EFFICACY AND SAFETY OF SELADELPAR IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS IN THE ASSURE STUDY: INTERIM RESULTS

Sponsor: CymaBay Therapeutics, Inc.

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DISCLOSURE INFORMATION

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I disclose the following financial relationship(s):

Consulting			Grants/contracts research paid to the Institution			DMSB
• Gilead	• Mirum	• Calliditas	• Gilead	• CymaBay	• Calliditas	• Cour
• Intercept	• CymaBay	• Kowa	• Intercept	• GSK	• Ipsen	
• Ipsen	• GSK		• Mirum	• Escient	• Kowa	
			• Zydus			

PRIMARY BILIARY CHOLANGITIS (PBC)

Approximately 1 in 1000 women over 40 years of age live with PBC

Chronic, progressive, autoimmune, cholestatic liver disease

Serum markers of cholestasis are prognostic

- Alkaline phosphatase (ALP)
- Total bilirubin (TB)

Frequently symptomatic

- Pruritus
- Fatigue

Ursodeoxycholic acid (UDCA) is an approved first-line therapy

- Approximately 40% of patients have an insufficient response
- Treatment does not improve pruritus

PATIENT PRIORITIES

- Disease control
- Symptom control
- Potent, safe, and tolerable therapy

1. European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-172. 2. American Liver Foundation. Primary biliary cholangitis (PBC). Updated September 7, 2023. Accessed October 31, 2023. https://liverfoundation.org/liver-diseases/autoimmune-liver-diseases/primary-biliary-cholangitis-pbc/ 3. Mayo Clinic. Primary biliary cholangitis. June 21, 2023. Accessed August 3, 2023. https://www.mayoclinic.org/diseases-conditions/primary-biliary-cholangitis/symptoms-causes/syc-20376874 4. Levy C, et al. *Clin Gastroenterol Hepatol.* 2023;21(8):2076-2087. 5. Lindor KD, et al. *Hepatology*. 2019;69(1):394-419. 6. Murillo Perez CF, et al. *Gastroenterology*. 2022;163(6):1630-1642.e3. 7. Invernizzi P, et al. *Dig Liver Dis*. 2017;49(8):841-846.

SELADELPAR: AN INVESTIGATIONAL, POTENT, SELECTIVE DELPAR (PPARδ AGONIST) TARGETING MULTIPLE CELL TYPES AND PROCESSES IN PBC

Improves Cholestasis

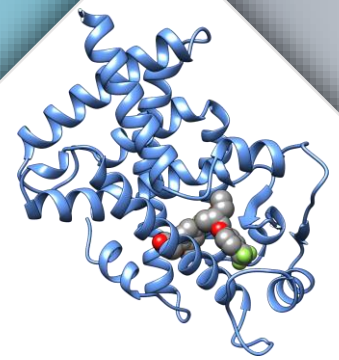
- ⇩ Bile acid synthesis
- ⇩ ALP
- ⇩ GGT

Hepatocytes and Cholangiocytes

Reduces Markers of Inflammation

- ⇩ Inflammatory cytokines
- ⇩ Inflammatory lipid mediators
- ⇩ ALT

Macrophages and Kupffer Cells



Seladelpar,
Potent PPARδ engagement

Reduces Pruritus

- ⇩ Bile acids
- ⇩ Serum IL-31

Hepatocytes

Increases Lipid Metabolism

- ⇩ Cholesterol/LDL-C/triglycerides
- ⇧ Fatty acid oxidation

Hepatocytes

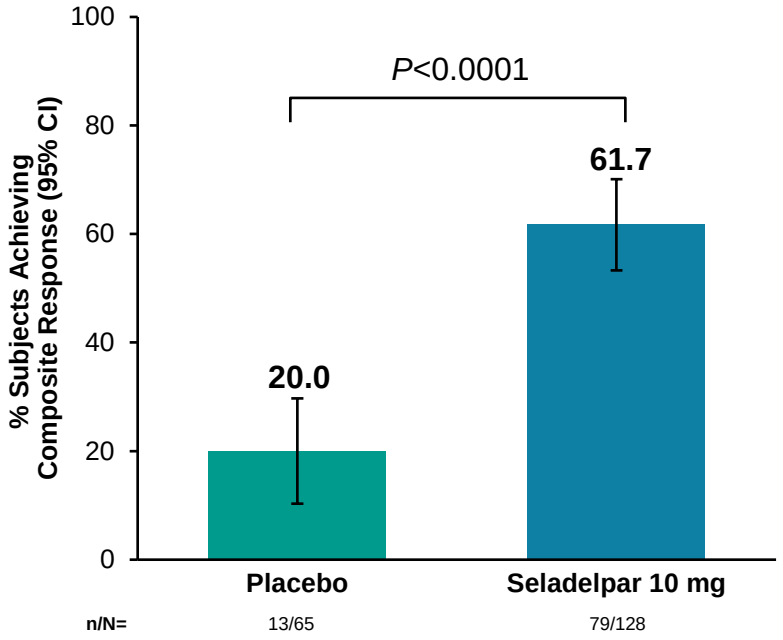
Seladelpar is an investigational drug that has not been approved for use in any indication by the FDA, EMA, or other regulatory agencies. Phase 3 clinical trials for seladelpar in PBC are ongoing.

ALT, alanine aminotransferase; EMA, European Medicines Agency; FDA, US Food and Drug Administration; GGT, gamma-glutamyltransferase; IL-31, interleukin-31; LDL-C, low-density lipoprotein cholesterol; PPARδ, peroxisome proliferator-activated receptor delta.

1. CymaBay Therapeutics, Inc. Seladelpar granted revised breakthrough therapy designation for the treatment of primary biliary cholangitis including pruritus in patients without cirrhosis or with compensated cirrhosis. October 23, 2023. Accessed October 28, 2023. https://www.cymabay.com/investors-media/news-events/press-releases/detail/577/seladelpar-granted-revised-breakthrough-therapy-designation 2. Hirschfield GM, et al. *Hepatology*. 2023;78(2):397-415. 3. Kremer AE, et al. *Liver Int.* 2022;42(1):112-123. 4. Kremer AE, et al. Presented at: ACG 2023 Annual Meeting; October 20-25, 2023; Vancouver, Canada. 5. Kuono T, et al. *J Biol Chem*. 2022;298(7):102056. 6. Choi Y, et al. Presented at: Discovery on Target; September 27-30, 2021; Boston, MA. 7. Choi Y, et al. Poster presented at: AASLD: The Liver Meeting; November 4-8, 2022; Washington, DC. Poster 4731. 8. Bowlus C, et al. Poster presented at: AASLD: The Liver Meeting; November 4-8, 2022; Washington, DC. Poster 4759.

