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SPECIAL ARTICLE

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Primary biliary cholangitis drug evaluation and regulatory approval: Where do we go from here?

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Abstract

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease. The management landscape was transformed 20 years ago with the advent of ursodeoxycholic acid. Up to 40% of patients do not, however, respond adequately to ursodeoxycholic acid and therefore still remain at risk of disease progression to cirrhosis. The introduction of obeticholic acid as a second-line therapy for patients failing ursodeoxycholic acid has improved outcomes for patients with PBC. There remains, however, a need for better treatment for patients at higher risk. The greatest threat facing our efforts to improve treatment in PBC is, paradoxically, the regulatory approval model providing conditional marketing authorization for new drugs based on biochemical markers on the condition that long-term, randomized placebo-controlled outcome trials are performed to confirm efficacy. As demonstrated by the COBALT confirmatory study with obeticholic acid, it is difficult to retain patients in the required follow-on confirmatory placebo-controlled PBC outcome trials when a licensed drug is commercially available. New PBC therapies in development, such as the peroxisome proliferator–activated receptor agonists, face even greater challenges in demonstrating outcome benefit through randomized placebo-controlled studies once following conditional marketing authorization, as there will be even more treatment options available. A recently published EMA Reflection Paper provides some guidance on the regulatory pathway to full approval but fails to recognize the importance of real-world data in providing evidence of outcome benefit in rare diseases. Here we explore the impact of the EMA reflection paper on PBC therapy and offer pragmatic solutions for generating evidence of long-term outcomes through real-world data collection.

WHERE WE ARE NOW

Primary biliary cholangitis (PBC) is a progressive chronic cholestatic liver disease. Predominantly affecting women, PBC can have a significant impact on patients through progression to cirrhosis with its associated complications and risk of death, and through the development of chronic and often life-altering symptoms including itch and fatigue.[1] Other implications include a decreased quality of life and stigma and discrimination.[2] In the early days of liver transplantation, despite being a rare disease, PBC was among the commonest indications for the procedure, reflecting the scale of its impact and lack of effective treatments.[3] However, the landscape is now very different with improved survival and the vast majority of patients not requiring transplantation (living and dying "with PBC" rather than "from PBC").[4] This change has come about through a combination of

Abbreviations: ALP, alkaline phosphatase; FXR, farnesoid X receptor; OCA, obeticholic acid; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator–activated receptor; RWE, real-world evidence; UDCA, ursodeoxycholic acid.

better awareness among patients and clinicians, increasing access to diagnostic tests, and, most notably, through the advent of effective treatment regimens and early prescription.

Also integral to the improvement in outcomes has been the move away from the traditional hepatology model of intervening to reduce transplant or death risk once advanced disease has developed, to a disease modification model of early intervention to prevent progression in the first place and improve quality of life.[1,5] Inherent in this changed thinking is that transplant is not a panacea for patients (there are challenges around access, especially for women with PBC and patients in minority groups, poor organ quality with long-term sequelae, and, crucially, quality of life after transplant[6]) and it is reasonable to aspire to avoid it if at all possible. This changed treatment model was a key factor in the name change from primary biliary cirrhosis to PBC.[7] Moving to the early diagnosis/early intervention model has, however, contributed significantly to the impasse in therapy development that inspired this white paper. We need to address the conundrum of how to demonstrate improved outcomes that may only be seen many years down the line in response to early therapy intervention, in a way that is acceptable to both patients and regulators. The danger that the PBC community faces is the need to demonstrate that therapies improve survival drives us to evaluate them in advanced disease (the only group of patients in whom a sufficient number of endpoint events would be seen within a feasible trial timeframe). At best this approach forces us to go back to the old, later-stage therapy model, potentially missing out on the maximum benefits of therapies that modify the whole disease course. At worst it means that we can't show that any therapy "works," leading us to potentially lose valuable treatment options.

