P4-10-07

Evaluation of pharmacokinetics and safety of imlunestrant in participants with hepatic impairment

Amita Datta-Mannan[1], Stephanie White[1], Elaine Shanks[2], Eunice Yuen[2], Stephen David Hall[1], Vivian Rodriguez Cruz[1], Xuejing Aimee Wang[1]

[1]Eli Lilly and Company, Indianapolis, IN, USA
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Study was sponsored by Eli Lilly and Company

OBJECTIVE

To compare the pharmacokinetics (PK) and safety of imlunestrant in women of nonchildbearing potential with hepatic impairment to those with normal hepatic function.

CONCLUSIONS

- Imlunestrant administered as a single oral dose in the fasted state was well tolerated in healthy FONCBP, as well as patients with mild, moderate and severe hepatic impairment (as determined by the Child Pugh's classification).
- There were no significant differences in the exposure profiles of imlunestrant in patients with mild hepatic impairment in comparison to participants with normal hepatic function.
- Patients with moderate and severe hepatic impairment presented significant increases in imlunestrant AUC (but not C_{max}) when compared with normal hepatic function.
- These data will inform imlunestrant dosing recommendations for patients with hepatic impairment

San Antonio Breast Cancer Symposium (SABCS); San Antonio, TX; Dec 10-13, 2024

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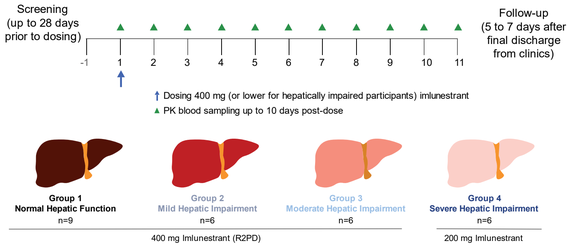
BACKGROUND

- Imlunestrant is a next-generation, oral selective estrogen receptor degrader designed to provide continuous ER-target inhibition, aimed to improve outcomes for patients with ER+ advanced breast and endometrial cancers.[1,2]
- Imlunestrant is mostly excreted in the feces and has an absolute bioavailability of ~10%.[3]
- Hepatic impairment (HI) is a common condition, especially among cancer patients, and it can modify the pharmacokinetics (PK) of anticancer drugs, impacting their safety.[4]
- Considering that the intended patient population for imlunestrant may include cancer patients with HI, it is essential to evaluate whether HI affects the imlunestrant PK and safety profile.
- Here we present PK and safety data for imlunestrant in postmenopausal females of nonchildbearing potential (FONCBP) with and without HI, following a single oral dose in a fasted state.

METHODS/STUDY DESIGN

- **Primary Objective**:
  - PK parameters based on Child-Pugh Classification
    - AUC(0-∞), and
    - Cmax
  - Exploratory analysis using NCI classification of HI
- **Secondary Objective**: Safety
- **Data cut-off date used for this analysis was February 1st 2024**

Child-Pugh classification: investigator assessed score calculated based on the sum of 5 parameters: serum albumin, total serum bilirubin, prothrombin time, ascites and hepatic encephalopathy



KEY ELIGIBILITY CRITERIA

- >18 years of age
- BMI: 18.0-42.0 kg/m2
- Female participants of non-childbearing potential
- **In addition, for Groups 2-4**
  - Investigator assessed Child-Pugh class A, B, or C (mild, moderate or severe)
  - Chronic Hepatic Impairment diagnosis (>6 months)

