SUPPLEMENTARY MATERIALS

SUPPLEMENTARY METHODS

The Cochrane risk of bias tool uses the following five specific domains to assess the quality of randomised controlled trials (RCTs): selection bias, performance bias, detection bias, attrition bias and reporting bias.

The Quality of Cohort studies (Q-Coh) tool assesses the risk of bias within non-randomised studies using eight domains: design of the study, representativeness, comparability of the groups, exposure measure, maintenance of the comparability, outcome measure, attrition and statistical analyses.

The National Institute of Health (NIH) assessment tool is recommended for studies without a control group.

Supplementary Table 1. Search terms, strings and strategy for the systematic literature review in (A) PubMed, (B) Embase, (C) Cochrane CENTRAL database and (D) WHO ICTRP database.

(A) Date of search: 31 March 2020

	Search #	Query	Number of citations
Disease	#1	("Pruritus"[Mesh]) AND (("Liver Cirrhosis, Biliary"[Mesh]) OR ("Cholestasis"[Mesh]))	864
	#2	("cholestatic pruritus") OR (("pruritus" OR "pruritus" OR itch*) AND (PBC OR "primary biliary cirrhosis" OR "primary biliary cholangitis" OR "cholestatic liver disease" OR "biliary liver cirrhosis" OR cholestasis OR PSC OR "primary sclerosing cholangitis"))	2112
	#3	#1 OR #2	2112
	#4	#3 NOT pregnancy	1604
Intervention	#5	drug OR treatment OR therapy OR cholestyramine OR Colestyramine OR colesevalam OR colestipol OR colestimide OR colestilan OR rifampicin OR rifampicin OR naltrexone OR nalmefene OR nalmetrene OR Nalfurafine OR Buprenorphine OR Naloxone OR sertraline OR gabapentin OR Phenobarbital OR phenobarbitone OR phenobarb OR Flumecinol OR Ondansetron OR Cimetidine OR Cetirizine OR Cyproheptadine OR Desloratadine OR Diphenhydramine OR Fexofenadine OR Hydroxyzine OR Loratadine OR Propofol OR Lidocaine OR Maralixibat OR Odevixibat OR Elobixibat OR Volixibat OR linerixibat OR Fenofibrate OR Bezafibrate OR "LPA inhibitors" OR "ATX inhibitors" OR Fibrates OR antibiotic OR "opiate antagonist" OR "serotonin reuptake inhibitor" OR barbituate OR "benzhydrol derivative" OR "5-HT3 antagonist" OR "H2 antagonist" OR anesthetic OR "bile acid sequestrant" OR anti-histamine OR antiepileptic OR anti-epileptic	13,324,940
Filters and Combination	#6	#4 AND #5	1297
	#7	#6 NOT (case reports[ptyp] OR letter[ptyp] OR comment[ptyp] OR editorial[ptyp] OR review[ptyp])	577

ATX, autotaxin; LPA, lysophosphatidic acid; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

(B) Date of search: 31 March 2020

	Search #	Query	Number of citations
Disease	#1	("cholestatic pruritus") OR (("pruritus" OR "pruritus" OR itch*) AND (PBC OR “primary biliary cirrhosis” OR "primary biliary cholangitis" OR "cholestatic liver disease" OR "biliary liver cirrhosis" OR cholestasis OR "chronic liver disease" OR PSC OR "primary sclerosing cholangitis"))	4557
Intervention	#2	drug OR treatment OR therapy OR cholestyramine OR Colestyramine OR colesevalam OR anti-histamine OR colestipol OR rifampicin OR rifampicin OR naltrexone OR nalmefene OR nalmetrene OR sertraline OR gabapentin OR Phenobarbital OR phenobarbitone OR phenobarb OR Cetirizine OR Cyproheptadine OR Desloratadine OR Diphenhydramine OR Fexofenadine OR Hydroxyzine OR Loratadine OR Nalfurafine OR Buprenorphine OR Naloxone OR Flumecinol OR Ondansetron OR Cimetidine OR Propofol OR Lidocaine OR Maralixibat OR Odevixibat OR Fenofibrate OR Bezafibrate OR "LPA inhibitors" OR "ATX inhibitors" OR Fibrates or colestimide or colestilan OR Elobixibat OR Volixibat OR linerixibat OR antibiotic OR "opiate antagonist" OR "serotonin reuptake inhibitor" OR barbituate OR "benzhydrol derivative" OR "5-HT3 antagonist" OR "H2 antagonist" OR anesthetic OR "bile acid sequestrant" OR antiepileptic OR anti-epileptic	16,946,819
Filters and Combinations	#3	#1 AND #2	35789
	#4	#3 NOT (case report OR nonhuman)	2317
	#5	#4 NOT ('intrahepatic cholestasis'/dm OR 'pregnancy complication'/dm)	1842
	#6	#5 NOT ('editorial'/it OR 'letter'/it OR 'review'/it OR 'short survey'/it)	1325

ATX, autotaxin; EMBASE, Excerpta Medica Database; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis

(C) Date of search: 31 March 2020

	Search #	Query	Number of citations
Disease	#1	("Pruritus") AND (("Biliary Liver Cirrhosis") OR ("Intrahepatic Cholestasis"))	53
	#2	("cholestatic pruritus") OR (("pruritus" OR "pruritus" OR itch*) AND (PBC OR “primary biliary cirrhosis” OR "primary biliary cholangitis" OR "cholestatic liver disease" OR "biliary liver cirrhosis" OR cholestasis OR PSC OR "primary sclerosing cholangitis"))	387
	#3	#1 OR #2	387
Intervention	#4	drug OR treatment OR therapy OR cholestyramine OR Colestyramine OR colesevalam OR anti-histamine OR colestipol OR rifampicin OR rifampicin OR naltrexone OR nalmefene OR nalmetrene OR sertraline OR gabapentin OR Phenobarbital OR phenobarbitone OR phenobarb OR Cetirizine OR Cyproheptadine OR Desloratadine OR Diphenhydramine OR Fexofenadine OR Hydroxyzine OR Loratadine OR Nalfurafine OR Buprenorphine OR Naloxone OR Flumecinol OR Ondansetron OR Cimetidine OR Propofol OR Lidocaine OR Maralixibat OR Odevixibat OR Fenofibrate OR Bezafibrate OR "LPA inhibitors" OR "ATX inhibitors" OR Fibrates or colestimide or colestilan OR Elobixibat OR Volixibat OR linerixibat OR antibiotic OR "opiate antagonist" OR "serotonin reuptake inhibitor" OR barbituate OR "benzhydrol derivative" OR "5-HT3 antagonist" OR "H2 antagonist" OR anesthetic OR "bile acid sequestrant" OR antiepileptic OR anti-epileptic	1,053,665
Filters and Combinations	#5	#4 AND #5	369

ATX, autotaxin; CENTRAL, Cochrane central register of controlled trials; LPA, lysophosphatidic acid; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

(D) Date of search: 12 March 2020

	Search #	Query	Number of citations
Disease	#1	Pruritus	1283
	#2	PBC OR primary biliary cholangitis OR cholestatic liver disease OR biliary liver cirrhosis OR cholestasis OR chronic liver disease	1280
Filters and Combinations	#3	#1 AND #2	41

PBC, primary biliary cholangitis; ICTRP, International Clinical Trials Registry Platform; WHO, World Health Organisation.

