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Livdelzi® (seladelpar) Effects on Lipids

This document is in response to your request for information on the effects of Livdelzi® (seladelpar [SEL]) on lipids.

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Summary

Clinical Data on the Effects of SEL on Lipids

In the multicenter, placebo-controlled, phase 3 RESPONSE study that evaluated SEL 10 mg ± UDCA in patients with PBC with inadequate response or intolerance to UDCA,[1] greater reductions from BL in TC, LDL, and TG levels were observed with SEL than with placebo; similar observations were reported for those who were and were not using a statin at BL. HDL levels in both groups generally remained stable.[2]

- No treatment-related SAEs or AEs that led to death occurred. No muscle-related AEs led to treatment DC; all muscle-related AEs in the SEL group were Grade 1 or 2 in severity.[2]

In a pooled analysis of lipid data from the phase 3, placebo-controlled ENHANCE study and an open-label phase 2 study, among participants with data at Month 6, significant reductions from BL to Month 6 in TC, LDL, TG, and HDL levels were observed with SEL.[3]

Clinical Data on the Effects of SEL on Lipids

RESPONSE Study

Study design

RESPONSE was a phase 3, international, randomized, placebo-controlled study that evaluated SEL 10 mg in participants with PBC and inadequate response to or intolerance of first-line treatment with UDCA. Participants (N=193) were randomly assigned (ratio of 2:1) to receive either SEL 10 mg (n=128) or placebo (n=65) once daily for 12 months. Participants were eligible if they had PBC, were aged 18 to 75 years, had received UDCA for ≥12 months or had an intolerance of UDCA (last dose >3 months from screening), and had an ALP level ≥1.67 × ULN, an AST/ALT level ≤3 × ULN, a TB level ≤2 × ULN, an eGFR >45 mL/min/1.73 m^2, an INR <1.1 × ULN, and a platelet count ≥100,000/mm^3. Those with advanced PBC (eg, albumin level < LLN and TB level > ULN), hepatic decompensation, or other chronic liver disease were excluded.[1]

The primary composite endpoint was the proportion of participants who achieved a biochemical response, which was defined as an ALP level <1.67 × ULN, an ALP level decrease by ≥15%, and a TB level ≤1 × ULN. Key secondary endpoints included ALP normalization (≤1 × ULN) at Month 12 and change from BL to Month 6 in weekly mean pruritus NRS score in those with an NRS score ≥4 (eg, moderate-to-severe pruritus) at BL.[1]

Subanalysis of lipid levels[2]

Study design and demographics

A subanalysis was performed to evaluate the change from BL in lipid levels in the SEL and placebo groups according to the use or non-use of statins at study BL, and to evaluate the safety of concomitant SEL and statins. Lipid panels were assessed at BL and every 3 months throughout the study. At BL, 28 participants (22%) in the SEL group and 17 participants (26%) in the placebo group were being treated with a statin (Table 1 and Table 2). At BL, HDL and TG levels were similar between those receiving and those not receiving statins, whereas TC and LDL levels were lower among those receiving statins than among those not receiving statins.

Table 1. RESPONSE Lipid Subanalysis: BL Demographics and Disease Characteristics[2]

Key Demographics and Characteristics		No Statin Use (n=148)		Statin Use (n=45)	
		SEL 10 mg (n=100)	Placebo (n=48)	SEL 10 mg (n=28)	Placebo (n=17)
Age, mean (SD), years		55.4 (10.1)	56.7 (10.1)	60.8 (8.7)	57.8 (6)
Female, n (%)		98 (98)	45 (94)	25 (89)	15 (88)
Race, White/Asian/Black/ American Indian or Alaska Native/missing, n (%)		90 (90)/4 (4)/ 2 (2)/2 (2)/2 (2)	42 (88)/2 (4)/ 1 (2)/3 (6)/0	24 (86)/3 (11)/ 0/1 (4)/0	14 (82)/2 (12)/ 1 (6)/0/0
Hispanic, n (%)		26 (26)	21 (44)	3 (11)	6 (35)
BMI, mean (SD), kg/m^2		27.1 (5.5)	26.6 (4.5)	27.7 (6)	27.5 (5.7)
Duration of PBC, mean (SD), years		7.6 (6)	8.2 (6.1)	10.2 (8.5)	9.7 (7.6)
Cirrhosis, n (%)		14 (14)	7 (15)	4 (14)	2 (12)
UDCA intolerance, n (%)		6 (6)	3 (6)	2 (7)	1 (6)
ALP level, mean (SD), U/L		320.3 (121.3)	297.1 (96.9)	294 (128.9)	361.1 (156.8)
Lipid levels, mean (SD), mg/dL	TC	251.6 (46.9)	247.5 (53.6)	202.3 (48.2)	206.6 (48.9)
	HDL	80.9 (21.5)	74.7 (20.9)	79.1 (28.5)	76.2 (26.7)
	LDL	146.9 (42.4)	148.4 (50.5)	100.4 (36.6)	106.3 (39.6)
	TG	118.7 (54.8)	122.3 (44.8)	113 (40.6)	120.6 (39.8)

