

The International PBC Summit  
c/o The PBC Foundation  
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Via email

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**Subject: Patients with PBC request your collaboration to establish a pathway to full approval of second-line therapies without long-term placebo controlled clinical trials**

Dear Doctors Sepodes, Musaus, Anania, Sharma, Kondowe, Hystad, and Trachsel

The International PBC Summit requests your urgent collaboration to find a solution to the conversion of Conditional / Accelerated Approval to traditional / full approval for second-line treatments for Primary Biliary Cholangitis (PBC). The International PBC Summit is a patient-led consortium of people interested in improving life for patients with PBC and consists of patients, patient advocacy groups, academic researchers, healthcare professionals, and industry, from 6 continents, and includes participants from Canada, the European Union, the United Kingdom and the United States. More details are provided in appendix 1.

For background, PBC is a life-long autoimmune cholestatic liver disease and unchecked, can lead to progressive fibrosis, cirrhosis, liver transplantation, and premature death. PBC mainly

affects women aged 40–70 years with global incidence rates between 0.84 and 2.75 patients per 100,000. Even in early stages of the disease, PBC is very burdensome in many but not all patients. Patients with PBC self-report a lower health-related quality of life (HRQoL) compared with control populations, with widespread effects on mental, social, emotional and physical health. Central and peripheral fatigue and pruritus are the most debilitating symptoms and significantly impair quality of life and daily functioning. PBC, as a rare disease, is disproportionally over-represented in liver transplant figures, particularly due to unmet clinical need. Living with PBC causes a greater burden for patients and our families / caregivers than living with other autoimmune liver diseases. As the disease progresses to liver cirrhosis and then decompensation, patients struggle with poor quality of life, an immense symptom burden and psychological stress associated with their worsened prognosis. (literature references provided in appendix 3)

At the International PBC Summit 2026 in April, we identified the need to engage with health authorities to agree on a mutually acceptable path forward.

We, patients with PBC and our teams of healthcare professionals and patient organizations, understand that regulatory Agencies consider randomized, placebo-controlled interventional clinical trials the gold standard evidence and we understand that trials incorporating real world data will leave a level of uncertainty because, despite ever-improving statistical methodology, the effects detected will always include some level of confounding due to the combined assessment of treatment decision and treatment effect. We also understand that the Agency has used regulatory flexibility to allow such data in regulatory decisions for other, more rare, orphan indications.

As a community, it is our considered opinion, based on the evidence described in Section 1.1 of the appended EASL-AASLD Delphi Consensus Statement, that the clinical benefits of alkaline phosphatase (ALP) lowering therapy for PBC have been established adequately. We accept the residual uncertainty of confounding in these studies. We are unwilling to accept living with prolonged periods of high levels of ALP and / or bilirubin because of the documented and real risk of our PBC progressing to liver decompensation, transplant and death while we are not receiving effective second-line treatment in the placebo arm of a long-term study. We believe the regulatory agencies and companies can explain the evidence and its limitations adequately in labeling, so we, patients and our healthcare providers, can jointly make the right treatment decisions.

In our lives, we never observe the effects of a medication in isolation; we always live the effects of the combination of the decision to take a medication and the effects of it. In that sense, the effects observed in real world studies will be a more accurate reflection of our reality. This, of course, represents both an opportunity and a challenge. However, the status quo of placebo-arm confirmatory trials for treatment of PBC are unattainable, and leave us only with challenges, most of which are unassailable.

We request that the Agencies work with patients, patient advocates, and our academic and company partners, to agree to non-placebo-controlled study designs for confirmatory trials for PBC as recommended in Section 2 of the appended Consensus Statement. These designs will enable us, as patients, to participate in these studies, and we believe they will allow you to take regulatory decisions based on their results.

Respectfully, we ask that you meet with selected representatives of the patient community to take this matter forward. Thank you very much for your attention in this matter. We are available to clarify or answer any questions you may have.

With kind regards,

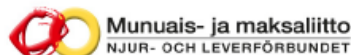
Patient advocacy group signatories

Contact: [robert@pbcfoundation.international](mailto:robert@pbcfoundation.international)

Asociación Albi-  
España  
Italy AMAF APS  
Australia Liver Foundation  
Botswana Organisation for  
Rare Diseases (BORDIS)  
Casa Hunter  
CBP Portugal  
Croatian Rare Liver Foundation  
Deutsche Leberhilfe e.V.