Supplementary Table 2. Inclusion and exclusion criteria for participants, interventions, outcomes and study design.

Category	Inclusion criteria	Exclusion criteria
Participants	• Adults (≥18 years) with cholestatic pruritus • ≥75% of participants with PBC or PSC	• Children/adolescents • Pruritus not related to cholestasis • >25% with non-PBC/PSC liver disease
Interventions	• **Bile acid sequestrants:** cholestyramine, colesevelam, colestipol, colestimide • **Antibiotics:** Rifampicin • **Opiate antagonists:** naltrexone, nalmefene, nalfurafine, buprenorphine, naloxone • **Serotonin reuptake inhibitor:** sertraline • **Antiepileptic:** gabapentin • **Barbiturate/benzhydrol derivative:** phenobarbital, flumecinol • **5-HT3 antagonist / H2 antagonist:** ondansetron, cimetidine • **Antihistamines:** cetirizine, cyproheptadine, desloratadine, diphenhydramine, fexofenadine, hydroxyzine, loratadine • **Anaesthetics:** propofol, lidocaine • **IBAT inhibitors:** elobixibat,linerixibat, maralixibat, odevixibat, volixibat • **Fibrates:** Fenofibrate, bezafibrate • **ATX and LPA inhibitors** • **Placebo/best supportive care**	• Non-pharmacologic treatment • Treatments targeting the underlying liver disease but not associated pruritus: UDCA, obeticholic acid, cyclosporine, methotrexate, colchicine

Outcomes	**Efficacy**
	• Pruritus meaure
	  ○ Numerical rating scale
	  ○ Visual analogue scale
	  ○ Adult itch reported outcome
	  ○ PBC-40/PBC-27 itch domain
	  ○ 5-D itch scale
	  ○ Measurements from activity monitoring devices
	Safety
	• Treatment-emergent adverse events
	• Treatment related adverse events
	• Serious adverse events
	• Specific adverse events
	• Withdrawals
	  ○ Due to adverse events
	  ○ Due to lack of efficacy
	HRQoL and other PROs
	• PBC-40/PBC-27
	• Generic measures (e.g., EQ-5D, SF-36, etc.)
	• Depression
	• Satisfaction with study medication
	• Patient Global Impression of Change
		• Relevant outcomes not reported

Study design	**Randomised controlled trials** • Parallel group • Crossover • Cluster **Non-randomised studies** • No restrictions on observational studies • No restrictions on design features	• Preclinical studies • Case reports

Timeframe/setting	• No restrictions on duration of follow-up • No restrictions on geographic setting • No restrictions on clinical setting	N/A
Report characteristics	• No temporal limit applied in the database searches • No restrictions on publication language • No restrictions on publication format or status	• Reviews • Letters • Comments • Case reports • Editorials

ATX, autotaxin; EQ-5D, EuroQol five-dimension scale; HRQoL, health-related quality of life; IBAT, ileal bile acid transporter; LPA, lysophosphatidic acid; N/A, not applicable; PBC, primary biliary cholangitis; PRO, patient-reported outcome; PSC, primary sclerosing cholangitis; SF-36, 36-Item Short Form survey; UDCA, ursodeoxycholic acid.

Supplementary Table 3. Key information extracted from relevant studies.

Data extraction fields	Information extracted
Study characteristics	Name, citation, related publications, objective, geography, single- or multi-centre, date, sponsorship, design, statistical methods, eligibility criteria, interventions, primary and secondary endpoints, duration, conclusions, assumptions, limitations and generalisability
Treatment characteristics	Treatments, administration, dosage(s) and schedule(s), concomitant treatments, duration, sample size for efficacy and/or safety
Baseline characteristics	Number of PBC or PSC patients, PBC or PSC histological stages, gender, age, primary liver diagnosis, baseline laboratory values, PBC treatment, prior and current pruritus treatments, comorbidities, BMI, history of transplant, outcome measurements of interest
Efficacy outcomes	NRS, VAS, pruritus severity reduction and/or improvement, adult ItchRO, PBC-40/PBC-27 itch domain, 5-D itch scale, measurements from activity monitoring devices, interference of itch on sleep, measures of fatigue (e.g., FACIT)
Safety outcomes	AEs, SAEs, treatment-related AEs and any AE specifically monitored, total withdrawals, withdrawals due to AEs, withdrawals due to lack of efficacy
Health-related quality of life and other PROs	PBC-40/PBC-27, EQ-5D/SF-36, depression, PROs related to patient satisfaction and impression of change

AEs, adverse events; BMI, body mass index; EQ-5D, EuroQol-5D; FACIT, Functional Assessment of Chronic Illness Therapy; NRS, numerical rating scale; PBC, primary biliary cholangitis; PRO, patient-reported outcome; PSC, primary sclerosing cholangitis; SAEs, serious AEs; SF-36, 36-Item Short Form survey; VAS, visual analogue scale.

Supplementary Table 4. Overview of pruritus efficacy measures and outcomes of included clinical trials

Study	Assessment	Timepoint	Interventions and dosage	N	Efficacy findings
Anion-exchange resins (n=8)					
Zuin 1991 [63]	Pruritus NRS: severe = 3; moderate = 2; slight = 1; none = 0	Baseline, Month 2	Cholestyramine 8–16 g/day	11	0.99 [mean; P<0.01]
		Baseline, Month 2	DEAE-Dextran 4–6 g/day	19	1.04 [mean; P<0.01]
	Disappearance of pruritus: severe = 3, moderate = 2, slight = 1, none = 0	Month 2	Cholestyramine 8–16 g/day	11	n=5 (45.5%)
		Month 2	DEAE-Dextran 4–6 g/day	19	n=7 (36.8%)
Datta 1966 [36]	Pruritus severity/intensity reduction/improvement	Month 13.2 (8.2) [mean (SD)]	Cholestyramine 3.3–10g/day	20	Relieved: n=14 Partial relief: n=3 No relief: 4
Van Berge Henegouwen 1974 [58]	Pruritus NRS: - no pruritus; + sporadic pruritus without scratch effects, only occurring during a warm environment; ++ moderate intermittent pruritus with scratch effects on the skin; +++ severe, often intolerable pruritus, present day and night, with scratch effects.	Baseline, Week 5	Cholestyramine 8–12 g/day	8	-1.71 (0.49) [mean (SD)] PBC patient with pruritus score of +++, only had + after treatment. 7 patients with pruritus score of ++ and +++ had no more pruritus. (5 patients with a pruritus score of ++ and 2 patients with + had no more pruritus at all during administration of cholestyramine.)
	Pruritus severity/intensity reduction/improvement: 1	Week 5		8	Intensity reduction: n=1 No pruritus: n=7
Taha 1994 [53]	Pruritus VAS median (IQR) (0, no pruritus; 100, severe pruritus preventing sleep)	Baseline, Week 2	Cholestyramine 4 g BID	8	18.43 (5.84, 40,85) mm
		Baseline, Week 2	None	8	33.27 (21.56, 75.08) mm
		Baseline, Week 2	UDCA 750 mg/day–12 mg/kg/day	8	28.97 (14.99, 50.13) mm
		Baseline, Week 2	Cholestyramine + UDCA 4 g BID + 750 mg/day–12 mg/kg/day	8	27.81 (16.73, 51.86) mm
Kuiper 2010 [41]	Pruritus severity/intensity reduction/improvement): ≥40% reduction in morning pruritus VAS	Baseline, Day 21	Colesevelam 1.875 g BID	17	6 (36.0%); Itch intensity 44 mm
		Baseline, Day 21	Placebo	18	6 (35.0%); Itch intensity 38 mm
Yokomori 2001 [14]	Pruritus NRS: from 1 (no itching) to 10 (severe and constant itching), via self-administered questionnaire containing 6 questions proposed by Ingham [68] and Lowrie et al. [69]	Week 4	UDCA 600 mg/day (8 weeks)	6	3.8 (0.4) [mean (SEM); nonsignificant vs baseline]
		Week 8	UDCA 600 mg/day (4 weeks)	5	2.5 (0.3) [mean (SEM); nonsignificant vs baseline]

