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EVALUATION OF THE EFFECT OF FOOD AND GASTRIC PH CHANGE ON THE PHARMACOKINETICS AND SAFETY OF IMLUNESTRANT IN HEALTHY VOLUNTEERS

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PURPOSE

Imlunestrant is a next-generation oral selective estrogen receptor (ER) degrader designed to deliver continuous ER target inhibition currently being investigated for the treatment of ER+ advanced breast and endometrial cancers.[1-4] As an orally administered drug, concomitant use of imlunestrant with proton pump inhibitors (PPIs)–that increase gastric pH–or food intake could alter its absorption leading to alterations in the pharmacokinetics (PK) and potentially, by extension, the clinical effects.[5-7]

OBJECTIVES

To evaluate the effect of food intake and gastric pH change on PK parameters as well as safety and tolerability of imlunestrant. Ultimately, these data will be used to better inform the design of the respective phase 3 clinical trials.

METHODS

- A Phase 1, open-label cohort study (NCT04840888) in healthy adult females of non-childbearing potential who received imlunestrant as a single 400 mg oral dose.
- **Cohort 1,** (N=8): In accordance with relevant FDA guidance,[8] a low-fat meal (400 calories meals with ≤25% fat) was used to assess food effect. The meal was administered 30 minutes prior to administration of study intervention and was aligned in terms of calories and content with that which oncology patients would be receiving; that is, a population-relevant meal (**Table 1**). Participants were 1:1 randomized to 1 of 2 crossover treatment sequences fasted/fed or fed/fasted (**Figure 1**). All participants received a single dose of 400 mg imlunestrant in the fed or fasted state with a washout period of 4 days between doses.
- **Cohort 2**, (N=10): Omeprazole was used to assess the PPI effect. All participants received imlunestrant, in the fasted state, in fixed treatment sequence with a washout period between doses (**Figure 2**).
  - Day 1: 400 mg imlunestrant alone
  - Days 2-5: no treatment
  - Days 5-8: 40 mg omeprazole alone once daily
  - Day 9: 400 mg imlunestrant + 40 mg omeprazole.
- The geometric least squares (GLS) mean for each treatment, GLS mean ratios (fed vs. fasted and control vs. omeprazole) were calculated for the following PK parameters: area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration [AUC(0-tlast)], AUC versus time curve from time zero to infinity [AUC(0-∞)], maximum observed drug concentration (Cmax), time of maximum observed drug concentration (tmax), half-life (t½), and apparent total body clearance of drug calculated after extravascular administration (CL/F).
- Safety assessments included all participants and involved monitoring of adverse events, clinical chemistry, hematology, vital signs, 12-lead electrocardiogram, and physical examination. All treatment emergent adverse events (TEAEs) and serious adverse events were listed and summarized by treatment, severity, and relationship to the study drug.

Figure 1. Cohort 1 – Food Effect Study Scheme

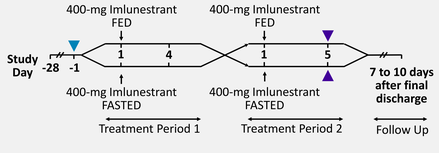


Figure 2. Cohort 2 – PPI Effect Study Scheme

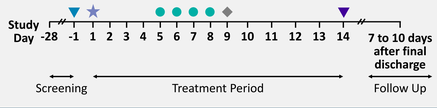


Table 1. Example of low-fat breakfast

	Protein	Fat	Carbohydrates	Calories
1c Special K Berry	2.0	0.0	27.0	116.0
4oz Fruit Cup (no citrus)	0.0	0.0	19.0	76.0
1 Slice Toast White Bread	3.0	0.5	12.0	64.5
1 oz Jelly (1 tablespoon)	0.0	0.0	13.0	52.0
1 Hard-Boiled Egg	6.3	5.3	0.6	77.0
8oz 1% Milk	8.0	1.0	12.0	89.0
Total	13.0	1.5	113.0	517.5
Total calories	**52.0**	**13.5**	**452.0**	
Percentage of total calories	**10 %**	**3%**	**87%**	

▼ Admission to clinical research unit
▼ Discharge from clinical research unit
★ 400-mg Imlunestrant alone
● 40-mg Omeprazole alone
◆ 400-mg Imlunestrant in combination with 40-mg omeprazole

