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Saudi Society for the Study of Liver Disease and Transplantation

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SASLT NEWSLETTER

New Beginning of New Era

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Introduction

New Beginning of New Era

A new era has begun for the SASLT newsletter. Henceforth, we both promise and aspire to hone our newsletter's focus towards more research-based analyses and clinical academia. First, I would like to express my gratitude to the former editors of SASLT for their commendable contributions to the inaugural issues of the newsletter. I would also like to extend my appreciation to the Board members and to the president of SASLT Dr. Fasial AbaAl-Khail for their confidence in nominating me to serve as editor in chief of the SASLT's newsletter for the year 2023. Furthermore, I'm pleased to introduce you my highly regarded and accomplished co-editors: Dr. Saad Al Ghamdi, a consultant in adult Gastroenterology ,Hepatology& transplant hepatology

In this edition, we'll examine the ways in which genetic intermediate diseases and nonalcoholic steatohepatitis (NASH) are becoming increasingly prevalent in pediatrics and adults alike. We will also discuss the most recent developments in the newly FDA-approved medical therapies for progressive familial intrahepatic cholestasis (PFIC), which have the potential to be ground-breaking. We are equally pleased and humbled by the significant role that King Faisal Specialist Hospital and Research Center, specifically the contribution of our Liver health Centre as principal investigators in this international study , has played in the success of this unprecedented achievement in the field of hepatology. Lastly, we hope you enjoy and are enriched by the contents of this newsletter.

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Non-Alcoholic Fatty liver Disease in Saudi Arabia (NAFLD)

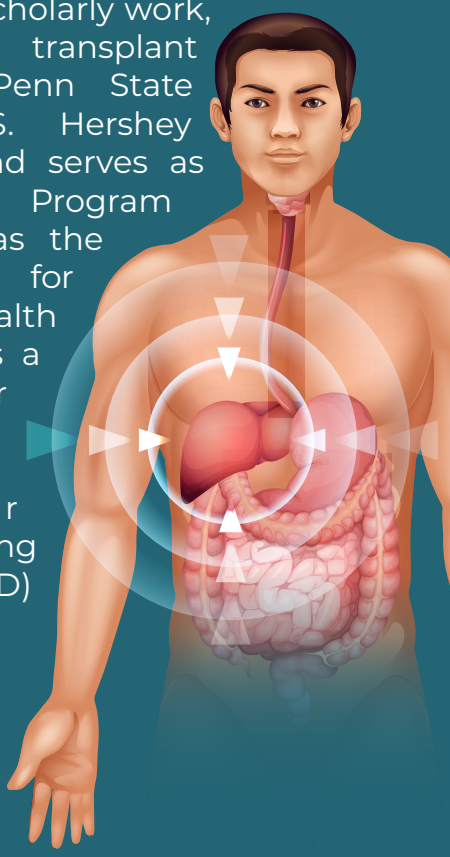
Non-alcoholic fatty liver disease (NAFLD) represents a major global health-care challenge. Medical professionals attribute this to the increasing prevalence of obesity, diabetes mellitus, and dyslipidemia worldwide. The global prevalence of NAFLD is estimated to be 25 - 30 % ,with affected patients showing an accompanying rise in the degree of advanced fibrosis. NAFLD is becoming a leading indication of liver transplantation worldwide after the advent of hepatitis C treatment with direct antiviral therapy.

The prevalence of NAFLD in Saudi Arabia, currently at %25, is among the highest in the world. It is estimated that, by %30 ,2030 of the Saudi population will have NAFLD, a figure that will be mirrored by a progressive rise in the incidence of decompensated liver disease, hepatocellular carcinoma (HCC), and death related to nonalcoholic steatohepatitis (NASH) cirrhosis.

Healthy dietary modification and a regular exercise program represent the foundation of NAFLD treatment. In this newsletter, we highlight a landmark study that illustrates the benefits of exercise in patients with NASH. We are very happy to have Dr. Stine from Penn State University as our guest.

Dr. Jonathan Stine is an Associate Professor of Medicine and Public Health Science at Penn State. As an internationally recognized liver expert with a research and clinical focus on nonalcoholic fatty liver disease (NAFLD) and exercise, he has authored more than 90 peer-reviewed papers, including multinational consensus guidelines, and several book chapters.

Stine is the recipient of multiple research grants and awards from the American Association for the Study of Liver Diseases, American Cancer Society and National Institutes of Health. He has been a study investigator on over 30 NAFLD clinical trials and is on the editorial board for several leading hepatology journals. Dr. Stine is the NAFLD consultant to the American College of Sports Medicine's Exercise is Medicine initiative and recently co-chaired the International Roundtable on NAFLD and Physical Activity for ACSM. He is also a member of the Global Liver Institute's NASH and Lifestyle councils. In addition to his scholarly work, Dr. Stine is a transplant hepatologist at Penn State Health Milton S. Hershey Medical Center and serves as the Fatty Liver Program Director as well as the Research Director for Penn State Health Liver Center. He is a founding member of the international METCON (Multicenter Exercise Training Cures NAFLD) Consortium.



By
Dr. Saad Alghamdi
Consultant, Adult Hepatology&Transplant Hepatology

International Overview of Non-Alcoholic Fatty liver Disease (NAFLD) & Exercise

We conducted the NASHFit study for several reasons, namely there are many key questions that remain unanswered in terms of exercise research in patients with NAFLD and NASH. The NASHFit study was our attempt to answer these questions and to better elucidate the benefits of regular exercise training in patients with NASH, including studying the impact of this intervention on PAI-1, an established biomarker of cardiovascular risk and clotting.

We are just beginning to see the tip of the iceberg in terms of the research investigating the link between exercise and NAFLD. Other key unanswered questions that we have begun investigating, many of which are possible through the work of the NASHFit Trial, include exploring the mechanisms underlying the benefit of exercise, understanding and developing the best tools necessary to effectively screen and assess a patient for NAFLD prior to starting an exercise program, determining the best way to translate our scientific knowledge to the patient and to improve the low rates of exercise counseling seen in clinical practice and also to better tease out the optimal exercise prescription including whether this improves long-term outcomes such as cardiovascular disease, cancer risk or prevent major adverse liver outcomes. We also need to determine how to best incorporate collaboration with an exercise specialist into the routine clinical care of patients with NAFLD.

