SUMMARY

~~**[0008a]** In an aspect of the present disclosure, there is provided an oligonucleotide for reducing expression of CYP27A1, the oligonucleotide comprising an antisense strand comprising a sequence as set forth in any one of SEQ ID NOs: 579-580, 598-614, 763-766, 786, and 788.~~

[~~0008b~~0008a] In an~~other~~ aspect of the present disclosure, there is provided an oligonucleotide for reducing expression of CYP27A1, the oligonucleotide comprising an antisense strand of 15 to 30 nucleotides in length, wherein the antisense strand has a region of complementarity to CYP27A1 that is complementary to at least 15 contiguous nucleotides of a sequence as set forth in SEQ ID NOs: 577-578, 581-597, 759-761, 785, 787, and 767-781, further comprising a sense strand of 19 to 50 nucleotides in length, wherein the sense strand comprises at its 3′-end a stem-loop set forth as: S_1-L-S_2, wherein S_1 is complementary to S_2, and wherein L forms a loop between S_1 and S_2 of 3 to 5 nucleotides in length, and wherein the antisense strand and the sense strand form a duplex region of at least 15 nucleotides in length but are not covalently linked.

[~~0008c~~0008b] In ~~a further~~another aspect of the present disclosure, there is provided an oligonucleotide for reducing expression of CYP27A1, the oligonucleotide comprising an antisense strand and a sense strand,

wherein the antisense strand is 21 to 27 nucleotides in length and comprises at least 15 contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 763-765 and 792~~has a region of complementarity with CYP27A1~~,

wherein the sense strand is 32 to 40 nucleotides in length and comprises at its 3′-end a stem-loop set forth as: S_1-L-S_2, wherein S_1 is complementary to S_2, and wherein L forms a loop between S_1 and S_2 of 3 to 5 nucleotides in length, and wherein the sense strand comprises at least 15 contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 759-761,

and wherein the antisense strand and the sense strand form a duplex region ~~structure~~ of at least 19 nucleotides in length but are not covalently linked.

[0008c] In a further aspect of the present disclosure, there is provided an oligonucleotide for reducing expression of CYP27A1, the oligonucleotide comprising a pair of sense and antisense strands selected from a row of the table

Sense Sequence/mRNA seq	S SEQ ID NO	Antisense Sequence	AS SEQ ID NO
UGCUACAUCCUGUUCGAGAAG CAGCCGAAAGGCUGC	577	UUCUCGAACAGGAUG UAGCAAA	579
UGCUACAUCCUGUUCGAGA_G CAGCCGAAAGGCUGC	785	UCUCGAACAGGAUGU AGCAAA	786
CAGAACUCACUCUAUGCCACG CAGCCGAAAGGCUGC	578	GUGGCAUAGAGUGA GUUCUGGA	580
CAGAACUCACUCUAUGCCA_G CAGCCGAAAGGCUGC	787	UGGCAUAGAGUGAG UUCUGGA	788
CGGAUGCUUUCAAUGAGGUAG CAGCCGAAAGGCUGC	581	UACCUCAUUGAAAGC AUCCGGG	598
AUGAGGUGAUUGAUGACUUUG CAGCCGAAAGGCUGC	582	AAAGUCAUCAAUCAC CUCAUGG	599
AGGUGAUUGAUGACUUUAUAG CAGCCGAAAGGCUGC	583	UAUAAAGUCAUCAAU CACCUGG	600
GUGAUUGAUGACUUUAUGAAG CAGCCGAAAGGCUGC	584	UUCAUAAAGUCAUCA AUCACGG	601
AUUGAUGACUUUAUGACUCAG CAGCCGAAAGGCUGC	585	UGAGUCAUAAAGUCA UCAAUGG	602
UCUACUACUUUGCCUUGGAAG CAGCCGAAAGGCUGC	586	UUCCAAGGCAAAGUA GUAGAGG	603
CUACUUUGCCUUGGAAGCUAG CAGCCGAAAGGCUGC	587	UAGCUUCCAAGGCAA AGUAGGG	604
AUUUGCUACAUCCUGUUCGAG CAGCCGAAAGGCUGC	588	UCGAACAGGAUGUAG CAAAUGG	605
UUGCUACAUCCUGUUCGAGAG CAGCCGAAAGGCUGC	589	UCUCGAACAGGAUGU AGCAAGG	606
UGUUCCAGAACUCACUCUAUG CAGCCGAAAGGCUGC	590	AUAGAGUGAGUUCU GGAACAGG	607
AGAAGCUGAUUGAUGAGAAAG CAGCCGAAAGGCUGC	591	UUUCUCAUCAAUCAG CUUCUGG	608
AGGACUUUGCCCACAUGCCAG CAGCCGAAAGGCUGC	592	UGGCAUGUGGGCAAA GUCCUGG	609
UCCCGGAUCAUAGAAAAGGAG CAGCCGAAAGGCUGC	593	UCCUUUUCUAUGAUC CGGGAGG	610
CGGAUCAUAGAAAAGGAAAUG CAGCCGAAAGGCUGC	594	AUUUCCUUUUCUAUG AUCCGGG	611
GAAAUUGAAGUUGAUGGCUUG CAGCCGAAAGGCUGC	595	AAGCCAUCAACUUCA AUUUCGG	612
AAGGCUGAUCCAGAAGUACAG CAGCCGAAAGGCUGC	596	UGUACUUCUGGAUCA GCCUUGG	613
GUCCUUGGGUAGAAUAUAAAG CAGCCGAAAGGCUGC	597	UUUAUAUUCUACCCA AGGACGG	614
CGGAACGCUACAAUUUUUAUG CAGCCGAAAGGCUGC	759	AUAAAAAUUGUAGC GUUCCGGU	763
ACAAUUUUUAUUCCAGCUAUG CAGCCGAAAGGCUGC	760	AUAGCUGGAAUAAA AAUUGUAG	764
ACGAGGUUAUCAGUGACUUUG CAGCCGAAAGGCUGC	761	AAAGUCACUGAUAAC CUCGUUU	765
UGCUACAUCCUGUUCGAGAAG CAGCCGAAAGGCUGC	577	UUCUCGAACAGGAUG UAGCAGG	791
ACAAUUUUUAUUCCAGCUAUG CAGCCGAAAGGCUGC	760	AUAGCUGGAAUAAA AAUUGUGG	792