RESULTS

Pharmacokinetics

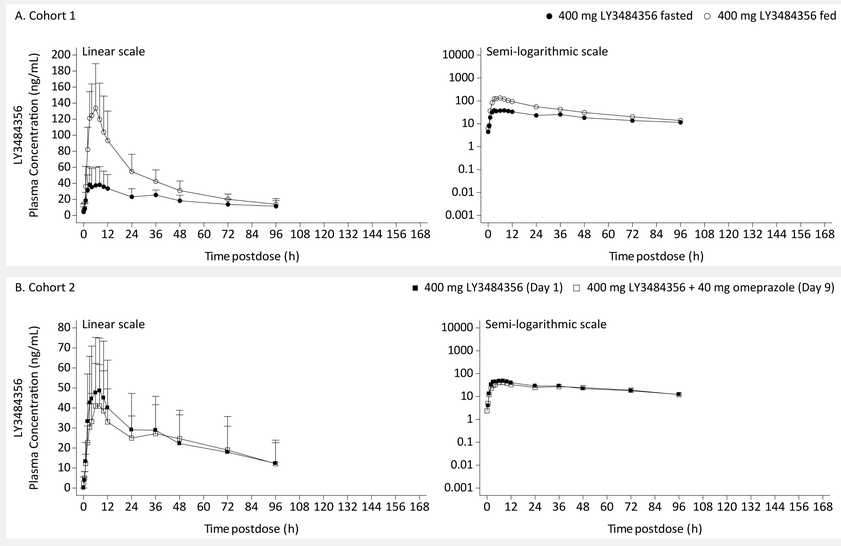
- Cohort 1: statistically significant increases in imlunestrant PK parameters GLS mean ratios (90% CI) following dosing in the fed state compared to the fasted state (**Table 1, Figure 3**):
  - AUC(0-tlast): 99% (1.67, 2.36) increase
  - AUC(0-∞): 104% (1.41, 2.94) increase
  - Cmax: 255% (2.83, 4.45) increase
  - The change in tmax was not statistically significant
- Cohort 2: The change in PK parameters of imlunestrant when dosed alone and in the presence of the PPI omeprazole were not statistically significant and were comparable (**Table 2, Figure 3**).

Table 2. Treatment periods and imlunestrant PK measurements by study cohort

	Cohort 1 - Food effect (N=8)		Cohort 2 - PPI effect (N=10)	
Geometric mean (Geometric CV%) [n]	**Imlunestrant Fasted**	**Imlunestrant Fed**	**Imlunestrant Alone (Day 1)**	**Imlunestrant + omeprazole (Day 9)**
AUC(0-tlast) ng.h/mL	1830 (43%) [8]	3900 (36%) [8]	2020 (66%) [10]	2010 (50%) [9]
AUC(0-∞) ng.h/mL	1810 (59%) [4]	4350 (39%) [6]	2270 (93%) [4]	1960 (46%) [4]
Cmax ng/mL	37.2 (51%) [8]	143 (28%) [8]	49.1 (61%) [10]	39.6 (47%) [9]
tmax (h)#	8.00 (3.0-35.8) [8]	3.02 (2.0-8.0) [8]	6.02 (1.0-10.0) [10]	6.00 (4.0-36.0) [9]
t½ (h)~	29.4 (26.7-35.8) [4]	31.3 (25.7-41.6) [6]	30.2 (23.5-37.7) [4]	30.2 (27.3-33.8) [4]
CL/F (L/h)	221 (59%) [4]	92.0 (39%) [6]	176 (93%) [4]	204 (46%) [4]
GLS mean ratios (90% CI)	**Imlunestrant Fed:Fasted**		**Imlunestrant Day 9:Day1**	
AUC (0-tlast) ng.h/mL	1.99 (1.67, 2.36)		1.05 (0.85, 1.29)	
AUC (0-∞) ng.h/mL	2.04 (1.41, 2.94)		n.a.	
Cmax ng/mL	3.55 (2.83, 4.45)		0.85 (0.65, 1.11)	
Geometric median of differences (90% CI)	**Fed-Fasted**		**Day 9-Day 1**	
tmax (h)#	-3.00 (-32.75, 0.00); p=0.0938		2.00 (-2.00, 5.00); p=0.1484	

