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Agents in Clinical Development for Other Chronic Liver Diseases Including HBV and PSC

Elizabeth K. Goacher, PA-C, MHS, AF-AASLD

Disclosures

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Disclosures

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Consultant: AbbVie, Clinical Area – Viral Hepatitis

Consultant: Gilead, Clinical Area – Viral Hepatitis

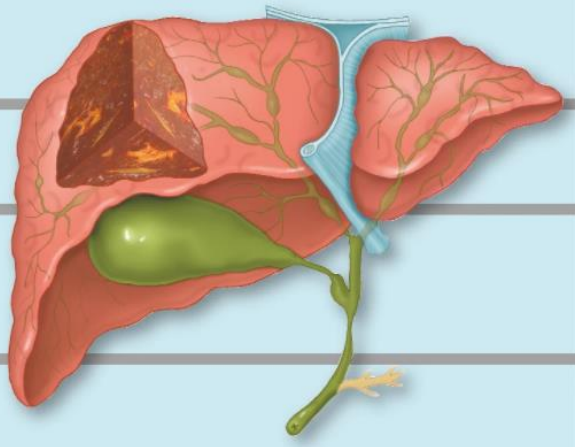
Consultant: Intercept, Clinical Area – PBC, NASH

Speakers Bureau: AbbVie, Clinical Area – Viral Hepatitis

Speakers Bureau: Gilead, Clinical Area – Viral Hepatitis

Speakers Bureau: Intercept, Clinical Area – PBC, NASH

PSC Agents Variety of MOA

Treatment	Biliary strictures and cholestasis	ALP signal
Bile-acid based therapy and PPARs • UDCA • *nor*UDCA • FXR and FGF19 analogues • Bezafibrate and fenofibrate		✓
Microbiota-based therapy • Antibiotics (e.g. vancomycin) • Fecal transplantation		✓
Immune-modulation therapy • Glucocorticoids and azathioprine • Calcineurin-inhibitors and MMF • Anti-TNFα • Vedolizumab • Simtuzumab (i.e. anti-fibrotic)		✗

Glossary by MOA

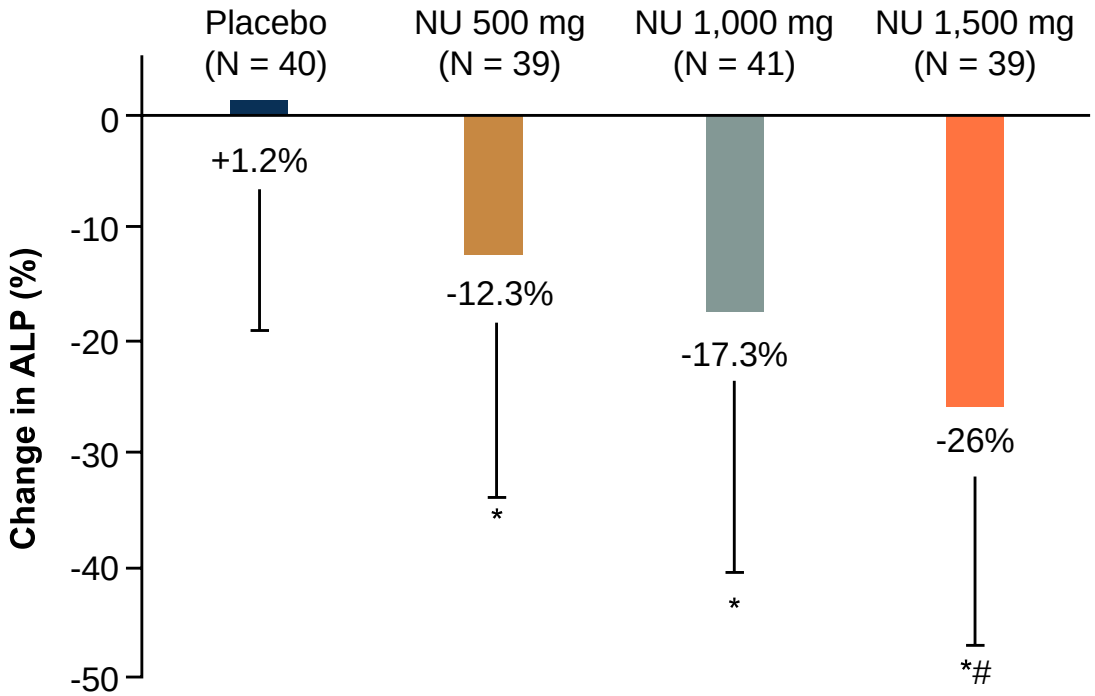
- Bile acid therapies
  - UDCA
  - norUDCA
- FXR agonists
  - OCA
  - Cilofexor
  - Tropifexor
- FGF
  - Aldafermin (NGM282)
- PPARs
  - Bezafibrate
  - Fenofibrate
- Microbiota based therapy
  - Vancomyocin
  - FMT
- Biologics
  - Infliximab
  - Vedolizumab
- Anti-inflammatories and antifibrotics
  - Cenicriviroc CCRx/CCR5 antagonist
  - Simtuzumab LOXL2 monoclonal antibody