		Week 4	UDCA 600 mg/day-colestilan 6.4 g/day (4 weeks)	5	1.2 (0.2) [mean (SEM); p<0.05 vs baseline]
Floreani 1988 [38]	Pruritus severity/intensity reduction/improvement: assayed by an intensity scale	Day 15	DEAE-Dextran 3000–6000 mg	12	Complete disappearance: n=5 Decrease: n=2 No change: n=5
		Day 15	Placebo	12	No change: n=12
Duncan 1984 [37]	Pruritus NRS: cumulative scores for the last 10 days of each treatment period (0 = no pruritus, 1 = mild, 2 = moderate, 3 = severe)	Baseline, Week 2	Cholestyramine 4 g BID	8	12.88 (8.82) [mean (SD)]; difference from placebo: -7.38 (7.21) [mean (SD)]
		Baseline, Week 2	Terfenadine 60 mg TID	8	15.75 (5.97) [mean (SD)]; difference from placebo: -4.50 (4.31) [mean (SD)]
		Baseline, Week 2	Chlorpheniramine 4 mg TID	8	19.25 (7.36) [mean (SD)]; difference from placebo: -1.00 (5.04) [mean (SD)]
		Baseline, Week 2	Placebo (lactose) 200 mg TID	8	20.25 (5.42) [mean (SD)
Antibiotics (n=8)					
Bachs 1992 [32]	Pruritus NRS: 3+ = continuous pruritus disturbing sleep pattern; 2+ = moderate pruritus present most of the time but tolerable and not interfering with sleep pattern; 1+ = mild intermittent pruritus which did not affect the patient's routine or disturb sleep pattern; 0 = no itching	Week 2	Rifampicin 10 mg/kg/day	16	Week 2: 0.6 (0.1) [mean (SE); degree; P<0.001 vs baseline]
		Month 3		14	Month 3: 0.2 (0.1) [mean (SE); P<0.001 vs baseline]
		Month 6		10	Month 6: 0.4 (0.2) [mean (SE); P<0.001 vs baseline]
		Month 9		10	Month 9: 0.3 (0.1) [mean (SE); P<0.001 vs baseline]
		Month 12		10	Month 12: 0 (0) [mean (SE); P<0.001 vs baseline]
		Month 15		9	Month 15: 0 (0) [mean (SE); P<0.001 vs baseline]
		Month 18		4	Month 18: 0 (0) [mean (SE); P<0.001 vs baseline]
		Month 24		2	Month 24: 0 (0) [mean (SE); P<0.001 vs baseline]
Loginov 1993 [44]	Measurements after the 2-week course of treatment. Scale for measure of intensity of pruritus not reported	Week 2	Rifampicin 450–600 mg/day	7	Significant decrease: 3 Complete resolution: 4
Webb 2018 [60]	Patients who reported resolution of pruritus and stopped taking rifampicin	n/a	Rifampicin 150–600 mg/day	105	17 (16.2%) 9 (8.6%) reported a lack of efficacy despite dose uptitration

Ghent 1988 [39]	Pruritus VAS: consisted of a card with a 100-mm line on which patients marked their itch severity ranging from none (0) to severe (100)	Baseline, Day 7, Day 14, Week 1, Week 2	Rifampicin 300–450 mg/day	9	Day 7: 29.2751 (mean) Day 14: 34.6058 (mean) Week 1: 265.7435 (mean) Week 2: 176.5454 (52.4262) [mean (SD)]
		Baseline, Day 7, Day 14, Week 1, Week 2	Placebo	9	Day 7: 49.4160 (mean) Day 14: 53.4190 (mean) Week 1: 408.5261 (66.2490) [mean (SD)] Week 2: 346.0124 (97.2144) [mean (SD)]
Podesta 1991 (RCT) [49]	Pruritus severity/intensity reduction/improvement: full response (pruritus disappeared) or partial response (50% reduction in pruritus scores)	Week 1	Rifampicin 300 mg BID	14	Full response: n=11 Partial response: n=3
		Week 1	Placebo	14	Full response: n=0 Partial response: n=2
	Change in Pruritus VAS: A scale from 0 to 100 where 100 = pruritus that interfered with sleep, altered daily activities, or resulted in self-inflicted skin breakdown. The pruritus score reported corresponds to the mean of the last 2 days of each period	Baseline, Week 1	Rifampicin 300 mg BID	14	-65.93 (23.08) [mean (SD)]
		Baseline, Week 1	Placebo	14	16.43 (33.71) [mean (SD)]
Podesta 1991 (OL) [49]	Pruritus severity/intensity reduction/improvement): Full response (pruritus disappeared) or partial response (50% reduction in pruritus scores)	8.2 (4.2) months [Mean (SD)]	Rifampicin 300 mg BID	18	Full response: 17 Partial response: 1
Tabibian 2017 [52]	5-D itch scale	Week 12	Rifaximin 1100 mg	13	7 (6–8) [median (IQR)]
Bachs 1989 [31]	Pruritus NRS: 3+ = continuous pruritus disturbing sleep pattern; 2+ = moderate pruritus present most of the time but tolerable and not interfering with sleep pattern; 1+ = mild intermittent pruritus which did not affect the patient's routine or disturb sleep pattern; 0 = no itching	Week 2	Rifampicin 10 mg/kg/day	21	0.8 (0.9) [mean (SD)]; -1.57 (0.81) [mean (SD); change from baseline/washout]
		Week 2	Phenobarbitone 3 mg/kg	18	1.4 (0.9) [mean (SD)]; -0.33 (0.69) [mean (SD); change from baseline/washout]
	Pruritus severity/intensity reduction/improvement	Week 2	Rifampicin 10 mg/kg/day	21	Pruritus improved (disappeared): n=19 (n=9)
		Week 2	Phenobarbitone 3 mg/kg	18	Pruritus improved (disappeared): n=8 (n=0)
Oral opiate agents (n=7)					
Yagi 2018 [62]	Pruritus VAS	Week 12	Nalfurafine hydrochloride 2.5 µg/day	44	29.3 (24.64) [mean (SD)]

