POPULATION PHARMACOKINETIC AND EXPOSURE-RESPONSE MODELING OF THE ORAL SELECTIVE ESTROGEN RECEPTOR DEGRADER RINTODESTRANT (G1T48) IN PATIENTS WITH ER+/HER2– ADVANCED BREAST CANCER

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BACKGROUND

- Rintodestrant is an orally bioavailable, potent, and selective estrogen receptor degrader (SERD) that competitively binds to the estrogen receptor (ER) and blocks ER signaling in tumors resistant to other endocrine therapies[1]
- Preliminary data from a first-in-human, open-label study of rintodestrant in patients with ER-positive (ER+)/human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC; NCT03455270) demonstrated that rintodestrant has a favorable safety profile and encouraging antitumor activity[2,3]
  - Updated clinical and pharmacodynamic (PD) data for rintodestrant are detailed in posters PS12-04[3] and PD8-07,[4] respectively
- Here, we report the results of population pharmacokinetic (PK) and exposure-response analyses to further characterize the PK profile of rintodestrant and identify potential exposure-response relationships

METHODS

Study Design

- The present PK and exposure-response analyses include data from 2 clinical studies:
  - **G1T48-01:** A phase 1, open-label, first-in-human study of rintodestrant monotherapy (200–1000 mg once daily [QD]) in women with ER+/HER2– ABC who had progressed on endocrine therapy (NCT03455270)
    - Part 1: 3 + 3 dose escalation (200–1000 mg QD)
    - Part 2: expansion of 600 and 1000 mg QD
    - Part 3: rintodestrant (800 mg QD) with palbociclib (125 mg QD on days 1–21 of each 28-day cycle) in patients who are less heavily pretreated
      - Only data from parts 1 and 2 were included in the analyses
  - **G1T48-10:** A 2-period fixed-sequence study in healthy subjects to investigate potential drug-drug interaction between rintodestrant (200 mg; dosed in periods 1 [day 1] and 2 [day 10]) and palbociclib (125 mg QD; dosed in period 2 [days 5–13])
    - PK data for rintodestrant in period 1 were included in the population PK analysis

PK Analysis

- Serial blood samples were collected pre dose and following rintodestrant administration on day 1 and day 29 (up to 72 hours post dose) of part 1 of the G1T48-01 study, and on day 1 (up to 96 hours post dose) of the G1T48-10 study
  - Sparse blood samples were collected during part 2 of the G1T48-01 study
- Nonlinear mixed-effect PK models were developed using NONMEM, Perl-speaks-NONMEM, and R to estimate PK parameters (including area under the curve [AUC] and maximum post hoc estimated plasma concentration) for individual patients (**Table 1**)
  - Drug concentrations below the lower limit of quantification were omitted from the analyses
  - Several models were fitted to the PK data to select the best base model
  - The quality of fit was evaluated using standard model discrimination processes, including objective function value and goodness-of-fit plots
  - The final model was established using a forward addition followed by backward elimination approach
- Steady-state exposure was analyzed against PD and efficacy endpoints

Table 1. Overview of Population PK and Exposure-Response Analyses

	Population PK	Exposure-Response
Analysis population	Subjects from both studies who received ≥ 1 rintodestrant dose and had ≥ 1 PK sample	The population PK model was used with response data from subjects in the patient study who received ≥ 1 rintodestrant dose and had ≥ 1 PK sample
Endpoints	PK parameters and predicted PK metrics	[18F]-FES PET; Ki67 cfDNA; ORR EPCAM+CD45– CTCs; Tumor size at week 8 ER degradation; PFS
Model	Nonlinear mixed-effect model	Linear logistic regression for binary endpoints Cox regression for time-to-event endpoints
Covariates	Age; Liver function Weight; Renal function BMI; UGT1A1 phenotype Food effect	Age ECOG PS Prior therapy in metastatic setting

[18F]-FES PET, [18F]-fluoroestradiol positron emission tomography; BMI, body mass index; cfDNA, cell-free DNA; CTC, circulating tumor cell; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetics.