PBC is now treated using a fully stratified approach, incorporated into routine clinical practice.[1,5] The goals of life-long therapy are the prevention of disease progression and the amelioration of disease-associated symptoms. The first-line treatment for all patients is with the hydrophilic bile acid ursodeoxycholic acid (UDCA) at a therapeutic dose of 13–15 mg/kg/d.[8] Patients showing an inadequate response are recommended to receive add-on second-line therapy. UDCA is safe but of relatively limited efficacy in people with more aggressive disease.[9,10] The challenges that we now face in relation to deriving the key evidence regarding the efficacy of second-line therapies in PBC were, in fact, presaged by exactly the same challenges faced with UDCA. Whereas UDCA was found, from the very outset, to significantly improve liver biochemical tests such as alkaline phosphatase (ALP), benefit in terms of death or transplant was much more limited, and nonexistent for how UDCA is currently used in normal practice (ie, early use to change the long-term disease trajectory), due to lack of informative data from randomized placebo-controlled trials. This led to a debate, over many years, as to whether UDCA actually "worked" in PBC. Indeed, there are some who suggest that its benefit is still unproven.[11] Why, in light of this uncertainty, is the use of UDCA in PBC recommended universally? The answer is that real-world clinical experience, collated in the form of extensive real-world evidence (RWE) studies has shown, beyond reasonable doubt, that it is both safe and effective in the majority of patients.[12–15]

A key step in the evolution of PBC treatment was the recognition that a significant minority of patients had an inadequate response to UDCA and were at an increased risk of disease progression and death or need for transplant. To identify and address this enhanced risk group, response to UDCA is assessed after a year of therapy,[9,10,13] and in those showing inadequate response, second-line therapy is introduced. UDCA response is assessed in clinical practice (as it has been in second-line therapy trials to date) by levels of blood biochemistry markers such as ALP, bilirubin (including indirect bilirubin), and transaminases; markers that have been strongly associated with risk of disease progression in RWE studies.[12] The options for second-line therapy are the first-in-class farnesoid X receptor (FXR) agonist obeticholic acid (OCA; licensed and labeled for this indication[16]), the peroxisome proliferator–activated receptor (PPAR) agonist bezafibrate (licensed but not labeled for this indication,[17] with fenofibrate replacing it in some jurisdictions[18]), the experimental approach of the combination of OCA and bezafibrate,[19] and the alternative PPAR agonists with different subtype specificity (elafibranor and seladelpar[20,21]) currently in clinical development. As is the case for UDCA, RWE evidence studies suggest that the improvement in ALP seen with OCA and bezafibrate is associated with improvement in transplant-free survival. Assessment of the need for second-line therapy due to UDCA under-response and the response to subsequent second-line therapy is assessed in routine practice as above. Elevation of ALP is strongly associated with a worse prognosis in PBC, and improvement with both UDCA and OCA has been associated with improved prognosis in large-scale cohort studies.[12,22,23]

WHERE WE NEED TO GO

Although the advent of the stratified treatment model has led to significant improvement in prognosis for patients with PBC (as demonstrated by RWE[22,23]), there remain areas of important unmet need:

(1) Ensuring that all patients who would benefit from the stratified approach get access to appropriate management and treatment.
(2) Understanding which treatment option might be best for which patient and supporting patients and clinicians in making these decisions.
(3) Understanding how we can more effectively treat the symptoms of PBC and improve quality of life.
(4) Creating an effective pathway for the development and approval of new medications (for both liver disease progression/control and symptom management) so that scientific advance and therapy development translates into patient benefit.

In terms of which treatments to use, uncertainty reflects a lack of data (especially head-to-head comparisons) and the rapid emergence of a number of options. Comparison of the outcomes of individual single-agent placebo-controlled trials in terms of ALP response can be complicated by differences in the entry criteria used (Table 1A). In simple terms, recruiting patients with lesser degrees of ALP elevation means that biochemical response criteria defined in terms of absolute values will be easier to achieve, but at the expense of relevance to the patients who are more badly affected; especially the very high ALP level younger patients who most need effective treatment.[13] Focus on just ALP can also lead to important, if subtle, effects that need to be understood better. FXR agonists may transcriptionally upregulate ALP,[27,28] masking some of their anticholestatic effects, while PPAR agonists have been suggested to downregulate ALP potentially leading to the converse, namely overestimation of anticholestatic actions.[29] Furthermore, there are differential effects on alanine aminotransferase, with FXR agonists giving a seemingly greater reduction than bezafibrate.[30] This is of importance due to the emerging link between alanine aminotransferase elevation and more aggressive forms of PBC, potentially through the process of interface hepatitis.[10,13] There are also important differences between the treatment types with regard to adverse effects. FXR agonists as a class can worsen PBC itch.[16] Although often manageable through dose adaptation and use of antipruritic therapies, the itch risk can lead to clinician avoidance and patient reticence especially in patients who are currently symptomatic or those with previous difficult-to-control itch. All PPAR agonists appear to improve itch (and certainly not worsen it).[31] They do, however, carry the risk of renal dysfunction[32]; a risk that is not seen with FXR agonists. The renal risk can be addressed in some patients with dose and formulation changes according to eGFR. There has also been concern about the potential for OCA to cause decompensation when used in advanced cirrhosis leading to prescribing restrictions.[33]. There are, as yet, only limited data on the long-term safety of PPAR agonists in PBC so it is unclear whether the same decompensation risk in patients with advanced PBC is present. Data on fenofibrate use in patients with cirrhosis suggesting worsening of bilirubin levels raises concerns that a similar effect may occur; however, further long-term safety data for fibrates are needed.[34]