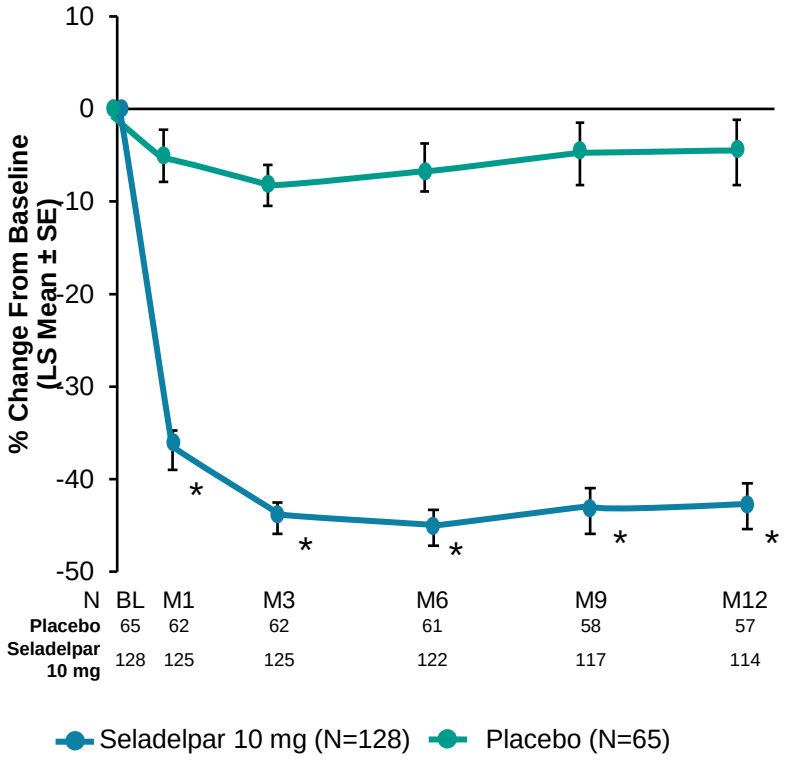
IN THE PIVOTAL PHASE 3 RESPONSE STUDY SELADELPAR SIGNIFICANTLY IMPROVED BIOCHEMICAL MARKERS AND PRURITUS

Primary Trial Outcome
COMPOSITE ENDPOINT AT MONTH 12

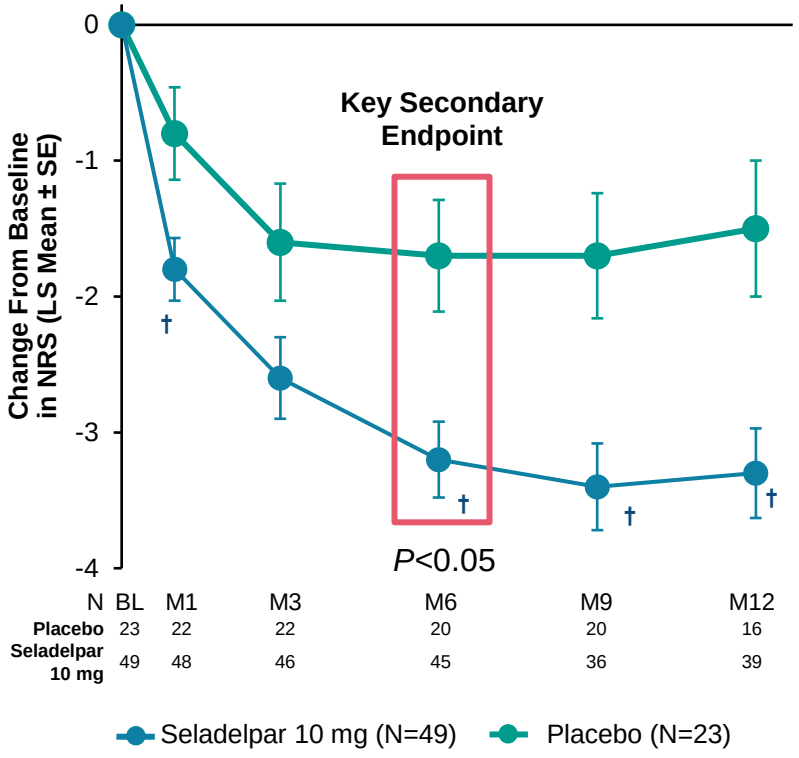


Composite endpoint: ALP <1.67× ULN; ALP decrease ≥15%; TB ≤1× ULN

ALP RELATIVE CHANGE FROM BASELINE



CHANGE IN NRS IN PATIENTS WITH BASELINE NRS ≥4

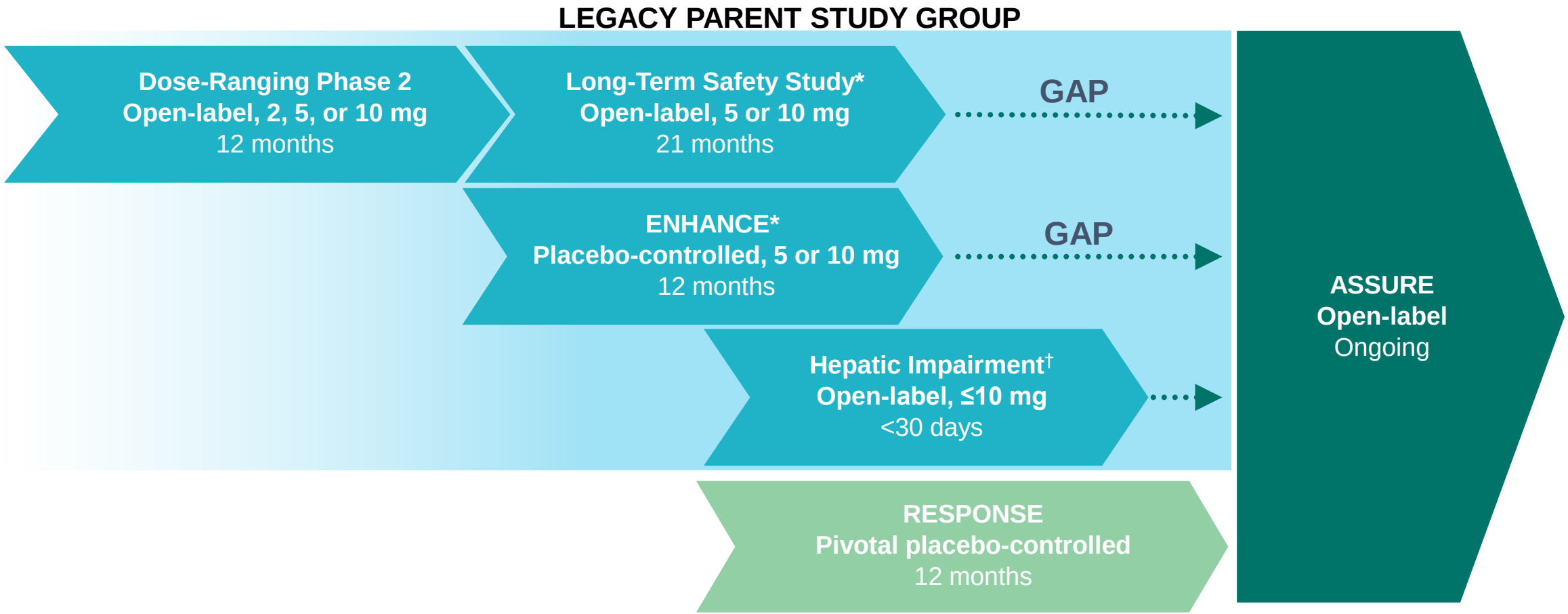


Patients treated with seladelpar had a similar incidence of adverse events to those in the placebo group

BL, baseline; LS, least-square; M, month; NRS, numerical rating scale; ULN, upper limit of normal.
*P<0.0001 vs placebo. †P<0.05 vs placebo.

1. Hirschfield GM, et al. *N Engl J Med*. 2024;390(9):783-794. 2. CymaBay Therapeutics, Inc. CymaBay announces an oral presentation of seladelpar Phase 3 pivotal results in primary biliary cholangitis at the late breaker session of the Liver Meeting®. November 13, 2023. Accessed April 29, 2024. https://www.cymabay.com/investors-media/news-events/press-releases/detail/583/cymabay-announces-an-oral-presentation-of-seladelpar-phase 3. CymaBay Therapeutics, Inc. Data on file [GAB Source Slides].