Exposure-Response Analysis

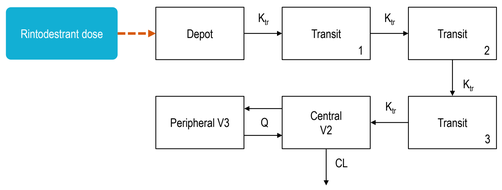
- As rintodestrant showed a favorable safety profile with limited grade ≥ 3 adverse events in the G1T48-01 and G1T48-10 studies, only exposure-efficacy and exposure-PD relationships were explored
- Exposure-response relationships for key PD markers, including ER target engagement ([18F]-fluoroestradiol positron emission tomography [[18F]-FES PET]), ER degradation, and proliferation (Ki67) in tumors, as well as dynamics of cell-free DNA (cfDNA) and enumeration of circulating tumor cells (CTCs) in peripheral blood were evaluated (**Table 1**)
  - [18F]-FES PET scan imaging was performed at baseline and cycle 2 day 2 to determine the impact of rintodestrant on ER occupancy/degradation
  - Tumor biopsies were obtained before starting rintodestrant and at 6 weeks on treatment
    - Proliferation (Ki67) and ER degradation were assessed using immunohistochemistry (IHC)
    - Samples were processed and analyzed at Epistem Ltd.
  - To evaluate mutational changes in cfDNA, peripheral blood samples collected at baseline and cycle 1 day 15 were analyzed
    - Samples were processed and analyzed at Guardant Health, Inc.
  - To evaluate CTCs, peripheral blood mononuclear cells collected at baseline and cycle 3 day 1 were analyzed
    - Antibodies to cytokeratin and CD45, and 4',6-diamidino-2-phenylindole (DAPI) were used for phenotypic identification of CTCs
    - Samples were processed and analyzed at Precision Medicine Group, LLC
- A tumor dynamic model was explored to characterize the relationship between rintodestrant concentrations and longitudinal tumor sizes according to Response Evaluation Criteria in Solid Tumors v1.1
- Relationships between model-predicted exposures and clinical outcomes (objective response rate [ORR], tumor size, and progression-free survival [PFS]) were also evaluated

RESULTS

PK Modeling

- PK data were obtained from 60 patients with ER+/HER2– ABC and 20 healthy subjects
- To explain the variable absorption PK profiles between subjects, rintodestrant PK was best described using a linear 2-compartment model with an absorption model with 3 transit compartments (**Figure 1**; **Table 2**)
  - Food had a minimal effect on the bioavailability of the drug (ie, relative bioavailability was fixed to 1) but decreased the drug absorption rate
  - Total clearance in UGT1A1 extensive metabolizers was ~35% higher than in intermediate/poor metabolizers (due to small sample size, intermediate and poor metabolizers were pooled for the covariate analysis), indicating that UGT1A1 is the major clearance pathway for rintodestrant
    - The UGT1A1 polymorphism did not have a clinically significant effect on rintodestrant exposure due to the relatively large intersubject variability that is not explained by the UGT1A1 polymorphism
  - Visual predictive check for goodness of fit is shown in **Figure 2**
- The simulated trough concentration of rintodestrant at the 800 mg recommended phase 2 dose (RP2D) was generated for 5000 virtual patients by resampling the set of between-subject random variables (ETAs) and exceeded the IC_{90} value for ER degradation established *in vitro* (**Table 3**)

Figure 1. Schematic Diagram of the Population PK Model



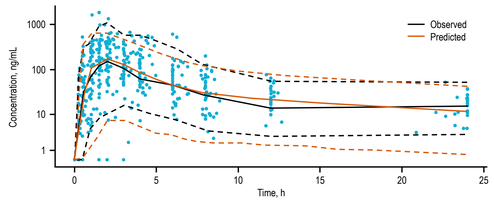
CL, clearance; K_{tr}, transit rate constant; PK, pharmacokinetics; Q, intercompartmental clearance; V, volume.

Table 2. Population PK Parameters of the Final Model

Population PK Parameters	Typical Values	BSV, %	BOV, %
CL, L/h	281 (×1.35 if UGT1A1 extensive metabolizer)	53	NE
V, L	795	110	NE
K_a/K_{tr}, h^{-1}	2.72 (×0.529 if fed)	3	51
Q, L/h	470	82	NE
Vp, L	5760	91	NE
rel F	1 (fixed parameter)	Fixed	26
Proportional residual error	0.307	NE	NE

BOV, between-occasion variability; BSV, between-subject variability; CL, clearance; K_a, absorption rate constant; K_{tr}, transit rate constant; NE, not estimated; PK, pharmacokinetics; Q, intercompartmental clearance; rel F, relative bioavailability; UGT, uridine glucuronyl transferase; V, volume of distribution of central compartment; Vp, volume of distribution of peripheral compartment.