Dutch Liver Patients  
Association (NLV)  
The Finnish Kidney and  
Liver Association  
Forening for Autoimmune  
Leversykdommer (FAL)  
Fundacion Sayani  
Hepactive  
Hepatitis Hilfe  
Hetz

Leverforeningen Denmark  
Liver Patients International  
Mijnlever  
PBC Föreningen Sverige  
PBC Foundation  
SLAP  
Swiss HePa - Swiss Liver  
Patients Association  
Friends of PBC Foundation

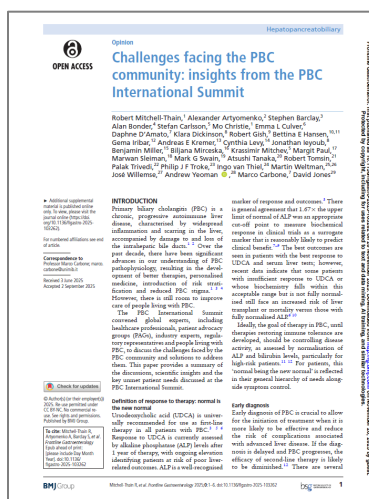


## Appendix 1 International PBC Summit

The International PBC Summit is an international annual event, recognised for its unique approach, which brings together all stakeholders in the PBC community to identify unmet needs and enable meaningful solutions. It has a deliberately bold and unconventional approach that gives more power to those on the floor than those on the stage. It is a uniquely collaborative and interactive event.

At the Summit every attendee comes as an equal: no surnames, positions, honorifics, or even companies. We come together as experts trying to bring our collective knowledge to the room to improve the lives of those affected by PBC. At the Summit, the power doesn't sit at the podium, but on the floor itself, as the room decides where to go next and which topics to work on throughout the year. Anybody can present their thoughts or ideas at the podium, or even in the group discussions, where we can discuss the merit together of each idea raised. There is an itinerary, but the agenda is set by Summit attendees throughout the course of the proceedings.

The appended paper entitled “Challenges facing the PBC community: insights from the PBC International Summit” provides a summary of the discussions, scientific insights and the key unmet patient needs discussed at the 2025 PBC International Summit.