Thornton 1988 [55]	Pruritus VAS: Pruritus was measured daily for 2 weeks before the study and then for 2 weeks at 1, 3, and 6 months; patients scored their pruritus on a VAS consisting of a 10 cm line ranging from "no itching" to "very itchy"	Month 1	Nalmefene 20-40 mg TID	9	Month 1: 0.2 (0.0-2.4); 0.5722 (0.8588) [median (range); mean (SD)]
		Month 3		9	Month 3: 0.2 (0.0-2.6); 0.6474 (0.8247) [median (range); mean (SD)]
		Month 6		8	Month 6: 0.3 (0.0-1.8); 0.4257 (0.6077) [median (range); mean (SD)]
Bergasa 1992 [33]	VAS: Mean (SD) change in mean VAS (%) relative to placebo number of centimetres (to the nearest millimetre) between 0 cm (i.e., no itching) and the point on the scale at which the patient made a mark; maximum is 10 cm (i.e., worst itching ever). Measured by scratching activity monitoring system designed specifically for this purpose; in units of counts per unit time	Baseline, 24 hours per infusion	Naloxone 0.2 µg/kg/min (total volume infused per 24 hours = 0.5L)	8	19.38% (68.53) Measured by scratching activity monitoring system designed specifically for this purpose; in units of counts per unit time
Summerfield 1980 [51]	Change in Pruritus VAS: this was a 10 cm horizontal line on a white card marked at the left end 'none' and at the right end 'unbearable'. The patient assessed the previous night's itching by marking a point along this line. The VAS were later estimated to within 1 mm. Patients could not refer to earlier assessments. The results were expressed as the change in itch score between the treatment night and the previous night	Baseline, Night 4	Naloxone 2 mg QD via IV for 5 months	20	-0.95 [mean; paired t-test vs PBO t=0.152]
		Baseline, Night 4	Placebo	20	1.33 [mean]
Terg 2002 (RCT) [54]	Pruritus VAS: Scale of 0 (absence of pruritus) to 10 (pruritus interfered with sleep, altered daily activities or resulted in self-inflicted skin breakdown); daytime pruritus was assessed before retiring to sleep while night-time pruritus was assessed at wake-up	Baseline, Week 2	Naltrexone-Placebo 50 mg/day	11	Daytime pruritus: 3.91 (2.39) [at the end of naltrexone treatment; mean (SD)] Night-time pruritus: 3.89 (2.17) [at the end of naltrexone treatment; mean (SD)]
		Baseline, Week 4	Placebo-Naltrexone 50 mg/day	9	Daytime pruritus: 3.06 (2.47) [at the end of naltrexone treatment; mean (SD)] Night-time pruritus: 3.05 (2.77) [at the end of naltrexone treatment; mean (SD)]
		Baseline, 2 weeks	Naltrexone 50 mg/day	18	Daytime pruritus: 3.55 (2.39) [at the end of naltrexone treatment; mean (SD)] Night-time pruritus: 3.55 (2.42) [at the end of naltrexone treatment; mean (SD)]
		Baseline, 2 weeks	Placebo	18	Daytime pruritus: 5.34 (2.41) [at the end of placebo treatment; mean (SD)] Night-time pruritus: 5.19 (2.55) [at the end of placebo treatment; mean (SD)]
Terg 2002 (OL) [54]	Ongoing response to treatment following RCT		Naltrexone 50 mg/day	7	Sustained response: 5

					Exacerbation of pruritus: 2
Wolfhagen 1997 [61]	Change in Pruritus VAS: the VAS scale consisted of 100-mm horizontal line without marks. The left side (0 mm) was labelled "no itching" and the right side (100 mm) was labelled "unbearable itching"	Baseline, Week 4	Naltrexone 50 mg/day	7	Daytime: -37.3992 (6.6136) [mean (SE)] % Change: -58.39% (9.47%) [mean (SEM)] Night-time: -29.9804 (10.6726) [mean (SE)] % Change: -44.58% (12.81%) [mean (SEM)]
		Baseline, Week 4	Placebo	8	Daytime: 3.1033 (4.2705) [mean (SE)] % Change: 8.1% (10.4%) [mean (SEM)] Night-time: 0.3433 (4.1284) [mean (SE)] % Change: 7.6% (9.4%) [mean (SEM)]
Selective Serotonin Reuptake Inhibitors (n=2)					
Mayo 2007 [45]	Pruritus severity/intensity reduction/improvement: at least 20% reduction in pruritus from baseline	Week 6	Sertraline (variable dosing)	12	n=8
		Week 6	Placebo	12	n=0
	Change in Pruritus VAS from baseline: measure in a daily itch diary where a continuous scale of exactly 100mm in length from 0 (no pruritus) to 10 (the worst pruritus imaginable) with points anchored and with facial expressions to guide patient's selection	Baseline, Week 6	Sertraline (variable dosing)	12	Reported mean change: -1.86
		Baseline, Week 6	Placebo	12	Reported mean change: 0.38
Ataei 2019 [30]	Pruritus VAS: 0–10 (at 4 weeks)	Baseline, Week 4	Sertraline 100 mg	18	3.33 (1.68) [mean (SD)]
		Baseline, Week 4	Rifampicin 300 mg	18	3.44 (2.749) [mean (SD)]
Fibrates (n=6)					
Kanda 2003 [40]	NR		Bezafibrate + UDCA 400 mg/day–600 mg/day	NR	NR
			UDCA 600 mg/day		
Reig 2018 [50]	Pruritus severity/intensity reduction/improvement: 38 months (median)	38 months (median)	Bezafibrate and continue UDCA 400 mg	26	No change: 1 Party disappeared: n=7 Completely disappeared: n=16
			None (discontinued bezafibrate) continue UDCA	NR	NR
	Pruritus VAS: Median (IQR) Presence and severity of pruritus was assessed before treatment and at the end of the observation period using the VAS from 0–10)	Month 38 (median)	Bezafibrate and continue UDCA 400 mg	26	0 (0, 1.4)
		Baseline, Month 3	None (discontinued bezafibrate) continue UDCA	11	4.6 (3.7, 6.5)
Corpechot 2018 [35]		Month 3	Bezafibrate 400 mg	49	Month 3: 0.0566 (0 - 2.9525) [median (IQR)]