Because the NASHFit study did not compare different exercise doses, we are conducting the NIH funded AMPED Trial in which we are directly comparing two different aerobic exercise doses of 750 MET-min per week (which is 150 min/wk of walking or the dose of exercise prescribed in the NASHFit study) and higher dose of 1,000 MET-min per week to standard clinical care in adults with biopsy proven NASH. Importantly, this study is designed to mimic a real-world setting, an adaptation in design that we learned through examining the few adherence issues that presented themselves in NASHFit, in which people's daily schedules are highly variable and our experienced team of exercise professionals may vary frequency and time of exercise in week so long as our study participant achieves the prescribed dose of exercise. More information on this study can be found on clinicaltrials.gov or https://research.med.psu.edu/liver

At this point in time, exercise remains a key component in the clinical management of NAFLD and NASH for all patients with this common condition and should be discussed at each and every healthcare visit in both the primary care and specialist setting. We need to do more as a medical society in helping to support our patients with NAFLD in making healthy lifestyle choices by providing a supportive environment that is rich with exercise-based information and resources. This will give our patients the best shot at making the healthy choices almost all patients self-report wanting to make (>%90 have a desire to be more physically active).

By
Dr. Jonathan Stine
Associate Professor of Medicine and Public Health Science at Penn State

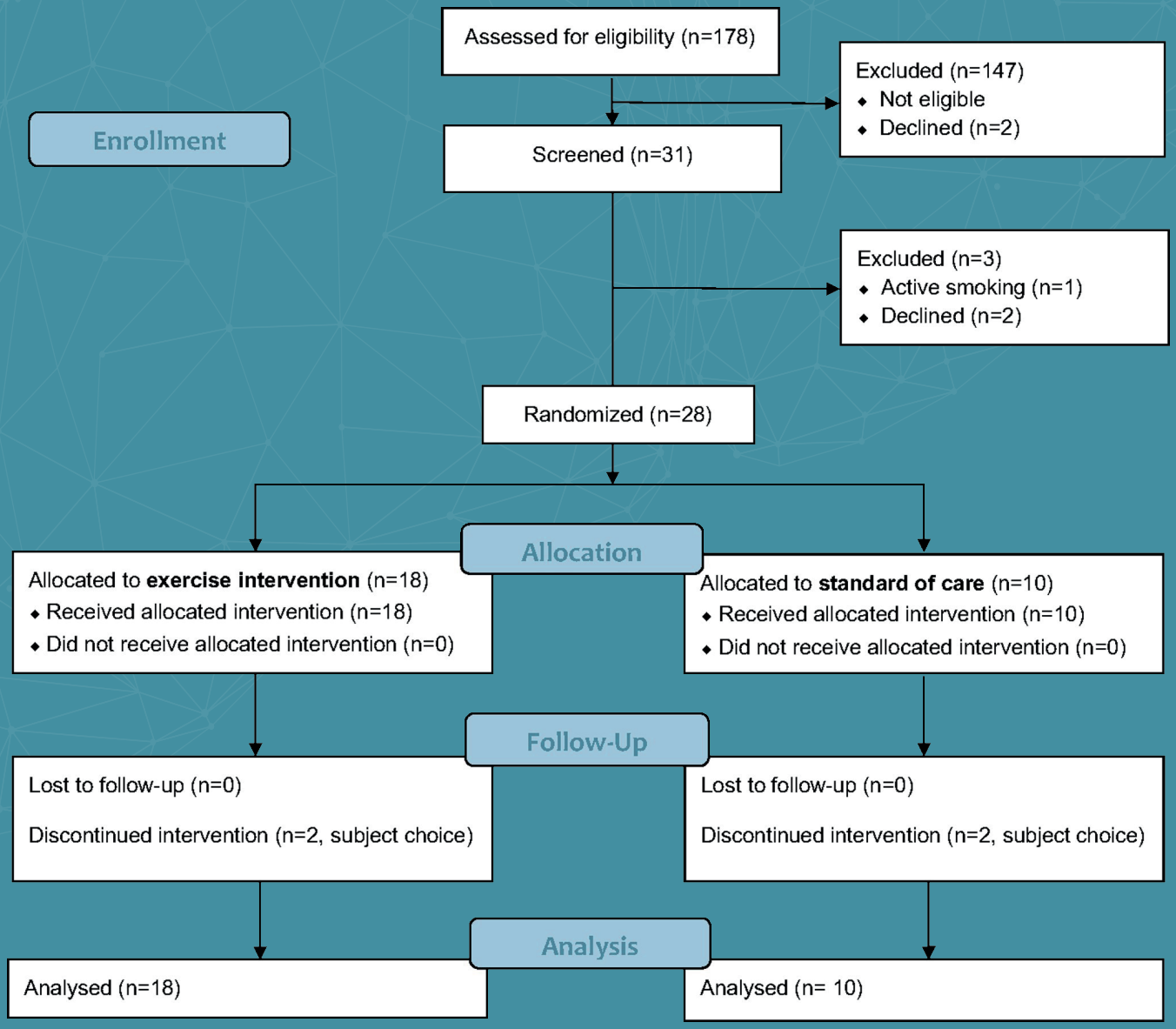
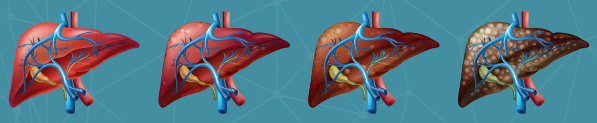


FIGURE 1 NASHFit Trial CONSORT diagram. Abbreviation: CONSORT, Consolidated Standards of Reporting Trials