.

[0008d] In another aspect of the present disclosure, there is provided a composition comprising an oligonucleotide disclosed herein, and an excipient.

[0008e] In a further aspect of the present disclosure, there is provided a composition disclosed herein, for use in delivering an oligonucleotide to a subject.

[0008f] In another aspect of the present disclosure, there is provided a use of the oligonucleotide disclosed herein, or a composition disclosed herein, in the manufacture of a medicament for attenuating bile acid accumulation in liver of a subject, decreasing the extent of liver fibrosis in a subject, and/or decreasing circulating bile acid concentrations in a subject.

~~**[0008g]** In a further aspect of the present disclosure, there is provided a use of a composition disclosed herein, in the manufacture of a medicament for decreasing the extent of liver fibrosis in a subject in need thereof.~~

~~**[0008h]** In another aspect of the present disclosure, there is provided a use of a composition disclosed herein, in the manufacture of a medicament for decreasing circulating bile acid concentrations in a subject in need thereof.~~

[~~0008i~~0008g] In a further aspect of the present disclosure, there is provided a composition disclosed herein for use in attenuating bile acid accumulation in liver of a subject, decreasing the extent of liver fibrosis in a subject, and/or decreasing circulating bile acid concentrations in a subject.

~~**[0008j]** In another aspect of the present disclosure, there is provided an oligonucleotide for reducing expression of CYP27A1, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand of 15 to 30 nucleotides in length, wherein the sense strand forms a duplex region with the antisense strand, wherein the sense strand comprises a sequence as set forth in any one of SEQ ID Nos: 577-578, 581-597, 759-762, 785, and 787 and wherein the antisense strand comprises a complementary sequence selected from SEQ ID Nos: 579-580, 598-614, 763-766, 786, and 788.~~

~~**[0008k]** In a further aspect of the present disclosure, there is provided an oligonucleotide for reducing expression of CYP27A1, the oligonucleotide comprising a pair of sense and antisense strands selected from a row of the table set forth in Appendix A.~~