Results of Non-UDCA Trials in PSC

Therapy	References	*N*	Design	Lab inclusion criteria	Primary endpoint	Result ALP	Other results
Therapy targeting bile acids							
norUDCA UDCA derivative	Fickert et al. [197]	161	RCT Multicenter Phase II 12 weeks	Bilirubin < 3.0 mg/dL	ΔALP at 12 weeks	Significant dose-dependent reduction in ALP; ΔALP (compared to placebo) – 12.3%, –17.3% and – 26.0% in the 500, 1000 and 1500 mg treatment groups	Favorable safety profile (no increase in pruritus)
NGM282 FGF-19 analogue	Hirschfield et al. [107]	62	RCT Phase II 12 weeks	N/A	ΔALP at 12 weeks	No significant change in ALP	Reduced BA Improved (reduced) fibrosis markers ELF test and PRO-C3
Obeticholic acid (OCA) FXR agonist AESOP trial	Kowdley et al. [100]	76	RCT Phase II 24 weeks	ALP ≥ 2.0*ULN Bilirubin < 2.5*ULN	ΔALP at 24 weeks	Significant reduction in ALP in the 5–10 mg treatment arm compared to placebo; ΔALP – 25% from baseline in the 5–10 mg treatment arm compared to ΔALP – 4.8% in placebo group; ΔALP – 14% vs – 25% in patients with and without UDCA at baseline in the 5–10 mg OCA arm	Increased pruritus; pruritus (severe pruritus) reported in 46% (8%), 60% (16%) and 67% (41%) in placebo, 1.5–3 mg and 5–10 mg groups; n = 15 dropouts prior to 24 week assessment
LUM001/maralixibat ASBT inhibitor CAMEO trial	Completed; Results at clinicaltrials.gov	27	Open label pilot 14 weeks	ALT and ALP ≤ 5*ULN	Δbile acid levels at 14 weeks	No reduction in ALP	ΔBA – 21.6 (– 38%)
Therapy targeting PPAR							
Bezafibrate 400 mg/day	Mizuno et al. [121]	7	Open-label pilot 6 months	ALP > 1.5 x ULN	ΔALP at 6 months	ALP reduction with 40% in 3/7 patients at 6 months	
Bezafibrate 400 mg/day	Mizuno et al. [122]	11	Open-label pilot 12 weeks		ΔALP at 12 weeks	ALP reduction at 12 weeks, ALP increase subsequent to treatment cessation	
Bezafibrate 400 mg/day or fenofibrate 200 mg/day	Lemoinne et al. [123]	20	Retrospective study	ALP > 1.5 x ULN on UDCA	ΔALP	Reduced ALP after at least 6 months; 40% reached ALP < 1.5 x ULN	Reduced ALT and pruritus
Fenofibrate	Dejman et al. [124]	8	Open label pilot 6 months	ALP > 1.5 x ULN	ΔALP at 6 months	Significant reduction; ΔALP – 43%	Reduced ALT No significant effect on Mayo risk score

Vesterhus, M, Karlsen, TH. Emerging therapies in primary sclerosing cholangitis: pathophysiological basis and clinical opportunities. *J Gastroenterol.* **55,** 588–614 (2020). https://doi.org/10.1007/s00535-020-01681-z.