TABLE 1 Baseline comparisons between control and exercise participants

	Control (*n* = 10)	Exercise (*n* = 18)	*p* Value
Demographics			
Age, years	45.0 (10.2)	52.9 (11.5)	0.082
Female sex, *n* (%)	5 (50.0)	12 (66.7)	0.444
BMI, kg/m^2	35.1 (4.9)	34.3 (4.9)	0.659
Alcohol consumption	2.1 (4.6)	0.7 (1.3)	0.362
Metabolic risk			
Comorbidities, *n* (%)			
Diabetes	5 (50.0)	6 (33.3)	0.444
Hyperlipidemia	7 (70.0)	11 (61.1)	0.703
Hypertension	5 (50.0)	14 (77.8)	0.210
Medication use, *n* (%)[a]			
Cholesterol lowering (all)	4 (40.0)	8 (44.4)	0.999
Statin	4 (40.0)	6 (33.3)	0.999
Fibrate	0 (0.0)	1 (5.6)	0.999
Antihyperglycemic (all)	5 (50.0)	7 (38.9)	0.698
Metformin	3 (30.0)	5 (27.8)	0.999
Sulfonylurea	1 (10.0)	1 (5.6)	0.999
GLP-1	0 (0.0)	1 (5.6)	0.999
SGLT2	1 (10.0)	0 (0.0)	0.357
Insulin	1 (10.0)	2 (11.1)	0.999
Antihypertensive (all)	5 (50.0)	14 (77.8)	0.210
Diuretic	0 (0.0)	5 (27.8)	0.128
ACE/ARB	4 (40.0)	4 (22.2)	0.400
BB	2 (20.0)	3 (16.7)	0.999
CCB	0 (0.0)	2 (11.1)	0.524
Aspirin 81 mg/d	0 (0.0)	2 (11.1)	0.524
HbA1c, %	6.3 (1.2)	6.3 (1.2)	0.961
HOMA-IR	9.5 (13.8)	13.8 (11.3)	0.365
VO_2 peak, ml/kg/min	23.9 (5.4)	20.3 (5.1)	0.096
NASH phenotyping			
Vitamin E, *n* (%)	2 (20.0)	3 (16.7)	0.999
Liver fat (MRI-PDFF), %	22.5 (10.5)	20.4 (7.7)	0.553
NAS	5.2 (0.6)	5.2 (1.0)	0.928
Steatosis	2.5 (1.0)	3.0 (2.0)	0.396
Lobular inflammation	1.0 (1.0)	1.5 (2.0)	0.341
HB	1.0 (2.0)	1. 0 (1.0)	0.327
Fibrosis stage, *n* (%)			0.125
0	1 (10.00)	2 (11.11)	
1	4 (40.00)	10 (55.56)	
2	4 (40.00)	2 (11.11)	
3	0 (0)	4 (22.22)	
4	1 (10.00)	0 (0)	



Note:
Randomization was upheld because there were no significant differences between the exercise intervention group and the standard-of- care control.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BB, beta blocker; CCB, calcium-channel blocker; GLP, glucagon-like peptide; HOMA-IR, homeostatic model assessment for insulin resistance; NAS, NAFLD Activity Score; SGLT, sodium-glucose transport

[a]No subjects were taking pioglitazone or obeticholic acid

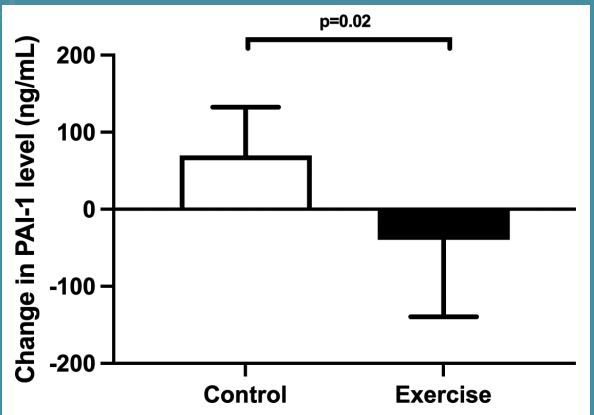


FIGURE 2 Change in PAI-1 comparing exercise training to standard clinical care. PAI-1 level was significantly decreased for he exercise training group when compared to the standard-of-care control group (−100 ± 40 vs. +63 ± 70 ng/ml; p = 0.02).