Recent large audits of clinical practice suggest, however, worrying gaps in the reach of treatment,[35] with UDCA use being seen at appropriately high levels, but with significant minorities of patients not being considered for second-line therapy despite meeting the criteria, not being asked about symptoms (including itch despite the availability of therapy), and some patients not being discussed with transplant units when in the end stage. The issues with access to effective therapy are even-more marked among minority groups.[36] This is despite clear guidelines as to the importance of each of these steps.[1,5,37] The reasons for variability in the use of optimal therapy regimes in PBC have not been formally studied. However, it may well be that the rapid pace of change with regard to therapy options, and the complexity of the diverse and numerous scoring systems for assessing treatment responses have been important contributors (although this may be simplified in the future if the growing interest in normalization of liver function tests as a goal of therapy leads to clinical practice change). There is a real need for clear, consistent education of the prescribing clinician (and patient) communities.

TABLE 1A Baseline alkaline phosphatase values for key phase 2 and 3 trials in PBC

Trial agent	Mean baseline ALP	Mean baseline ALP:ULN ratio
OCA phase 2[24]	287 ± 164	2.2
OCA phase 3 ("POISE")[16]	326 ± 196	2.5
OCA phase 3 confirmatory ("COBALT")[25]	490 ± 285	**3.8**
Bezafibrate phase 3[17]	243 ± 114	1.8
Elafibranor phase 3 ("ELATIVE")[21]	322 ± 151	3.1
Seladelpar phase 3 ("ENHANCE")[20]	292 ± 171	2.3
Budesonide phase 2[26]	341 ± 182	2.6

Abbreviation: ALP, alkaline phosphatase.

THE EMERGING CHALLENGE

The current iterative model for therapy has led to all the advances outlined in the first section and could, all things being equal, reasonably be expected to address many of the outstanding issues outlined in the second section. There is a significant emerging challenge that has the potential to reverse much of the recent progress made in PBC, however. This is the threat to the regulatory approvals of the second-line therapies that are integral to the stratified treatment model.

There are 2 linked issues that have given rise to the problem. These are the conditional marketing approval model that has allowed access to licensed second-line therapy in the form of OCA (with seladelpar and elafibranor potentially following down the same path) and the challenge of undertaking the confirmatory trials that are required to convert conditional to full approval. OCA conditional approval was granted based on a consistent pattern of improvement in ALP and other purely biochemical markers that have repeatedly been shown to be associated with the risk of death or need for transplantation in PBC. These are, however, surrogate markers, albeit ones that are deemed to be "reasonably likely to predict" outcomes in the lexicon of regulatory authority evidence grades. Bezafibrate, also widely used off-label for the treatment of PBC, did not require any form of approval as it was already available in many countries for the treatment of hyperlipidemia. Following the approval of OCA, and the evidence showing ALP and other biochemical improvements with bezafibrate, both drugs have become widely used in the stratified PBC therapy model; use that is recommended by all major guidelines. To both clinicians and patients, this use made complete sense. Their use was associated with a rapid and significant improvement (and even normalization) in liver blood tests that have been used to monitor disease severity for more than 50 years. The pivotal trial that led to the conditional approval of OCA (POISE) targeted a group of patients who were UDCA nonresponders (mean ALP: 326 U/L [ULN: 130] and normal bilirubin levels), and thus at an increased future risk of progression to cirrhosis, but not the patients with more severe PBC who were at an imminent risk of progression and deterioration. The selected population fully fitted with the targeted earlier intervention model (ie, the group whom, the consensus view in the field is, that we should be treating aggressively), but were also the group in whom the trial duration was not going to be able to demonstrate an impact on actual rates of progression to hard disease endpoints of death or need for transplant.