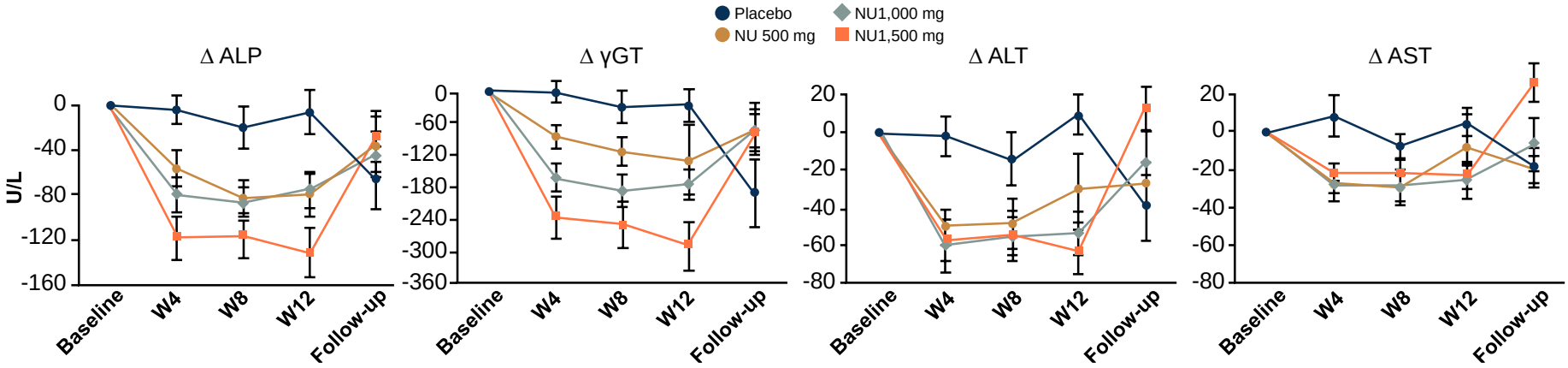
*nor*Ursodeoxycholic Acid: Change in Alk Phos at 12 Weeks



Fickert P, et al. European PSC norUDCA Study Group. norUrsodeoxycholic acid improves cholestasis in primary sclerosing cholangitis. *J Hepatol*. 2017 Sep;67(3):549-558.