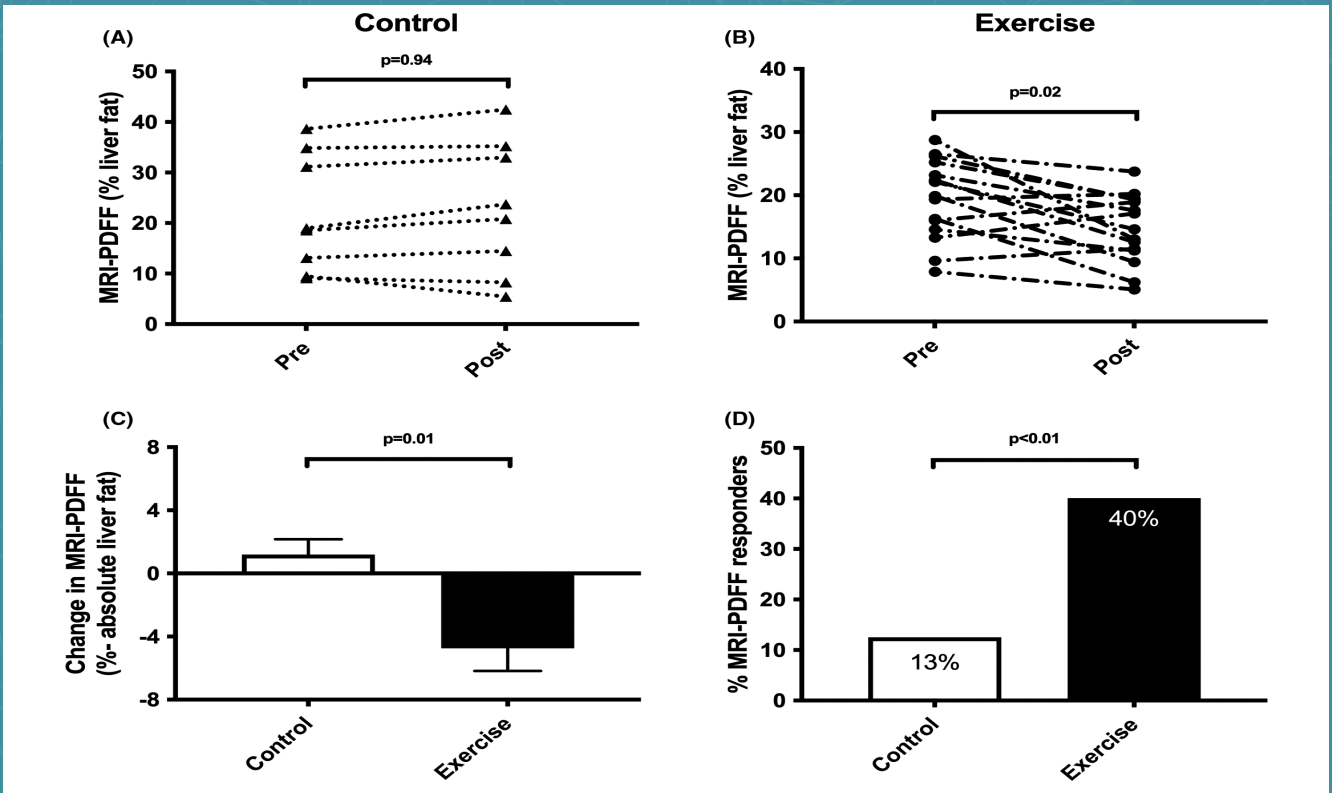


FIGURE 3 Change in MRI-PDFF measured liver fat comparing exercise training to standard clinical care. (A) No significant change was observed in MRI-PDFF in standard-of-care subjects. (B) MRI-PDFF significantly decreased following exercise training. (C) Exercise training decreased liver fat, as measured by MRI-PDFF (−5.6 ± 4.7 vs. %2.8 ± 1.2 absolute liver fat; p = 0.01). (D) Forty percent of exercise subjects had a ≥%30 relative reduction in MRI-PDFF, the threshold for histological response, compared to %13 of standard-of-care subjects

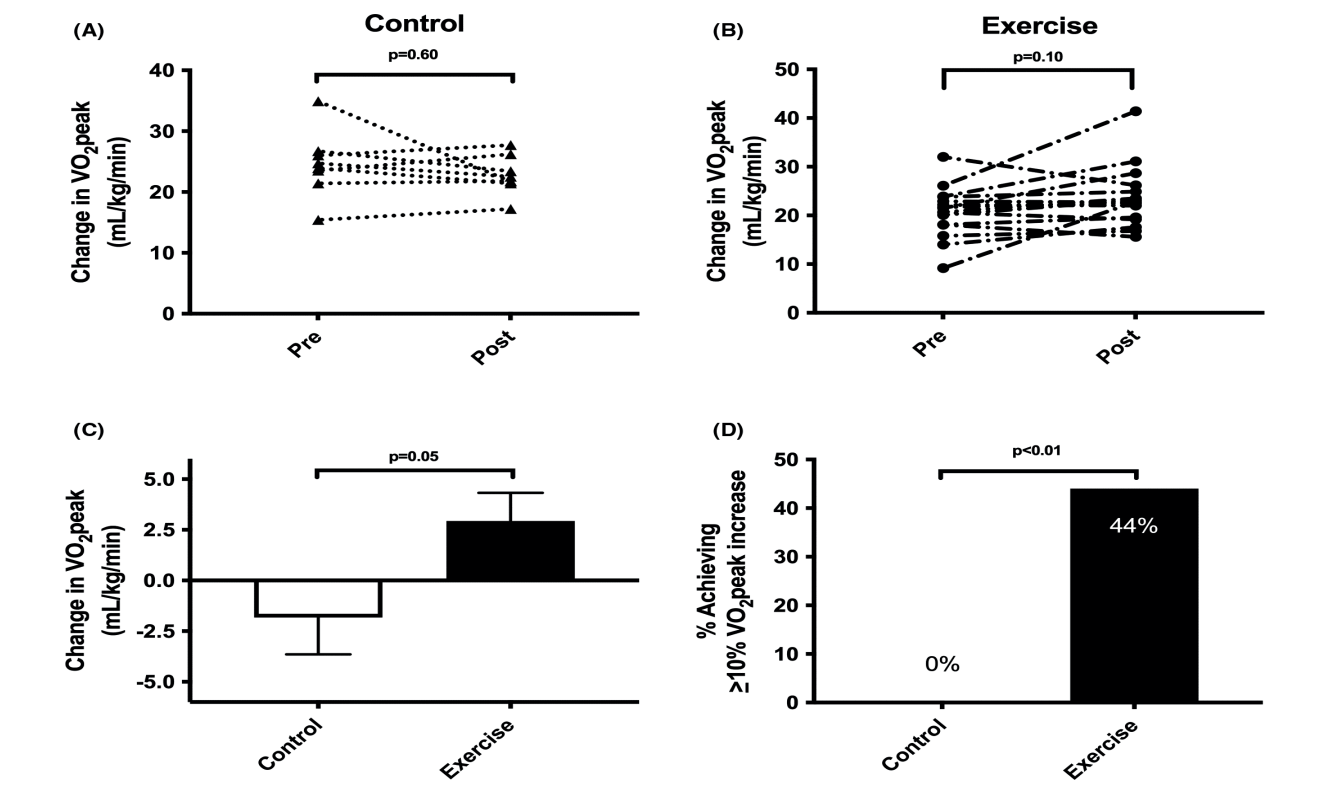


FIGURE 4 Change in cardiorespiratory fitness comparing exercise training to standard clinical care. (A) No significant change was observed in VO2 peak for standard-of-care subjects. (B) There was a trend toward significance in VO2 peak improvement following exercise training. (C) Cardiorespiratory fitness improved more with exercise training given that greater gain in VO2 peak (+5.6 ± 3.0 vs. −5.1 ± 1.8 ml/ kg/min; p = 0.05) was observed in comparison to standard clinical care. (D) Forty-four percent of exercise subjects had a ≥%10 gain in VO2 peak, the threshold to improve overall mortality, compared to %0 of standard clinical care subjects

One Milestone toward treatment of Progressive Familial Intrahepatic cholestasis in children and adult

Production of bile is a critical liver function that playas major role in detoxification, cholesterol homeostasis, nutrition, and endocrine signaling. Cholestasis is the final common biochemical phenotype of a wide-range of liver pathologies. It can also represent a highly selective impairment of one of many steps involved in the synthesis, secretion and modification of bile acids, which in turn leads to liver damage. Advanced cholestatic liver disease, therefore, comprises a highly heterogeneous group of conditions .Genetic causes of cholestatic liver disease are more probably to present in the pediatric age group but also in adult.

Although the exact contribution of genetic causes is unknown because many cases labeled as 'idiopathic'cholestatic liver disease may in fact be caused by single gene mutations in known or hitherto un identified disease genes, estimates suggest that at least %45 of cholestatic liver disease in children are genetic in etiology .

Known genetic causes include metabolic diseases, cystic fibrosis, Alagille syndrome, progressive familial intrahepatic cholestasis (PFIC), and bile acid synthesis and absorption defects. Mutation identification in these patients has historically aimed at empowering families with information to pursue informed reproductive choices. However, recent advances have raised the possibility that the management itself can be personalized based on the knowledge of the underlying gene. This places increasing emphasis on the importance of providing a genetic diagnosis early in the work up.