# Appendix 2 EASL-AASLD Delphi Consensus Statement

## a. Existing evidence (Section 1.1)

## b. Alternative study designs without long-term placebo (Section 2)

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| <p><b>1.1. What is the role of liver biochemistry in a biomarker in PBC clinical trials?</b></p> <p>During liver biochemistry, ALP and total bilirubin are the most commonly studied. ALP levels are directly related to disease progression<sup>1,2,3</sup> and subsequent mortality in ALP and total bilirubin. ALP levels are directly related to disease progression, LT, and death in real-world retrospective cohorts. These associations have been proven in several clinical trials, including clinical trials in patients with ALP and total bilirubin as primary endpoints. However, ALP and total bilirubin are not directly related to liver disease progression, although they have not been directly related to survival endpoints<sup>4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225,226,227,228,229,230,231,232,233,234,235,236,237,238,239,240,241,242,243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261,262,263,264,265,266,267,268,269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284,285,286,287,288,289,290,291,292,293,294,295,296,297,298,299,300,301,302,303,304,305,306,307,308,309,310,311,312,313,314,315,316,317,318,319,320,321,322,323,324,325,326,327,328,329,330,331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547,548,549,550,551,552,553,554,555,556,557,558,559,560,561,562,563,564,565,566,567,568,569,570,571,572,573,574,575,576,577,578,579,580,581,582,583,584,585,586,587,588,589,590,591,592,593,594,595,596,597,598,599,600,601,602,603,604,605,606,607,608,609,610,611,612,613,614,615,616,617,618,619,620,621,622,623,624,625,626,627,628,629,630,631,632,633,634,635,636,637,638,639,640,641,642,643,644,645,646,647,648,649,650,651,652,653,654,655,656,657,658,659,660,661,662,663,664,665,666,667,668,669,670,671,672,673,674,675,676,677,678,679,680,681,682,683,684,685,686,687,688,689,690,691,692,693,694,695,696,697,698,699,700,701,702,703,704,705,706,707,708,709,710,711,712,713,714,715,716,717,718,719,720,721,722,723,724,725,726,727,728,729,730,731,732,733,734,735,736,737,738,739,740,741,742,743,744,745,746,747,748,749,750,751,752,753,754,755,756,757,758,759,760,761,762,763,764,765,766,767,768,769,770,771,772,773,774,775,776,777,778,779,780,781,782,783,784,785,786,787,788,789,790,791,792,793,794,795,796,797,798,799,800,801,802,803,804,805,806,807,808,809,810,811,812,813,814,815,816,817,818,819,820,821,822,823,824,825,826,827,828,829,830,831,832,833,834,835,836,837,838,839,840,841,842,843,844,845,846,847,848,849,850,851,852,853,854,855,856,857,858,859,860,861,862,863,864,865,866,867,868,869,870,871,872,873,874,875,876,877,878,879,880,881,882,883,884,885,886,887,888,889,890,891,892,893,894,895,896,897,898,899,900,901,902,903,904,905,906,907,908,909,910,911,912,913,914,915,916,917,918,919,920,921,922,923,924,925,926,927,928,929,930,931,932,933,934,935,936,937,938,939,940,941,942,943,944,945,946,947,948,949,950,951,952,953,954,955,956,957,958,959,960,961,962,963,964,965,966,967,968,969,970,971,972,973,974,975,976,977,978,979,980,981,982,983,984,985,986,987,988,989,990,991,992,993,994,995,996,997,998,999,1000,1001,1002,1003,1004,1005,1006,1007,1008,1009,1010,1011,1012,1013,1014,1015,1016,1017,1018,1019,1020,1021,1022,1023,1024,1025,1026,1027,1028,1029,1030,1031,1032,1033,1034,1035,1036,1037,1038,1039,1040,1041,1042,1043,1044,1045,1046,1047,1048,1049,1050,1051,1052,1053,1054,1055,1056,1057,1058,1059,1060,1061,1062,1063,1064,1065,1066,1067,1068,1069,1070,1071,1072,1073,1074,1075,1076,1077,1078,1079,1080,1081,1082,1083,1084,1085,1086,1087,1088,1089,1090,1091,1092,1093,1094,1095,1096,1097,1098,1099,1100,1101,1102,1103,1104,1105,1106,1107,1108,1109,1110,1111,1112,1113,1114,1115,1116,1117,1118,1119,1120,1121,1122,1123,1124,1125,1126,1127,1128,1129,1130,1131,1132,1133,1134,1135,1136,1137,1138,1139,1140,1141,1142,1143,1144,1145,1146,1147,1148,1149,1150,1151,1152,1153,1154,1155,1156,1157,1158,1159,1160,1161,1162,1163,1164,1165,1166,1167,1168,1169,1170,1171,1172,1173,1174,1175,1176,1177,1178,1179,1180,1181,1182,1183,1184,1185,1186,1187,1188,1189,1190,1191,1192,1193,1194,1195,1196,1197,1198,1199,1200,1201,1202,1203,1204,1205,1206,1207,1208,1209,1210,1211,1212,1213,1214,1215,1216,1217,1218,1219,1220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,2221,2222,2223,2224,2225,2226,2227,2228,2229,2230,2231,2232,2233,2234,2235,2236,2237,2238,2239,2240,2241,2242,2243,2244,2245,2246,2247,2248,2249,2250,2251,2252,2253,2254,2255,2256,2257,2258,2259,2260,2261,2262,2263,2264,2265,2266,2267,2268,2269,2270,2271,2272,2273,2274,2275,2276,2277,2278,2279,2280,2281,2282,2283,2284,2285,2286,2287,2288,2289,2290,2291,2292,2293,2294,2295,2296,2297,2298,2299,2300,2301,2302,2303,2304,2305,2306,2307,2308,2309,2310,2311,2312,2313,2314,2315,2316,2317,2318,2319,2320,2321,2322,2323,2324,2325,2326,2327,2328,2329,2330,2331,2332,2333,2334,2335,2336,2337,2338,2339,2340,2341,2342,2343,2344,2345,2346,2347,2348,2349,2350,2351,2352,2353,2354,2355,2356,2357,2358,2359,2360,2361,2362,2363,2364,2365,2366,2367,2368,2369,2370,2371,2372,2373,2374,2375,2376,2377,2378,2379,2380,2381,2382,2383,2384,2385,2386,2387,2388,2389,2390,2391,2392,2393,2394,2395,2396,2397,2398,2399,2400,2401,2402,2403,2404,2405,2406,2407,2408,2409,2410,2411,2412,2413,2414,2415,2416,2417,2418,2419,2420,2421,2422,2423,2424,2425,2426,2427,2428,2429,2430,2431,2432,2433,2434,2435,2436,2437,2438,2439,2440,2441,2442,2443,2444,2445,2446,2447,2448,2449,2450,2451,2452,2453,2454,2455,2456,2457,2458,2459,2460,2461,2462,2463,2464,2465,2466,2467,2468,2469,2470,2471,2472,2473,2474,2475,2476,2477,2478,2479,2480,2481,2482,2483,2484,2485,2486,2487,2488,2489,2490,2491,2492,2493,2494,2495,2496,2497,2498,2499,2500,2501,2502,2503,2504,2505,2506,2507,2508,2509,2510,2511,2512,2513,2514,2515,2516,2517,2518,2519,2520,2521,2522,2523,2524,2525,2526,2527,2528,2529,2530,2531,2532,2533,2534,2535,2536,2537,2538,2539,2540,2541,2542,2543,2544,2545,2546,2547,2548,2549,2550,2551,2552,2553,2554,2555,2556,2557,2558,2559,2560,2561,2562,2563,2564,2565,2566,2567,2568,2569,2570,2571,2572,2573,2574,2575,2576,2577,2578,2579,2580,2581,2582,2583,2584,2585,2586,2587,2588,2589,2590,2591,2592,2593,2594,2595,2596,2597,2598,2599,2600,2601,2602,2603,2604,2605,2606,2607,2608,2609,2610,2611,2612,2613,2614,2615,2616,2617,2618,2619,2620,2621,2622,2623,2624,2625</sup></p> 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