	Pruritus VAS: itch intensity score (0–10 VAS, with 0 indicating no itch and 10 indicating the worst itch imaginable)	Month 12		47	Month 12: 0.0792 (0 - 1.9570) [median (IQR)]
		Month 24		47	Month 24: 0.0566 (0 - 1.4706) [median (IQR)]
		Month 3	Placebo	46	Month 3: 2.7376 (0.2036 - 5.9502) [median (IQR)]
		Month 12		44	Month 12: 2.3869 (0.0226 - 5.9502) [median (IQR)]
		Month 24		40	Month 24: 2.3303 (0.9955 - 4.9434) [median (IQR)]
de Vries 2019 [64]	Pruritus severity/intensity reduction/improvement: ≥50% reduction in pruritus (VAS)	Week 3	Bezafibrate 400 mg	37	n=14 (38.0%)
		Week 3	Placebo	33	n=4 (12.0%)
Levy 2011 [7]	Pruritus severity/intensity reduction/improvement: 0 = absent; 1 = mild; 2 = moderate; and 3 = severe	Week 48	Fenofibrate 160 mg	20	Stable: 44.0% Improved: 28.0% Deteriorated: 28.0%
Lemoinne 2018 [42]	Pruritus severity/intensity reduction/improvement: Intensity of pruritus was defined on a semi-quantitative scale: grade 0, none: grade 1, mild; grade 2, moderate; grade 3, severe	1.56 years (0.56-5.12)	Fibrate 200 mg/day or 400 mg/day	8	Improved: n=7
IBAT Inhibitors (n=3)					
Hegade 2017 [20]	Pruritus NRS: Itch Intensity. Absolute score difference vs placebo [LS mean (SE)]	Week 2	Linerixibat 90 mg BID	21	LS mean (SE): 1.58 (0.450)
		Week 2	Linerixibat 90 mg BID – Sequence 1	11	LS mean (SE); 95% CI: 2.66 (0.733; 1.17, 4.15)
		Week 2	Linerixibat 90 mg BID – Sequence 2	10	LS mean (SE); 95% CI: 1.58 (0.755; 0.05, 3.11)
		Week 2	Placebo – Sequence 1	11	LS mean (SE); 95% CI: 2.80 (0.733; 1.31, 4.29)
		Week 2	Placebo – Sequence 2	10	LS mean (SE); 95% CI: 4.60 (0.755; 3.07, 6.13)
	PBC-40/PBC-27 itch domain	Week 2	Linerixibat 90 mg BID	21	LS mean (SE): -0.59 (0.176)
		Week 2	Linerixibat 90 mg BID – Sequence 1	11	LS mean (SE); 95% CI: 2.73 (0.343); 2.03, 3.43
		Week 2	Linerixibat 90 mg BID – Sequence 2	10	LS mean (SE); 95% CI: 1.99 (0.349); 1.28, 2.70)
		Week 2	Placebo – Sequence 1	11	LS mean (SE); 95% CI: 2.61 (0.343); 1.90, 3.31)

		Week 2	Placebo – Sequence 2	10	LS mean (SE); 95% CI: 3.29 (0.349); 2.58, 4.00)
	5-D itch scale	Week 2	Linerixibat 90 mg BID	21	Degree (1-5) [LS mean (SE)]: [-0.65 (0.207)] Direction (1-5) [LS mean (SE)]: [-0.92 (0.298)] Disability (1-5) [LS mean (SE)]: [-1.03 (0.294)] Distribution (1-5) [LS mean (SE)]: [-1.03 (0.247)] Duration (1-5) [LS mean (SE)]: [-0.92 (0.293)] Domain (5-25) [LS mean (SE)]: [-4.55 (1.030)]
		Week 2	Linerixibat 90 mg BID – Sequence 1	11	Degree (1-5) [LS mean (SE); 95% CI]: [2.45 (0.276); 1.90, 3.01)] Direction (1-5) [LS mean (SE); 95% CI]: [2.64 (0.311); 2.02, 3.25)] Disability (1-5) [LS mean (SE); 95% CI]: [3.36 (0.360); 2.64, 4.08)] Distribution (1-5) [LS mean (SE); 95% CI]: [3.00 (0.413); 2.16, 3.84)] Duration (1-5) [LS mean (SE); 95% CI]: [1.55 (0.421); 0.70, 2.39)] Overall domain (5-25) [LS mean (SE); 95% CI]: [13.00 (1.342); 10.31, 15.69)]
		Week 2	Linerixibat 90 mg BID – Sequence 2	10	Degree (1-5) [LS mean (SE); 95% CI]: [1.96 (0.285); 1.39, 2.53)] Direction (1-5) [LS mean (SE); 95% CI]: [2.18 (0.326); 1.53, 2.83)] Disability (1-5) [LS mean (SE); 95% CI]: [2.29 (0.374); 1.54, 3.04)] Distribution (1-5) [LS mean (SE); 95% CI]: [2.47 (0.422); 1.61, 3.32)] Duration (1-5) [LS mean (SE); 95% CI]: [1.22 (0.433); 0.35, 2.09)] Overall domain (5-25) [LS mean (SE); 95% CI]: [10.13 (1.388); 7.35, 12.91)]
		Week 2	Placebo – Sequence 1	11	Degree (1-5) [LS mean (SE); 95% CI]: [2.55 (0.276); 1.99, 3.10)]

					Direction (1-5) [LS mean (SE); 95% CI]: [3.27 (0.311); 2.65, 3.89)] Disability (1-5) [LS mean (SE); 95% CI]: [3.73 (0.360); 3.01, 4.45)] Distribution (1-5) [LS mean (SE); 95% CI]: [3.45 (0.413); 2.62, 4.29)] Duration (1-5) [LS mean (SE); 95% CI]: [2.09 (0.421); 1.24, 2.94)] Overall domain (5-25) [LS mean (SE); 95% CI]: [15.09 (1.342); 12.40, 17.78)]
		Week 2	Placebo – Sequence 2	10	Degree (1-5) [LS mean (SE); 95% CI]: [3.16 (0.285); 2.59, 3.73)] Direction (1-5) [LS mean (SE); 95% CI]: [3.38 (0.326); 2.73, 4.03)] Disability (1-5) [LS mean (SE); 95% CI]: [3.99 (0.374); 3.24, 4.74)] Distribution (1-5) [LS mean (SE); 95% CI]: [4.07 (0.422); 3.21, 4.92)] Duration (1-5) [LS mean (SE); 95% CI]: [2.52 (0.433); 1.65, 3.39)] Overall domain (5-25) [LS mean (SE); 95% CI]: [17.13 (1.388); 14.35, 19.91)]
Mayo 2019 [47]	Adult Itch RO	Week 13/ET	Maralixibat 10 mg	21	Week 13/ET Absolute value [mean (SD)]: 6.7 ± 2.92 Week 13/ET LS mean change from baseline (95% CI): -4.0 (-5.3, -2.8) Week 13/ET LS mean difference from placebo (95% CI): -0.3 (-2.0, 1.5)
		Week 13/ET	Maralixibat 20 mg	21	Week 13/ET Absolute value [mean (SD)]: 24.4 ± 19.93 Week 13/ET LS mean change from baseline (95% CI): -27.3 (-34.8, -19.8) Week 13/ET LS mean difference from placebo (95% CI): -4.0 (-14.2, 6.2) n: 21
		Week 13/ET	Placebo	23	Week 13/ET Absolute value [mean (SD)]: 27.5 ± 19.69 Week 13/ET LS mean change from baseline (95% CI): -23.4 (-30.3, -16.4) n: 24

