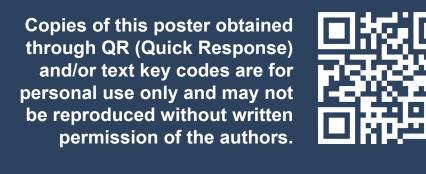
REAL

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Conclusions

- Despite available treatments, alkaline phosphatase (ALP) normalization is uncommon among individuals with primary biliary cholangitis (PBC)
- In this study, ALP normalization was associated with reduced mortality and improved clinical outcomes
- Given the benefits of ALP normalization in terms of reduced clinical burden and mortality, additional effective and well-tolerated treatments are needed for individuals with PBC

Plain Language Summary

- Primary biliary cholangitis is a long-term liver disease that gets worse over time and can have a significant impact on patients and their families
- This study evaluated the relationship between alkaline phosphatase levels and health outcomes
- This study found that alkaline phosphatase levels often remain elevated and that, when alkaline phosphatase levels are normal, patients have a lower risk of dying, needing a liver transplant, or experiencing severe liver damage, complications, or cirrhosis
- These findings highlight the need for more effective and safe treatments for people with primary biliary cholangitis

References: 1. Lleo A, et al. Lancet. 2020;396:1915-26. 2. European Association for the Study of the Liver. J Hepatol. 2017;67:145-72. **3.** Lindor KD, et al. *Hepatology*. 2019;69:394-419. **4.** Hirschfield GM, et al. *N Engl J Med*. 2024;390:783-94. **5.** Lammers WJ, et al. *Gastroenterology*. 2014;147:1338-49.e5.

Acknowledgments: We gratefully acknowledge the study participants, investigators, site staff, and the REAL team. This analysis was sponsored by CymaBay Therapeutics, a Gilead Sciences, Inc., company. Medical writing and editorial assistance were provided by Stratevi and Ellie Manca, MPH, and Allison Yankey, PhD, of Red Nucleus, and were funded by Gilead Sciences, Inc.

Disclosures: KVK declares research support from CymaBay Therapeutics; grants and/or contracts from 89Bio; Genfit; Gilead Sciences, Inc.; GSK; Hanmi Pharmaceuticals; HighTide Therapeutics; Intercept Pharmaceuticals; Madrigal Pharmaceuticals; Mirum Pharmaceuticals; NGM Biopharmaceuticals; Pfizer; Pliant Therapeutics; and Viking Therapeutics; royalties/ licenses from UpToDate; consulting fees from 89Bio; Calliditas Therapeutics; CymaBay Therapeutics; Genfit; Gilead Sciences, Inc.; Inipharm; Intercept Pharmaceuticals; Madrigal Pharmaceuticals; Mirum Pharmaceuticals; NGM Biopharmaceuticals; and Pliant Therapeutics; payment/honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from AbbVie; Gilead Sciences, Inc.; and Intercept Pharmaceuticals; payment for expert testimony from the Department of Justice; participation in a data safety monitoring board or advisory board for CTI BioPharma, Durect, and Labcorp; stock or stock options for Inipharm; and receipt of equipment, materials, drugs, medical writing, gifts, or other services from Sonic Incytes. JI and CFMP are employees of CymaBay Therapeutics, a Gilead Sciences, Inc., company. YP, MS, and DI are employees of Stratevi, a research consulting firm that received funding from Gilead Sciences, Inc., to conduct this study.