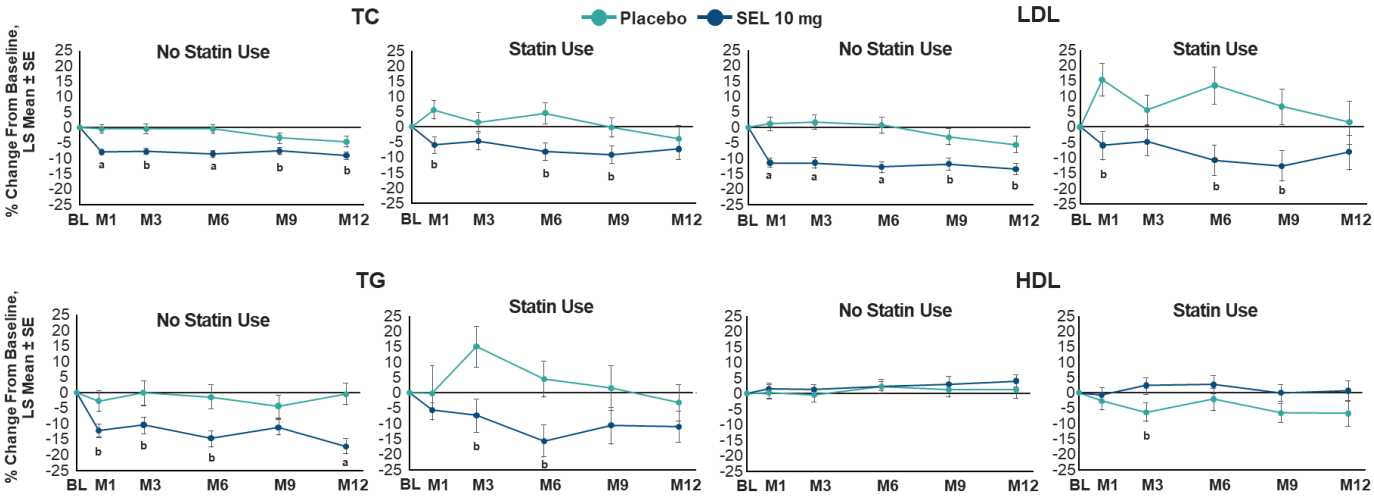
Table 2. RESPONSE Lipid Subanalysis: Statins Used at BL[2]

Parameter, n (%)		SEL 10 mg	Placebo
Participants on statin at BL		28 (22)	17 (26)
Statins used at BL	Atorvastatin	9 (32)	7 (41)
	Atorvastatin calcium	4 (14)	2 (12)
	Rosuvastatin calcium	4 (14)	2 (12)
	Simvastatin	4 (14)	1 (6)
	Rosuvastatin	3 (11)	2 (12)
	Pravastatin	3 (11)	1 (6)
	Ezetimibe/rosuvastatin	1 (4)	0
	Ezetimibe/atorvastatin	0	1 (6)
	Ezetimibe/simvastatin	0	1 (6)

Lipid panel results

Greater reductions from BL in TC, LDL, and TG levels were observed with SEL than with placebo; similar observations were reported for those who were and were not using a statin at BL. HDL levels in both groups generally remained stable over 12 months of treatment.

Figure 1. RESPONSE Lipid Subanalysis: Mean % Change From BL in Lipid Levels Through Month 12 According to Treatment and by Statin Use[2]



Abbreviation: LS=least squares; M=month.
[a]*P*<0.0001. [b]*P*<0.05.