Figure 2. Visual Predictive Check of the PK Model



Dashed lines = 5th and 95th percentiles; solid line = 50th percentile.
PK, pharmacokinetics.

Table 3. Simulated Trough Concentration of Rintodestrant After Repeated 800 mg QD Dosing and *In Vitro* IC for ER Degradation

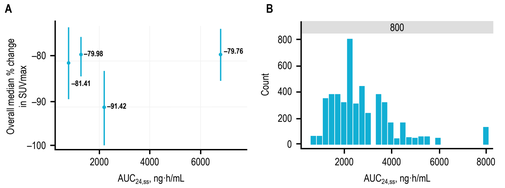
	Virtual Subjects, N = 5000
Total trough concentration, ng/mL	
Mean (SD)	61.8 (48.6)
Median	49.1
90% CI	8.4–153
Range	1.9–439.2
Free trough concentration, ng/mL	
Mean (SD)	0.97 (0.76)
Median	0.77
90% CI	0.13–2.40
Range	0.03–6.90
IC_{50} for *in vitro* ER degradation, ng/mL	0.0152
IC_{90} for *in vitro* ER degradation, ng/mL[a]	0.137

[a] IC_{90} was calculated by assuming $IC_{90} = IC_{50} \times 9$ (ie, Hill coefficient of 1).
ER, estrogen receptor; IC, inhibitory concentration; QD, once daily.

Exposure-Response Relationships

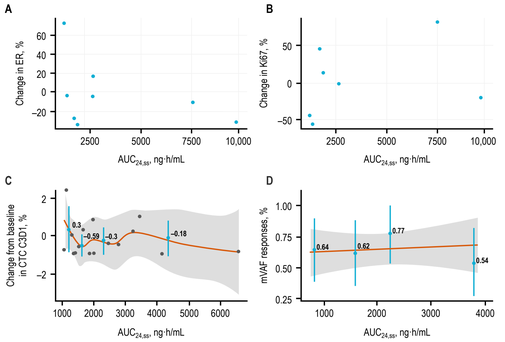
- A positive exposure-response relationship was identified between total exposure and target ER engagement, as measured by [18F]-FES PET up to 2000 ng·h/mL (**Figure 3A**)
  - Above 2000 ng·h/mL, the relationship showed a U-shaped curve, which may be due to an unknown covariate effect
  - For dose selection, it is reasonable to target 2000 ng·h/mL
  - Simulated area under the plasma concentration-time curve over the dosing interval with rintodestrant 800 mg QD showed that the majority of subjects (66%) had exposure higher than 2000 ng·h/mL, supporting 800 mg as the RP2D (**Figure 3B**)
- In the ER degradation analysis, most patients had an AUC of ~2000 ng·h/mL and above, and 6 of 8 patients (75%) had a decrease in ER IHC score, indicating that this dose leads to a pharmacologically active exposure, supporting 800 mg as the RP2D (**Figure 4A**)
- A clear exposure-response relationship was not identified between any PK parameter and proliferation (Ki67), CTCs, and cfDNA (**Figure 4B–D**), potentially due to confounding effects from covariates in the model (eg, prior SERD treatment, *ESR1* variants) and limited data
- Because of limited data on tumor size (ie, in most cases, data on tumor size were only collected once post treatment [up to the data-cut date]), the longitudinal tumor size model could not be meaningfully fitted. Therefore, only an exploratory analysis of tumor size versus exposure was conducted
  - There was no obvious correlation between tumor size and exposure (**Figure 5A**)
- The analysis of ORR and exposure included patients with unconfirmed responses
  - There was a relatively flat exposure-response relationship between ORR and exposure quartiles (**Figure 5B**)
- No correlation was observed for PFS and exposure quartiles (**Figure 5C**)

Figure 3. A) Exposure vs ER Modulation ([18F]-FES PET) and B) Distribution Histogram of Exposure Simulated from 5000 Virtual Patients at 800 mg