ASSURE IS OPEN TO PBC PATIENTS WHO HAVE PARTICIPATED IN PREVIOUS SELADELPAR STUDIES



*These studies had an early termination. †Patients were eligible to enroll in ASSURE after completing the study, but they had to meet screening criteria and had variable time to entry into ASSURE.

Phase 3 registrational study RESPONSE (NCT04620733). Legacy studies: Phase 3 study ENHANCE (NCT03602560), CB8025-21629 (NCT02955602), CB8025-31731 (NCT03301506), and CB8025-21838 (NCT04950764).

INTERIM ANALYSIS OF ASSURE CONDUCTED TO ASSESS LONG-TERM EFFICACY AND SAFETY IN LEGACY PATIENTS

Interim analysis was performed on all data through June 29, 2023

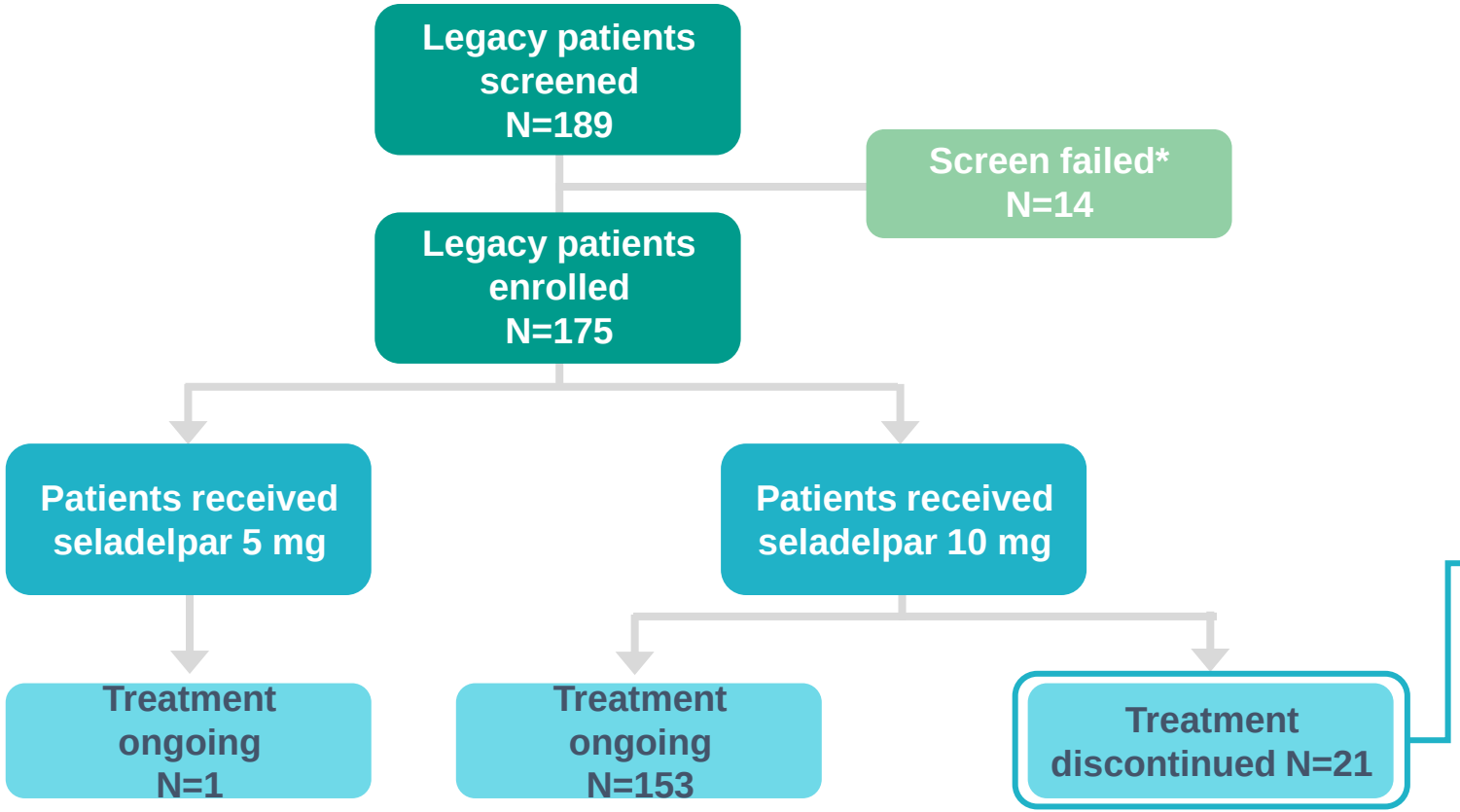
Efficacy analyses included the following:

- Composite biochemical response (ALP <1.67× ULN, ≥15% decrease in ALP, TB ≤1× ULN)
- ALP normalization
- Change is liver enzymes (ALP, TB, GGT, and ALT)
- Change in pruritus NRS score for patients with baseline ≥4

Overall safety profile

RESPONSE rollover subjects will be reported separately

PATIENT DISPOSITION



ONGOING STUDY
PATIENTS AS OF JUNE 29, 2023

Time point, months	≥6	≥12	≥18	≥24
Number of patients	169	140	89	19

REASONS FOR DISCONTINUATION

- Closure of sites in Russia (7)
- Adverse events (7)
  - Liver safety monitoring (2)
- Withdrawal of informed consent (2)
- Pregnancy (1)
- Noncompliance (1)
- Lost to follow-up (1)
- Other (2)

AST, aspartate aminotransferase.
*Reasons for screen failures: AST or ALT >3× ULN; TB >2× ULN; advanced PBC by Rotterdam criteria; Estimated glomerular filtration rate <60; previous treatment-related adverse event; Model for End-Stage Liver Disease (MELD) score >15; autoimmune hepatitis; use of prohibited medications.