Introduction

- Primary biliary cholangitis (PBC) is a progressive chronic inflammatory liver disease that imposes a significant clinical burden^{1,2}
- Ursodeoxycholic acid (UDCA) is a first-line treatment for PBC, followed by second-line treatments, including obeticholic acid (OCA), for patients with inadequate response or intolerance to UDCA^{2,3}
- Treatment efficacy is demonstrated through surrogate biochemical markers, including alkaline phosphatase (ALP)
- ALP normalization is associated with improved liver-related clinical outcomes^{2,4,5}
- However, real-world evidence of treatment effectiveness on ALP normalization and the association with clinical outcomes remains limited

Objectives

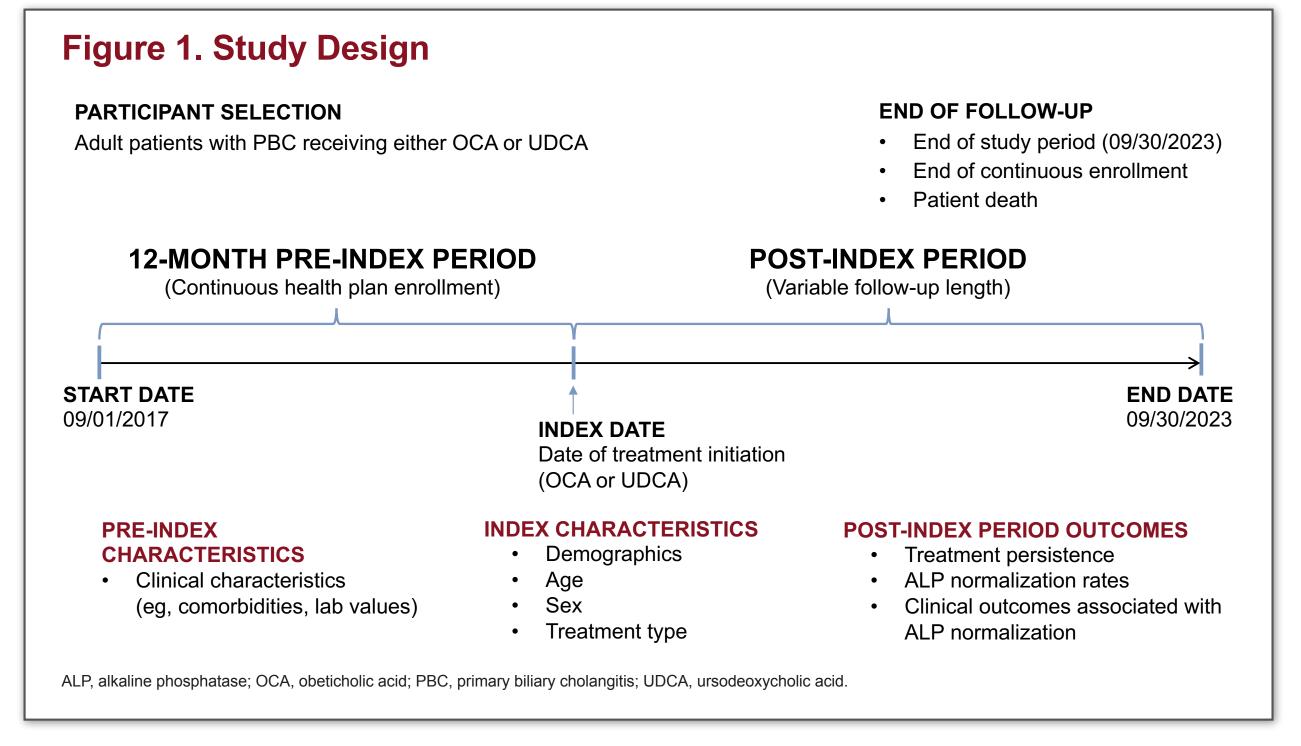
- Using a large, national, and geographically, demographically, and clinically diverse sample from the US, this study:
- Evaluated ALP normalization rates associated with UDCA, OCA, or concurrent UDCA/OCA
- Assessed the association between normal ALP and clinical outcomes

Methods

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Data and Statistical Analyses

- An intent-to-treat analysis was conducted using Komodo's Healthcare Map claims linked with Quest Diagnostics laboratory data of individuals with PBC (Figure 1)
- Three cohorts were created based on the initial treatment received after a 12-month baseline period
- UDCA monotherapy (no prior UDCA treatment during the baseline period)