[0009] Examples of the disclosure relate to compositions and related methods for reducing expression of genes affecting liver metabolic functions, particularly genes affecting bile acid levels in a subject. In some examples, the disclosure relates to a recognition that CYP27A1 is a useful target for the treatment of hepatobiliary diseases, particularly such diseases that are associated with bile acid accumulation. In further examples it has been discovered that oligonucleotides for reducing expression or activity of CYP27A1 are useful for treating conditions in which the accumulation of bile acids in the liver contributes to cellular toxicity (*e.g.*, to toxicity hepatocytes and/or cholangiocytes) and/or promotes liver fibrosis. Accordingly, in some examples, the disclosure relates to the use of oligonucleotides, including RNAi oligonucleotides, antisense oligonucleotides, and other similar modalities, for reducing expression or activity of CYP27A1 for the treating of

hepatobiliary diseases, including, for example, cholestasis, cholangitis, nonalcoholic steatohepatitis (NASH) and/or alagille syndrome.

[00010] In further examples, potent RNAi oligonucleotides have been developed for selectively inhibiting CYP27A1 expression in a subject. In some examples, the RNAi oligonucleotides are useful for reducing CYP27A1 activity, and thereby decreasing or preventing the accumulation of bile acid in a subject. In some examples, key regions of CYP27A1 activity mRNA (referred to as hotspots) have been identified herein that are particularly amenable to targeting using such oligonucleotide-based approaches (See Example 1). In some examples, oligonucleotides developed herein to inhibit CYP27A1 expression are useful for reducing or preventing liver fibrosis associated with bile acid accumulation (see, e.g., Example 1, FIG. 7 and FIG. 8).

[00011] One example of the present disclosure provides oligonucleotides for reducing expression of CYP27A1. In some examples, the oligonucleotides comprise an antisense strand comprising a sequence as set forth in any one of SEQ ID NOs: 579-580, 598-614, 763-766, 786, and 788. In some examples, the oligonucleotides further comprise a sense strand that comprises a sequence as set forth in any one of SEQ ID NOs: 577-578, 581-597, 759-762, 785, and 787. In some examples, the antisense strand consists of a sequence as set forth in any one of SEQ ID NOs: 579-580, 598-614, 763-766, 786, and 788. In some examples, the sense strand consists of a sequence as set forth in any one of SEQ ID NOs: 577-578, 581-597, 759-762, 785, and 787.

[00012] One example of the present disclosure provides oligonucleotides for reducing

CLAIMS

What is claimed is:

~~1. An oligonucleotide for reducing expression of CYP27A1, the oligonucleotide comprising an antisense strand comprising a sequence as set forth in any one of SEQ ID NOs: 579-580, 598-614, 763-766, 786, and 788.~~

~~2. The oligonucleotide of claim 1, further comprising a sense strand comprises a sequence as set forth in any one of SEQ ID NOs: 577-578, 581-597, 759-762, 785, and 787.~~

~~3. The oligonucleotide of claim 1 or 2, wherein the antisense strand consists of a sequence as set forth in any one of SEQ ID NOs: 579-580, 598-614, 763-766, 786, and 788.~~

~~4. The oligonucleotide of any one of claims 1 to 3, wherein the sense strand consists of a sequence as set forth in any one of SEQ ID NOs: 577-578, 581-597, 759-762, 785, and 787.~~

~~5~~1. An oligonucleotide for reducing expression of CYP27A1, the oligonucleotide comprising an antisense strand of 15 to 30 nucleotides in length, wherein the antisense strand has a region of complementarity to CYP27A1 that is complementary to at least 15 contiguous nucleotides of a sequence as set forth in SEQ ID NOs: 577-578, 581-597, 759-761, 785, 787, and 767-781, further comprising a sense strand of 19 to 50 nucleotides in length, wherein the sense strand comprises at its 3′-end a stem-loop set forth as: S_1-L-S_2, wherein S_1 is complementary to S_2, and wherein L forms a loop between S_1 and S_2 of 3 to 5 nucleotides in length, and wherein the antisense strand and the sense strand form a duplex region of at least 15 nucleotides in length but are not covalently linked.

~~6. The oligonucleotide of claim 1, wherein the antisense strand is 19 to 27 nucleotides in length.~~

~~7. The oligonucleotide of claim 1, wherein the antisense strand is 21 to 27 nucleotides in length.~~

~~8. The oligonucleotide of any one of claims 2 to 4, wherein the sense strand is 15 to 50 nucleotides in length, wherein the sense strand forms a duplex region with the antisense strand.~~

~~9. The oligonucleotide of claim 5, wherein the sense strand is 19 to 50 nucleotides in length.~~

~~10~~2. The oligonucleotide of claim ~~5 or 6~~1, wherein the antisense strand and the sense strand form a duplex region ~~is~~ of at least 19 nucleotides in length.