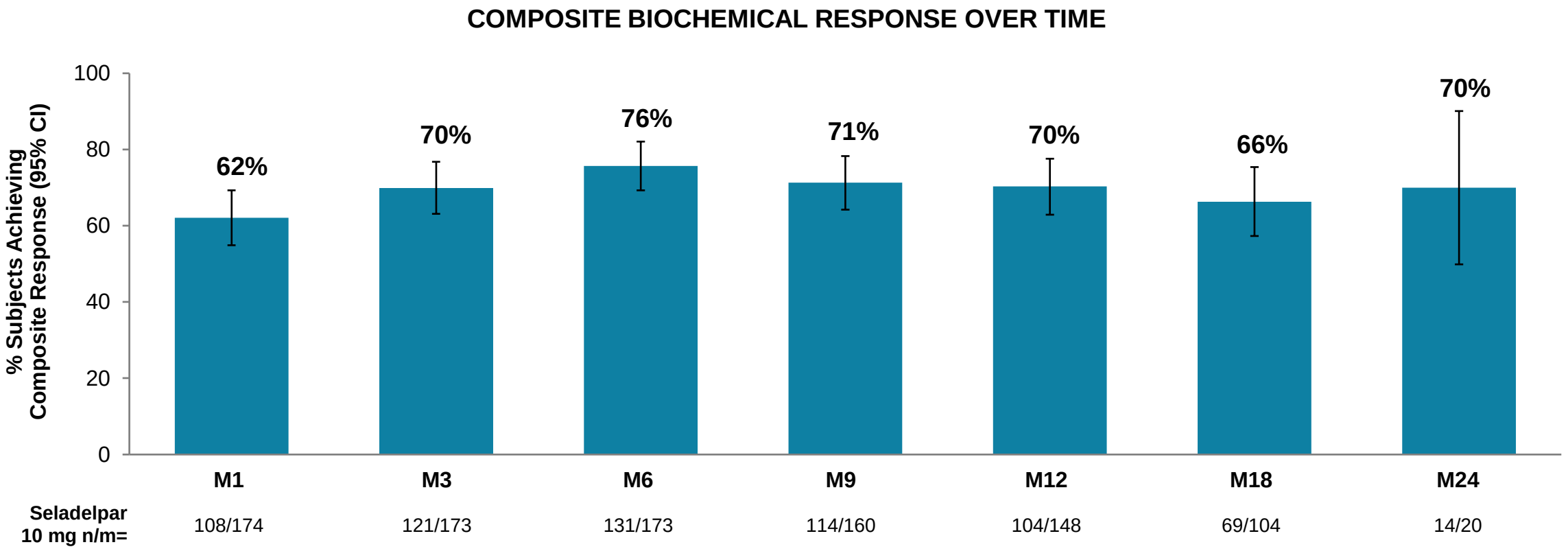
KEY DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Age Years, Mean (SD)	58.6 (9.6)
Age at Diagnosis Years, Mean (SD)	47.7 (8.5)
Female Sex, n (%)	164 (94.3)
Race, n (%)*	
White	150 (86.2)
Asian	13 (7.5)
American Indian or Alaska Native	6 (3.4)
Black or African American	3 (1.7)
Ethnicity, n (%)†	
Hispanic or Latino	23 (13.2)
BMI kg/m^2, Mean (SD)	27.5 (6.0)
Prior Use of OCA and/or Fibrates, n (%)	32 (18.4)
UDCA Intolerance, n (%)	6 (3.4)

Liver Stiffness kPa, Mean (SD)	10.3 (8.3)
Pruritus History, n (%)	
Yes	118 (67.8)
NRS Mean	2.875 (2.9)
NRS ≥4, n (%)	60 (34.5)
ALP U/L, Mean (SD)	270.5 (124.4)
Baseline ALP <350 U/L, n (%)	132 (75.9)
TB mg/dL, Mean (SD)	0.75 (0.34)
Bilirubin <1× ULN, n (%)	150 (86.2)
Bilirubin <0.6× ULN, n (%)	84 (48.3)
GGT U/L, Mean (SD)	208.1 (178.0)
ALT U/L, Mean (SD)	41.0 (23.6)
MELD Score, Mean (SD)	6.9 (1.1)

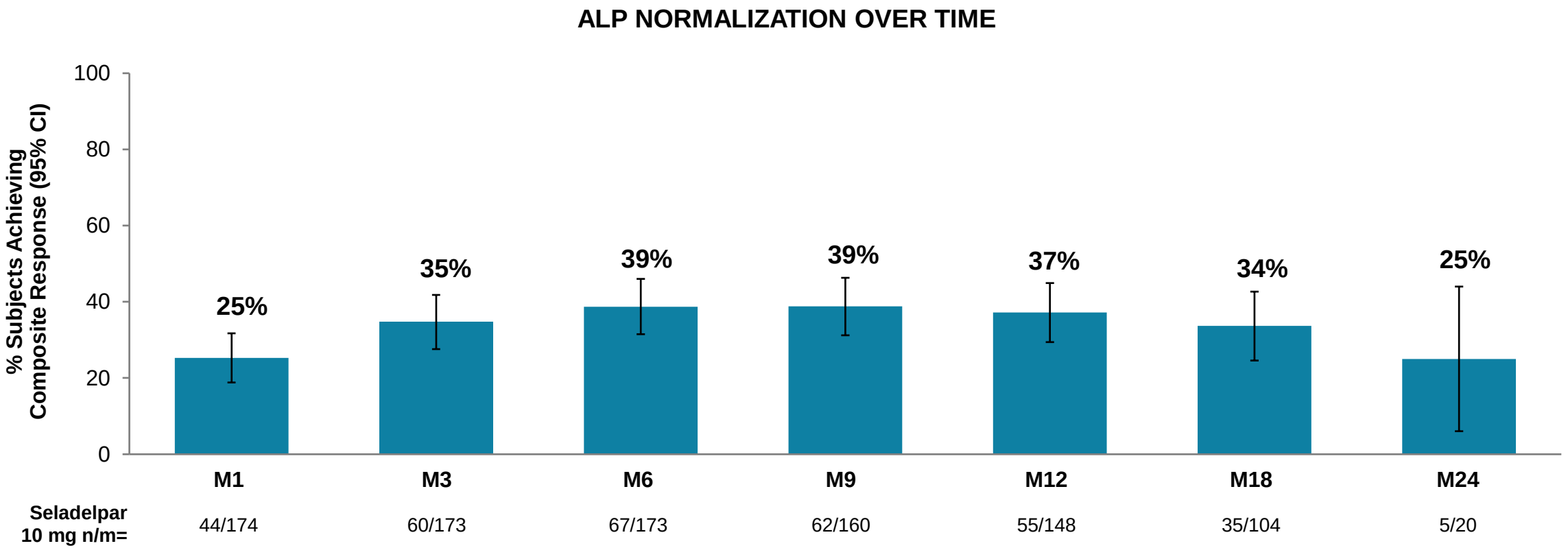
BMI, body mass index; OCA, obeticholic acid.
*Missing data: 1 (0.6%) patient declined to answer and 1 (0.6%) patient had missing race data.
†Missing data: 3 (1.7%) patients declined to answer and 1 (0.6%) patient had missing ethnicity data.

LEGACY PATIENTS ACHIEVED RAPID AND DURABLE COMPOSITE BIOCHEMICAL RESPONSE



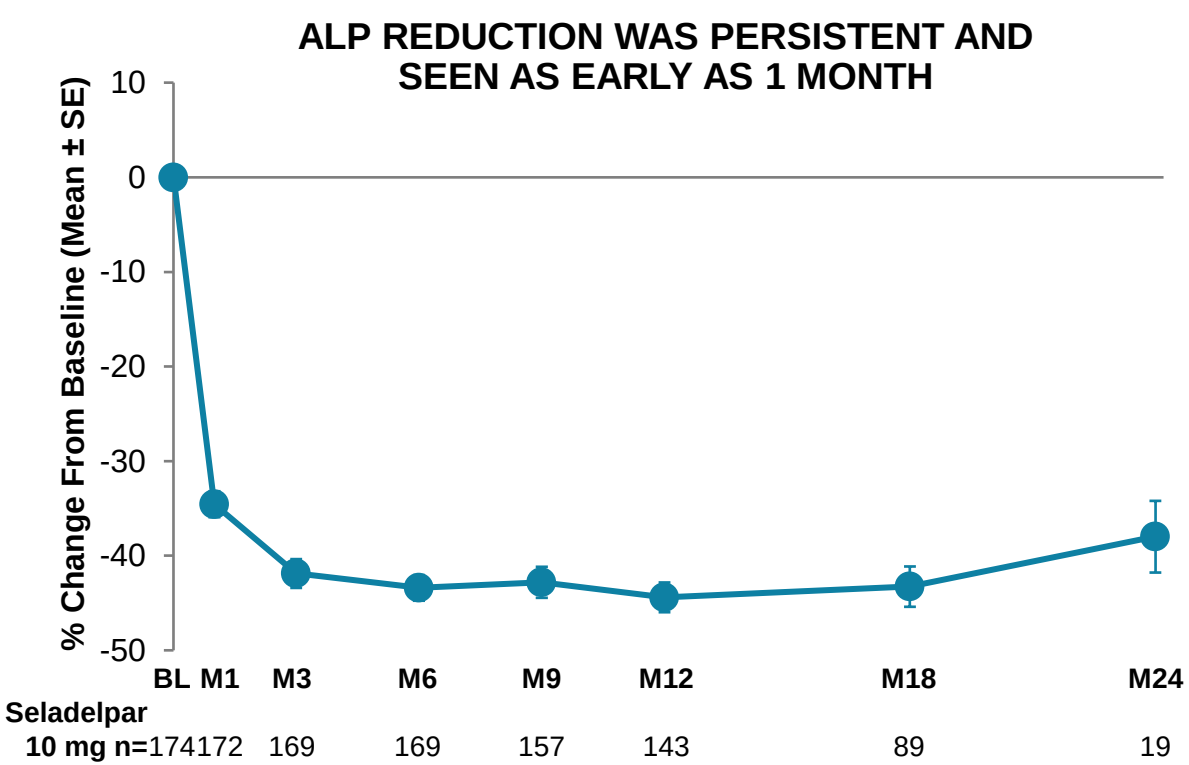
n/m, number of responders/number of evaluable subjects.
Composite response defined as ALP<1.67× ULN, ≥15% decrease in ALP, and TB 1× ≤ULN.
Data are for legacy parent study group (CB8025-21629, CB8025-31735, CB8025-31731, and CB8025-21838) as of June 29, 2023.