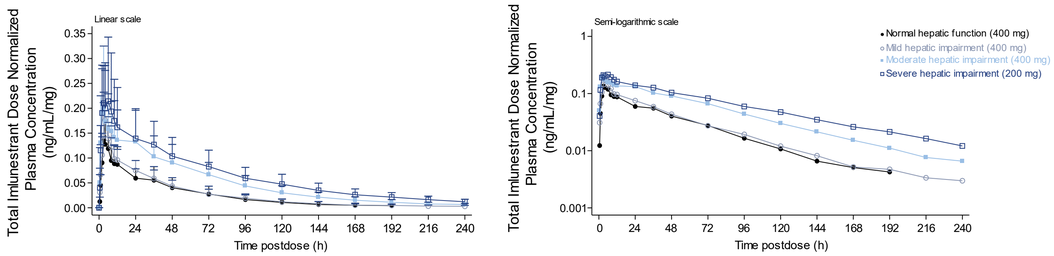
National Cancer Institute (NCI) classification: comprises total bilirubin and glutamic-oxaloacetic transaminase/aspartate aminotransferase ratio

RESULTS

BASELINE CHARACTERISTICS

	Child-Pugh Classification				National Cancer Institute Classification			
	Normal Hepatic Function	Mild Hepatic Impairment	Moderate Hepatic Impairment	Severe Hepatic Impairment	Normal Hepatic Function	Mild Hepatic Impairment	Moderate Hepatic Impairment	Severe Hepatic Impairment
	n=9	n=6	n=6	n=6	n=12	n=9	n=5	n=1
Age, yrs (Median, range)	60.0 (52-67)	68.0 (61-70)	60.0 (45-71)	57.0 (53-61)	60.5 (52-70)	61.0 (45-71)	56.0 (53-61)	61.0 (N/A)
Race (n, %)								
American Indian or Alaska Native	0	0	1 (16.7%)	0	0	1 (11.1%)	0	0
Black or African American	1 (11.1%)	0	0	0	1 (8.3%)	0	0	0
White	8 (88.9%)	6 (100%)	5 (83.3%)	6 (100%)	11 (91.7%)	8 (88.9%)	5 (100%)	1 (100%)
Body Mass Index (kg/m²) (Median, range)	31.0 (21.8-38.6)	32.2 (21.6-41.8)	32.0 (23.0-39.3)	35.0 (25.8-39.5)	31.4 (21.8-39.3)	32.4 (21.6-41.8)	34.4 (25.8-34.9)	39.5 (N/A)
Score	N/A	6 (5-6)	7.5 (7-8)	10 (10-11)	N/A	N/A	N/A	N/A

MEAN DOSE NORMALIZED IMLUNESTRANT PLASMA CONCENTRATIONS ACROSS NORMAL HEPATIC FUNCTION AND HEPATIC IMPAIRMENT PARTICIPANTS

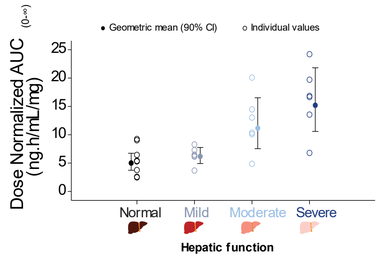


PHARMACOKINETIC RESULTS

Parameter	Child-Pugh Classification				National Cancer Institute Classification	
	Normal Hepatic Function[a]	Mild Hepatic Impairment[a]	Moderate Hepatic Impairment[a]	Severe Hepatic Impairment[b,c]	Mild Hepatic Impairment[a]	Moderate Hepatic Impairment[b,c]
	n=9	n=6	n=6	n=6	n=9	n=5
Unbound Imlunestrant (Mean)	0.0658	0.0603	0.0524	0.0478	N/A	N/A
Elimination Half-Life (h; Median; min, max)	33.1 (26.2, 51.7)	42.8 (24.7, 58.5)	46.3 (38.2, 56.7)	67.0 (47.2, 74.1)	N/A	N/A
AUC(0-t_{last}) (GLSM ratio; 90% CI)	N/A	1.23 (0.822, 1.83)	2.20 (1.49, 3.32)	2.91 (1.80, 4.70)	1.56 (1.10, 2.22)	3.02 (1.97, 4.62)
AUC(0-t_{last}) Unbound (GLSM ratio; 90% CI)	N/A	1.14 (0.717, 1.80)	1.80 (1.13, 2.85)	2.22 (1.33, 3.70)	1.62 (1.16, 2.27)	2.69 (1.79, 4.03)
AUC(0-∞) (GLSM ratio; 90% CI)	N/A	1.23 (0.826, 1.84)	2.22 (1.49, 3.32)	3.06 (1.90, 4.91)	1.56 (1.09, 2.22)	3.15 (2.05, 4.85)
AUC(0-∞) Unbound (GLSM ratio; 90% CI)	N/A	1.14 (0.719, 1.80)	1.82 (1.15, 2.88)	2.33 (1.40, 3.88)	1.62 (1.15, 2.27)	2.81 (1.86, 4.24)
C_{max} (GLSM ratio; 90% CI)	N/A	1.29 (0.824, 2.02)	1.51 (0.965, 2.37)	1.24 (0.748, 2.04)	1.50 (1.05, 2.14)	1.73 (1.13, 2.67)
C_{max} Unbound (GLSM ratio; 90% CI)	N/A	1.19 (0.734, 1.94)	1.24 (0.760, 2.01)	1.6 (1, 2.7)	1.56 (1.10, 2.21)	1.54 (1.01, 2.36)