A confirmatory trial of OCA effectiveness in terms of these hard disease endpoints was a requirement of conditional approval. The COBALT trial was initiated but not completed because of the challenge of recruiting and retaining the necessary participants (who had a higher level of disease severity than the participants in the OCA phase 2 and pivotal 3 trials to allow a reasonable number of endpoint events).[25] In the experience of all investigators, recruiting patients at high-risk into a long-term trial with a placebo arm was impossible (and arguably unethical). Patients, and clinicians, felt it was unreasonable to run the risk of getting placebo when the trial drug, with its demonstrable rapid benefits in terms of standard clinical severity markers, was freely available (as, of course, was bezafibrate). Given that the applications for regulatory approval of seladelpar and elafibranor will follow the same pathway of conditional approval and confirmatory trial, it is likely that they will encounter exactly the same challenges of recruiting patients and maintaining therapy while awaiting hard endpoints of liver failure, portal hypertension, transplant, and death as were faced by OCA.

COBALT did, however, recruit a substantial number of patients (334) and, at face value, the outcomes challenge the efficacy of OCA, with no difference in hard endpoint frequency between the ITT active drug and placebo groups. On this basis, confirmation of benefit has not been achieved and the ongoing approval of OCA is in the balance. If marketing authorization for OCA be withdrawn, we would potentially still have access to bezafibrate as a second-line therapy (in those countries where it is licensed), but there is no more clinical trial evidence for the benefit of bezafibrate on hard disease endpoints than there is for OCA. As clinicians managing patients with PBC, we are therefore faced with the prospect of having to withdraw a treatment that patients are established on and watch as their liver biochemical tests deteriorate. This would probably be rapid given that they improve quickly when the drug is first introduced. If this eventuality does arise, it will be crucial to quantify and evaluate the clinical changes associated with drug withdrawal. This loss of benefit to patients will all be in the name of withdrawal of a drug that is deemed to not be benefitting them. At the very least patients are going to find this hard to understand.

At the heart of this conundrum is a paradox. We have a series of drugs that clearly improve liver blood tests that when elevated are associated with the risk of liver complications and death in PBC, but have struggled to prove directly that these new agents actually reduce that risk. There are 2 potential explanations for this paradox, and understanding which is correct will be crucial in the next stage of the journey of PBC therapy.

The first potential explanation is that our understanding of the association between liver biochemical tests and the risk of death for OCA is incorrect. The association has been proven for patients who are untreated and those who are treated with UDCA but may not hold true for OCA as a second-line therapy. At face value, this "null hypothesis" feels implausible and difficult to explain biologically. The blood test–based

improvement with OCA is multifaceted, with benefits for ALP, alanine aminotransferase, bilirubin, and gamma-glutamyl transferase that are unrelated in terms of their transcription or formation and elimination. Moreover, any effect of OCA in terms of transcription of ALP (as opposed to modification of the biological process of cholestasis) actually leads to underestimation rather than overestimation of its benefits.

The second, and alternative, potential explanation is that the COBALT trial was flawed and its apparent finding of no benefit on survival cannot be relied on. There are 2 strands of evidence to suggest that this is indeed the case. The first is that, in addition to recruitment challenges, retaining participants in COBALT was also difficult. A significant proportion, especially in the placebo arm, dropped out. Why might there have been an imbalance between active drug and placebo participants withdrawing? The answer is probably a simple one. The rapid and significant improvement of blood tests such as ALP (which is integral to the paradox) allowed participants to effectively unblind themselves. Our own direct experience was of participants showing no ALP improvement choosing to withdraw from the trial to go on to commercially available OCA or bezafibrate. In this setting, an ITT analysis will be biased because of the skewed dropout/serious cross-over to OCA/bezafibrate in both arms, whereas in a per-protocol analysis there is informative censoring, meaning that the assumptions for performing Kaplan-Meier Cox survival analysis do not hold and conclusions cannot be drawn. In simple terms, in the reported ITT analysis, participants who dropped out from the placebo arm and went on to clinically indicated and available second-line therapy were still regarded as being in the placebo arm. There is evidence to suggest that this is indeed the case. The reduction in ALP seen in the "placebo" arm in OCA is over 10 times greater than that seen across the average of all key PBC trials to date (Table 1B); a spontaneous improvement rate that is also completely out of keeping with all clinical experience of the natural history of PBC. It is possible, therefore, that there was no apparent difference in the outcomes in the 2 arms because they were both, de facto, treated with a second-line therapy. If this were the case, and second-line therapy does indeed confer survival benefit, we would expect another important impact; survival benefit in the "placebo" as well as OCA-treated arms. This appears to indeed be the case when the COBALT participant group survival is compared with multiple different real-world patient cohorts. Furthermore, fully real-world data sets, comparing propensity-matched groups of OCA-treated and untreated groups from the same cohorts confirm better survival for patients treated with OCA.