~~11~~3. The oligonucleotide of claims 1 or 2~~any one of claims 1 to 7~~, wherein the region of complementarity ~~with~~ to CYP27A1 is complementary to at least 19 contiguous nucleotides of a sequence as set forth in SEQ ID NOs: 577-578, 581-597, 759-761, 785, 787, and 767-781.

~~12~~4. The oligonucleotide of any one of claims ~~5~~ 1 to ~~9~~3, wherein the sense strand comprises at least 15 contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 577-578, 581-597, 759-~~762~~761, 785, and 787.

~~13. The oligonucleotide of any one of claims 10, wherein the antisense strand comprises a sequence as set forth in any one of SEQ ID NOs: 579-580, 598-614, 763-766, 786, and 788.~~

5. The oligonucleotide of claim 4, wherein the sense strand comprises at least 16 contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 577-578, 581-597, 759-761, 785, and 787.

6. The oligonucleotide of claim 4, wherein the sense strand comprises at least 17 contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 577-578, 581-597, 759-761, 785, and 787.

7. The oligonucleotide of claim 4, wherein the sense strand comprises at least 18 contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 577-578, 581-597, 759-761, 785, and 787.

8. The oligonucleotide of claim 4, wherein the sense strand comprises at least 19 contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 577-578, 581-597, 759-761, 785, and 787.

9. The oligonucleotide of any one of claims 1-8, wherein the antisense strand comprises at least 15 contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 579-580, 598-614, 763-765, 786, 788, and 792.

10. The oligonucleotide of claim 9, wherein the antisense strand comprises at least 16 contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 579-580, 598-614, 763-765, 786, 788, and 792.

11. The oligonucleotide of claim 9, wherein the antisense strand comprises at least 17 contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 579-580, 598-614, 763-765, 786, 788, and 792.

12. The oligonucleotide of claim 9, wherein the antisense strand comprises at least 18 contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 579-580, 598-614, 763-765, 786, 788, and 792.

13. The oligonucleotide of claim 9, wherein the antisense strand comprises at least 19 contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 579-580, 598-614, 763-765, 786, 788, and 792.

14. The oligonucleotide of any one of claims ~~5~~ 1 to ~~9~~13, wherein the sense strand consists of a sequence as set forth in any one of SEQ ID NOs: 577-578, 581-597, 759-~~762~~761, 785, and 787.

15. The oligonucleotide of any one of claims ~~10~~1 to 14, wherein the antisense strand consists of a sequence as set forth in any one of SEQ ID NOs: 579-580, 598-614, 763-~~766~~765, 786, ~~and~~ 788, and 792.

~~16. The oligonucleotide of any one of claims 8 to 15, wherein the sense strand comprises at its 3′-end a stem-loop set forth as: S_1-L-S_2, wherein S_1 is complementary to S_2, and wherein L forms a loop between S_1 and S_2 of 3 to 5 nucleotides in length.~~

~~17~~16. An oligonucleotide for reducing expression of CYP27A1, the oligonucleotide comprising an antisense strand and a sense strand,

wherein the antisense strand is 21 to 27 nucleotides in length and comprises at least 15 contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 763-765 and 792~~has a region of complementarity with CYP27A1~~,

wherein the sense strand is 32 to 40 nucleotides in length and comprises at its 3′-end a stem-loop set forth as: S_1-L-S_2, wherein S_1 is complementary to S_2, and wherein L forms a loop between S_1 and S_2 of 3 to 5 nucleotides in length, and wherein the sense strand comprises at least 15 contiguous nucleotides of a sequence as set forth in any one of SEQ ID NOs: 759-761,

and wherein the antisense strand and the sense strand form a duplex region~~structure~~ of at least 19 nucleotides in length but are not covalently linked.

~~18. The oligonucleotide of claim 17, wherein the region of complementarity is complementary to at least 19 contiguous nucleotides of CYP27A1 mRNA.~~

17. The oligonucleotide of claim 16, wherein the antisense strand comprises at least 16 contiguous nucleotides of a sequence as set forth in SEQ ID NO: 763, and the sense strand comprises at least 16 contiguous nucleotides of a sequence as set forth in SEQ ID NO: 759.

