) with efficacy measures
- Assess the relationships between PK parameters and efficacy parameters

METHODS

Study Design (NCT02983071; EudraCT Number 2016-001485-29)

- Part 1: open-label, 3 + 3, parallel-dose escalation of lerociclib 200 mg–850 mg QD and 100 mg–425 mg BID administered continuously
- Part 2: open-label expansion of lerociclib doses 400 mg QD, 500 mg QD, 150 mg BID, and 200 mg BID administered continuously
- Fulvestrant 500 mg on days 1, 15, and 29, then once monthly as per standard of care
- Pre or perimenopausal patients also received goserelin as per local standard of care for the duration of study treatment. A luteinizing hormone-releasing hormone agonist must have started ≥ 28 days before the first dose of lerociclib

Key Inclusion Criteria

- HR+/HER2- ABC
- Women of any menopausal status ≥ 18 years of age
- Progressed during or within 12 months after adjuvant therapy or progressed during or within 2 months after endocrine therapy for advanced disease
- Part 1: ≤ 2 chemotherapy regimens in the advanced setting
- Part 2: ≤ 1 chemotherapy regimen in the advanced setting
- Eastern Cooperative Oncology Group performance status 0–1

Key Exclusion Criteria

- Parts 1 and 2: prior treatment with fulvestrant
- Part 2: prior treatment with a CDK4/6 inhibitor
- Known active uncontrolled or symptomatic central nervous system metastases

Pharmacodynamic Analysis

- To evaluate mutational changes in cfDNA, peripheral blood samples were collected at baseline, cycle 1 day 15 (C1D15; week 3 day 1), each tumor assessment, and at a post-treatment visit 30 days (+ 5 days) after the last dose of study treatment. Samples were processed and analyzed at Guardant Health, Inc. and Fios Genomics Ltd.

RESULTS

Patient Demographics, Baseline Characteristics, Disposition, and Lerociclib Exposure

- As of April 17, 2020, 110 patients have been treated (46 in part 1 and 64 in part 2); 39 patients (35.5%) remain on lerociclib treatment overall; 10 of 20 patients (50.0%) treated with 150 mg BID remain on treatment
- Nine patients (45.0%) treated with 150 mg BID discontinued lerociclib treatment due to progressive disease and 1 patient (5.0%) due to an adverse event (AE). Across all dose cohorts, 65 patients (59.1%) discontinued lerociclib treatment due to progressive disease, 4 (3.6%) due to an AE, and 2 (1.8%) withdrew by choice
- Median (range) duration of lerociclib exposure was 9.3 (1.7–27.8) months for the 150 mg BID dose cohort and 9.4 (1.0–37.3) months across all dose cohorts
- Patient demographics and baseline characteristics are summarized in **Table 1**. Refer to Bulat et al for doses not shown[7]