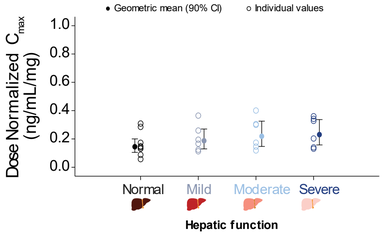
[a]Imlunestrant dose 400 mg (R2PD); [b]Imlunestrant dose 200 mg; [c]Dose normalized values; ; GLSM – Geometric Least Squares Mean; N/A – not available; R2PD - recommended phase 2 dose

IMLUNESTRANT AUC $_{(0-\infty)}$ IS INCREASED IN PARTICIPANTS WITH MODERATE AND SEVERE HEPATIC IMPAIRMENT



- No significant differences between participants with mild HI compared to participants with normal hepatic function;
- Patients with moderate and severe HI present increases in AUC, compared to patients with normal hepatic function

IMLUNESTRANT C_{MAX} IS SIMILAR ACROSS PARTICIPANTS WITH NORMAL HEPATIC FUNCTION AND HEPATIC IMPAIRMENT



- The imlunestrant C_{max} was similar between patients with normal hepatic function and those with mild, moderate and severe HI.

SAFETY

	Child-Pugh Classification							
	Normal Hepatic Function		Mild Hepatic Impairment		Moderate Hepatic Impairment		Severe Hepatic Impairment	
	n=9		n=6		n=6		n=6	
	TEAEs	TRAEs	TEAEs	TRAEs	TEAEs	TRAEs	TEAEs	TRAEs
Adverse Event (n%)	All Grade	All Grade	All Grade	All Grade	All Grade	All Grade	All Grade	All Grade
Patients with ≥1 AE	0	0	0	0	2 (33.3%)	1 (16.7%)	2 (33.3%)	1 (16.7%)
Nausea	0	0	0	0	2	0	1	0
Headache	0	0	0	0	1	1	1	0
Upper Abdominal Pain	0	0	0	0	1	0	0	0
Arthralgia	0	0	0	0	1	1	0	0
Back Pain	0	0	0	0	0	0	1	0
Fall	0	0	0	0	0	0	1	0
Insomnia	0	0	0	0	1	1	0	0
Portal Vein Thrombosis	0	0	0	0	1	0	0	0
Pruritus	0	0	0	0	1	0	0	0
Rash	0	0	0	0	0	0	1	1
Vomiting	0	0	0	0	1	0	0	0

[a]TEAE: Treatment emergent-adverse event; [b]TRAE: Treatment related-adverse event

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1. Jhaveri KL et al. *JCO* (2024) **0**. JCO.23.02733. DOI:10.1200/JCO.23.02733
2. Jhaveri KL et al. *Ann Oncol* (2023) 34(2). S338-S339. DOI 10.1016/j.annonc.2023.09.560
3. Datta-Mannan et al. AAPS PharmSci (2024): T0930-02-07
4. Krens SD, et al. *Lancet Oncology* (2019); 20(4): e200-e207.DOI: 10.1016/S1470-2045(19)30145-7

ACKNOWLEDGMENTS

We would like to thank the clinical trial participants and their caregivers, without whom this work would not be possible. We would like to thank the trial investigators and study staff. Medical writing support was provided by Joana Cruz Pereira, Eli Lilly and Company.
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- Here we present PK and safety data for imlunestrant in postmenopausal females of nonchildbearing potential (FONCBP) with and without HI, following a single oral dose in a fasted state.