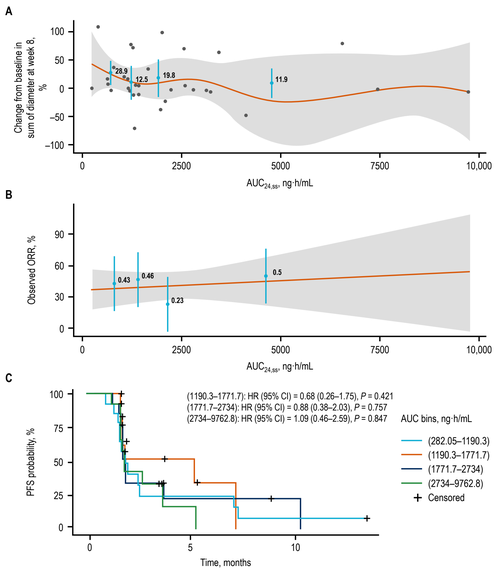
A) AUC was split into 4 quartiles. Error bars represent the variability of exposure in each quartile.
[18F]-FES PET, [18F]-fluoroestradiol positron emission tomography; AUC, area under the curve; AUC_{24}, area under the curve over 24 hours; ER, estrogen receptor; ss, steady state; SUVmax, maximum standard uptake values.

Figure 4. Exposure vs Biomarkers Results: (A) Exposure-ER Degradation, (B) Exposure-Proliferation, (C) Exposure-CTCs, and (D) Exposure-Variant Allele Fractions



A and **B)** each data point corresponds to 1 patient; **C)** n = 5, 4, 4, and 4 for each exposure quartile. Error bars represent the variability of exposure in each quartile. Orange line represents LOESS fit and gray area represents 90% CI; **D)** n = 13 or 14 for each exposure quartile. Error bars represent the variability of exposure in each quartile. For logistic regression, percentage mutant allele fractions were treated as binary variables (increase vs decrease).
AUC_{24}, area under the curve over 24 hours; C, cycle; CTC, circulating tumor cell; D, day; ER, estrogen receptor; LOESS, locally estimated scatterplot smoothing; mVAF, mean variant allele fraction; ss, steady state.

Figure 5. Exposure-Efficacy Results: (A) Tumor Size at Week 8 vs Exposure, (B) ORR vs Exposure, and (C) Exposure-PFS Analysis Using Kaplan-Meier Plot



A) AUC was split into 4 exposure quartiles (13–14 subjects per bin). Error bars represent the variability of exposure in each quartile. Blue line represents LOESS fit and gray area represents 90% CI; **B)** exposure was split into 4 quartiles. Error bars represents the variability of exposure in each quartile. ORR was modeled by logistic regression; **C)** AUC was split into 4 bins represented by different colors. Light blue line = lowest 25th percentile; orange line = 25th–50th percentile; dark blue line = 50th–75th percentile; green line = highest 25th percentile. Exposure bins were treated as categorical variables in the Cox Proportional-Hazards model and used 282.05–1190.3 as the reference.
AUC, area under the curve; AUC_{24}, area under the curve over 24 hours; HR, hazard ratio; LOESS, locally estimated scatterplot smoothing; ORR, objective response rate; PFS, progression-free survival; ss, steady state.

CONCLUSIONS

- Rintodestrant PK was best described using a linear 2-compartment model with an absorption model with 3 transit compartments
- Rintodestrant has variable PK; UGT1A1 polymorphism was identified as a significant covariate impacting rintodestrant exposure, but the effect may not be clinically significant
- Simulated trough concentration at 800 mg QD exceeded *in vitro* IC_{50}/IC_{90} values for ER degradation, supporting the selection of 800 mg QD as the RP2D
- [18F]-FES PET and IHC data for ER engagement and degradation, respectively, indicate that a regimen of rintodestrant 800 mg QD results in a pharmacologically active exposure of ~2000 ng·h/mL in the majority of patients
- Exposure-response relationships with other PD biomarkers, including proliferation of tumor cells, CTCs, and cfDNA, were not observed, presumably due to other prognostic factors and/or limited sample size
- Across the dose range studied, relationships between exposure to rintodestrant and tumor size or clinical outcome (ORR and PFS) were not observed
  - These analyses are limited by the relatively small patient sample size

Acknowledgments:
- We thank all the investigators and site staff, with special thanks to the patients and their families
- We thank Chloe Katz, Christina Sipes, and Daniel Klem for operational support
- Study sponsored by G1 Therapeutics. Medical writing assistance was provided by Alligent Europe (Envision Pharma Group), funded by G1 Therapeutics

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