— OCA (those treated with OCA monotherapy at baseline with or without prior UDCA)

- Concurrent UDCA/OCA (treated with both UDCA and OCA or had prior UDCA and added OCA to their treatment, with a required overlap of ≥60 days to ensure stable concurrency)
- Inclusion criteria
- Aged ≥18 years as of the start of treatment
- Continuous enrollment in a health plan and a diagnosis of PBC (ICD-10-CM code K74.3) in the 12 months (baseline period) prior to or on the treatment start (index) date
- ALP normalization rates were evaluated using the most recent measurement at or prior to the 24-month mark, but ≥6 months from the index date
- Associations between normal ALP at the first ALP test months from the index date and subsequent clinical outcomes were evaluated using multivariable Cox proportional hazard models

Results

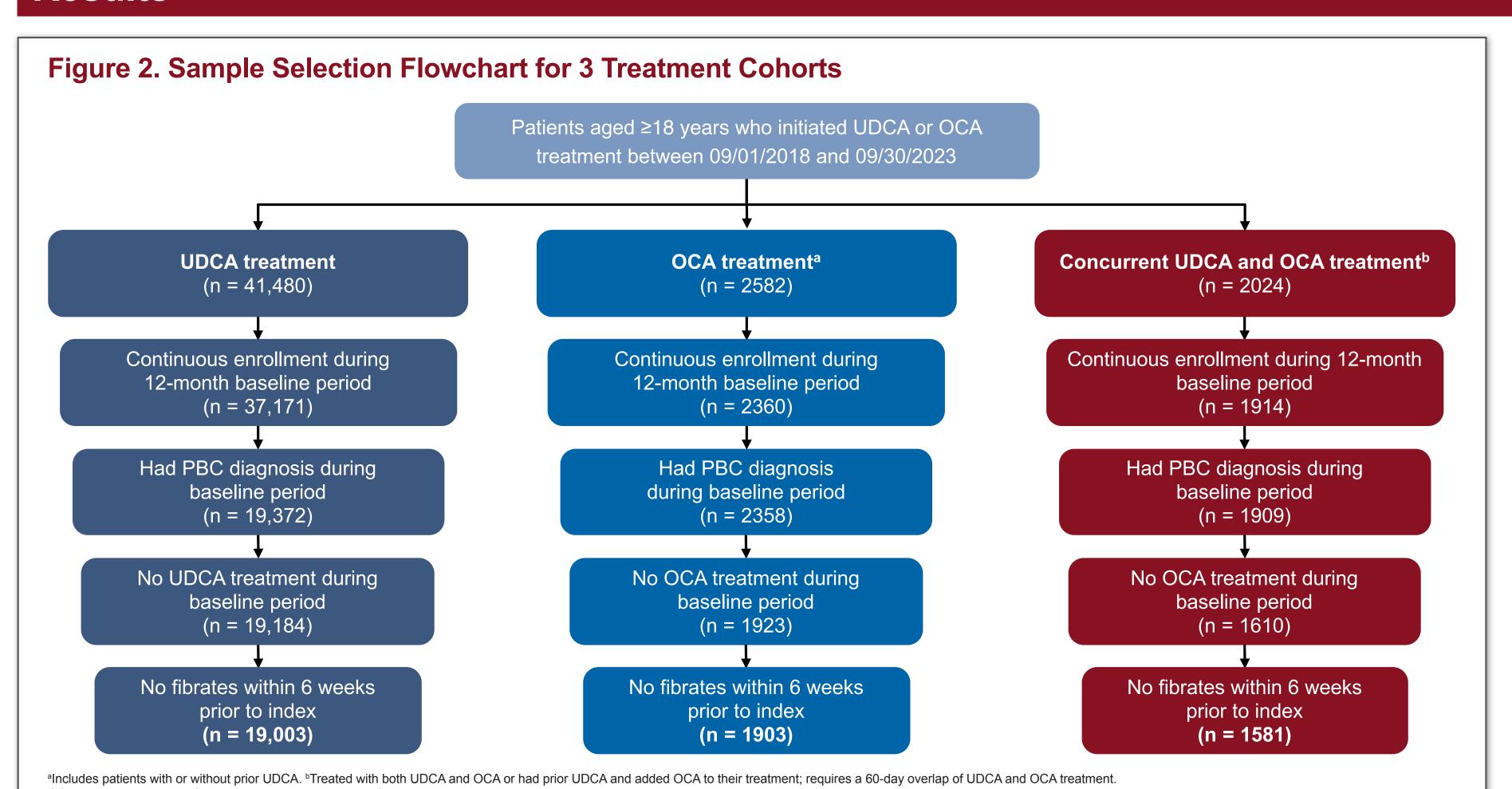


Table 1. Demographic and Clinical Characteristics at Baseline

Baseline Characteristics	(n = 19,003)	(n = 1903)	P-value*	(n = 1581)	P-value ^s	(n = 22,487)
Age						
Mean (SD)	62.5 (13.2)	59.9 (11.7)	<.001	59.0 (11.0)	<.001	62.1 (13.0)
Payer type, n (%)						
Commercial	6644 (35.0)	767 (40.3)	N/A	804 (50.9)	N/A	8215 (36.5)
Medicaid	2019 (10.6)	221 (11.6)	N/A	166 (10.5)	N/A	2406 (10.7)