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  - PK parameters based on Child-Pugh Classification
    - AUC(0-∞), and
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Child-Pugh classification: investigator assessed score calculated based on the sum of 5 parameters: serum albumin, total serum bilirubin, prothrombin time, ascites and hepatic encephalopathy

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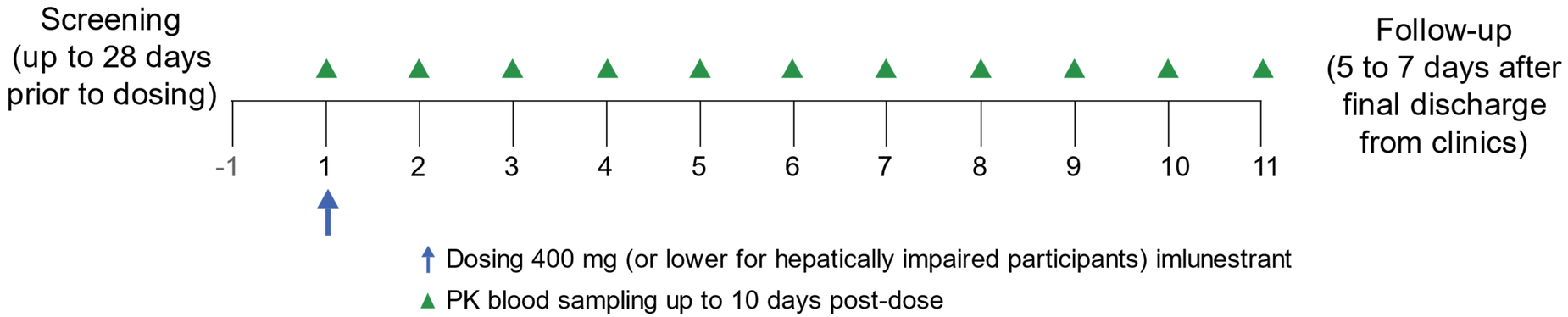
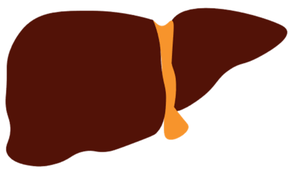
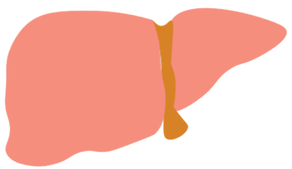




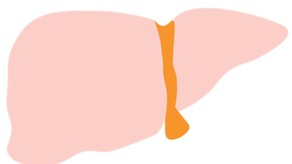
Group 1
Normal Hepatic Function
n=9

Group 2
Mild Hepatic Impairment
n=6



Group 3
Moderate Hepatic Impairment
n=6

400 mg Imlunestrant (R2PD)



Group 4
Severe Hepatic Impairment
n=6

200 mg Imlunestrant

METHODS/STUDY DESIGN

KEY ELIGIBILITY CRITERIA

- >18 years of age
- BMI: 18.0-42.0 kg/m2
- Female participants of non-childbearing potential
- **In addition, for Groups 2-4**
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American Indian or Alaska Native	0	0	1 (16.7%)	0	0	1 (11.1%)	0	0
Black or African American	1 (11.1%)	0	0	0	1 (8.3%)	0	0	0
White	8 (88.9%)	6 (100%)	5 (83.3%)	6 (100%)	11 (91.7%)	8 (88.9%)	5 (100%)	1 (100%)
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Score	N/A	6 (5-6)	7.5 (7-8)	10 (10-11)	N/A	N/A	N/A	N/A