	PBC-40/PBC-27	Week 13/ET	Maralixibat 10 mg	21	Week 13/ET Absolute value [mean (SD)]: 6.7 ± 2.92
		Week 13/ET	Maralixibat 20 mg	21	Week 13/ET Absolute value [mean (SD)]: 6.3 ± 2.88
		Week 13/ET	Placebo	23	Week 13/ET Absolute value [mean (SD)]: 7.2 ± 3.76
	5-D itch scale	Week 13/ET	Maralixibat 10 mg	21	Week 13/ET Absolute value [mean (SD)]: 12.1 ± 3.97 Week 13/ET LS mean change from baseline (95% CI): -6.9 (-8.9, -4.8) Week 13/ET LS mean difference from placebo (95% CI): -0.5 (-3.4, 2.3)
		Week 13/ET	Maralixibat 20 mg	21	Week 13/ET Absolute value [mean (SD)]: 12.4 ± 4.69 Week 13/ET LS mean change from baseline (95% CI): -6.7 (-8.8, -4.6) Week 13/ET LS mean difference from placebo (95% CI): -0.4 (-3.2, 2.5)
		Week 13/ET	Placebo	23	Week 13/ET Absolute value [mean (SD)]: 12.7 ± 5.63 Week 13/ET LS mean change from baseline (95% CI): -6.3 (-8.3, -4.4
Al-Dury 2018 [18]	PBC-40/PBC-27 itch domain	4 weeks	Selective IBAT inhibitor (A4250/odevixibat) 0.75 mg/day or 1.5 mg/day or 3 mg/day	4	Overall domain score: 4.50 (2.38) [mean (SD)]
		4 weeks	Cholestyramine or Colestipol	4	Overall domain score: 10.50 (3.32) [mean (SD)]
Other (n=8)					
Turner 1990 [56]	Pruritus VAS: 100 mm VAS (0=no itch, 100= severe, continuous day and night intolerable itch) - last 7 days	Baseline, Week 3	Flumecinol 600 mg	21	30.7 [mean; pruritus level fell significantly compared with placebo (p=0.017; ANOVA)]
		Baseline, Week 3	Placebo	20	37.3 [mean]
Turner 1994 (LD) [57]	Change in Pruritus VAS: For each patient, mean VAS scores (itching and quality of life) for consecutive 7-day periods of observation were computed as summary measures	Baseline, Week 3	Flumecinol 600 mg	24	-9.4 (-29, -2) [Median (IQR)] median difference vs PBO: -8.0 (-20.8, 2.1) [median (95% CI)]
		Baseline, Week 3	Placebo	26	-4.2 (-13, 6) [Median (IQR)]
Turner 1994 (HD) [57]	Change in Pruritus VAS: For each patient, mean VAS scores (itching and quality of life) for	Baseline, Week 3	Flumecinol 300 mg	10	-21.7 (-28, -12) [Median (IQR)] median difference vs PBO: -19.8 (-40.7, -3.3) [median (95% CI)]

	consecutive 7-day periods of observation were computed as summary measures	Baseline, Week 3	Placebo	9	-21.7 (-28, -12) [Median (IQR)]
Villamil 2005 [59]	Pruritus VAS: used average over 7 days using "The mean of the values of the daily visual analogue scale scores for the 7 days of the study were analyzed" Patients were asked to record the severity of their pruritus on a VAS at baseline and every 12 hours (before going to bed and after awakening) for the following 7 days. Scales were designed according to standard principles and consisted of 100-mm horizontal lines without intermediate marks	7 days	Lidocaine 100 mg IV over 5 minutes	11	50.5 (25.4) [mean (SD)]
		7 days	Placebo	5	71.7 (8.9) [mean (SD)]
Mayo 2018 [46]	Pruritus VAS: VAS: visual analogue scale; Improved: decrease of 20% or greater from baseline value; Worsened: increase of 20% or greater from baseline value	Baseline, Day 28	NGM282 3 mg SC	7	Improved: 3 No change: 2 Worsened: 0 Missing/not reported: 2 Change in VAS score: 12.6 (24.9) [mean (SD)] −4.5 (−13.2, 4.3) [LSM (95% CI); vs placebo]
		Baseline, Day 28	Placebo	10	Improved: 3 No change: 5 Worsened: 1 Missing/not reported: 1
Mayo 2019 (NGM282) [47]	NRS (ranging from 0–10) at week 12	Week 12	NGM282 1 mg	21	Change from baseline: 0.01 [LS mean] difference vs placebo: -0.47 (-1.93–0.99) [mean (95% CI)]
		Week 12	NGM282 3 mg	21	Change from baseline: -0.32 [LS mean] difference vs placebo: -0.52 (-1.96–0.92) [mean (95% CI)]
		Week 12	Placebo	20	Change from baseline: 0.36 [LS mean]
Bloomer 1975 [34]	Pruritus NRS: 0 = None, 1 = mild, 2 = moderate, 3 = Marked. Average duration of Pruritus therapy (months) = 2.86 (1.41) [mean (SD)]	2.86 (1.41) months	Phenobarbital 120 mg/day–250 mg/day	9	0.67 (0.5) [mean (SD)] Change from baseline: -1.11 (0.78) [mean (SD)]
O'Donohue 2005 [48]	Pruritus severity/intensity reduction/improvement: >50% reduction in the severity of pruritus (VAS) vs Day 0	Day 1, Day 5	Ondansetron 8 mg BID; IV injection (Day 1) + oral (Day 1–5)	9	n=2 (Day1) n=1 (5-day treatment period)
		Day 1, Day 5	Placebo (saline)	10	n=1 (Day1) n=2 (5-day treatment period)

	Change in Pruritus VAS: 0 = no pruritus and 10 = the worst imaginable pruritus	Baseline, Day 1, Day 5	Ondansetron 8 mg BID; IV injection (Day 1) + oral (Day 1–5)	9	17.0% (mean reduction Day 1 vs Day 0) 21.0% (mean reduction over 5-day treatment period vs Day 0);
		Baseline, Day 1, Day 5	Placebo (saline)	10	17.0% (mean reduction Day 1 vs Day 0) 22.0% (mean reduction over 5-day treatment period vs Day 0)

ANOVA, analysis of variance; BID, twice daily; CI, confidence interval; DEAE, diethylaminoethyl; ET, early termination; IBAT, ileal bile acid transporter; IQR, interquartile range; IV, intravenous; LS, least squares; n/a, not available; NR, not reported; NRS, numerical rating scale; OL, open label; PBC, primary biliary cholangitis; PBO, placebo; QD, once daily; RCT, randomised controlled trial; SD, standard deviation; SE, standard error; SEM, standard error of the mean; TID, three times daily; UDCA, ursodeoxycholic acid; VAS, visual analogue scale.

Supplementary Table 5. Overview of safety data from included clinical trials.