Medicare	9710 (51.1)	841 (44.2)	N/A	565 (35.7)	N/A	11,116 (49.4)
Unknown	630 (3.3)	74 (3.9)	<.001	46 (2.9)	<.001	750 (3.3)
Female, n (%)	16,369 (86.1)	1742 (91.5)	<.001	1411 (89.2)	.060	19,522 (86.8)
Race/ethnicity, n (%)						
Asian or Pacific Islander	584 (3.1)	40 (2.1)	<.001	46 (2.9)	<.001	670 (3.0)
Black or African American	1083 (5.7)	130 (6.8)	N/A	70 (4.4)	N/A	1283 (5.7)
Hispanic or Latino	2606 (13.7)	298 (15.7)	N/A	206 (13.0)	N/A	3110 (13.8)
Other	495 (2.6)	55 (2.9)	N/A	50 (3.2)	N/A	600 (2.7)
Unknown	3976 (20.9)	431 (22.6)	N/A	424 (26.8)	N/A	4831 (21.5)
White	10,259 (54.0)	949 (49.9)	N/A	785 (49.7)	N/A	11,993 (53.3)
Charlson comorbidity index						
Mean (SD)	4.89 (3.10)	4.23 (2.62)	<.001	3.91 (2.48)	<.001	4.76 (3.04)
Other comorbidities, n (%)						
Pruritus diagnosis or any pruritus treatment	2643 (13.9)	397 (20.9)	<.001	340 (21.5)	<.001	3380 (15.0)
Cirrhosis	5402 (28.4)	583 (30.6)	.045	463 (29.3)	.486	6448 (28.7)
ALP/bilirubin at index, n (%)						
Normal ALP ^b (≤1 × ULN)	1198 (42.4)	54 (17.5)	N/A	27 (12.3)	N/A	1279 (38.1)
Abnormal ALP ^b (>1 × ULN)	1629 (57.6)	254 (82.5)	<.001	192 (87.7)	<.001	2075 (61.9)
Abnormal bilirubin ^c (>1 × ULN)	415 (14.6)	53 (17.0)	.303	19 (8.4)	.014	487 (14.4)