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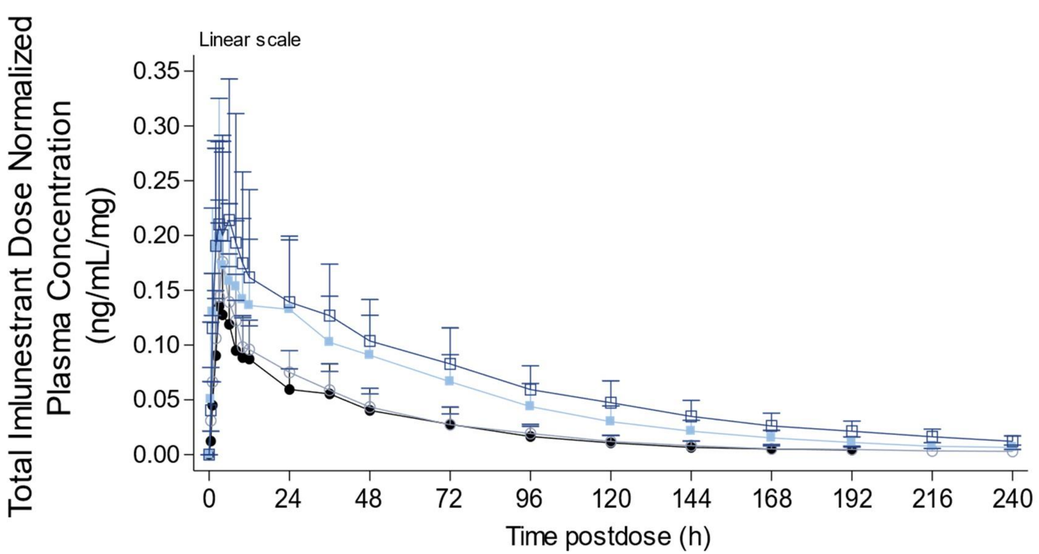