Safety results

Rates of AEs, SAEs, and Grade ≥3 AEs according to statin use are shown in Table 3. No treatment-related SAEs or AEs that led to death occurred. No muscle-related AEs led to treatment DC; all muscle-related AEs in the SEL group were Grade 1 or 2 in severity, and one Grade 3 AE of myalgia occurred in the placebo group (Table 3). No AEs associated with CK elevations were noted, and no participants who were receiving statins at BL had increases of CK levels to >3 × ULN.

Table 3. RESPONSE Lipid Subanalysis: Safety Outcomes by Treatment and According to Statin Use[2]

Safety Outcome, n (%)		No Statin Use (n=148)		Statin Use (n=45)	
		SEL 10 mg (n=100)	Placebo (n=48)	SEL 10 mg (n=28)	Placebo (n=17)
Any AEs		84 (84)	41 (85)	27 (96)	14 (82)
Grade ≥3 AEs (per CTCAE)		12 (12)	3 (6)	2 (7)	2 (12)
SAEs		8 (8)	2 (4)	1 (4)	2 (12)
AEs that led to treatment DC		4 (4)	2 (4)	0	1 (6)
AEs that led to study DC		3 (3)	2 (4)	0	1 (6)
Any muscle-related AEs		6 (6)	5 (10)	2 (7)	0
Muscle-related AEs	Myalgia	2 (2)	2 (4)	1 (4)	0
	Fibromyalgia	2 (2)	1 (2)	0	0
	Muscle spasms	2 (2)	1 (2)	0	0
	Musculoskeletal stiffness	0	1 (2)	0	0
	Musculoskeletal pain	0	0	1 (4)	0

Abbreviation: CTCAE=Common Terminology Criteria for Adverse Events.

More participants in the placebo group than in the SEL group began a statin or increased their statin dose (Table 4).

Table 4. RESPONSE Lipid Subanalysis: Statin Status Changes During the Study[2]

Statin Status Changes, n or n (%)	SEL 10 mg (n=128)	Placebo (n=65)
Participants not using a statin at BL	100	48
Participants who began statin during study	4 (4)	7 (15)
Participants using a statin at BL	28	17[a]
Participants who stopped any statin during study	1 (4)	0
Participants who had a statin dosage increase during study	1 (4)	1 (6)

[a]One participant began a statin at BL. Their dose was reduced from Day 143 to Day 274 and increased again to their BL dose from Day 275 through the end of the study; therefore, they were not counted as having stopped their statin or being in the dose-change category.

Pooled Analysis of ENHANCE Study and Open-Label Phase 2 Study[3]

Study design and demographics

A pooled analysis of lipid panel data from the phase 3, placebo-controlled ENHANCE study and a phase 2, open-label study was conducted. Participants were eligible if they had PBC, an ALP level ≥1.67 × ULN, and had received a stable UDCA dose for the previous 12 months (unless they were UDCA intolerant). Those with a TB level >2 mg/dL (ENHANCE) or >2 × ULN (phase 2 study), advanced PBC (eg, albumin level <LLN and TB level >ULN), an INR >ULN, a platelet count <100 × 10^9/L (ENHANCE), and clinically significant hepatic decompensation were excluded. Participants received once-daily SEL 10 mg (n=144), SEL 5 mg (n=142), or placebo (n=87); if tolerated, concomitant UDCA treatment was used. Lipid data were collected at BL, and changes at Month 6 were assessed.

At BL, 23% of all participants were receiving lipid-lowering medications (Table 5); however, many participants had high lipid levels at BL: TC (≥200 mg/dL); LDL (≥130 mg/dL), 54%; and TG (≥150 mg/dL), 21%.77%. Most participants (75%) had a high HDL level (≥60 mg/dL) at BL.

Table 5. Pooled Analysis: BL Demographics and Disease Characteristics[3]