18. The oligonucleotide of claim 16, wherein the antisense strand comprises at least 16 contiguous nucleotides of a sequence as set forth in SEQ ID NO: 764, and the sense strand comprises at least 16 contiguous nucleotides of a sequence as set forth in SEQ ID NO: 760.

19. The oligonucleotide of claim 16, wherein the antisense strand comprises at least 16 contiguous nucleotides of a sequence as set forth in SEQ ID NO: 765, and the sense strand comprises at least 16 contiguous nucleotides of a sequence as set forth in SEQ ID NO: 761.

20. The oligonucleotide of claim 16, wherein the antisense strand comprises at least 17 contiguous nucleotides of a sequence as set forth in SEQ ID NO: 763, and the sense strand comprises at least 17 contiguous nucleotides of a sequence as set forth in SEQ ID NO: 759.

21. The oligonucleotide of claim 16, wherein the antisense strand comprises at least 17 contiguous nucleotides of a sequence as set forth in SEQ ID NO: 764, and the sense strand comprises at least 17 contiguous nucleotides of a sequence as set forth in SEQ ID NO: 760.

22. The oligonucleotide of claim 16, wherein the antisense strand comprises at least 17 contiguous nucleotides of a sequence as set forth in SEQ ID NO: 765, and the sense strand comprises at least 17 contiguous nucleotides of a sequence as set forth in SEQ ID NO: 761.

23. The oligonucleotide of claim 16, wherein the antisense strand comprises at least 18 contiguous nucleotides of a sequence as set forth in SEQ ID NO: 763, and the sense strand comprises at least 18 contiguous nucleotides of a sequence as set forth in SEQ ID NO: 759.

24. The oligonucleotide of claim 16, wherein the antisense strand comprises at least 18 contiguous nucleotides of a sequence as set forth in SEQ ID NO: 764, and the sense strand comprises at least 18 contiguous nucleotides of a sequence as set forth in SEQ ID NO: 760.

25. The oligonucleotide of claim 16, wherein the antisense strand comprises at least 18 contiguous nucleotides of a sequence as set forth in SEQ ID NO: 765, and the sense strand comprises at least 18 contiguous nucleotides of a sequence as set forth in SEQ ID NO: 761.

26. The oligonucleotide of any one of claims 1 to 25, wherein the antisense strand is 22 nucleotides in length.

27. The oligonucleotide of any one of claims 1 to 26, wherein the sense strand is 36 nucleotides in length.

~~19~~28. The oligonucleotide of any one of claims ~~16~~ 1 to ~~18~~27, wherein L is a tetraloop.

~~20. The oligonucleotide of any one of claims 16 to 19, wherein L is 4 nucleotides in length.~~

~~21~~29. The oligonucleotide of any one of claims ~~16~~ 1 to ~~20~~28, wherein L comprises a sequence set forth as GAAA.

~~22. The oligonucleotide of any one of claims 8 to 15, wherein the antisense strand is 27 nucleotides in length and the sense strand is 25 nucleotides in length.~~

~~23. The oligonucleotide of claim 22, wherein the antisense strand and sense strand form a duplex region of 25 nucleotides in length.~~

~~24. The oligonucleotide of claim 19, further comprising a 3′-overhang sequence on the antisense strand of two nucleotides in length.~~

~~25. The oligonucleotide of any one of claims 8 to 15, wherein the oligonucleotide comprises an antisense strand and a sense strand that are each in a range of 21 to 23 nucleotides in length.~~

~~26. The oligonucleotide of claim 25, wherein the oligonucleotide comprises a duplex structure in a range of 19 to 21 nucleotides in length.~~

~~27~~30. The oligonucleotide of any one of claims 1-29~~claim 25 or 26~~, wherein the oligonucleotide comprises a 3′-overhang sequence of one or more nucleotides in length, wherein the 3′-overhang sequence is present on the antisense strand, the sense strand, or the antisense strand and sense strand.

31~~28~~. The oligonucleotide of claim 30~~25 or 26~~, wherein ~~the oligonucleotide comprises~~ a 3′-overhang sequence of two nucleotides in length~~, wherein the 3′ overhang sequence~~ is ~~present~~ on the antisense strand~~, and wherein the sense strand is 21 nucleotides in length and the antisense strand is 23 nucleotides in length, such that the sense strand and antisense strand form a duplex of 21 nucleotides in length~~.