In our cohort, Shagrani et al (1) which was the first to study genetic profiling of liver disease in Saudi Arabia, half of PFIC cases hadABCB11mutations. MDR3 deficiency caused by ABCB4mutations accounted for most of the remaining PFIC cases with less than %2 of ATP8B1 mutation (PFIC1)

Unfortunately the only treatment option for most PFIC cases was liver transplantation.

High disease burden of autosomal recessive cholestatic liver disease was observed in our cohort study Consistent with our experience with other autosomal recessive diseases, most of the mutations were private young mutations that were rendered homozygous through the consanguinity loop (%68). This translates into a minimum disease burden of cholesteric liver disease in Saudi Arabia of 1:7246, a very high estimate even when compared with countries with high burden of cholestatic liver disease in children like Japan.

Baes on all the previous points we were one the major player to start the first international clinical trial aiming to find medical therapy for PFIC patients

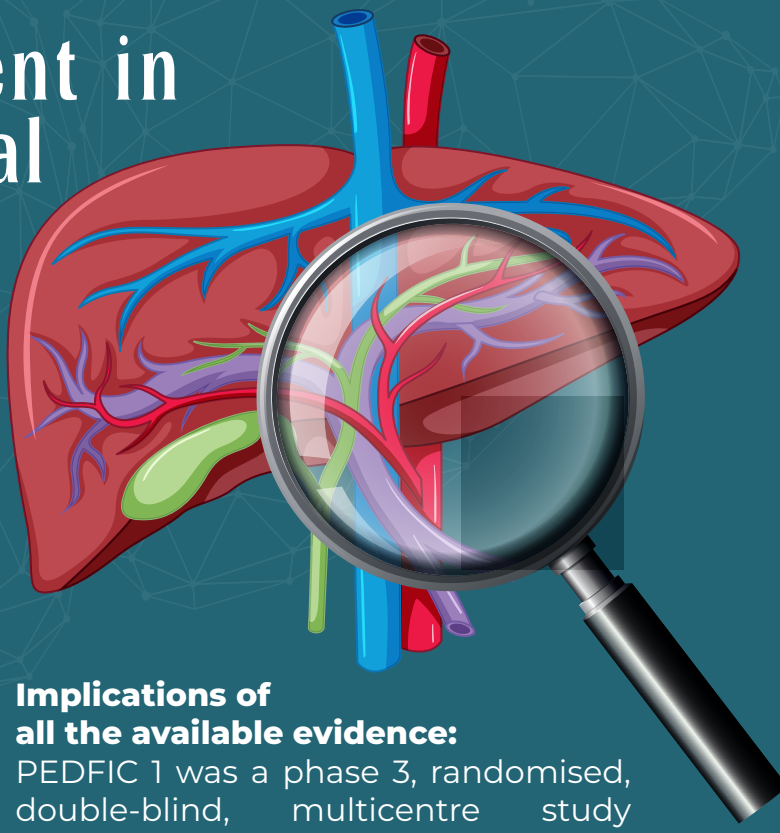
By
Dr. Mohammad Shagrani
Consultant Pediatric Hepatology & Transplant Hepatology

Professor Henkjan J. Verkade

is a pediatric gastro/hepatologist at the Beatrix Children's Hospital of the University Medical Center Groningen, The Netherlands.
Henkjan Verkade combines clinical work in pediatric gastro/hepatology, in particular hepatology of rare liver diseases and liver transplantation.
The relationship with Henkjan evolved in collaboration in research at various Espghan meetings.

In 2017 Verkade initiated with Bettina Hansen the global NAPPED registry (Natural Course and Prognosis of PFIC and Effect of Biliary Diversion) which KFSH&RC was one the co-founders. The aim was to increase the insights into the natural history, genotype-phenotype associations and the associations between treatments and long-term outcome in patients with either of two types of PFIC; severe deficiency of the Familial Intrahepatic Cholestasis Protein type 1 (FIC1), encoded by ATP8B1, also known as Progressive Familial Intrahepatic Cholestasis type 1 (PFIC1) or severe deficiency of the Bile Salt Export Pump (BSEP), encoded by ABCB11, also known as PFIC2. FIC1 and BSEP are canalicular proteins involved in bile formation by contributing to the canalicular membrane bilayer asymmetry and by transporting bile acids, respectively. Patients affected by these diseases present a phenotype of progressive cholestasis, normal/low serum gamma-glutamyl transferase activity level, elevated serum bile acids, severe pruritus and in case of the PFIC1 spectrum, extrahepatic manifestations such as diarrhea and pancreatitis The NAPPED registry has been helpful to further characterize the natural history of progressive familiar intrahepatic cholestasis syndromes and to identify prognostic parameters for the course of disease and for responsiveness to treatments. At present, we have accumulated the largest genetically defined cohort of patients with severe FIC1 and BSEP deficiency known to date (>800 patients included). The data allow tailoring medical and surgical therapies to the level of individual patients, based on the specific mutations causing these rare diseases. For example, patients could be identified that do but also patients that do not benefit from biliary diversion surgery, as well as those that are at high risk (up to %34) of developing hepatocellular carcinoma in childhood (van Wessel et al., 2020).
The insights obtained from the NAPPED study, including with many patient data from the Kingdom of Saudi-Arabia, have been published in high ranked journals (among others, J Hepatology, Hepatology, J Hepatology Reports). It is expected that the insights will also have great influence on the understanding of the novel medical treatments for these diseases, such the drugs that inhibit the intestinal reabsorption of bile acids (so called ASBT inhibitors). Finally, the natural cohort allows to search for surrogate endpoints and supports sample size calculations for design of new studies.

Odevixibat treatment in progressive familial intrahepatic cholestasis



Introduction:
Historically, initial treatments for PFIC were limited to nutritional supplementation and off-label agents aimed at increasing bile flow or reducing pruritus. PFIC can also be treated with surgical interventions, such as partial external biliary diversion and liver transplantation. However, these therapies might not be effective in all patients with PFIC or provide sustained relief.

The ileal bile acid transporter (IBAT), also known as the apical sodium-dependent bile acid transporter (ASBT), is a critical regulator of the enterohepatic circulation of bile acids, taking up bile acids in the distal intestine for return to the liver via the portal circulation. Small-molecule inhibition of IBAT has been investigated as a therapeutic approach to treat a number of disease states, including cholestatic liver diseases.

