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Abstract #300
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ZN-c5, an oral selective estrogen receptor degrader (SERD), in women with advanced estrogen receptor-positive (ER+)/ human epidermal growth factor receptor 2 negative (HER2-) breast cancer

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INTRODUCTION

- ZN-c5 is a novel, potent, orally bioavailable selective estrogen receptor degrader (SERD) that binds effectively to the estrogen receptors alpha and beta. It shows improved activity over fulvestrant in human tumor xenograft models and in tumor models that are resistant to tamoxifen.[1]
- Based on these preclinical data, a First-in-Human study of ZN-c5 in advanced/metastatic estrogen receptor positive (ER+) / human epidermal growth factor receptor 2 (HER2)-negative breast cancer was initiated (ZN-c5-001, NCT03560531; EudraCT 2018-001364-27).
- Study ZN-c5-001 is an evaluation of ZN-c5 both as monotherapy and in combination with the CDK4/6 inhibitor palbociclib.
- Updated interim results from the Phase 1 monotherapy dose escalation and expansion parts of the study are reported here. The cut-off date for this analysis was 15 September 2021.

METHODS

- Single-agent ZN-c5 is being evaluated at sequentially escalating doses starting at 50 mg/day, administered orally, once daily (QD) or twice daily (BID).
- Objectives and Endpoints

Phase 1 Protocol Part	Primary Endpoint
Monotherapy Dose Escalation (3+3 design)	Maximum tolerated dose/ Recommended Phase 2 Dose
Monotherapy Expansion	Safety and tolerability

Key Secondary Endpoints

- Pharmacokinetics
- Anti-tumor activity (RECIST): objective response rate (ORR), clinical benefit rate (CBR), duration of response, progression-free survival, overall survival

Key Inclusion Criteria

- Prior treatment with CDK4/6 inhibitors was allowed.
- Subjects had to have a documented prior response to endocrine therapy for advanced/metastatic disease (stable disease [SD], partial response [PR], or complete response [CR]) lasting > 6 months or disease recurrence after at least 24 months of adjuvant endocrine treatment.
- Prior therapies
  - For monotherapy dose escalation, >1% ER+ required: unlimited endocrine-based therapies and 0-2 chemotherapies for advanced/metastatic disease
  - For monotherapy expansion, >10% ER+ required: 0-2 endocrine-based therapies and 0-1 chemotherapies for advanced/metastatic disease

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RESULTS

Subjects

- A total of 56 subjects are included.
- Subjects were enrolled in the ZN-c5 monotherapy parts from December 19, 2018 to January 05, 2021.
- ZN-c5 dose levels of 50, 75, 100, 150, and 300 mg QD and 75 and 150 mg BID were assessed; ZN-c5 was taken on an empty stomach.
- **Table 1** summarizes the demographics and baseline characteristics of the treatment groups.
- All subjects were female.
- Subjects had a median of 2 prior therapies for advanced/metastatic disease, with a median of 2 prior endocrine-based therapies and a median of 0 prior chemotherapies.
- **Table 2** shows treatment discontinuation data for all groups.