Table 1. Baseline Characteristics at Selected Dose Levels

	QD				BID			Total
	300 mg (n = 3)	400 mg (n = 15)	500 mg (n = 30)	All QD Doses (n = 60)	150 mg (n = 20)	200 mg (n = 21)	All BID Doses (n = 50)	All Doses (N = 110)
Median (range) age, years	46.0 (45–72)	56.0 (50–68)	57.0 (25–85)	57.5 (25–85)	55.0 (33–84)	55.0 (34–78)	55.0 (33–84)	56.0 (25–85)
Race, n (%) Black/African American White Not reported	0 3 (100) 0	0 14 (93.3) 1 (6.7)	0 26 (86.7) 4 (13.3)	0 55 (91.7) 5 (8.3)	0 20 (100) 0	1 (4.8) 20 (95.2) 0	2 (4.0) 48 (96.0) 0	2 (1.8) 103 (93.6) 5 (4.5)
ECOG PS, n (%) 0 1	1 (33.3) 2 (66.7)	13 (86.7) 2 (13.3)	21 (70.0) 9 (30.0)	44 (73.3) 16 (26.7)	17 (85.0) 3 (15.0)	17 (81.0) 4 (19.0)	42 (84.0) 8 (16.0)	86 (78.2) 24 (21.8)
Menopausal status, n (%) Postmenopausal Pre/perimenopausal	3 (100) 0	13 (86.7) 2 (13.3)	22 (73.3) 8 (26.7)	49 (81.7) 11 (18.3)	14 (70.0) 6 (30.0)	15 (71.4) 6 (28.6)	37 (74.0) 13 (26.0)	86 (78.2) 24 (21.8)
Median (range) number of prior lines of therapy for advanced disease	1 (1–2)	2 (0–4)	1 (0–4)	1.5 (0–6)	1 (0–6)	1 (0–6)	1 (0–6)	1 (0–6)
Number of prior lines of therapy for advanced disease, n (%) 0 1 2 3 ≥ 4	0 2 (66.7) 1 (33.3) 0 0	4 (26.7) 3 (20.0) 4 (26.7) 3 (20.0) 1 (6.7)	6 (20.0) 12 (40.0) 6 (20.0) 5 (16.7) 1 (3.3)	12 (20.0) 18 (30.0) 15 (25.0) 11 (18.3) 4 (6.7)	7 (35.0) 5 (25.0) 4 (20.0) 2 (10.0) 2 (10.0)	9 (42.9) 2 (9.5) 7 (33.3) 2 (9.5) 1 (4.8)	21 (42.0) 8 (16.0) 13 (26.0) 5 (10.0) 3 (6.0)	33 (30.0) 26 (23.6) 28 (25.5) 16 (14.5) 7 (6.4)
Prior anticancer therapy for advanced disease, n (%) Chemotherapy Endocrine therapy AI (steroidal) AI (nonsteroidal) SERM[a] Targeted therapy[b] mTOR inhibitor	3 (100) 2 (66.7) 2 (66.7) 0 1 (33.3) 1 (33.3) 0 0	11 (73.3) 5 (33.3) 10 (66.7) 3 (20.0) 8 (53.3) 5 (33.3) 3 (20.0) 2 (13.3)	24 (80.0) 14 (46.7) 22 (73.3) 2 (6.7) 18 (60.0) 6 (20.0) 1 (3.3) 1 (3.3)	48 (80.0) 28 (46.7) 44 (73.3) 8 (13.3) 35 (58.3) 17 (28.3) 5 (8.3) 4 (6.7)	13 (65.0) 10 (50.0) 11 (55.5) 2 (10.0) 6 (30.0) 5 (25.0) 1 (5.0) 1 (5.0)	12 (57.1) 6 (28.6) 12 (57.1) 6 (28.6) 10 (47.6) 4 (19.0) 2 (9.5) 2 (9.5)	29 (58.0) 20 (40.0) 27 (54.0) 8 (16.0) 19 (38.0) 11 (22.0) 3 (6.0) 3 (6.0)	77 (70.0) 48 (43.6) 71 (64.5) 16 (14.5) 54 (49.1) 28 (25.5) 8 (7.3) 7 (6.4)
Bone-only disease, n (%)[c]	0	1 (7.1)	0	3 (5.1)	2 (10.0)	3 (14.3)	6 (12.0)	9 (8.3)
Visceral metastasis, n (%)	3 (100)	12 (80.0)	23 (76.7)	46 (76.7)	16 (80.0)	14 (66.7)	38 (76.0)	84 (76.4)

[a] Includes tamoxifen and toremifene; [b] No patients had prior exposure to CDK4/6 inhibitors; [c] One patient had missing bone assessment data and was not included in the denominator
AI, aromatase inhibitor; BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; mTOR, mammalian target of rapamycin; QD, once daily; SERM, selective estrogen receptor modulator

Safety and Tolerability

- The selected dose of lerociclib 150 mg BID demonstrated an improved tolerability profile relative to QD dosing and other BID doses, including decreased rates of gastrointestinal AEs as well as lower rates of neutropenia considered related to lerociclib treatment (**Table 2**)
  - Grade 4 neutropenia was reported in 1 patient (5.0%) treated with 150 mg BID, and no other lerociclib-related Grade 4 AEs were reported at this dose level; Grade 3 febrile neutropenia was reported in 1 patient (5.0%) treated with 150 mg BID
  - Most common Grade 3/4 laboratory abnormalities in patients treated with 150 mg BID were observed in absolute neutrophils (40.0%), leukocytes (20.0%), and lymphocytes (10.0%)
  - No lerociclib dose interruptions or reductions were required for Grade 3 neutropenia without associated infection or fever
  - No lerociclib-related Grade ≥ 3 nausea, vomiting, diarrhea, or fatigue was reported in patients treated with 150 mg BID
  - Grade 2 stomatitis was reported in 1 patient (5.0%) treated with 150 mg BID
  - Alopecia was reported in 1 patient (5.0%) treated with 150 mg BID. Across all dose levels, all lerociclib-related alopecia was Grade 1
  - Lerociclib-related serious AEs were reported in 1 patient (5.0%) treated with 150 mg BID (Grade 2 pneumonitis)
  - Lerociclib treatment discontinuation due to an AE occurred in 1 patient (5.0%) treated with 150 mg BID (Grade 2 pneumonitis, resolved)
- Lerociclib dose reduction occurred in 2 patients (10.0%) treated with 150 mg BID and in 36 patients (32.7%) overall
- No cases of QTcF prolongation (≥ 480-ms) or venous thromboembolism were reported at any dose level