Literature search and basis of research:
Published and presented results of phase 2 studies of IBAT inhibitors in PFIC have shown evidence of improvement in key features of PFIC, such as reduced serum bile acid concentrations and pruritus, but these studies had no placebo controls. These searches revealed that, to date, there have been no completed, published, placebo-controlled trials of an IBAT inhibitor in patients with PFIC.

Implications of all the available evidence:
PEDFIC 1 was a phase 3, randomised, double-blind, multicentre study conducted at 33 sites in the USA, Canada, Europe, Australia, and the Middle East, from May 2018, to July 2020. This outpatient study consisted of a screening phase and parallel-design treatment period Study results from PEDFIC 1 indicated that odevixibat can reduce pruritus and lower serum bile acids in patients with PFIC, both of which might have long-term implications for patients (ie, potentially reduce the need for liver transplantation and delay disease progression, respectively). The findings from this study formed the basis for the approval of odevixibat for the treatment of pruritus in patients aged 3 months and older with PFIC in the USA and for the treatment of PFIC in patients aged 6 months and older in the EU. Odevixibat represents a non-surgical, pharmacological option to interrupt the enterohepatic circulation and could provide significant treatment benefits in PFIC, a disease with high unmet medical needs. The ongoing open-label extension study of odevixibat in PFIC, called PEDFIC 2, will provide long-term efficacy and safety information on Odevixibat in patients with PFIC.

Study design and participants:
Children (aged 5·0 to 18 years) with a clinical diagnosis of PFIC1 or PFIC2 and genetic confirmation of biallelic pathogenic mutations in the ATP8B1 (ie, PFIC1) or ABCB11 (ie, PFIC2) genes, elevated serum bile acids (≥100 μ mol/L), history of significant pruritus as determined by the investigator, and an average caregiver-reported observed scratching score of 2 or greater (calculated from daily electronic diary [eDiary] entries) in the 14 days preceding randomisation were eligible for inclusion. Additionally, caregivers or age-appropriate patients (≥8 years of age) agreed to use the eDiary device to record symptoms. Patients or their caregivers provided written informed consent before entering the study.

Patients with two mutations in ABCB11 predicting a complete absence of functional bile salt export pump protein were excluded. Patients were also excluded if they had a medical history or ongoing presence of other types of liver disease (eg, biliary atresia, benign recurrent intrahepatic cholestasis, liver cancer, histopathologic evidence of non-PFIC aetiology of cholestasis); diseases or conditions known to interfere with bile acid metabolism (eg, inflammatory bowel disease); chronic (>3 months) diarrhoea; active, clinically significant, acute or chronic infection or infection requiring hospitalisation or parenteral anti-infective treatment within 4 weeks of treatment start; or chronic kidney disease. Patients were also excluded from the study if they had biliary diversion surgery within the 6 months preceding the screening period; had a liver transplant or one planned within 6 months of randomisation; signs of decompensated liver disease (eg, ascites); or pruritus caused by any condition other than PFIC (eg, treatment-refractory atopic dermatitis, other primary pruritic skin disease).

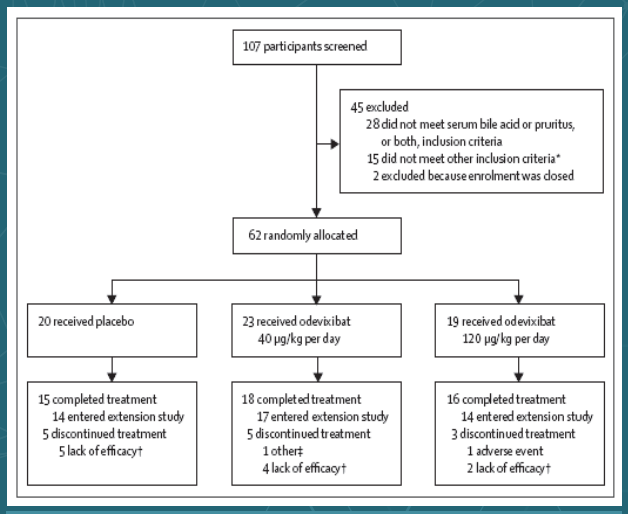
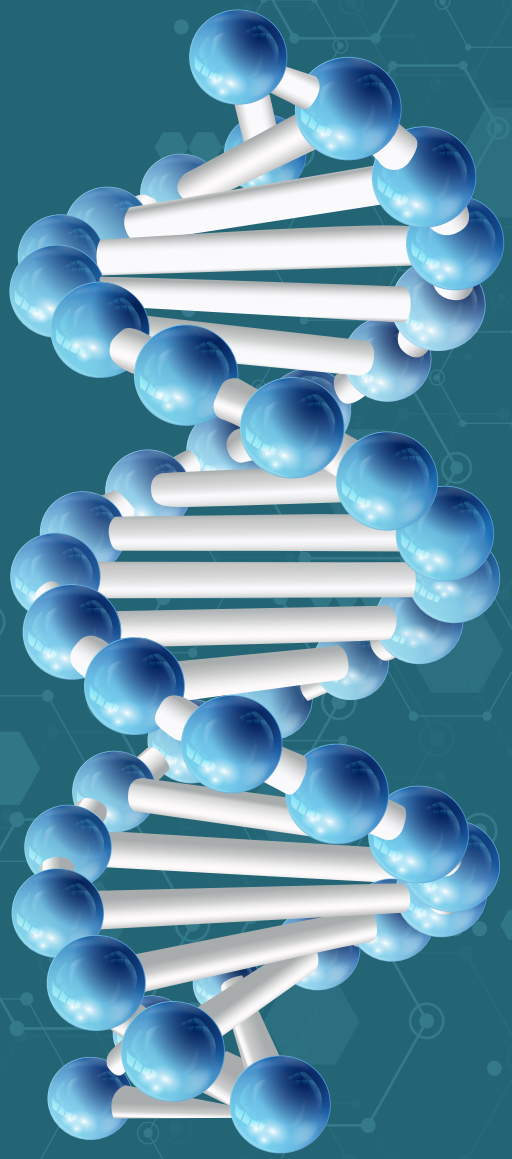


FIGURE 1: PEDFIC 1 Trial profile



Results

In total, 45 patients were excluded during screening and 62 patients were randomly allocated to treatment (odevixibat 40 µg/kg per day, n=23 and odevixibat 120 µg/kg per day, n=19) or placebo (n=20). These randomly allocated patients comprised the population assessed for efficacy and safety analyses. Overall, (79%) 49 of 62 patients completed the 24-week treatment period . 11 patients (placebo, n=5; odevixibat 40 µg/kg per day, n=4; odevixibat 120 µg/kg per day, n=2) discontinued treatment due to patient or caregiver judgment of no improvement or intolerable symptoms (ie, perceived lack of efficacy, as patients and clinicians were blinded to study outcomes until the last patient completed the study) and rolled over into the long-term extension study before completing 24 weeks of treatment. Additionally, one patient treated with odevixibat 40 µg/kg per day discontinued due to non-compliance and inability to travel to the clinic, and one patient treated with odevixibat 120 µg/kg per day discontinued early due to a TEAE of diarrhoea.treatment-refractory atopic dermatitis, other primary pruritic skin disease).