*nor*Ursodeoxycholic Acid: Absolute Changes in Alk Phos, vGT, ALT and AST

Fig. 4



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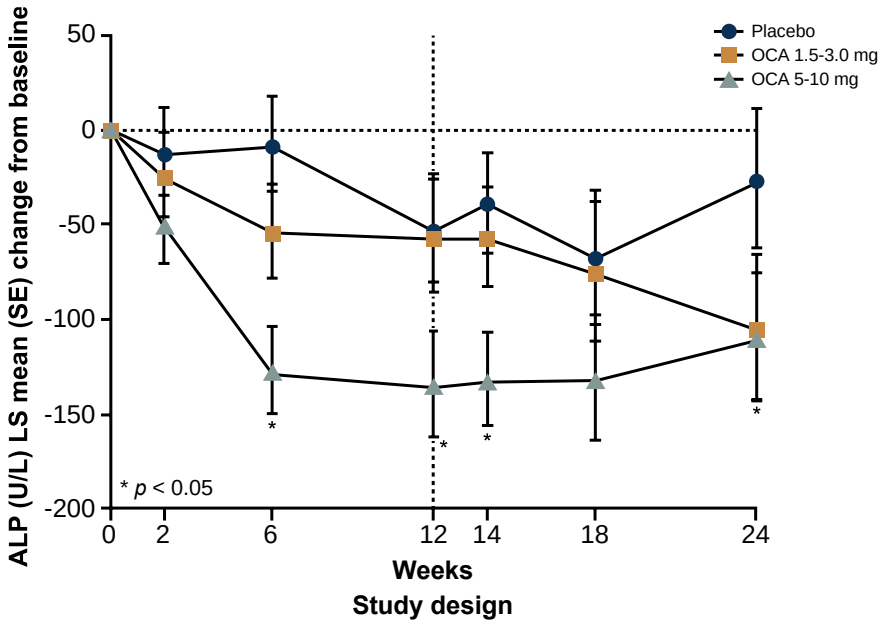
A Randomized, Placebo-Controlled, Phase II Study of Obeticholic Acid for Primary Sclerosing Cholangitis



Mean change from baseline in ALP over time by treatment group

Kowdley KV, et al. AESOP Study Investigators. A randomized, placebo-controlled, phase II study of obeticholic acid for primary sclerosing cholangitis. *J Hepatol*. 2020 Jul;73(1):94-101. doi: 10.1016/j.jhep.2020.02.033. Epub 2020 Mar 10. PMID: 32165251.

Fenofibrate and Benzafibrate

- 4 studies (2 each)
- Total of 46 patients
- Alk phos decrease promising
  - Range 30-54%
- Multicenter RCT Bezafibrate on itch in PBC and PSC ongoing

Results of Non-UDCA Trials in PSC

Therapy	References	N	Design	Lab inclusion criteria	Primary endpoint	Result ALP	Other results
Therapy targeting gut microbiota							
Vancomycin vs metronidazole	Tabibian et al. [137]	28	RCT Phase II-III Multicenter 12 weeks	ALP > 1.5*ULN	ΔALP at 12 weeks	Non-dose dependent ALP reduction in all 4 treatment arms (low vs high dose vancomycin or metronidazole)	
Vancomycin	Rahimpour et al. [138]	29	RCT 12 weeks	No	ΔMayo risk score	ALP reduction at 12 weeks; ΔALP – 18.2%	Reduced Mayo risk score
Metronidazole	Farkkila et al. 2004 [139]	80	RCT Phase III 36 months	No / not specified (possibly ALP or ALT > ULN)	ΔALP or other liver enzymes, Mayo risk score, symptoms or histology at 36 months	ALP reduction at 36 months; ΔALP – 52.4% vs – 37.7% in metronidazole + UDCA group vs UDCA + placebo group	Reduced Mayo risk score; higher proportion of patients showed histologic improvement of stage or grade
Minocycline	Silveira et al. [143]	16	Open-label pilot 12 months	ALP > 1.5*ULN	ΔALP at 12 months	ALP reduction at 12 months; ΔALP – 20%	Reduced Mayo risk score
Rifaximin	Tabibian et al. [140]	16	Open-label pilot 3 months	ALP > 1.5*ULN	50% ALP reduction at 3 months	No significant ALP reduction	No significant reduction in bilirubin, GGT, Mayo risk score
Fecal transplantation	Allegretti et al. [41]	10	Open-label pilot 24 weeks	ALP > 1.5*ULN	≥ 50% ALP reduction at week 24	30% (3/10) experienced a ≥ 50% decrease in ALP	
Immune modulating therapy							
All-trans retinoic acid	Assis et al. [115]	15	Open-label pilot 12 weeks	ALP > 1.5 x ULN on UDCA	ΔALP – 30% at 12 weeks	Non-significant ALP reduction; 3/15 achieved ≥ 30% ALP reduction	Reduced ALT and C4; ALT returned to pre-treatment values after washout period
Infliximab	Hommes et al. [167]	10	RCT 52 weeks	ALP > 2*ULN	≥ 50% ALP reduction at week 18	Failed to demonstrate effect in the n = 6 treatment group	No change in histologic stage or symptom scores