This whole debate has been crystallized by the publication, in December 2023, of a long-awaited EMA reflection paper around acceptable evidence of efficacy in PBC (as well as primary sclerosing cholangitis; https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-regulatory-requirements-development-medicinal-products-primary-biliary-cholangitis-pbc-and-primary-sclerosing-cholangitis-psc_en.pdf). Does this reflection paper "answer the question" and allow us to move forward? The paper allows us all to agree on some key areas while leaving other areas open for debate. This at least has the benefit of focusing the discussion.

(1) The paper acknowledges that ALP and bilirubin are "used and are accepted endpoints for studies to support conditional marketing approval" in second-line therapy. This is important as it validates the design for all phase 2 and phase 3 pivotal studies of second-line therapy for PBC to date, and brings the regulatory view into line with normal hepatology clinical practice where these measures form the core of disease monitoring. It is recommended, however, that the conventional "POISE" endpoint (incorporating ALP and bilirubin[16]) be expanded by the inclusion of transaminases, gamma-glutamyl transferase, symptoms, and composite risk scores.

(2) The paper also accepts that confirmation of clinical benefit "may be difficult." This, we feel, the whole

TABLE 1B Change in the alkaline phosphatase values for the active drug and placebo groups in the key phase 2 and 3 trials in PBC

Trial agent	Maximum percentage change in ALP in active drug group from baseline	Percentage improvement in ALP in the placebo group from baseline
OCA phase 2[24]	−25	−3
OCA phase 3 ("POISE")[16]	−41	−4
OCA phase 3 confirmatory ("COBALT") (12-month data)[25]	−28	**−18**
Bezafibrate phase 3[17]	−60	0
Elafibranor phase 3 ("ELATIVE")[21]	−39	1.7
Seladelpar phase 3 ("ENHANCE")[20]	−42	0
Budesonide phase 2[26]	−29	−2.5

Abbreviation: ALP, alkaline phosphatase.

field can agree on. The paper recommends that for confirmatory studies there is, again, a broadening of endpoints to include the progression to cirrhosis and MELD >14.

(3) The paper recommends that "the intake of rescue medication……be considered as a treatment failure" in addition to liver-related events and deaths of any cause (our interpretation of the term "rescue medication" is that it largely refers to OCA or bezafibrate prescribed as part of normal clinical practice). This is important because it represents an acknowledgment that the intake of rescue medication is an unavoidable issue in confirmatory trials where we are enriching for patients at higher risk in a disease area where there is a high level of patient awareness of the significance of blood test values, and freely available second-line therapy. Points (2) and (3) set the tone for the debate about where we go next.

(4) The paper suggests "an alternative regulatory strategy to consider would be to aim for full approval, using pivotal data in patient populations with different stages of the disease." This is important as we continue to clarify our thinking about when in the disease course individual therapy approaches are appropriate. There is increasingly a move to "earlier/better" treatment in patients at high baseline risk before progression occurs. This would include using models that are peer-reviewed and also RWE using current best practices.

(5) The paper highlights the potential value of noninvasive surrogate markers for liver fibrosis, such as FibroScan, in composite endpoints. Progression to cirrhosis is clearly associated with adverse outcomes in PBC, and liver stiffness measurement as assessed using FibroScan (or alternative technologies) is highly predictive of the presence, or future risk of cirrhosis.[38,39] This makes the approach potentially highly attractive as a future trial outcome measure, although its advent does not help us address the legacy issue around previous pivotal trials where FibroScan data capture did not happen or was incomplete. The integration of biochemical and FibroScan data appears to be particularly potent for predicting survival,[39] presumably reflecting the fact that ductopenia occurring in the absence of significant fibrosis (but giving rise to significant biochemical abnormality) is one of the risk variants of PBC.[40]

(6) The EMA remains concerned about the use of RWE which the paper describes as being "*limited by methodological challenges* related to the nature of the source." On this basis, the EMA view remains that it is an "exploratory approach" not appropriate for generating pivotal evidence. RWE approaches may also be more limited with respect to FibroScan data because of a lack of availability of the technology in routine clinical practice in many centers, at least until recently.