Key Demographics and Characteristics	Overall (N=373)	SEL 10 mg (n=144)	SEL 5 mg (n=142)	Placebo (n=87)
Female, n (%)	351 (94)	133 (92)	133 (94)	85 (98)
Age, mean (SD), years	56 (9)	56 (9)	56 (9)	56 (8)
Age ≥65 years, n (%)	58 (16)	24 (17)	22 (16)	12 (14)
BMI, mean (SD), kg/m^2	28 (6)	28 (6)	27 (6)	28 (6)
BMI >30 kg/m^2, n (%)	106 (28)	41 (28)	37 (26)	28 (32)
Duration of PBC, mean (SD), years	9 (6)	9 (6)	9 (7)	8 (6)
UDCA intolerance, n (%)	24 (6)	11 (8)	11 (8)	2 (2)
UDCA dose, mean (SD), mg/kg/day	15 (4)	15 (4)	15 (4)	15 (3)
ALP level, mean (SD), U/L	300 (126)	293 (120)	311 (143)	293 (106)
Key comorbid conditions, HTN/DM[a]/CAD, n (%)	88 (24)/32 (9)/ 8 (2)	36 (25)/15 (10)/ 4 (3)	32 (23)/8 (6)/ 3 (2)	20 (23)/9 (10)/ 1 (1)
Concomitant lipid-lowering medications, overall/statins, n (%)	86 (23)/69 (19)	31 (22)/27 (19)	38 (27)/28 (20)	17 (20)/14 (16)

Key Demographics and Characteristics		Overall (N=373)	SEL 10 mg (n=144)	SEL 5 mg (n=142)	Placebo (n=87)
Lipid levels, mean (SD), mg/dL	TC	238 (52)	237 (53)	238 (53)	239 (50)
	LDL	138 (43)	137 (44)	138 (44)	139 (39)
	TG	116 (50)	119 (56)	110 (47)	121 (44)
	HDL	77 (24)	76 (23)	78 (24)	76 (25)
	Non-HDL	161 (47)	161 (49)	160 (47)	163 (43)

Abbreviations: CAD=coronary artery disease; DM=diabetes mellitus; HTN=hypertension.
[a]Included the following preferred terms: type 2 DM, DM, and type 1 DM.

Lipid panel results

At Month 6, data for 164 participants were available: SEL 10 mg, n=70; SEL 5 mg, n=71; and placebo, n=23. Improvements from BL in lipid levels were observed for those in the SEL arm (*P*<0.05 for all comparisons vs placebo), whereas changes observed in the placebo group were not significant (Table 6).

Table 6. Pooled Analysis: Mean Change From BL to Month 6 in Lipid Levels[3]

Mean Change From BL, mg/dL	SEL 10 mg (n=70)	SEL 5 mg (n=71)	Placebo (n=23)
TC	-20[a]	-18	-4
LDL	-18[a]	-15[a]	+0.5
TG	-25[a]	-17[a]	-8
HDL	+2[a]	0	-3
Non-HDL	-23[a]	-18[a]	-1

[a]*P*<0.05 vs placebo.

Changes in lipid levels in the SEL 10 mg group were similar between participants regardless of the concomitant lipid-lowering treatment they were receiving.

References

1. Hirschfield GM, Bowlus CL, Mayo MJ, et al. A Phase 3 Trial of Seladelpar in Primary Biliary Cholangitis. *N Engl J Med.* 2024;390(9):783-794.
2. Bowlus C, Yilmaz Y, Zigmond E, et al. Seladelpar and Reductions In Lipids In Patients With Primary Biliary Cholangitis With and Without Statin Use In The Phase 3 Placebo Controlled Response Study [Poster 4342]. The Liver Meeting; 15-19 November, 2024; USA.
3. Bowlus CL, Choi YJ, Yang K, Crittenden B, Kim D, McWherter CA. Seladelpar Improved the Lipid Profile of Patients With Primary Biliary Cholangitis (PBC): Results From Phase 2 and 3 Clinical Studies.[Poster 4759]. Paper presented at: American Association for the Study of Liver Diseases (AASLD); November 4-8, 2022; Washington, D.C.

Abbreviations

AE=adverse event
ALP=alkaline phosphatase
BL=baseline
CK=creatine kinase
DC=discontinuation
LLN=lower limit of normal
NRS=numerical rating scale
PBC=primary biliary cholangitis
SAE=serious adverse event
SEL=seladelpar
TB=total bilirubin
TC=total cholesterol
TG=triglycerides
UDCA=ursodeoxycholic acid
ULN=upper limit of normal

Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Livdelzi US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/pbc/livdelzi/livdelzi_pi.

Follow-Up

For any additional questions, please contact Gilead Medical Information at:

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FDA MedWatch Program by ☎ 1-800-FDA-1088 or ✉MedWatch, FDA, 5600 Fishers Ln, Rockville, MD 20852 or www.accessdata.fda.gov/scripts/medwatch

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