32~~29~~. The oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified nucleotide.

33~~30~~. The oligonucleotide of claim 32~~29~~, wherein the modified nucleotide comprises a 2′-modification.

34~~31~~. The oligonucleotide of claim 33~~30~~, wherein the 2′-modification is a modification selected from: 2′-aminoethyl, 2′-fluoro, 2′-O-methyl, 2′-O-methoxyethyl, and 2′-deoxy-2′-fluoro-β-d-arabinonucleic acid.

35~~32~~. The oligonucleotide of any one of claims 32~~29~~ to 34~~31~~, wherein all of the nucleotides of the oligonucleotide are modified.

3633. The oligonucleotide of any one of the preceding claims, wherein the oligonucleotide comprises at least one modified internucleotide linkage.

3734. The oligonucleotide of claim 3633, wherein the at least one modified internucleotide linkage is a phosphorothioate linkage.

3835. The oligonucleotide of any one of the preceding claims, wherein the 4′-carbon of the sugar of the 5′-nucleotide of the antisense strand comprises a phosphate analog.

3936. The oligonucleotide of claim 3835, wherein the phosphate analog is oxymethyl phosphonate, vinyl phosphonate, or malonyl phosphonate.

4037. The oligonucleotide of any one of the preceding claims, wherein at least one nucleotide of the oligonucleotide is conjugated to one or more targeting ligands.

4138. The oligonucleotide of claim 4037, wherein each targeting ligand comprises a carbohydrate, amino sugar, cholesterol, polypeptide or lipid.

4239. The oligonucleotide of claim 4138, wherein each targeting ligand comprises a N-acetylgalactosamine (GalNAc) moiety.

4340. The oligonucleotide of claim 4239, wherein the GalNac moiety is a monovalent GalNAc moiety, a bivalent GalNAc moiety, a trivalent GalNAc moiety, or a tetravalent GalNAc moiety.

4441. The oligonucleotide of any one of claims 116 to 4319, wherein up to 4 nucleotides of L of the stem-loop are each conjugated to a monovalent GalNAc moiety.

4542. The oligonucleotide of claim 4037, wherein the targeting ligand comprises an aptamer.

46. An oligonucleotide for reducing expression of CYP27A1, the oligonucleotide comprising a pair of sense and antisense strands selected from a row of the table