Table 1. Subject Demographics and Baseline Characteristics

	50 mg QD (N = 16)	75 mg QD (N = 3)	100 mg QD (N = 3)	75 mg BID (N = 6)	150 mg QD (N = 15)	150 mg BID (N = 3)	300 mg QD (N = 10)	Total (N = 56)
Median age, years (range)	59 (49 - 73)	55 (51 - 60)	58 (55 - 64)	62.5 (56 - 77)	57 (38 - 73)	56 (47 - 72)	67 (46 - 89)	58.5 (38 - 89)
Race, n								
White	12	3	3	5	12	3	9	47
Black or African American	1	—	—	—	1	—	—	2
Asian	2	—	—	1	—	—	—	3
Not reported	1	—	—	—	2	—	1	4
ECOG status, n (%)								
0	12 (75%)	1 (33%)	2 (67%)	4 (67%)	4 (27%)	2 (67%)	5 (50%)	30 (54%)
1	4 (25%)	2 (67%)	1 (33%)	1 (17%)	11 (73%)	1 (33%)	5 (50%)	25 (45%)
Not reported	—	—	—	1 (17%)	—	—	—	1 (2%)
Prior lines of therapy, median (range)	2 (0 - 4)	4 (3 - 9)	4 (4 - 5)	3 (1 - 5)	1 (0 - 3)	1 (0 - 4)	2 (1 - 6)	2 (0 - 9)
Endocrine-based, median (range)	1 (0 - 3)	3 (3 - 6)	3 (3 - 4)	2 (1 - 3)	1 (0 - 2)	1 (0 - 3)	2 (0 - 5)	2 (0 - 6)
Chemotherapy, median (range)	1 (0 - 2)	1 (0 - 3)	1 (1 - 1)	1 (0 - 2)	0 (0 - 1)	0 (0 - 1)	1 (0 - 1)	0 (0 - 3)
CDK4/6i, n (%)	7	2	3	6	13	1	7	39 (70%)
Fulvestrant, n (%)	3	3	3	5	8	1	3	26 (46%)
PI3Ki, n (%)	—	1	1	-	-	-	2	4 (7%)
Measurable disease, n (%)	14 (88%)	2 (67%)	3 (100%)	3 (50%)	11 (73%)	2 (67%)	6 (60%)	41 (73%)
Visceral disease, n (%)	11	1	2	1	9	1	3	28 (50%)
Bone-only disease, n (%)	1	1	0	3	3	1	3	12 (21%)
ESR1 mutations,* n/N (%)	9/14 (64%)	1/1 (100%)	2/3 (67%)	2/6 (33%)	2/14 (14%)	1/3 (33%)	3/8 (38%)	20/49(41%)
D538G, n	7	1	2	1	1	-	2	14
Y537N, n	3	—	1	—	—	1	-	5
Y537S, n	3	—	1	1	—	1	1	7
L536H, n	1	—	1	—	—	—	—	2
E380Q, n	2	—	—	—	—	—	—	3
Other, n	3	—	—	1	1	1	—	5
Not done, n	2	2	—	—	1	—	2	7

*Dose Escalation: Local test, Dose Expansion: Central laboratory; Subjects can have > 1 mutation.

Table 2. Treatment Discontinuation

	50 mg QD (N = 16)	75 mg QD (N = 3)	100 mg QD (N = 3)	75 mg BID (N = 6)	150 mg QD (N = 15)	150 mg BID (N = 3)	300 mg QD (N = 10)	Total (N = 56)
Treatment discontinued n (%)	12 (75%)	3 (100%)	3 (100%)	5 (83%)	12 (80%)	3 (100%)	9 (90%)	47 (84%)
Reason								
Disease progression, n	10	2	3	5	12	3	8	43
Investigator discretion, n	2	1	—	—	—	—	—	3
Unacceptable toxicity, n	—	—	—	—	—	—	1*	1

*Grade 3 hypersensitivity.

Safety

- No dose-limiting toxicities were observed at any dose level.
- No subject experienced a fatal event, and 1 (2%) of 56 subjects experienced a treatment-related serious adverse event (SAE) of hypersensitivity.
- 54 (96%) of 56 subjects experienced at least 1 treatment-emergent adverse event (TEAE) (**Table 3**).
- Grade 3 TEAEs occurring in ≥ 2 subjects included abdominal pain, hypertension, hyponatremia, pain in extremity (n = 2 each), and gamma-glutamyl transferase (GGT) increase (n = 3). Of these, only 1 TEAE each of abdominal pain and GGT increase were deemed related to ZN-c5. Grade 4 events were not reported.
- 33 (59%) of 56 subjects experienced at least 1 ZN-c5-treatment-related adverse event (TRAE), mainly of Grade 1 or 2 in severity (**Table 3**). Grade 3 TRAEs were hypersensitivity, abdominal pain, GGT increase, and dyspnea (n = 1 each).
- A few subjects had TRAEs of diarrhea (4%) and nausea (14%), all Grade 1 or 2.
- No dose relationship was observed.
- Only 1 subject had a ZN-c5 dose reduction, due to GGT increase.