(7) The paper recommends consideration of an endpoint of complete response (normalization of ALP and Bili $<0.7\times$ ULN[41]) as primary or secondary endpoints for final approval for second-line therapy. This is in keeping with emerging clinical and mechanistic data to suggest that UDCA responders with abnormal liver biochemistry retain a degree of both disease inflammatory activity and excess mortality risk[42,43]; however, it would lead to significant changes in clinical practice.

(8) In terms of safety, the paper acknowledges the challenge of distinguishing between DILI and disease progression (something we are sure all hepatologists would agree with) and makes recommendations as to how liver enzymes and function test abnormality should be assessed.

(9) Broadening out our approach from therapy aimed at reducing the risk to life/need for transplantation, the paper explores the route to approval for therapies targeting symptoms (focusing on itch, but with relevance to other symptoms). This is an important step forward for patients, for whom difficult-to-control symptoms are a major issue. The noteworthy points include:

- a need to understand the degree of improvement that will be meaningful to patients;
- guidance about assessing the broader impacts of itch beyond its direct effects (including on sleep and broader quality of life);
- clear guidance to undertake studies that enroll patients with a sufficient degree of symptoms to allow meaningful assessment of change (previously an issue in PBC where some of the therapies have been evaluated in populations where only a minority of the patients are symptomatic).

There is one final aspect that is important to not lose sight of. As discussed earlier, we run the risk of failing to learn from the issues we encountered with understanding the true benefits of UDCA. If we fail to learn from the experience with UDCA, of almost missing what we now know to be a significant beneficial effect, we run the risk of making the same mistakes again. What ultimately confirmed the benefits were not RCTs, but RWE. RWE, in fact, continues to show us ways to better use UDCA in PBC with the recent, entirely RWE-driven move to the use of UDCA to prevent PBC recurrence following liver transplantation.[44]

We are, therefore, at a fork in the road in PBC. Requiring the hard endpoint, placebo-controlled trials to show the efficacy of second-line therapies that show clear effects at the level of surrogate biochemical markers are practically (and ethically we would argue) not deliverable. RWE strongly suggests hard endpoint benefit, but such evidence is not currently considered by regulatory agencies as sufficient to provide confirmation. That leaves us with 2 options. The first option is we, as a community, can build on the EMA reflection paper (which accepts the difficulties of the current evidence pathway and challenges us to develop better

approaches) to move forward, develop better trial models including endpoints that strike a practical balance between clinical meaning and plausibility of seeing change within a reasonable trial duration, and put RWE approaches to effect confirmation on a robust and acceptable footing (something the patient and academic communities in PBC would be keen to work with the regulators to do). The alternative is that we move backward and be faced with the complete loss of our stratified therapy model and the need to withdraw treatments that are benefitting patients in terms of biochemical markers which have been at the heart of assessing and monitoring PBC for 50 years.

AUTHOR CONTRIBUTIONS

David E.J. Jones Devised the concept for this Special article and wrote the first draft. All authors undertook critical review and revision for important intellectual content. All authors have seen and approved the final version. The opinions expressed are the shared views of all the authors.