Study	Interventions	N	Treatment-related AEs	Treatment-related SAEs	Withdrawals due to AEs	AEs occurring in ≥5% of patients, n (%)
Anion-exchange resins (n=8)						
Datta 1966 [36]	Cholestyramine 3.3–10.0 g/day	17	NR	NR	NR	NR
Van Berge Henegouwen 1974 [58]	Cholestyramine 8–12 g/day	NR	NR	NR	0	NR
Duncan 1984 [37]	Cholestyramine 4 g BID	8	NR	NR	2	Diarrhoea, n=4 (50.0) Vomiting, n=2 (25.0)
	Terfenadine 60 mg TID	8	NR	NR	0	Emotional lability (rapid changes in mood), n=1 (12.5)
	Chlorpheniramine 4 mg TID	8	NR	NR	0	Drowsiness, n=2 (25.0) Headache, n=1 (12.5)
	Placebo (lactose) 200 mg TID	8	NR	NR	1	Nausea, n=1 (12.5) Cutaneous burning, n=1 (12.5)
Floreani 1988 [38]	DEAE-dextran 3000–6000 mg vs placebo	NR	NR	NR	NR	NR
Zuin 1991 [63]	Cholestyramine 8–16 g/day	15	NR	NR	NR	Diarrhoea, n=6 (40.0) Constipation, n=1 (6.7) Abdominal pain, n=1 (6.7)
	DEAE-Dextran 4–6 g/day	19	NR	NR	NR	Diarrhoea, n=3 (15.8) Abdominal pain, n=2 (10.5)
Taha 1994 [53]	Cholestyramine 4 g BID vs no treatment vs UDCA vs cholestyramine 4 g BID + UDCA 750 mg/day–12 mg/kg/day	8	NR	NR	NR	NR
Yokomori 2001 [14]	UDCA 600 mg/day (8 weeks)	6	0	0	NR	NR
	UDCA 600 mg/day (4 weeks)	5	0	0	NR	NR
	UDCA-colestilan (4 weeks)	5	0	0	NR	NR
Kuiper 2010 [41]	Colesevelam 1.875 g BID vs placebo	NR	NR	NR	NR	NR

Antibiotics (n=8)						
Ghent 1988 [39]	Rifampicin 300-450 mg/day	9	0	0	0	NR
	Placebo	9	0	0	0	NR
Bachs 1989 [31]	Rifampicin 10 mg/kg	22	1	NR	1	NR ≥5%
	Phenobarbitone 3 mg/kg	21	3	NR	3	Rash, 3 (14.3)
Podesta 1991 (RCT) [49]	Rifampicin	14	0	0	0	NR
	Placebo	14	0	0	0	NR
Podesta 1991 (OL) [49]	Rifampicin	18	NR	NR	NR	NR
Bachs 1992 [32]	Rifampicin 10 mg/kg/day	16	NR	NR	6	Liver transplantation, n=3 (18.8) Toxic hepatitis, n=2 (12.5) Peripheral oedema, n=1 (6.3)
Loginov 1993 [44]	Rifampicin 450–600 mg	7	NR	NR	1	Upper abdominal pain, n=2 (28.6) Nausea, n=1 (14.3) Drop in leukocyte level, n=1 (14.3)
Tabibian 2017 [52]	Rifaximin 1100 mg	16	NR	NR	3	Headache, n=2 (12.5) Dyspepsia, n=2 (12.5) Dizziness, n=1 (6.3) Rapid increase in liver enzymes, n=1 (6.3) Endoscopic retrograde cholangiography: n=1 (6.3)
Webb 2018 [60]	Rifampicin 150–600 mg/day	105	NR	NR	19	Liver transplantation, n=21 (20.0) Hepatitis, n=5 (4.8)
Oral opiate agents (n=8)						
Summerfield 1980 [51]	Naloxone: 2 mg QD via IV for 5 months vs placebo	NR	NR	NR	NR	NR
Thornton 1988 [55]	Nalmefene 20–40 mg TID	9	NR	NR	1	Severe opioid withdrawal, n=9 (100) Bilirubin increase, n=1 (11.1) Deepening jaundice, n=1 (11.1)
Bergasa 1992 [33]	Naloxone 0.2 µg/kg/min (total volume infused per 24 hours = 0.5L)	8	0	0	NR	NR
	Placebo (5% dextrose/0.45% NaCl)	8	0	0	NR	NR
Wolfhagen 1997 [61]	Naltrexone	8	NR	NR	0	Abdominal cramps, n=5 (62.5) Opioid withdrawal, n=4 (50.0) Nausea, n=4 (50.0) Dizziness, n=3 (37.5) Drowsiness, n=2 (37.5) Dry mouth, n=2 (25.0) Flushing, n=2 (25.0) Headache, n=1 (12.5) Tremor, n=1 (12.5)

						Peripheral oedema, n=1 (12.5) Nightmares, n=1 (12.5) Night sweating, n=1 (12.5)
	Placebo	8	NR	NR	0	Abdominal cramps, n=1 (12.5) Dry mouth, n=1 (12.5) Night sweating, n=1 (12.5) Epistaxis, n=1 (12.5) Swelling of the hands, n=1 (12.5)
Terg 2002 (RCT) [54]	Naltrexone 50 mg/day	20	NR	NR	2	Dizziness, n=10 (50.0) Nausea, n=8 (40.0) Vomiting, n=6 (30.0) Abdominal cramps, n=5 (25.0) Headache, n=5 (25.0) Asthenia, n=3 (15.0) Drowsiness, n=3 (15.0) Irritability, n=3 (15.0) Dry mouth, n=3 (15.0) Insomnia, n=2 (10.0) Tremor, n=1 (5.0) Tachycardia, n=1 (5.0) Anorexia, n=1 (5.0) Flushing, n=1 (5.0) Hypertension, n=1 (5.0)
	Placebo	20	NR	NR	0	Headache, n=3 (15.0) Vomiting, n=2 (10.0) Drowsiness, n=2 (10.0) Irritability, n=2 (10.0) Abdominal cramps, n=1 (5.0) Nausea, n=1 (5.0)
Terg 2002 (OL) [54]	Naltrexone 50 mg/day	7	NR	NR	NR	NR
Yagi 2018 [62]	Nalfurafine hydrochloride 2.5 µg/day	NR	NR	NR	NR	NR
Selective serotonin reuptake inhibitors (n=2)						
Mayo 2007 [45]	Sertraline (variable dosing) initial dose of 25 mg QD, increased in 25 mg increments at 4-week intervals to a maximum of 100 mg QD.	21	NR	NR	1	Insomnia, n=3 (14.3) Fatigue, n=2 (9.5) Liver transplantation, n=2 (9.5) Increased bowel frequency, n=2 (9.5) Visual hallucinations, n=2 (9.5) Nausea, n=1 (4.8) Dizziness, n=1 (4.8)
	Placebo	12	NR	NR	1	Insomnia, n=6 (50)