Table 3. Treatment-Related Adverse Events in ≥ 10% of Subject per Cohort and Total, and Total Treatment-Emergent Adverse Events

Preferred Term	50 mg QD (N = 16)		75 mg QD (N = 3)		100 mg QD (N = 3)		75 mg BID (N = 6)		150 mg QD (N = 15)		150 mg BID (N = 3)			300 mg QD (N = 10)			Total TRAEs (N = 56)				Total TEAEs (N = 56)			
NCI CTCAE Grade	1	2	1	2	1	2	1	2	1	2	1	2	3	1	2	3	1	2	3	All	1	2	3	All
Any AE, n (%)	6	2	1	0	0	0	2	2	5	4	1	1	1	4	3	1	19 (34%)	12 (21%)	2 (4%)	33 (59%)	13 (23%)	27 (48%)	14 (25%)	54 (96%)
Hot flush, n (%)	0	0	0	0	0	0	2	0	3	0	0	0	0	1	2	0	6 (11%)	2 (4%)	0	8 (14%)	6 (11%)	2 (4%)	0	8 (14%)
Nausea, n (%)	1	0	0	0	0	0	1	0	1	1	0	1	0	1	2	0	4 (7%)	4 (7%)	0	8 (14%)	12 (21%)	5 (9%)	0	17 (30%)
Fatigue, n (%)	1	0	0	0	0	0	1	0	2	0	1	0	0	1	1	0	6 (11%)	1 (2%)	0	7 (13%)	12 (21%)	3 (5%)	0	15 (27%)

Pharmacokinetics

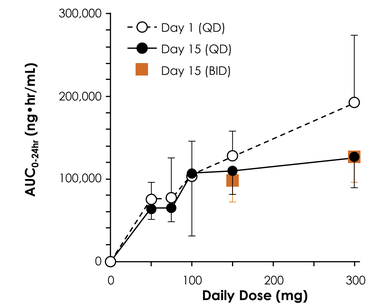
- PK analyses were conducted for 54 (96%) of 56 subjects in fasted conditions during Cycle 1 of the Phase 1 monotherapy dose escalation and expansion. (**Table 4**)
- The preliminary PK was characterized by fast absorption with median T_{max} values of 1 to 2 hrs. The exposures were approximately dose-proportional at the dose levels of 50 to 100 mg and less than dose-proportional between 100 and 300 mg. No accumulation of ZN-c5 was observed after 15 days of QD dosing. The estimated mean elimination half-lives ranged between 11 to 18 hrs.

Table 4. Preliminary Pharmacokinetic Data for ZN-c5 (Mean ± SD)

Dose and Number of Subjects (Day1/Day15)	Day 1 C_{max} (ng/mL)	Day 1 T_{max}* (hr)	Day 1 $AUC_{0\text{-}24hr}$ (ng•h/mL)	Day 15 C_{max} (ng/mL)	Day 15 T_{max}* (hr)	Day 15 $AUC_{0\text{-}24hr}$ (ng•h/mL)	Day 15/ Day 1 AUC Ratio
50 mg (N = 16/14)	5,790 ± 1,260	2 (0.5-4)	75,700 ± 20,800	5,270 ± 803	1 (1-4)	64,300 ± 13,800	0.88 ± 0.22
75 mg (N = 3/3)	6,700 ± 4,080	2 (1-4)	77,300 ± 47,800	6,700 ± 1,040	2 (1-2)	64,400 ± 16,000	1.1 ± 0.66
100 mg (N = 3/3)	7,120 ± 2,550	4 (2-6)	103,000 ± 42,100	9,250 ± 5,350	2 (1-2)	107,000 ± 75,700	0.97 ± 0.31
150 mg (N = 15/13)	10,100 ± 2,530	2 (1-6)	129,000 ± 29,600	9,320 ± 2,880	2 (1-8)	110,000 ± 28,700	0.86 ± 0.22
75 mg BID† (150 mg/day) (N = 4/4)	7,800 ± 3,200	1.5 (1-2)	NA	7,360 ± 3,030	2 (1-2)	101,000 ± 29,900	NA
300 mg (N = 10/9)	13,600 ± 5,380	3 (2-6)	192,000 ± 81,800	11,500 ± 4,570	2 (2-6)	126,000 ± 36,700	0.68 ± 0.11
150 mg BID† (300 mg/day) (N = 3/3)	10,100 ± 3,320	2 (1-2)	NA	8,170 ± 1,430	2 (2-2)	127,000 ± 30,800	NA

*T_{max}: median and range; †$AUC_{0\text{-}24hr}$ on Day 15 estimated as 2 x $AUC_{0\text{-}12hr}$.