Abbreviations: AUC, area under the concentration; versus time curve from time zero to infinity; AUC(0-tlast), area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; CI, confidence interval; CL/F, apparent total body clearance of drug calculated after extravascular administration; Cmax, maximum observed drug concentration; n, number of observations; GLS, geometric least squares; n.a.; not applicable; p, p-values reported from the Wilcoxon signed rank test; PK, pharmacokinetics; PPI, proton pump inhibitor; tmax, time of maximum observed drug concentration.
Model: Log (PK) =treatment + sequence + period + participant + random error, where participant was fitted as a random effect

Figure 3. Arithmetic mean plasma concentration profile of Imlunestrant administered (A) in the fasted and fed states, and (B) alone and in the presence of omeprazole.



Mean concentration values are plotted using nominal sampling times and only presented when at least 2/3 of the values are present and within time window.

Safety assessments

- Imlunestrant was generally well tolerated when administered in the fasted or fed state, alone and in the presence of omeprazole (**Table 3**).
- There were no clinically meaningful findings in clinical laboratory assessments, vital signs, 12-lead electrocardiogram, and physical examination.
- In cohort 1, all TEAEs were mild. One participant experienced abdominal pain in the fasted state and another participant experienced constipation in the fed state.
- In cohort 2, on Day 1 of imlunestrant administration (alone) one participant experienced mild diarrhea and another participant experienced mild constipation.
- In cohort 2, on Days 5 to 8 of omeprazole administration (alone), one participant experienced mild abdominal pain and moderate diarrhea that led to study discontinuation.

Table 3. TEAEs Related to Study Treatment, by Treatment

	Treatment period	Number of TEAEs (number of participants)	Type	Severity	Outcome
Cohort 1 – Food effect (N=8)	Imlunestrant, Fasted	1 (1)	Abdominal pain	Mild	Resolved
	Imlunestrant, Fed	1 (1)	Constipation	Mild	Resolved
	Other Safety assessments*	0 (0)	n.a.	n.a.	n.a.
Cohort 2 – PPI effect (N=10)	Imlunestrant Alone (Day 1)	2 (2)	Diarrhea	Mild	Resolved
			Constipation	Mild	Resolved
	Omeprazole alone (Days 5-8)	2 (1)	Diarrhea	Moderate	Patient discontinued on Day 8
			Abdominal pain	Mild	Resolved
	Imlunestrant + Omeprazole (Day 9)	0 (0)	n.a.	n.a.	n.a.
	Other Safety assessments*	0 (0)	n.a.	n.a.	n.a.

Abbreviations: n.a.; not applicable; PPI, proton pump inhibitor; TEAEs, treatment-emergent adverse events. *clinical chemistry, hematology, vital signs, 12-lead electrocardiogram, and physical examination

CONCLUSIONS

- Low fat diet significantly affected the imlunestrant exposure resulting in increases of ~2-fold in AUC and ~3.6-fold in Cmax. Therefore, imlunestrant will be advised to be taken one hour after or two hours before food consumption.
- There were no statistically significant impact on PK in the presence of PPI omeprazole indicating PPI may be taken concomitantly with imlunestrant.
- A single oral dose of 400 mg imlunestrant was generally well tolerated in healthy females regardless of food or PPI intake.

REFERENCES

1. Shripad V. et al., AACR; Cancer Res 2021;81(13_Suppl):Abstract nr 1236.
2. Lim et al., AACR; Cancer Res 2021;81(4 Suppl):Abstract nr OT-09-03.
3. Komal L. et al., JCO 40, 1021-1021(2022). 4. Jhaveri K. et al, AACR; Cancer Res 2022;82(4 Suppl):Abstract nr OT2-11-01. 5. Raoul JL, et al., ESMO Open. 2023 Feb;8(1):100880. 6. Patel D, et al., Clin Pharmacokinet. 2020 Apr;59(4):447-462. 7. Di Maio S and Carrier RL. J Control Release. 2011 Apr 30;151(2):110-22. 8. FDA. June 2022 Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations

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CONFLICT OF INTERESTS

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