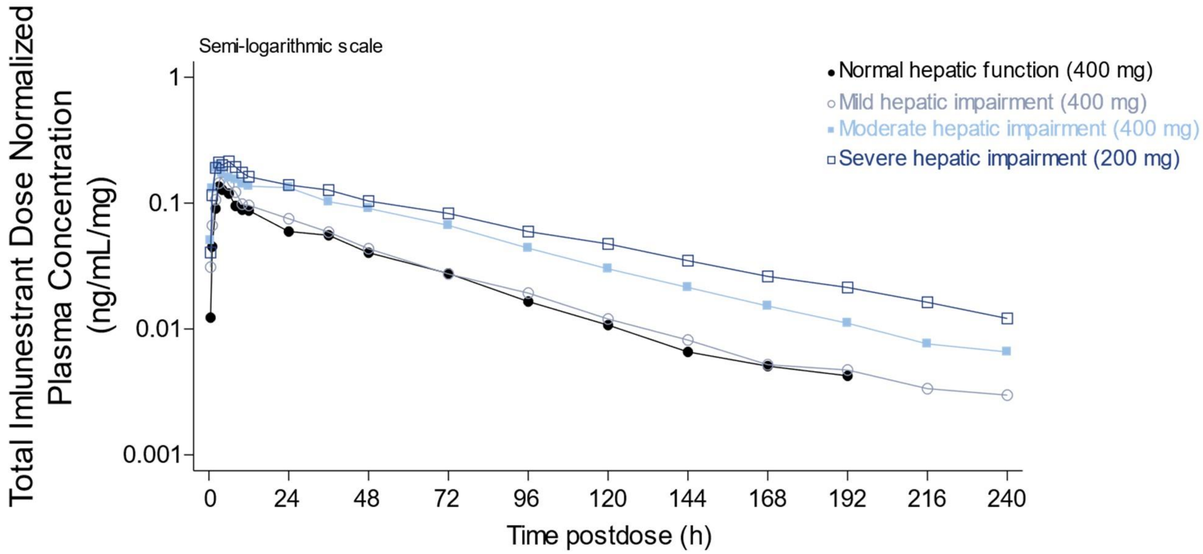

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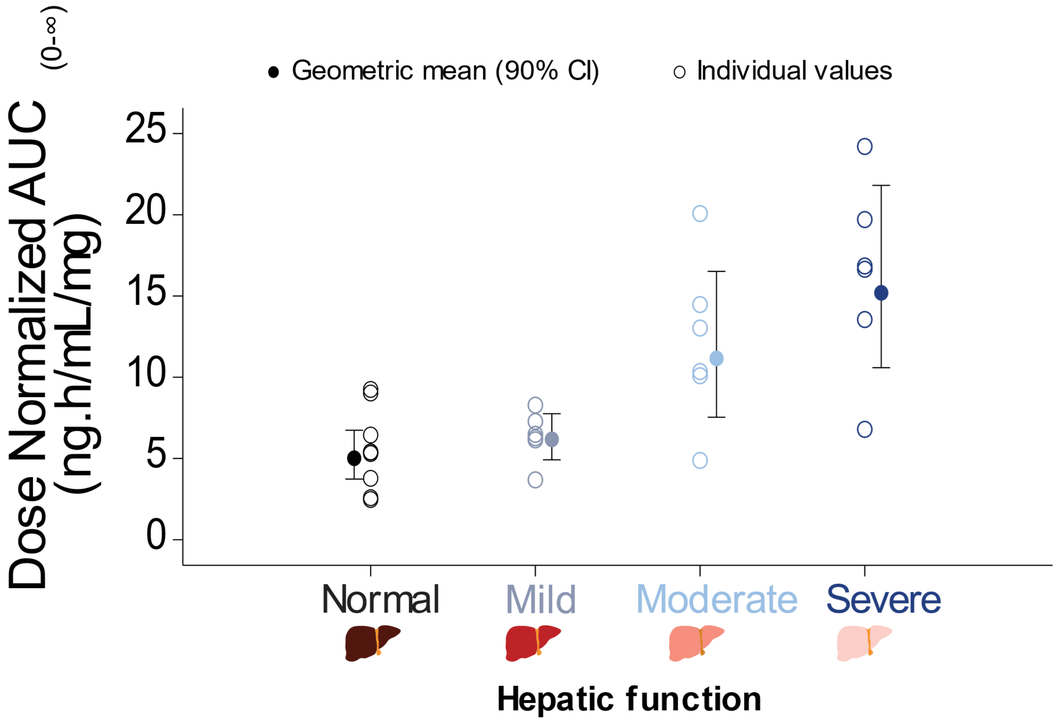
[a]Imlunestrant dose 400 mg (R2PD); [b]Imlunestrant dose 200 mg; [c]Dose normalized values
GLSM – Geometric Least Squares Mean; N/A – not available; R2PD - recommended phase 2 dose