Table 2. Most Common Lerociclib-Related AEs (≥ 10% of All Patients) at Selected Dose Levels

Patients, n (%)	QD								BID				Total			
	300 mg (n = 3)		400 mg (n = 15)		500 mg (n = 30)		All QD Doses (n = 60)		150 mg (n = 20)		200 mg (n = 21)		All BID Doses (n = 50)		Total TRAEs (N = 110)		Total TEAEs (N = 110)	
Grade	All	≥ 3	All	≥ 3	All	≥ 3	All	≥ 3	All	≥ 3	All	≥ 3	All	≥ 3	All	≥ 3	All	≥ 3
Any AE	3 (100)	2 (66.7)	15 (100)	6 (40.0)	29 (96.7)	24 (80.0)	57 (95.0)	40 (66.7)	15 (75.0)	7 (35.0)	21 (100)	9 (42.9)	44 (88.0)	19 (38.0)	101 (91.8)	59 (53.6)	108 (98.2)	69 (62.7)
Neutropenia[a]	3 (100)	2 (66.7)	15 (100)	6 (40.0)	25 (83.3)	19 (63.3)	53 (88.3)	33 (55.0)	11 (55.0)	7 (35.0)	13 (61.9)	9 (42.9)	30 (60.0)	19 (38.0)	83 (75.5)	52 (47.3)	85 (77.3)	54 (49.1)
Nausea	3 (100)	0	13 (86.7)	0	21 (70.0)	3 (3.3)	42 (70.0)	1 (1.7)	3 (15.0)	0	10 (47.6)	0	18 (36.0)	0	60 (54.5)	1 (0.9)	63 (57.3)	1 (0.9)
Leukopenia[b]	2 (66.7)	0	8 (53.3)	3 (20.0)	13 (43.3)	9 (30.0)	32 (53.3)	17 (28.3)	8 (40.0)	3 (15.0)	10 (47.6)	7 (33.3)	24 (48.0)	11 (22.0)	56 (50.9)	28 (25.5)	56 (50.9)	28 (25.5)
Diarrhea	2 (66.7)	0	10 (66.7)	1 (6.7)	19 (63.3)	3 (10.0)	38 (63.3)	5 (8.3)	5 (25.0)	0	8 (38.1)	1 (4.8)	15 (30.0)	1 (2.0)	53 (48.2)	6 (5.5)	57 (51.8)	6 (5.5)
Anemia[c]	1 (33.3)	0	6 (40.0)	0	12 (40.0)	2 (6.7)	25 (41.7)	1 (1.7)	4 (20.0)	1 (5.0)	4 (19.0)	0	11 (22.0)	2 (4.0)	36 (32.7)	3 (2.7)	39 (35.5)	3 (2.7)
Vomiting	2 (66.7)	0	7 (46.7)	0	9 (30.0)	1 (3.3)	23 (38.3)	1 (1.7)	3 (15.0)	0	1 (4.8)	0	5 (10.0)	0	28 (25.5)	1 (0.9)	31 (28.2)	1 (0.9)
Fatigue	2 (66.7)	0	5 (33.3)	0	12 (40.0)	1 (3.3)	21 (35.0)	1 (1.7)	2 (10.0)	0	2 (9.5)	0	5 (10.0)	0	26 (23.6)	1 (0.9)	33 (30.0)	1 (0.9)
Thrombocytopenia[c]	1 (33.3)	0	5 (33.3)	0	9 (30.0)	1 (3.3)	16 (26.7)	2 (3.3)	2 (10.0)	1 (5.0)	4 (19.0)	1 (4.8)	9 (18.0)	2 (4.0)	25 (22.7)	4 (3.6)	26 (23.6)	4 (3.6)
Lymphocytopenia[a]	0	0	1 (6.7)	1 (6.7)	4 (13.3)	1 (3.3)	8 (13.3)	3 (5.0)	1 (5.0)	0	4 (19.0)	3 (14.3)	5 (10.0)	3 (6.0)	13 (11.8)	6 (5.5)	14 (12.7)	7 (6.4)

[a] Includes neutropenia and neutrophil count decreased
[b] Includes leukopenia and white blood cell count decreased
[c] Includes anemia, anemia macrocytic, red blood cell count decreased, and hemoglobin decreased
[d] Includes thrombocytopenia and platelet count decreased
[e] Includes lymphocytopenia, lymphopenia, and lymphocyte count decreased
No Grade 5 AEs were reported
AE, adverse event; BID, twice daily; QD, once daily; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event