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Results of Non-UDCA Trials in PSC

Therapy	References	N	Design	Lab inclusion criteria	Primary endpoint	Result ALP	Other results
Other or undefined targets							
Cenicriviroc Anti-inflammatory effects (CCR2/CCR5 antagonist) PERSEUS trial	Completed, not published; results at clinicaltrials.gov	20	Open label Phase II 24 weeks	ALP > 1.5*ULN Bilirubin ≤ 2.0 mg/dL	ALP (%Δ)	50% (*n* = 10) of patients achieved ALP reduction to 1.5*ULN at 24 weeks. Mean ALP reduction – 4.5% at 24 weeks. No patients achieved ALP normalization or 50% ALP reduction	
Curcumin Anti-inflammatory effects, upregulation of PPAR-***γ***	Completed, not published	15	Phase I-II Open-label	ALP > 1.5*ULN	ALP 40% reduction or reduction to < 1.5*ULN	Results submitted to clinicaltrials.gov, but not posted	

Currently Registered and Ongoing Therapeutic Trials in Adult PSC

Therapy	Pathophysiologic target	Trial Phase	Design	Lab inclusion criteria	Primary endpoint	Secondary endpoint
Bile acid based therapy						
*Nor*UDCA	UDCA derivative Unknown receptor	III	Double-blind RCT Multicenter	No (?)	ALP partial normalization	Histology
Cilofexor	FXR agonist	III	Double-blind RCT	ALT ≤ 8*ULN Bilirubin ≤ 2.0 mg/mL	Histology	ΔALP Δother liver biochemistries ΔLSM (TE) + +
Therapy targeting PPAR						
Seladelpar	Selective PPAR-***δ*** agonist	II	Double-blind RCT	ALP ≥ 1.5*ULN and < 8*ULN Bilirubin ≤ 2*ULN ALT and AST ≤ 5*ULN Platelets ≥ 140,000	ΔALP at 24 w	LTX ΔMELD Hepatic decompensating events HCC
Bezafibrate	PPAR-***α*** agonist	III	Double-blind RCT	No	Proportion of patients reaching 50% reduction in itch intensity at 3 weeks	Δliver biochemistries Δautotaxin activity Δcholesterol, CK, creatinine
Therapy targeting gut microbiota						
Vancomycin	Antibiotic	III	Double-blind RCT Multicenter	ALP ≥ 1.5*ULN	ALP normalization at 6, 12, 18, 21, 24, months	ΔTE at 18 months