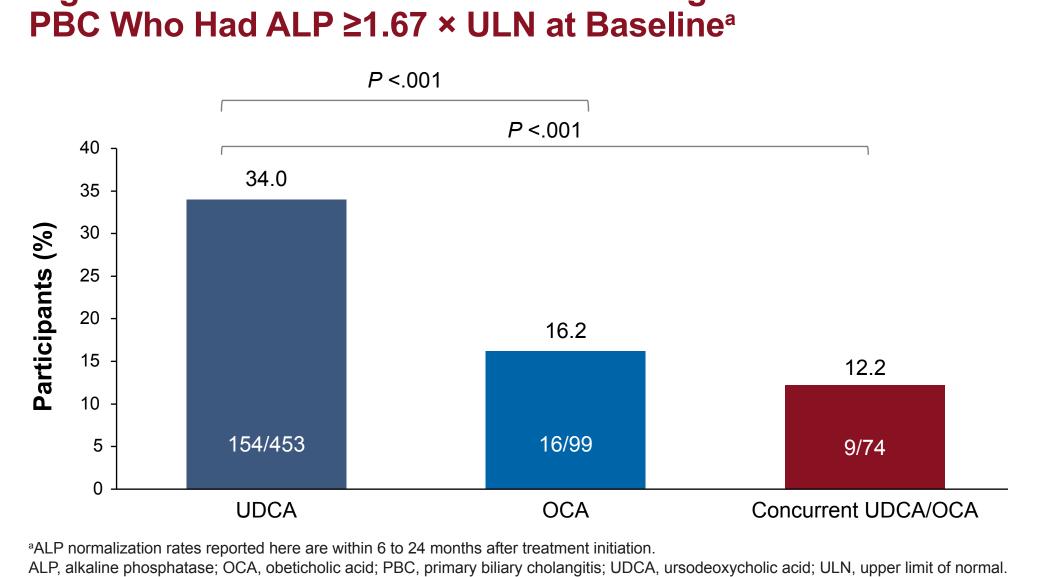
Concurrent UDCA & OCA

• A total of 22,487 individuals initiating UDCA monotherapy (n = 19,003), OCA (n = 1903), or concurrent UDCA/OCA therapy (n = 1581) were identified (Figure 2)

^aCompared with UDCA cohort. ^bn = 2827 for UDCA, n = 308 for OCA, and n = 219 for concurrent UDCA and OCA. ^cn = 2823 for UDCA, n = 312 for OCA, and n = 225 for concurrent UDCA and OCA.

• Study participants' average age was 62 years, 87% were female, and their average Charlson Comorbidity Index score was 4.76 (**Table 1**)

Figure 3. ALP Normalization Rates Among Individuals With



 Among participants with baseline ALP levels ≥1.67 × ULN (n = 626), ALP normalization rates remained low primarily in the OCA and concurrent treatment groups in the 6- to 24-month follow-up (Figure 3)

— ALP normalization rates were 34.0%, 16.2%, and 12.2% in the UDCA, OCA, and concurrent UDCA/OCA groups, respectively