						Fatigue, n=2 (16.7) Nausea, n=1 (8.3)
Ataei 2019 [30]	Sertraline 100 mg	18	NR	NR	0	Nausea, n=3 (16.7)
	Rifampicin 300 mg	18	NR	NR	0	Nausea, n=1 (5.6)
Fibrate (n=6)						
Kanda 2003 [40]	Bezafibrate 400 mg/day + UDCA 600 mg/day	11	NR	0	0	Polydipsia, n=1 (9.1)
	UDCA 600 mg/day	11	NR	0	0	NR
Levy 2011 [43]	Fenofibrate 160 mg	20	NR	NR	2	Heartburn, n=5 (25.0) Nausea, n=3 (15.0) Diarrhoea, n=2 (10.0) Elevated ALT and AST, n=2 (10.0) Fatigue, n=1 (5.0) Dishydrotic eczema, n=1 (5.0) Renal insufficiency, n=1 (5.0) Arthralgia, n=1 (5.0) Weight gain, n=1 (5.0) Increased appetite, n=1 (5.0) Hot flushes, n=1 (5.0) Rigours, n=1 (5.0) Nasopharyngitis, n=1 (5.0)
Reig 2018 [50]	Bezafibrate 400 mg/day and continue UDCA 13–16 mg/kg/day	48	NR	0	NR	NR
Corpechot 2018 [35]	Bezafibrate 400 mg QD for 24 months	50	NR	NR	1	Myalgia, n=10 (20.0) Nasopharyngitis, n=9 (18.0) Abdominal pain, n=7 (14.0) Arthralgia, n=7 (14.0) Depressive mood, n=7 (14.0) Flu-like syndrome, n=5 (10.0) Bronchitis, n=4 (8.0) Pruritus, n=4 (8.0)
	Placebo	50	NR	NR	2	Arthralgia, n=11 (22.0) Nasopharyngitis, n=10 (20.0) Bronchitis, n=9 (13.0) Depressive mood, n=8 (16.0) Pruritus, n=7 (14.0) Diarrhoea, n=6 (12.0) Abdominal pain, n=6 (12.0) Myalgia, n=5 (10.0) Flu-like syndrome, n=5 (10.0)

Lemoinne 2018 [42]	Fibrate 200 mg/day or 400 mg/day	20	NR	NR	10	Carcinoma (gall bladder), n=1 (5.0)
de Vries 2019 [64]	Bezafibrate 400 mg vs placebo	NR	NR	NR	NR	NR
IBAT inhibitor (n=3)						
Hegade 2017 [20]	Linerixibat 90 mg BID	21	NR	0	0	Diarrhoea, n=7 (33.0) Headache, n=6 (29.0) Upper abdominal pain, n=3 (14.0) Abdominal distension, n=3 (14.0) Abdominal pain, n=3 (14.0) Nausea, n=2 (10.0) Nasopharyngitis, n=2 (10.0) Fatigue, n=2 (10.0) Vomiting, n=1 (5.0) Dizziness, n=1 (5.0)
	Placebo	21	NR	0	0	Headache, n=7 (33.0) Vomiting, n=2 (10.0) Dizziness, n=2 (10.0) Paraesthesia/dysaesthesia, n=2 (10) Diarrhoea, n=1 (5.0) Upper abdominal pain, n=1 (5.0) Abdominal distension, n=1 (5.0)
Al-Dury 2018 [18]	Odevixibat 0.75 mg/day or 1.5 mg/day or 3 mg/day	10	NR	NR	5 [abdominal pain (5/5), diarrhoea (4/5), melena and significantly decreased haemoglobin (1/5)]	NR
Mayo 2019 [21]	Maralixibat 10 mg	20	15 (75.0)	1 (5.0)	1 (5.0)	Diarrhoea, n=14 (70.0) Nausea, n=5 (25.0) Upper abdominal pain, n=4 (20.0) Abdominal pain, n=4 (20.0) Abdominal distension, n=3 (15.0) Fatigue, n=3 (15.0) Headache, n=3 (15.0)
	Maralixibat 20 mg	21	15 (71.4)	0	0	Diarrhoea, n=11 (52.4) Upper abdominal pain, n=6 (28.6) Abdominal pain, n=5 (23.8) Nausea, n=4 (19.0) Headache, n= 2 (9.5)
	Placebo	24	11 (45.8)	0	0	Headache, n=8 (33.3)

						Diarrhoea, n=6 (25.0) Upper abdominal pain, n=2 (8.3) Abdominal distension, n=3 (12.5) Nausea, n=4 (16.7) Pruritus, n=3 (12.5)
Other (n=8)						
Bloomer 1975 [34]	Phenobarbital 120–250 mg/day	9	NR	NR	1	Drowsiness, 9 (100) Gastrointestinal bleeding, n=2 (22.2) Rash, 1 (11.1)
Turner 1990 [56]	Flumecinol 600 mg vs placebo	NR	NR	NR	NR	NR
Turner 1994 (LD) [57]	Flumecinol 600 mg	24	NR	NR	0	NR
	Placebo	26	NR	NR	0	NR
Turner 1994 (HD) [57]	Flumecinol 300 mg	10	NR	NR	0	NR
	Placebo	9	NR	NR	0	NR
Villamil 2005 [59]	Lidocaine 100 mg IV over 5 minutes	12	NR	NR	NR	Tinnitus (mild), n=5 (41.7) Paraesthesia/dysaesthesia (lingual), n=2 (16.7)
	Placebo IV over 5 minutes	6	NR	NR	NR	NR
O'Donohue 2005 [48]	Ondansetron 8 mg BID	9	NR	NR	0	Constipation, n=4 (44.4)
	Placebo (saline)	10	NR	NR	0	Nausea, n=3 (30.0) Headache, n=2 (20.0) Bilirubin increase, n=1 (10.0)
Mayo 2018 [46]	NGM282 0.3 mg SC	14	3 (21.4)	0	0	Diarrhoea, n=3 (21.4) Nausea, n=2 (14.3) Headache, n=2 (14.3) Mouth ulceration, n=2 (14.3) Dry eye, n=2 (14.3) Upper respiratory tract infection, n=2 (14.3) Injection-site bruising/erythema, 1 (7.1)
	NGM282 3 mg SC	16	11 (68.8)	0	1	Diarrhoea, n=4 (25.0) Headache, n=4 (25.0) Increased appetite, n=4 (25.0) Abdominal pain, n=2 (12.5) Nausea, n=2 (12.5) Fatigue, n=2 (12.5) Injection-site bruising/erythema, n=2 (12.5) Loose stools/faecal urgency, n=2 (12.5) Faces discoloured/pale, n=2 (12.5) Vitamin D deficiency, n=2 (12.5) Mouth ulceration, n=1 (6.3) Upper respiratory tract infection, n=1 (6.3)

	Placebo SC	15	7 (46.7)	0	1	Abdominal pain, n=4 (26.7) Injection-site bruising/erythema, n=3 (20.0) Upper respiratory tract infection, n=3 (20.0) Diarrhoea, n=1 (6.7) Nausea, n=1 (6.7) Fatigue, n=1 (6.7) Headache, n=1 (6.7) Loose stools/faecal urgency, 1 (6.7)
Mayo 2019 (NGM 282) [47]	NGM282 1 mg SC	21	NR	NR	NR	Pruritus, n=1, (5.0)
	NGM282 3 mg SC	21	NR	NR	NR	Pruritus, n=1, (5.0)
	Placebo SC	20	NR	NR	NR	Pruritus, n=2, (10.0)

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate transferase; BID, twice daily; DEAE, diethylaminoethyl; HD, high dose; IV, intravenous; LD, low dose; NaCl, sodium chloride; NR, not reported; OL, open label; QD, once daily; RCT, randomised controlled trial; QD, once daily; SAEs, serious AEs; SC, subcutaneous; TID, three-times daily; UDCA, ursodeoxycholic acid.