Sense Sequence/mRNA seq	S SEQ	Antisense Sequence	AS SEQ

	ID NO		ID NO
UGCUACAUCCUGUUCGAGAAG CAGCCGAAAGGCUGC	577	UUCUCGAACAGGAUG UAGCAAA	579
UGCUACAUCCUGUUCGAGA_G CAGCCGAAAGGCUGC	785	UCUCGAACAGGAUGU AGCAAA	786
CAGAACUCACUCUAUGCCACG CAGCCGAAAGGCUGC	578	GUGGCAUAGAGUGA GUUCUGGA	580
CAGAACUCACUCUAUGCCA_G CAGCCGAAAGGCUGC	787	UGGCAUAGAGUGAG UUCUGGA	788
CGGAUGCUUUCAAUGAGGUAG CAGCCGAAAGGCUGC	581	UACCUCAUUGAAAGC AUCCGGG	598
AUGAGGUGAUUGAUGACUUUG CAGCCGAAAGGCUGC	582	AAAGUCAUCAAUCAC CUCAUGG	599
AGGUGAUUGAUGACUUUAUAG CAGCCGAAAGGCUGC	583	UAUAAAGUCAUCAAU CACCUGG	600
GUGAUUGAUGACUUUAUGAAG CAGCCGAAAGGCUGC	584	UUCAUAAAGUCAUCA AUCACGG	601
AUUGAUGACUUUAUGACUCAG CAGCCGAAAGGCUGC	585	UGAGUCAUAAAGUCA UCAAUGG	602
UCUACUACUUUGCCUUGGAAG CAGCCGAAAGGCUGC	586	UUCCAAGGCAAAGUA GUAGAGG	603
CUACUUUGCCUUGGAAGCUAG CAGCCGAAAGGCUGC	587	UAGCUUCCAAGGCAA AGUAGGG	604
AUUUGCUACAUCCUGUUCGAG CAGCCGAAAGGCUGC	588	UCGAACAGGAUGUAG CAAAUGG	605
UUGCUACAUCCUGUUCGAGAG CAGCCGAAAGGCUGC	589	UCUCGAACAGGAUGU AGCAAGG	606
UGUUCCAGAACUCACUCUAUG CAGCCGAAAGGCUGC	590	AUAGAGUGAGUUCU GGAACAGG	607
AGAAGCUGAUUGAUGAGAAAG CAGCCGAAAGGCUGC	591	UUUCUCAUCAAUCAG CUUCUGG	608
AGGACUUUGCCCACAUGCCAG CAGCCGAAAGGCUGC	592	UGGCAUGUGGGCAAA GUCCUGG	609
UCCCGGAUCAUAGAAAAGGAG CAGCCGAAAGGCUGC	593	UCCUUUUCUAUGAUC CGGGAGG	610
CGGAUCAUAGAAAAGGAAAUG CAGCCGAAAGGCUGC	594	AUUUCCUUUUCUAUG AUCCGGG	611
GAAAUUGAAGUUGAUGGCUUG CAGCCGAAAGGCUGC	595	AAGCCAUCAACUUCA AUUUCGG	612
AAGGCUGAUCCAGAAGUACAG CAGCCGAAAGGCUGC	596	UGUACUUCUGGAUCA GCCUUGG	613
GUCCUUGGGUAGAAUAUAAAG CAGCCGAAAGGCUGC	597	UUUAUAUUCUACCCA AGGACGG	614
CGGAACGCUACAAUUUUUAUG CAGCCGAAAGGCUGC	759	AUAAAAAUUGUAGC GUUCCGGU	763
ACAAUUUUUAUUCCAGCUAUG CAGCCGAAAGGCUGC	760	AUAGCUGGAAUAAA AAUUGUAG	764
ACGAGGUUAUCAGUGACUUUG CAGCCGAAAGGCUGC	761	AAAGUCACUGAUAAC CUCGUUU	765
UGCUACAUCCUGUUCGAGAAG CAGCCGAAAGGCUGC	577	UUCUCGAACAGGAUG UAGCAGG	791
ACAAUUUUUAUUCCAGCUAUG CAGCCGAAAGGCUGC	760	AUAGCUGGAAUAAA AAUUGUGG	792

.

4743. A composition comprising an oligonucleotide of any one of the preceding claims and an excipient.

4844. A composition of claim 4743, for use in delivering an oligonucleotide to a subject.

4945. Use of the oligonucleotide of any one of claims 1 to 46, or a composition of claim 4743 in the manufacture of a medicament for attenuating bile acid accumulation in liver of a subject, decreasing the extent of liver fibrosis in a subject, and/or decreasing circulating bile acid concentrations in a subject.

~~46. Use of a composition of claim 43 in the manufacture of a medicament for decreasing the extent of liver fibrosis in a subject in need thereof.~~

~~47. Use of a composition of claim 43 in the manufacture of a medicament for decreasing circulating bile acid concentrations in a subject in need thereof.~~

5048. A composition of claim 4743 for use in attenuating bile acid accumulation in liver of a subject, decreasing the extent of liver fibrosis in a subject, and/or decreasing circulating bile acid concentrations in a subject.

5149. The use or composition for use of any one of claims 4844 to 5048, wherein the subject suffers from hepatobiliary disease.

~~50. An oligonucleotide for reducing expression of CYP27A1, the oligonucleotide comprising a sense strand of 15 to 50 nucleotides in length and an antisense strand of 15 to 30 nucleotides in length, wherein the sense strand forms a duplex region with the antisense strand, wherein the sense strand comprises a sequence as set forth in any one of SEQ ID NOs: 577-578, 581-597, 759-762, 785, and 787 and wherein the antisense strand comprises a complementary sequence selected from SEQ ID NOs: 579-580, 598-614, 763-766, 786, and 788.~~

~~51. An oligonucleotide for reducing expression of CYP27A1, the oligonucleotide comprising a pair of sense and antisense strands selected from a row of the table set forth in Appendix A.~~

52. The use or composition for use of any one of claims 48~~44~~ to 50~~48~~, wherein the subject suffers from parenteral nutrition-associated liver disease (PNALD).