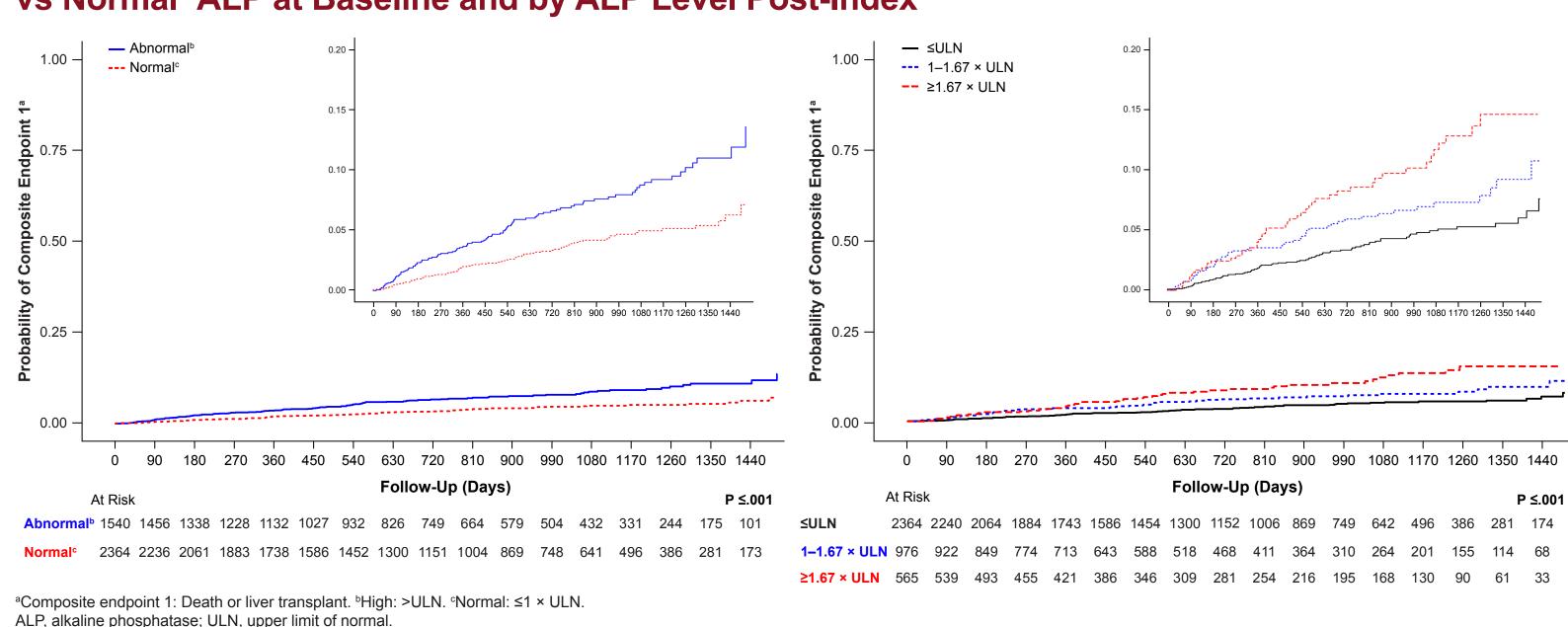


Table 2. Association Between Having Normal ALP Levels at First ALP Test After 6 Months Following **Treatment Initiation and Subsequent Clinical Outcomes**

Outcome	Hazard Ratio (95% CI)ª	<i>P</i> -Value		
Death	0.59 (0.42–0.83)	.003		
Liver transplant	0.30 (0.16–0.55)	<.001		
Cirrhosis	0.65 (0.53–0.80)	<.001		
Decompensated cirrhosis	0.36 (0.26–0.50)	<.001		
Ascites requiring treatment	0.22 (0.14–0.34)	<.001		
Hospitalization ^b	0.22 (0.06–0.86)	.029		
Composite endpoint 1 ^c	0.51 (0.37–0.50)	<.001		
Composite endpoint 2 ^d	0.44 (0.33–0.59)	<.001		

 ALP normalization was significantly associated with a reduced risk for mortality, incident liver transplant, cirrhosis, decompensated cirrhosis, ascites requiring treatment, hospitalization, and composite clinical endpoints (Figure 4, Table 2)

^dComposite endpoint 2: Death, liver transplant, hospitalization (with a primary diagnosis of esophageal/gastric variceal bleeding, hepatic encephalopathy, or spontaneous bacterial peritonitis), or ascites requiring treatment.

Limitations

- Only a subset of participants with PBC had results from ALP tests, which reduced statistical power and may have led to bias
- As in all observational studies, there was a potential for bias due to unobserved confounding, missing data, and inaccurate data coding (eg, patients with higher ALP may be more likely to have advanced disease)
- The study was based on an intent-to-treat approach and did not evaluate treatment switching patterns and how they may affect ALP normalization rates