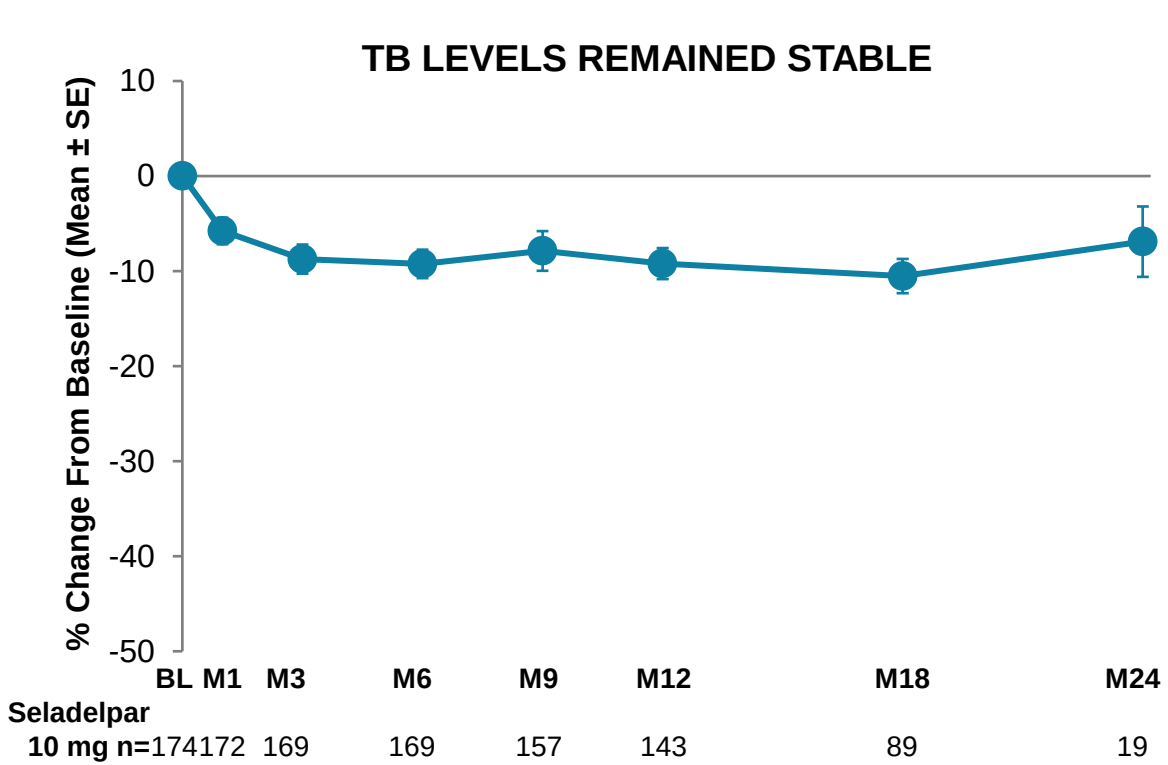
LEGACY PATIENTS ACHIEVED RAPID AND DURABLE ALP NORMALIZATION



Responder is defined as ALP ≤1.0× ULN. Intention-to-treat (ITT) analysis set.
n/m, number of responders/number of evaluable subjects.
Data are for legacy parent study group (CB8025-21629, CB8025-31735, CB8025-31731, and CB8025-21838) as of June 29, 2023.