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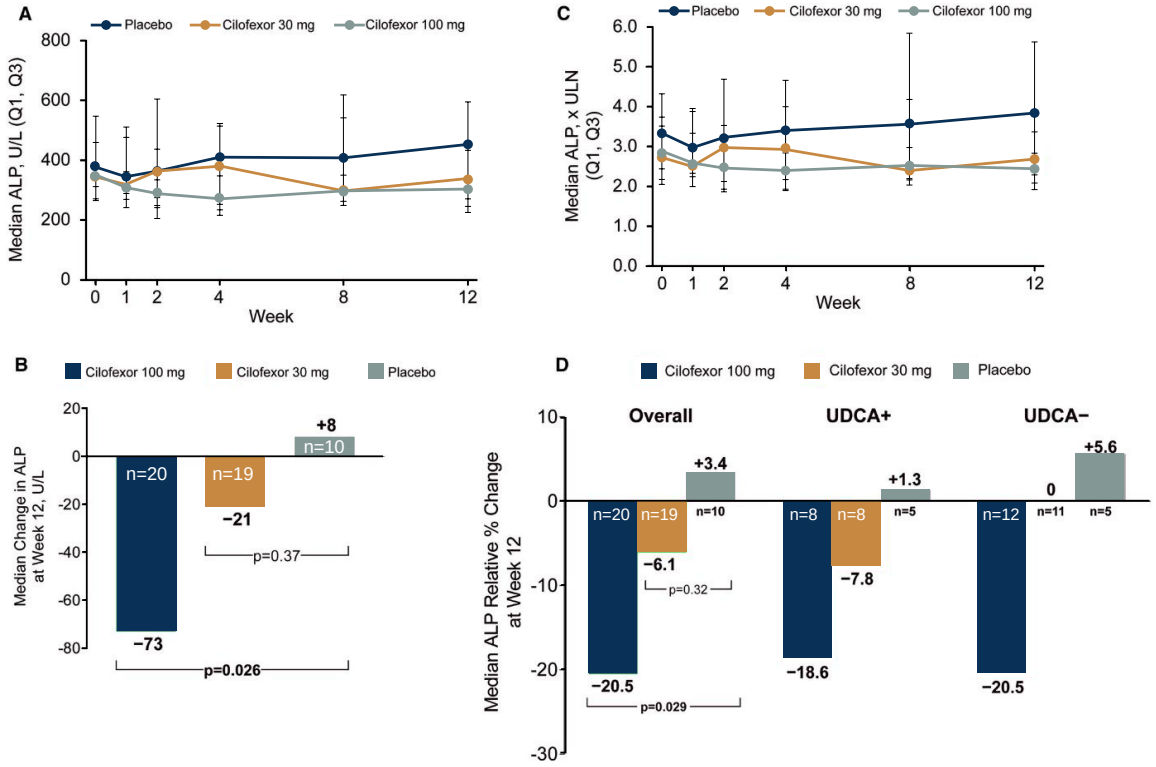
The Nonsteroidal Farnesoid X Receptor Agonist Cilofexor (GS-9674) Improves Markers of Cholestasis and Liver Injury in Patients With Primary Sclerosing Cholangitis



Hepatology. Volume: 70, Issue: 3, Pages: 788-801, First published: 19 January 2019, DOI: (10.1002/hep.30509).

Currently Registered and Ongoing Therapeutic Trials in Adult PSC

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Cilofexor	FXR agonist	III	Double-blind RCT	ALT ≤ 8*ULN Bilirubin ≤ 2.0 mg/mL	Histology	ΔALP Δother liver biochemistries ΔLSM (TE) + +
Therapy targeting PPAR						
Seladelpar	Selective PPAR-***δ*** agonist	II	Double-blind RCT	ALP ≥ 1.5*ULN and ≤ 3*ULN Bilirubin ≤ 2 ULN ALT and AST ≤ 5*ULN Platelets ≥ 140,000	ΔALP at 24 w	LTX ΔMELD Hepatic decompensating events HCC
Bezafibrate	PPAR-***α*** agonist	III	Double-blind RCT	No	Proportion of patients reaching 50% reduction in itch intensity at 3 weeks	Δliver biochemistries Δautotaxin activity Δcholesterol, CK, creatinine
Therapy targeting gut microbiota						
Vancomycin	Antibiotic	III	Double-blind RCT Multicenter	ALP ≥ 1.5*ULN	ALP normalization at 6, 12, 18, 21, 24, months	ΔTE at 18 months

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Currently Registered and Ongoing Therapeutic Trials in Adult PSC