CONFLICTS OF INTEREST

David E.J. Jones consults, is on the speakers' bureau, and received grants from Intercept. He consults and is on the speakers' bureau for GlaxoSmithKline and Ipsen. He consults for Advanz and CymaBay. He is on the speakers' bureau for Dr Falk. Ulrich Beuers consults for Abacus and CSL Behring. He is on the speakers' bureau for GlaxoSmithKline and Zambon. He received grants from the Amsterdam UMC Foundation and ZonMW. He is employed by AASLD and EASL. Alan Bonder consults and received grants from Chemomab, CymaBay, Ipsen, and GlaxoSmithKline. He consults for GuidePoint and Intercept/Alfasigma. He received grants from CARA Therapeutics, GENFIT, Gilead, Intercept, and Mirium. He has other interests with AASLD and Pfizer. Marco Carbone consults and advises CymaBay and Ipsen. He consults for Advanz, Calliditas, Intercept, and Mayoly Spindler. Emma Culver consults, advises, and is on the speakers' bureau for Dr Falk, Horizon, Ipsen, and Zenus. She consults and advises Moderna and Sanofi. She advises and is on the speakers' bureau for Intercept. She is on the speakers' bureau and received grants from Janssen. She consults for AstraZeneca, Avicenna, Gilead, and Mirum. She is on the speakers' bureau for Advance, GlaxoSmithKline, and Intercept. Jessica Dyson is on the speakers' bureau and received grants from GlaxoSmithKline and Ipsen. She consults for Umecrine and NICE. She is on the speakers' bureau for Dr Falk and Intercept. Robert G. Gish consults, advises, and is on the speakers' bureau for AbbVie, Genentech, and Intercept. He consults, advises, and owns stock in Genlantis, HepQuant, and HepaTx. He consults and advises Arrowhead, Dynavax, Enyo, Gilead, Helios, Janssen, Merck, and Pfizer. He consults and is on the speakers' bureau for AstraZeneca, Eisai, and Ipsen. He consults and owns stock in Abacus, Eiger, JBS Science, and Virion. He consults for Abbott, Albireo, Aligos, Altimmune, Antios, Audentes, Corcept, Effectus, Fibronostics, Fujifilm/Wako, Gerson Lehrman Group, GlaxoSmithKline, Kinnate Bio, Perspectum, Precision BioSciences, Quest, Seres, Sonic Incytes, Topography Health, Tune, and Venatorx. He advises CymaBay, Durect, Kezar Life Sciences, Prodigy, Sagimet, and Takeda. He is on the speakers' bureau for Bristol Myers Squibb, Diasorin, Mallinckrodt, and VBI Vaccines. He owns stock in AngioCrine. Bettina E. Hansen consults, advises, and received grants from Ipsen. She consults and advises Advanz. She advises and received grants from CymaBay. She consults for Albireo, Calliditas, Chemomab, Enyo, Intercept, and Mirum. She advises Pliant. She received grants from Calliditas. Gideon Hirschfield consults for Advanz, CymaBay, Dr Falk, Escient, GlaxoSmithKline, Intercept, Ipsen, Kowa, Mirum, and Pliant. Kris Kowdley consults, is on the speakers' bureau, and received grants from Gilead and Intercept. He consults and received grants from 89bio, CymaBay, GENFIT, GlaxoSmithKline, Ipsen, Madrigal, Mirum, NGM, Pfizer, and Zydus. He consults and owns in stock in Inipharm. He consults for Enanta and HighTide. He is on the speakers' bureau for AbbVie. He received grants from Boston, Corcept, Hanmi, Janssen, Novo Nordisk, Pliant, Terns, and Viking. He received compensation from UpToDate. Andreas E. Kremer consults, advises, and is on the speakers' bureau, and received grants from Intercept. He consults, advises, and is on the speakers' bureau for Advanz, CymaBay, Dr Falk, GlaxoSmithKline, Ipsen, and Mirum. He consults and advises Escient. Marlyn Mayo consults and received grants from CymaBay, GlaxoSmithKline, and Ipsen. She consults for Intra-Sana Laboratories. She received grants from Intercept and Mirum. George Mells received grants from Advanz and Intercept. James Neuberger consults for Umecrine. He is on the speakers' bureau for Advanz and GlaxoSmithKline. Mark Swain consults, advises, and received grants from GlaxoSmithKline, Ipsen, and Novo Nordisk. He consults and advises Advanz. He consults and is on the speakers' bureau for Abbott. He advises Abbott. He received grants from AbbVie, Altimmune, AstraZeneca, Axcella, Bristol Myers Squibb, Calliditas, CymaBay, Galectin, Gilead, GlaxoSmithKline, Intercept, Ipsen, Kowa, Madrigal, Merck, Novartis, Novo Nordisk, Pfizer, and Roche. Atsushi Tanaka advises GlaxoSmithKline, EA Pharma, and Kowa. He is on the speakers' bureau for Gilead. Douglas Thorburn consults and is on the speakers' bureau for Ipsen. He consults for Chemomab and Pliant. He is on the speakers' bureau for Advanz. Michael Trauner consults, is on the speakers' bureau, and received grants from Albireo, Dr Falk, Gilead, Intercept, and MSD. He consults and is on the speakers' bureau for Janssen and Madrigal. He

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