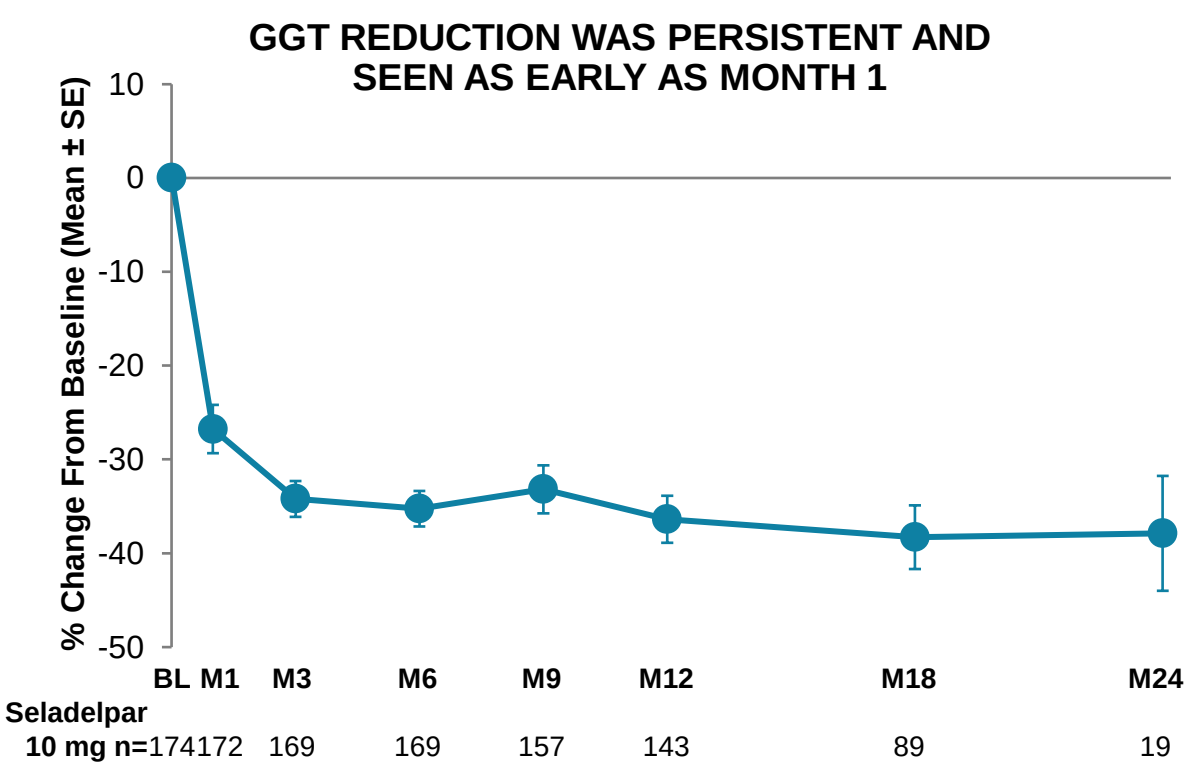
ALP REDUCTION WAS RAPID AND DURABLE, WHILE TOTAL BILIRUBIN REMAINED STABLE

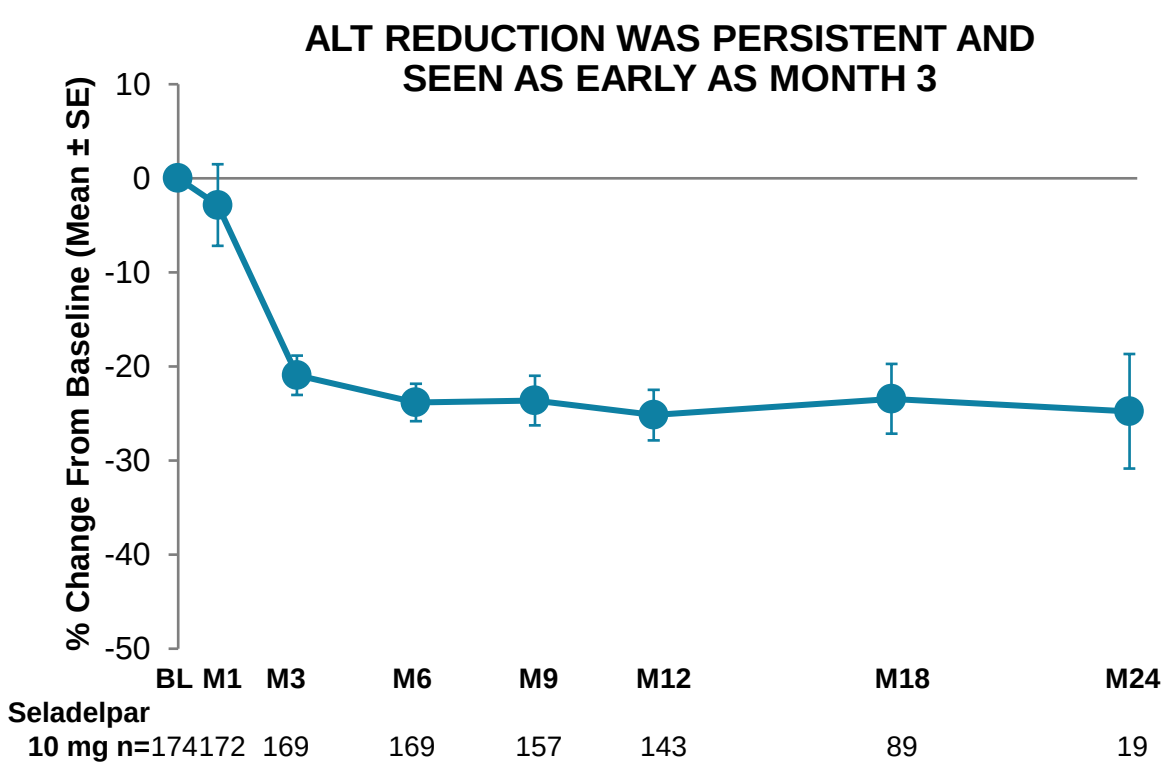




ITT analysis set. n=number of evaluable subjects.
Data are for legacy parent study group (CB8025-21629, CB8025-31735, CB8025-31731, and CB8025-21838) as of June 29, 2023.

GGT AND ALT REDUCTIONS WERE RAPID AND DURABLE





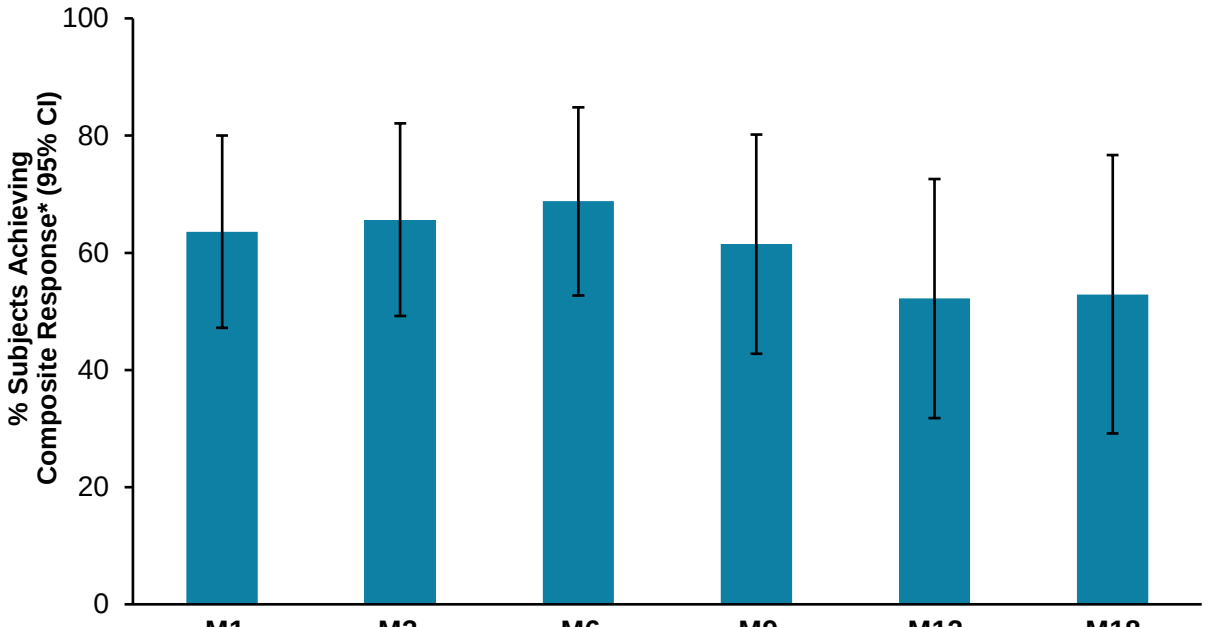
ITT analysis set. n=number of evaluable subjects.
Data are for legacy parent study group (CB8025-21629, CB8025-31735, CB8025-31731, and CB8025-21838) as of June 29, 2023.

CHARACTERISTICS OF PATIENTS WITH CIRRHOSIS

Number of Subjects With Cirrhosis at Screening, n (%)	**33**
Child-Pugh A	31 (93.9)
Child-Pugh B	2 (6.1)
Cirrhosis with portal hypertension	8 (24.2)
MELD Score, n (%)	
n	33
Mean (SD)	7.2 (1.52)
Min, Max	6, 12
Supporting Information for the Diagnosis of Cirrhosis as Indicated by the Primary Investigator	
Liver biopsy, n (%)	6 (18.2)
Liver stiffness via FibroScan®, n (%)	18 (54.5)
Radiological evidence, n (%)	13 (39.4)
Laboratory findings, n (%)	4 (12.1)
Clinical determination by the investigator, n (%)	7 (21.2)
Current decompensated liver disease, n (%)	2 (6.1)
Portal Hypertension, n (%)	8 (24.2)
Esophageal varices, n (%)	5 (15.2)
Ascites	0
Splenomegaly, n (%)	7 (21.2)
Thrombocytopenia, n (%)	3 (9.1)
Nonesophageal varices	0