Prespecified subgroup analyses were performed to assess effects on serum bile acids and pruritus in patients with PFIC1 or PFIC2. Results are displayed in figures 2A and figure 2B

Treatment with odevixibat led to reductions from baseline in standard liver-associated tests: at week 12, mean changes in serum ALT were −5·20 U/L (SD 3·97) with odevixibat and 7·1 U/L (5·44) with placebo, and at week 24, these values were −7·26 U/L (1·79) and 7·3 U/L (4·16), respectively (secondary endpoints). None of the 62 patients underwent surgical interruption of the enterohepatic circulation or liver transplantation during the study (secondary endpoint).

No patients in this study had dose reductions. One patient who had received odevixibat 120 µg/kg per day discontinued due to a drug-related TEAE of diarrhoea. All severe and serious TEAEs observed during the study are shown in the table 2. No deaths, treatment-related serious adverse events, or TEAEs related to liver decompensation occurred.

Mean changes in clinical chemistry, haematology, and laboratory parameters were generally small and not considered clinically meaningful. In addition, there were only minimal changes in fat-soluble vitamins during treatment with odevixibat, and no patients experienced new or worsening fat-soluble vitamin deficiency refractory to clinically recommended vitamin supplementation.

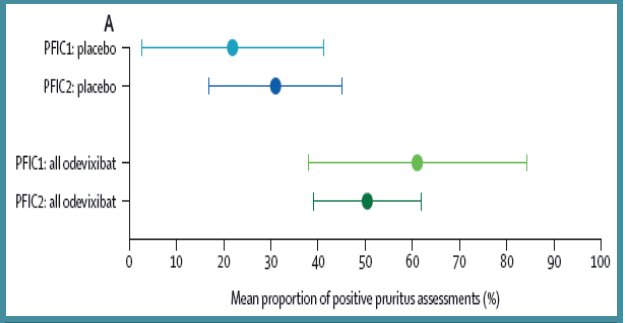


FIGURE 2A

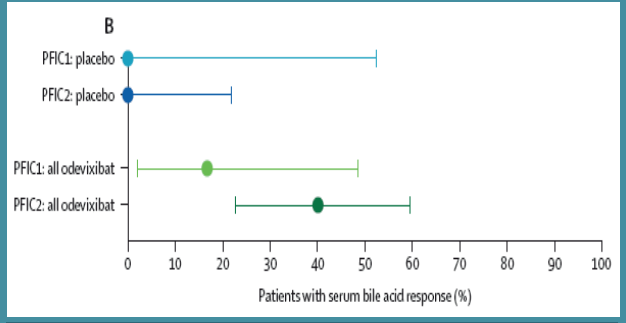


FIGURE 2B

Most patients ([%60] 34 of 57 with available assessments) had abnormal liver findings on abdominal ultrasound at baseline, primarily hepatomegaly. Clinically significant improvements from baseline in liver echogenicity were reported for three patients (two in the odevixibat 120 µg/kg per day group and one in the placebo group), and liver findings worsened for one patient in the odevixibat 40 µ g/kg per day group.

Discussion

In this study, odevixibat 40 and 120 µg/kg per day effectively reduced pruritus and serum bile acids relative to placebo in children with PFIC1 or PFIC2, meeting both primary efficacy endpoints. These effects occurred rapidly and were sustained through week 24. Overall, there were no unexpected TEAEs observed, and odevixibat was generally well tolerated, with similar safety profiles observed for both doses of odevixibat.

Two potentially serious features of PFIC are cholestasis leading to progressive hepatic damage and unrelenting pruritus. Excess retained intrahepatic bile acids (reflected in elevated serum bile acids) have been associated with, and are thought to contribute to, the progressive hepatic damage seen in these children. Surgical interruption of the enterohepatic circulation can reduce serum bile acids and pruritus, as well as improve other clinical outcomes; importantly, patients who had lower serum bile acids after diversion surgery have longer transplant-free survival. However, the response to biliary diversion can wane over time, and many patients experience recurring cholestasis or pruritus after surgery. Liver transplantation is considered when patients with PFIC have end-stage liver disease, hepatocellular carcinoma, or pruritus unresponsive to off-label medical therapy or biliary diversion surgery. However, liver transplantation is not curative in all patients.

In the present study, odevixibat-associated reductions in pruritus were clinically meaningful. Interestingly, odevixibat also reduced concentrations of autotaxin, a proposed pruritogen,by approximately half with 24 weeks of treatment. Reductions in pruritus and serum bile acids might result in reduced need for diversion surgery in patients treated with odevixibat; avoidance of such surgery and the potentially associated consequences (eg, surgical complications; permanent stoma) could lead to enhanced quality of life. In addition, to the extent that accumulation of bile acids contributes to ongoing liver damage, reduction of bile acid concentrations by odevixibat could also result in improved hepatic health and delay of liver transplantation; this potential is also supported by the improvement in hepatic biochemical parameters observed in patients receiving odevixibat. Therefore, odevixibat might have the potential to delay, or perhaps even prevent, surgical interventions in this patient population.

The findings on pruritus should be considered in light of general limitations associated with subjective measures; however, these study results are strengthened by several factors, namely: inclusion of a placebo control and positive findings on two primary endpoints, with one based on subjective measurement of symptoms and the other based on a biological parameter. In addition, due to the study's eligibility criteria (ie, exclusion of patients with extreme perturbations in hepatic parameters), these study findings might not be fully generalisable to all patients with PFIC with these characteristics; thus, further research into these populations is warranted.

Although part of this study was conducted during the COVID-19 pandemic, no patient was lost to follow-up during this time. Overall, most patients ([%79] 49 of 62) completed the treatment period, with (%18) 11 rolling over early to the ongoing long-term extension study, PEDFIC 2.