Efficacy

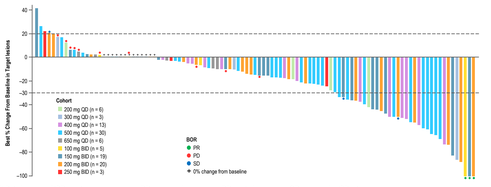
- Confirmed objective partial response (PR) rate was 31.6% in patients treated with lerociclib 150 mg BID and 29.5% across all dose levels (**Table 3; Figures 1 and 2**)
- CBR (complete response + PR + stable disease lasting ≥ 24 weeks) was 73.7% in patients treated with lerociclib 150 mg BID and 70.5% across all dose levels (**Table 3**)
- Subgroup analyses revealed the following:
  - Patients who received no prior chemotherapy in the advanced setting (n = 58) had a CBR of 74.1%, compared with a CBR of 66.0% in patients who received ≥ 1 prior line of chemotherapy in the advanced setting (n = 47)
  - Patients without visceral disease at baseline (n = 23) had a CBR of 78.3%, compared with a CBR of 68.3% in patients with visceral disease at baseline (n = 82)
  - Postmenopausal patients (n = 83) had a CBR of 72.3%, compared with a CBR of 63.6% in pre/perimenopausal patients (n = 22)
- Median PFS (95% CI) in patients treated with lerociclib 150 mg BID was 28.6 (3.7, 28.6) months (60.0% censored at last follow-up) and 12.9 (9.3, 16.6) months in all patients (45.5% censored at last follow-up)

Table 3. Best Overall Response (Confirmed) in Patients With Measurable Disease at Selected Dose Levels

Patients, n (%) [95% CI][a]	QD				BID			Total
	300 mg (n = 3)	400 mg (n = 13)	500 mg (n = 30)	All QD Doses (n = 58)	150 mg (n = 19)	200 mg (n = 20)	All BID Doses (n = 47)	All Doses (N = 105)[b]
CR	0	0	0	0	0	0	0	0
PR	1 (33.3) [0.8, 90.6]	6 (46.2) [19.2, 74.9]	10 (33.3) [17.3, 52.8]	18 (31.0) [19.5, 44.5]	6 (31.6) [12.6, 56.6]	6 (30.0) [11.9, 54.3]	13 (27.7) [15.6, 42.6]	31 (29.5) [21.0, 39.2]
SD	1 (33.3) [0.8, 90.6]	7 (53.8) [25.1, 80.8]	18 (60.0) [40.6, 77.3]	35 (60.3) [46.6, 73.0]	9 (47.4) [24.4, 71.1]	12 (60.0) [36.1, 80.9]	25 (53.2) [38.1, 67.9]	60 (57.1) [47.1, 66.8]
PD	1 (33.3) [0.8, 90.6]	0	2 (6.7) [0.8, 22.1]	5 (8.6) [2.9, 19.0]	4 (21.1) [6.1, 45.6]	2 (10.0) [1.2, 31.7]	9 (19.1) [9.1, 33.3]	14 (13.3) [7.5, 21.4]
Objective response[c]	1 (33.3) [0.8, 90.6]	6 (46.2) [19.2, 74.9]	10 (33.3) [17.3, 52.8]	18 (31.0) [19.5, 44.5]	6 (31.6) [12.6, 56.6]	6 (30.0) [11.9, 54.3]	13 (27.7) [15.6, 42.6]	31 (29.5) [21.0, 39.2]
Clinical benefit[d]	2 (66.7) [9.4, 99.2]	10 (76.9) [46.2, 95.0]	22 (73.3) [54.1, 87.7]	41 (70.7) [57.3, 81.9]	14 (73.7) [48.8, 90.9]	14 (70.0) [45.7, 88.1]	33 (70.2) [55.1, 82.7]	74 (70.5) [60.8, 79.0]

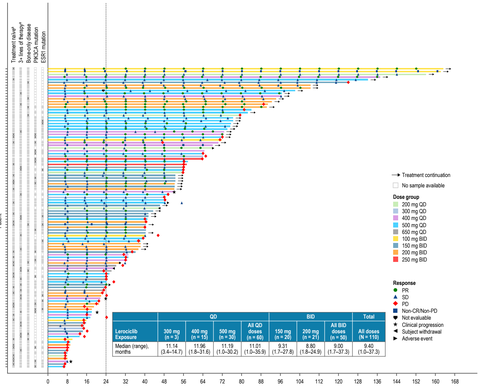
Based on Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1
[a] Clopper-Pearson exact method used to calculate 95% CI
[b] Five patients (4.5%) did not have measurable disease
[c] Objective response = CR + PR
[d] Clinical benefit = CR + PR + SD lasting ≥ 24 weeks
BID, twice daily; CR, complete response; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease

Figure 1. Best Relative Change From Baseline in Tumor Size for Target Lesions by Dose Level in All Patients



BID, twice daily; BOR, best overall response; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease

Figure 2. Treatment Duration and Response by Group in All Patients



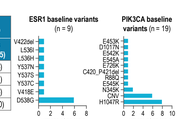
[a] In advanced setting
BID, twice daily; CR, complete response; ESR1, estrogen receptor 1; PD, progressive disease; PIK3CA, phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha; PR, partial response; QD, once daily; SD, stable disease

Pharmacodynamics

- 67/110 patients (61%) had samples analyzed for cfDNA: 63 at baseline, 61 at C1D15, and 22 at time of progression (**Table 4; Figure 3**)
- A higher number of genes with variants, as well as variants in MYC, ERBB2, CCND1, or CCNE1, were significantly associated with lack of clinical benefit (**Figure 4A**)
  - ESR1 and PIK3CA status did not impact response
- 36/45 patients (80%) had a decrease in mean variant allele frequency (mVAF) at C1D15 (**Figure 4B**)
  - PFS did not correlate with change in mVAF due to the low number of events in patients with a mVAF increase
  - At C1D15, > 90% of variants in BRCA2, GNAS, and TP53 were still present; 80% of variants in ATM and APC were absent
- For additional cfDNA results, refer to the mini oral by Krastev et al (ESMO Abstract #1417)[8]

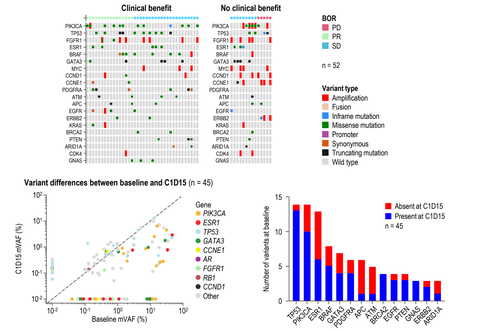
Table 4 and Figure 3. Baseline Characteristics

Baseline		Visceral disease		Prior endocrine therapy[a]		Prior chemotherapy[a]	
	Total	No (n = 14)	Yes (n = 49)	0–1 (n = 46)	2+ (n = 17)	No (n = 38)	Yes (n = 25)
ESR1 variant, n (%)	9 (14)	2 (14)	7 (14)	5 (11)	4 (24)	5 (13)	4 (16)
PIK3CA variant, n (%)	19 (30)	1 (7)	18 (37)	16 (35)	3 (18)	13 (34)	6 (24)
> 3 genes altered, n (%)	20 (32)	4 (29)	16 (33)	14 (30)	6 (35)	11 (29)	9 (36)
> 3 variants, n (%)	22 (35)	4 (29)	18 (37)	16 (35)	6 (35)	12 (32)	10 (40)



[a] In advanced setting
Variants include amplifications and inframe, missense, promoter, and truncating mutations

Figure 4. cfDNA Results: (A) Variants at Baseline Associated With Clinical Response and (B) cfDNA Dynamics After 2 Weeks of Treatment



BOR, best overall response; C1D15, cycle 1 day 15; mVAF, mean variant allele frequency; PD, progressive disease; PR, partial response; SD, stable disease

CONCLUSIONS

- Lerociclib 150 mg BID shows a differentiated safety profile and is the selected dose for future studies
  - Low rates of Grade 4 neutropenia support continuous lerociclib dosing without a drug holiday
  - Low rates of diarrhea, nausea, vomiting, fatigue, stomatitis, and alopecia were observed
- The efficacy data are consistent with marketed CDK4/6 inhibitors used in combination with fulvestrant[3-5]
  - Lerociclib 150 mg BID treatment resulted in a CBR of 73.7% and 70.5% across all doses
  - Subgroup analyses of all treated patients revealed a CBR of 74.1% in patients who received no prior chemotherapy in the advanced setting, a CBR of 78.3% in patients without visceral disease at baseline, and a CBR of 72.3% in postmenopausal patients
  - Preliminary median PFS was 28.6 months for the 150 mg BID dose and 12.9 months across all doses
- Preliminary exploratory cfDNA results indicate genetic variants present at baseline are associated with clinical response, which warrant prospective validation in future studies. Two weeks of lerociclib with fulvestrant treatment decreased the number of cfDNA variants detectable, indicative of clinical activity

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Conflicts of Interest:
Dr Bulat has nothing to disclose

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