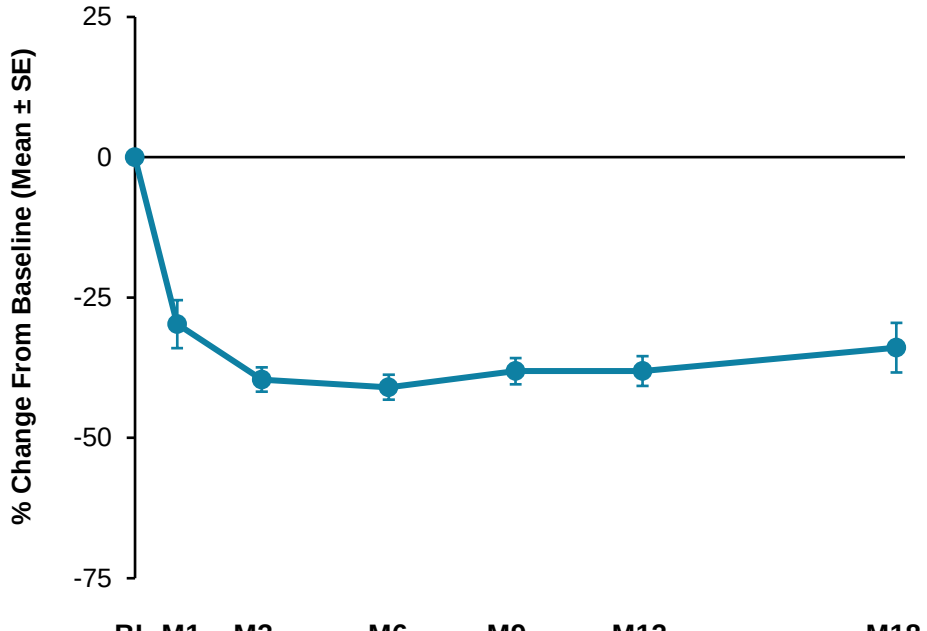
33 PATIENTS IN THIS STUDY POPULATION HAD CIRRHOSIS AND EFFICACY RESULTS WERE CONSISTENT WITH THE OVERALL POPULATION

COMPOSITE RESPONSE



	M1	M3	M6	M9	M12	M18
Seladelpar 10 mg n/m=	21/33	21/32	22/32	16/26	12/23	9/17

ALP RELATIVE CHANGE FROM BASELINE

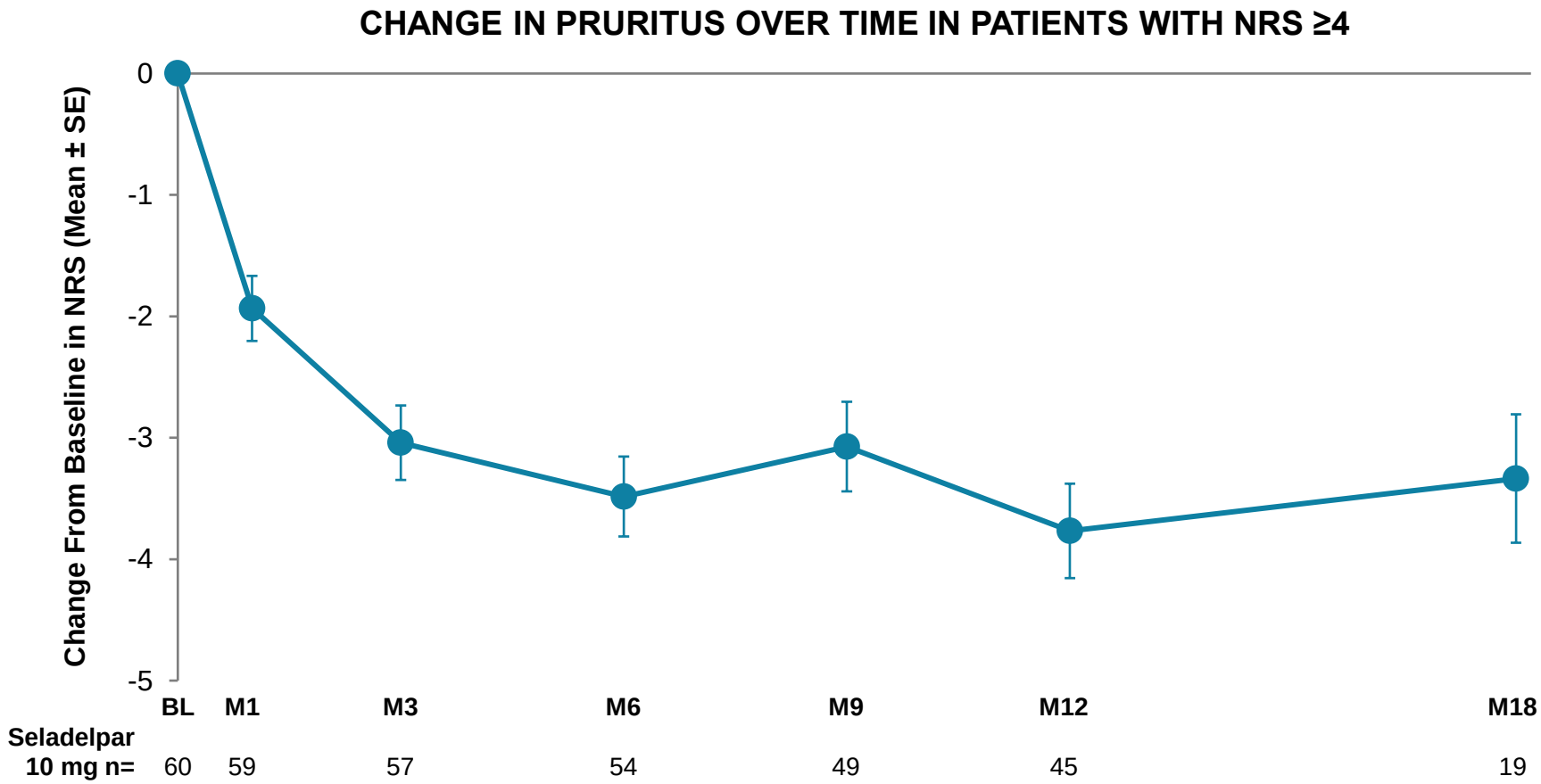


	BL	M1	M3	M6	M9	M12	M18
Seladelpar 10 mg n=	33	33	32	32	26	23	16

Safety was generally similar to the overall study population

n/m=number of responders/number of evaluable subjects.
Legacy studies include CB8025-21629, CB8025-31735, and CB8025-31731. CB8025-31731-RE is an ongoing study, and data are as of June 29, 2023. Data shown through Month 18.
*Composite response defined as ALP <1.67× ULN, ≥15% decrease in ALP, and TB ≤1× ULN. ITT analysis set.

CHANGE IN PRURITUS OVER TIME WAS RAPID AND DURABLE IN PATIENTS WITH NRS ≥4



Note: This is a snapshot (June 29, 2023) of an ongoing study.

Data are for legacy parent study group (CB8025-21629, CB8025-31735, CB8025-31731, and CB8025-21838). Time points with ≤5 subjects are not shown.