In conclusion, odevixibat, administered as once a day oral capsules, represents a non-surgical, pharmacological option to interrupt the enterohepatic circulation in patients with PFIC. Odevixibat has the potential to improve the standard of care in patients with PFIC and provide treatment benefits in a disease group with high unmet medical needs.

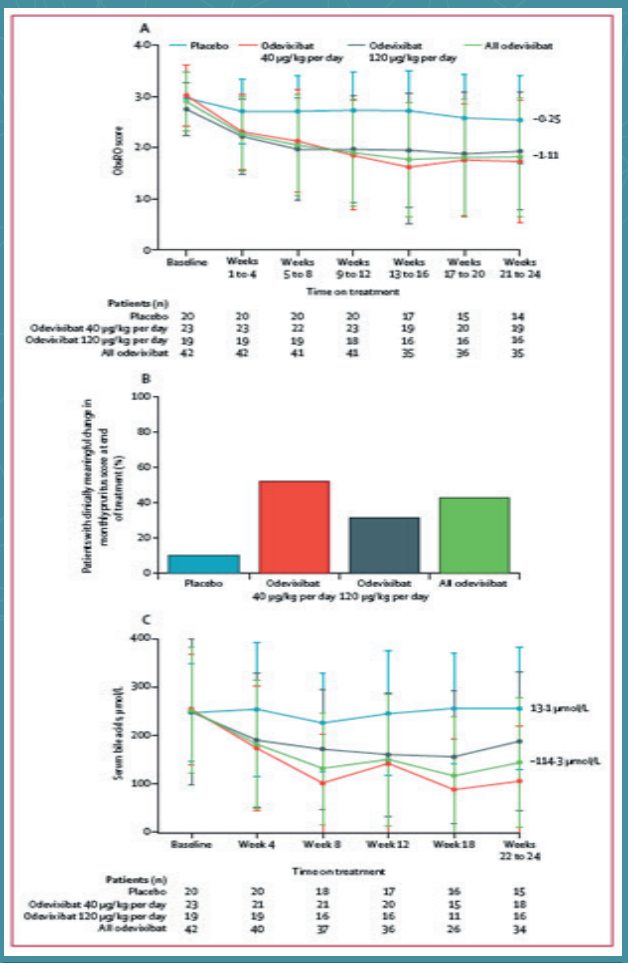


Figure 3: Additional efficacy outcomes
Mean pruritus scores over time (A); proportion of patients with clinically meaningful change in monthly pruritus score at end of treatment (B); and mean fasting serum bile acid concentrations over time (C). The two values to the right in (A) and (C) depict the mean changes from baseline in the placebo and odevixibat groups at the last time point assessed. Error bars show SD. ObsRO=observer-reported outcome.

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	Placebo (n=20)	Odevixibat 40 µg/kg per day (n=23)	Odevixibat 120 µg/kg per day (n=19)	Odevixibat, all doses (n=42)
Any TEAE	17 (85%)	19 (83%)	16 (84%)	35 (83%)
Mild	6 (30%)	11 (48%)	8 (42%)	19 (45%)
Moderate	9 (45%)	7 (30%)	6 (32%)	13 (31%)
Severe	2 (10%)	1 (4%)	2 (11%)	3 (7%)
Serious TEAEs	5 (25%)	0	3 (16%)	3 (7%)
TEAEs leading to discontinuation	0	0	1 (5%)	1 (2%)
Liver-related TEAEs*	4 (20%)	5 (22%)	6 (32%)	11 (26%)
TEAEs occurring in ≥5% of patients overall, by preferred term				
Diarrhoea or frequent bowel movements	2 (10%)	9 (39%)	4 (21%)	13 (31%)
Pyrexia	5 (25%)	7 (30%)	5 (26%)	12 (29%)
Upper respiratory tract infection	3 (15%)	3 (13%)	5 (26%)	8 (19%)
Vomiting	0	4 (17%)	3 (16%)	7 (17%)
ALT increased	1 (5%)	3 (13%)	3 (16%)	6 (14%)
Total bilirubin increased	2 (10%)	3 (13%)	2 (11%)	5 (12%)
Abdominal pain	0	2 (9%)	1 (5%)	3 (7%)
AST increased	1 (5%)	2 (9%)	1 (5%)	3 (7%)
Blood ALP increased	1 (5%)	1 (4%)	2 (11%)	3 (7%)
Nasopharyngitis	1 (5%)	1 (4%)	2 (11%)	3 (7%)
Pruritus	1 (5%)	2 (9%)	1 (5%)	3 (7%)
Cough	3 (15%)	0	2 (11%)	2 (5%)
Urinary tract infection	3 (15%)	1 (4%)	1 (5%)	2 (5%)
Epistaxis	1 (5%)	1 (4%)	1 (5%)	2 (5%)
Viral upper respiratory tract infection	1 (5%)	2 (9%)	0	2 (5%)
Vitamin D deficiency	1 (5%)	0	2 (11%)	2 (5%)
Blood creatine phosphokinase increased	2 (10%)	0	1 (5%)	1 (2%)
Influenza	2 (10%)	0	1 (5%)	1 (2%)
Scratch	2 (10%)	1 (4%)	0	1 (2%)
Constipation	4 (20%)	0	0	0
Rash	3 (15%)	0	0	0
Drug-related TEAEs	3 (15%)	7 (30%)	7 (37%)	14 (33%)
Drug-related TEAEs occurring in ≥5% of patients overall, by preferred term				
ALT increased	1 (5%)	2 (9%)	2 (11%)	4 (10%)
AST increased	1 (5%)	2 (9%)	1 (5%)	3 (7%)
Total bilirubin increased	1 (5%)	2 (9%)	2 (11%)	4 (10%)
Diarrhoea or frequent bowel movements	1 (5%)	2 (9%)	2 (11%)	4 (10%)

Data are patients, n (%). TEAE=treatment-emergent adverse event. ALT=alanine aminotransferase. AST=aspartate aminotransferase. ALP=alkaline phosphatase. *Study investigators were asked to indicate which reported events were considered liver related; the most commonly reported liver-related TEAEs were increased ALT (7% [n=3/42] with odevixibat vs 0% [n=0/20] with placebo) and increased blood bilirubin (5% [n=2/42] with odevixibat vs 5% [n=1/20] with placebo).

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