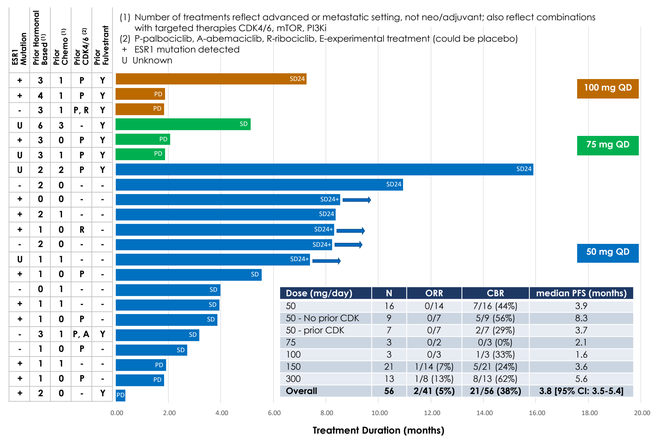
Figure 1. Dose Dependence of ZN-c5 Exposure



Clinical Activity

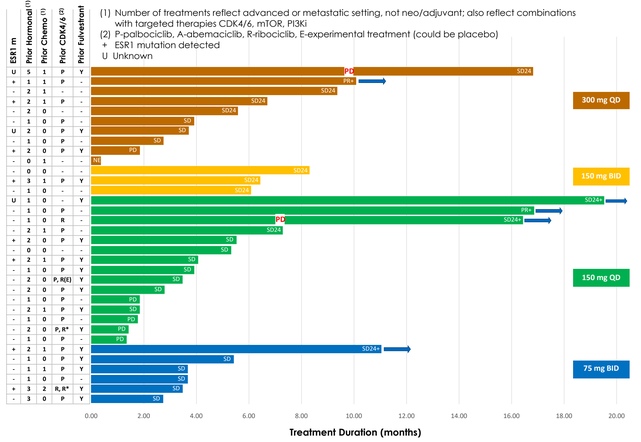
- ZN-c5 achieved a best response of confirmed PR (as per RECIST) in 2 (5%) of 41 subjects with measurable disease, the majority of whom had received prior CDK4/6 inhibitors. The clinical benefit rate (CBR = PR + SD ≥ 24 weeks) was 38%. In addition, the median progression-free survival (PFS) was 3.8 months (95% CI, 3.5-5.4).

Figure 2. ZN-c5-001 Monotherapy Phase 1: 50-100 mg Treatment Duration (months) and Response by Dose



Dose (mg/day)	N	ORR	CBR	median PFS (months)
50	16	0/14	7/16 (44%)	3.9
50 - No prior CDK	9	0/7	5/9 (56%)	8.3
50 - prior CDK	7	0/7	2/7 (29%)	3.7
75	3	0/2	0/3 (0%)	2.1
100	3	0/3	1/3 (33%)	1.6
150	21	1/14 (7%)	5/21 (24%)	3.6
300	13	1/8 (13%)	8/13 (62%)	5.6
Overall	**56**	**2/41 (5%)**	**21/56 (38%)**	**3.8 [95% CI: 3.5-5.4]**

Figure 3. ZN-c5-001 Monotherapy Phase 1: 150-300 mg Treatment Duration (months) and Response by Dose



CONCLUSIONS

- This is an updated interim analysis of the First-in-Human Study ZN-c5-001. The study is ongoing.
- These Phase 1 data demonstrated that ZN-c5 monotherapy was well tolerated and showed clinical benefit, including radiographic disease stabilizations and confirmed PRs, in subjects with advanced ER+/HER2- breast cancer.
- PK data demonstrate expected plasma exposure across the entire tested dose range.
- These interim monotherapy data warrant further evaluation of ZN-c5 in this setting. A Phase 2 part is ongoing in this study, with ZN-c5 dosed at 50 mg QD and possibly at 25 mg QD.

REFERENCE: **1.** Samatar AA, et al. *Cancer Res.* 2020;80(16 Suppl):abs 4373.