RESULTS

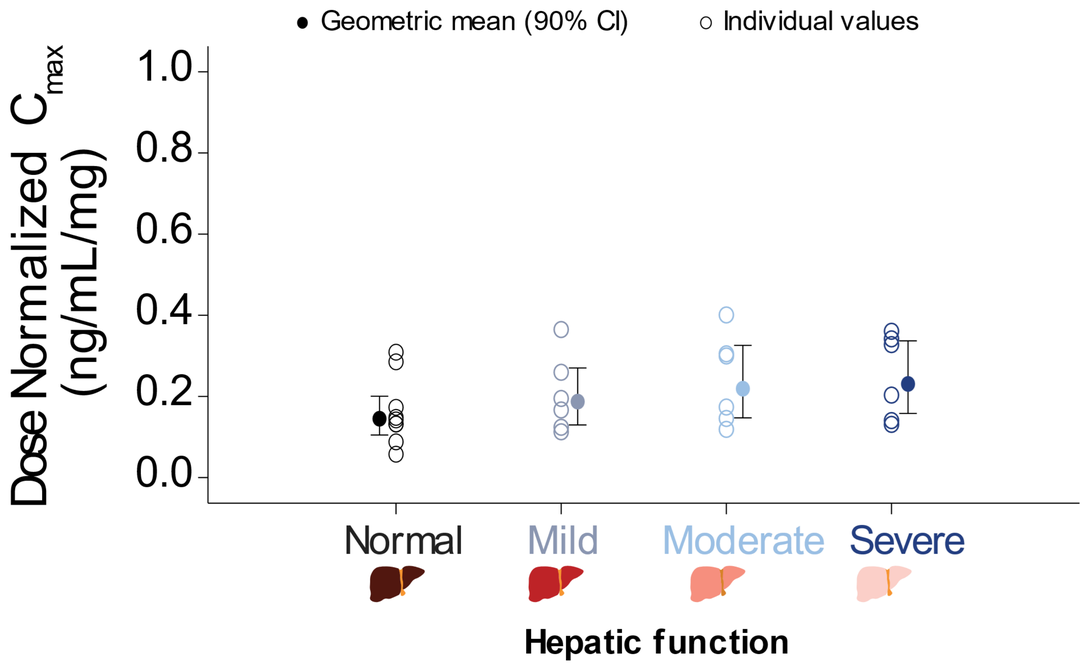
IMLUNESTRANT AUC (0-∞) IS INCREASED IN PARTICIPANTS WITH MODERATE AND SEVERE HEPATIC IMPAIRMENT



- No significant differences between participants with mild HI compared to participants with normal hepatic function;
- Patients with moderate and severe HI present increases in AUC, compared to patients with normal hepatic function

RESULTS

IMLUNESTRANT CMAX IS SIMILAR ACROSS PARTICIPANTS WITH NORMAL HEPATIC FUNCTION AND HEPATIC IMPAIRMENT



- The imlunestrant C_{max} was similar between patients with normal hepatic function and those with mild, moderate and severe HI.

RESULTS

SAFETY

	Child-Pugh Classification							
	Normal Hepatic Function		Mild Hepatic Impairment		Moderate Hepatic Impairment		Severe Hepatic Impairment	
	n=9		n=6		n=6		n=6	
	TEAEs	TRAEs	TEAEs	TRAEs	TEAEs	TRAEs	TEAEs	TRAEs
Adverse Event (n%)	All Grade	All Grade	All Grade	All Grade	All Grade	All Grade	All Grade	All Grade
Patients with ≥1 AE	0	0	0	0	2 (33.3%)	1 (16.7%)	2 (33.3%)	1 (16.7%)
Nausea	0	0	0	0	2	0	1	0
Headache	0	0	0	0	1	1	1	0
Upper Abdominal Pain	0	0	0	0	1	0	0	0
Arthralgia	0	0	0	0	1	1	0	0
Back Pain	0	0	0	0	0	0	1	0
Fall	0	0	0	0	0	0	1	0
Insomnia	0	0	0	0	1	1	0	0
Portal Vein Thrombosis	0	0	0	0	1	0	0	0
Pruritus	0	0	0	0	1	0	0	0
Rash	0	0	0	0	0	0	1	1
Vomiting	0	0	0	0	1	0	0	0

[a]TEAE: Treatment emergent-adverse event; [b]TRAE: Treatment related-adverse event

CONCLUSIONS

- Imlunestrant administered as a single oral dose in the fasted state was well tolerated in healthy FONCBP, as well as patients with mild, moderate and severe hepatic impairment (as determined by the Child Pugh's classification).
- There were no significant differences in the exposure profiles of imlunestrant in patients with mild hepatic impairment in comparison to participants with normal hepatic function.
- Patients with moderate and severe hepatic impairment presented significant increases in imlunestrant AUC (but not C_{max}) when compared with normal hepatic function.
- These data will inform imlunestrant dosing recommendations for patients with hepatic impairment

Acknowledgements and References

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