Therapy	Pathophysiologic target	Trial Phase	Design	Lab inclusion criteria	Primary endpoint	Secondary endpoint
Immune modulating therapy						
Simvastatin	Immune modulating receptor?	III	Double-blind RCT Multicenter	No	Overall survival; Listing of liver transplantation Time to first varices bleeding or CCA, GBC, HCC	ΔALP Δbilirubin ΔMELD or ΔChild-Pugh MRCP progression ΔLSM (TE) or Δserum fibrosis markers Progression of symptoms, biliary dysplasia, colon cancer or dysplasia
Timolumab BTT1023 BUTEO trial	Anti-VAP-1 antibody	II	Open label	ALP > 1.5*ULN Stable ALP i.e. < 25% variation between screening visits 1 and 2	ALP 25% reduction by day 99	
All-trans retinoic acid	FXR/RXR complex activation	II	Open label ALP ≥ 1.5*ULN	ALP ≥ 1.5*ULN	ΔALP at 24 w	ALP > 1.5*ULN ΔALT Δbile acids ΔELF test ΔLSM (TE)
Sulfasalazine	Immune modulating	II	Double-blind RCT Multicenter	ALP ≥ 1.67*ULN Bilirubin ≤ 3 mg/dL INR ≤ 1.4 Platelets ≥ 100,000 MELD ≤ 10	APL ≥ 1.5 at 22 w	Δother liver biochemistries ΔMayo risk score Symptoms
Vidofludimus calcium	Blocks IL-17 production	II	Open label	ALP > 1.5*ULN Indirect bilirubin < 1.2*ULN	ΔALP at 3 and 6 months	Δother liver biochemistries IL-17 and IFNγ levels at 3 and 6 months

Vesterhus M, Karlsen TH. Emerging therapies in primary sclerosing cholangitis: pathophysiological basis and clinical opportunities. *J Gastroenterol.* **55,** 588–614 (2020). https://doi.org/10.1007/s00535-020-01681-z.

Conclusions – PSC

- Multiple mechanisms of action being evaluated
- No single agent ready for prime time
- Combination agents may be the ticket
- Surrogate endpoint of alkaline phosphatase and small numbers of patients challenge clinical trial conclusions

Hepatitis B: Cure? Really?

- Challenges
  - cccDNA eradication requires more than viral suppression
  - Clinical trial endpoint definition
- Many MOAs in trials
  - Antiviral
  - Immunomodulatory

Hepatitis B Drugs in Development by Stage

Table 1. Therapeutics in clinical development for chronic hepatitis B

Drug Class	Drug	Company	Phase 1	Phase 2	Phase 3
DAAs					
Core protein inhibitors	AB-506 ABI-H0731 ABI-H2158 EDP-514 JNJ-6379 JNJ-0440 RO7049389	Arbutus Biopharma Assembly Biosciences Assembly Biosciences Enanta Pharmaceuticals Johnson & Johnson Johnson & Johnson Roche	→	→	
siRNA, antisense RNA	AB-729 DCR-HBVS GSK/IONIS-HBV-L_{Rx} IONIS-HBV_{Rx} JNJ-3989 (ARO-HBV) RO7062931 Vir-2218 (ALN-HBV02)	Arbutus Biopharma Dicerna Pharmaceuticals Ionis/GlaxoSmithKline Ionis/GlaxoSmithKline Johnson & Johnson Roche Vir Biotechnology/Alnylam	→	→	
pol/RT inhibitor	Tenofovir exalidex	ContraVir Pharmaceuticals	→	→	
HBsAg secretion inhibitors	REP-2139 REP-2165	Replicor Replicor	→	→	
Indirect-acting antivirals and immunotherpeutics					
HBV entry inhibitor	Bulevirtide	Hepatera Ltd	→	→	
TLR-7 agonists	AL-034 RG-7854 RO7020531	Johnson & Johnson/Alios Roche Roche	→		
TLR-8 agonist	GS-9688	Gilead Sciences	→	→	
Therapeutic vaccines	AIC-649 INO-1800 TG1050	AiCuris Inovio Pharmaceuticals Transgene	→		
RIG-I and NOD2 agonist	Inarigivir	Spring Bank	→	→	
Apoptosis inducer	APG-1387	Ascentage Pharma	→		
FXR agonist	EYP-001	Enyo Pharma	→	→	

Abbreviations: NOD2, nucleotide-binding oligomerization domain-containing protein 2; RIG-I, retinoic acid-inducible gene-I.

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