SERIOUS ADVERSE EVENTS, EVENTS LEADING TO DISCONTINUATION, AND LIVER- AND MUSCLE-RELATED EVENTS WERE UNCOMMON

Patient incidence	Legacy Patients (N=174) n (%)
Adverse Events	140 (80.5)
Serious Adverse Events	17 (9.8)
Grade 3 Adverse Events	20 (11.5)
Adverse Events Leading to Treatment Discontinuation	8 (4.6)
Liver-Related Adverse Events	11 (6.3)
Muscle-Related Adverse Events	12 (6.9)

Liver-related adverse events

- Clinical events were mild or moderate and did not lead to treatment discontinuation
- Lab-related events were generally mild or moderate and transient
  - 2 patients with increased blood bilirubin discontinued treatment

Muscle-related adverse events

- All events were mild/moderate
- Muscle spasms occurred in 5 patients without treatment discontinuations
- Myalgia occurred in 4 patients, with 1 transient CK elevation (<5× ULN) resolved without dose interruption or reduction

CK, creatine kinase.
Liver, muscle, renal, and pancreatic adverse events were identified by prespecified search strategy.

KEY TAKEAWAYS

Seladelpar is being developed as a potential second-line treatment for patients with PBC

Data from legacy patients in the ASSURE long-term extension study demonstrated:

- Durable effect on markers of cholestasis and liver injury for up to 2 years
- Sustained reduction in pruritus in patients with baseline NRS ≥4
- Seladelpar appears safe and well tolerated, including in patients with cirrhosis
- Results are consistent with the pivotal Phase 3 RESPONSE study

THANK YOU!

CymaBay gratefully acknowledges the study patients, investigators, and site staff who have made this and other seladelpar trials possible.

APPENDIX

DDW2024
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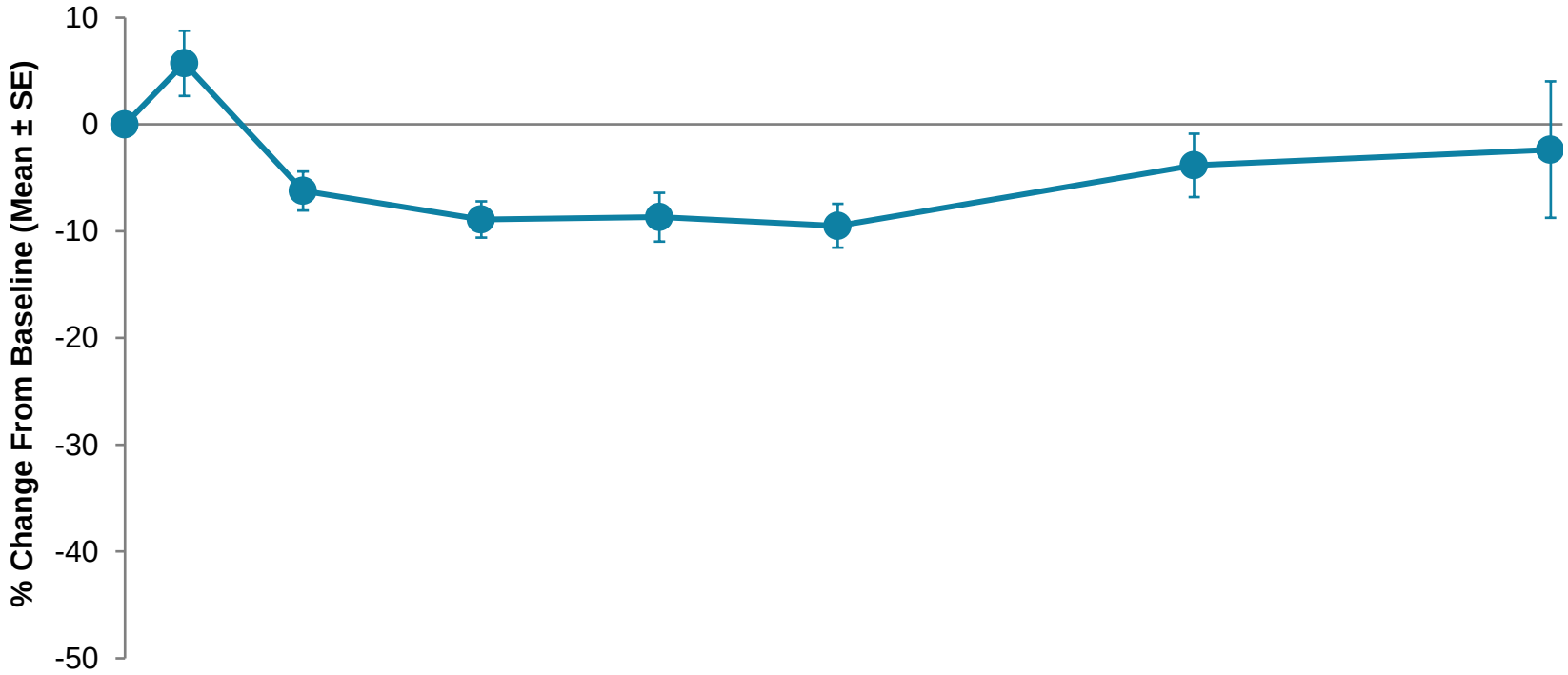
EXHIBIT DATES: MAY 19–21, 2024

PERCENT CHANGE IN AST LEVELS FROM BASELINE OVER TIME

Legacy and hepatic impairment study parent group*



	BL	M1	M3	M6	M9	M12	M18	M24
Seladelpar 10 mg n=	174	172	169	169	157	143	89	19

AST levels remained overall stable throughout the treatment period

ITT analysis set. n=number of evaluable subjects.
*Data are for legacy and parent study group (CB8025-21629, CB8025-31735, CB8025-31731, and CB8025-21838) as of June 29, 2023.

ASSURE STUDY CIRRHOSIS CRITERIA

A diagnosis of cirrhosis required a patient meeting one or more of the following criteria:

- **Historical liver biopsy** demonstrating cirrhosis (eg, Ludwig Stage 4 or Ishak Stage 5)
- **Current or prior history** of decompensated liver disease, including ascites, hepatic encephalopathy, esophageal varices, or other clinical conditions consistent with liver cirrhosis and/or portal hypertension
- **Liver stiffness** >16.9 kPa by FibroScan® at screening
- **Combination of platelets** <140×10^3/μL with the following:
  - Serum albumin <3.5 g/dL
  - INR >1.3 (not due to antithrombotic agent use)
  - TB >1.0× ULN
- **Presence of radiological evidence** of cirrhosis (nodular liver) with concurrent splenomegaly
- **Clinical determination** by the investigator

INR, international normalized ratio.

MOST COMMON ADVERSE EVENTS WERE SIMILAR TO THOSE OBSERVED ACROSS THE CLINICAL TRIAL PROGRAM

MOST COMMON ADVERSE EVENTS (≥5% OF PATIENTS)

Preferred Term	Legacy Patients (N=174) n (%)
Subjects With ≥1 Treatment-Emergent Adverse Event	140 (80.5)
COVID-19	36 (20.7)
Pruritus	20 (11.5)
Nasopharyngitis	15 (8.6)
Urinary Tract Infection	14 (8.0)
Nausea	14 (8.0)
Diarrhea	13 (7.5)
Fatigue	9 (5.2)

SERIOUS ADVERSE EVENTS BY PREFERRED TERM

Blood Bilirubin Increased	Hemorrhoids
Cartilage Injury	Leukocytosis
Cerebral Infarction	Nephrolithiasis
Chronic Myeloid Leukemia	Noncardiac Chest Pain
COVID-19 Pneumonia	Pancreatitis Acute
Essential Hypertension	Quadrantanopia
Femoral Neck Fracture	Radius Fracture
Groin Abscess	Rotator Cuff Syndrome
Hematuria	Sepsis
Hemoperitoneum	Urinary Tract Infection