(i) the antisense strand comprises the antisense sequence of AD-61193, and/or the sense strand comprises the sense sequence of AD-61193, wherein the antisense and/or sense sequence comprises all of the modified nucleotides of AD-61193, or
(ii) the antisense strand consists of the antisense sequence of AD-61193, and/or the sense strand consists of the sense sequence of AD-61193, wherein the antisense and/or sense sequence comprises all of the modified nucleotides of AD-61193.

23. The dsRNA of claim 2, wherein:
(i) the antisense strand comprises the antisense sequence of AD-60819, and/or the sense strand comprises the sense sequence of AD-60819, wherein the antisense and/or sense sequence comprises all of the modified nucleotides of AD-60819, or
(ii) the antisense strand consists of the antisense sequence of AD-60819, and/or the sense strand consists of the sense sequence of AD-60819, wherein the antisense and/or sense sequence comprises all of the modified nucleotides of AD-60819.

24. A vector encoding at least one strand of a dsRNA of any one of claims 1 to 23.

25. A cell comprising the dsRNA of any one of claims 1 to 23 or the vector of claim 24.

26. A pharmaceutical composition for inhibiting expression of an ALAS1 gene, the composition comprising the dsRNA of any one of claims 1 to 23.

27. The pharmaceutical composition of claim 26, wherein dsRNA is administered in an unbuffered saline or water solution.

28. The pharmaceutical composition of claim 26 or 27, wherein said composition is suitable for subcutaneous administration.

29. ~~A method of inhibiting ALAS1 expression in a cell, the method comprising:~~

~~(a) introducing into the cell the~~ Use of a dsRNA of any one of claims 1 to 23 in the manufacture of a medicament for inhibiting ALAS1 expression in a cell, wherein said medicament is (a) introduced into the cell, and

~~(b) wherein said use maintaining~~ maintains the cell of step (a) for a time sufficient to obtain degradation of the mRNA transcript of an ALAS1 gene, thereby inhibiting expression of the ALAS1 gene in the cell,

optionally wherein the expression of ALAS1 is inhibited by at least 20% or at least 30%.

30. ~~A method for decreasing a level of a porphyrin or a porphyrin precursor (e.g., ALA or PBG) in a cell (e.g., a hepatocyte), comprising contacting the cell with~~ Use of the dsRNA of any one of claims 1 to 23 in the manufacture of a medicament for decreasing a level of a porphyrin or a porphyrin precursor (e.g., ALA or PBG) in a cell (e.g., a hepatocyte), wherein said medicament is to be administered in an amount effective to decrease the level of the porphyrin or the porphyrin precursor in the cell.

31. ~~A method of treating a porphyria, the method comprising administering to a subject in need of such treatment~~ Use of a therapeutically effective amount of

(i) the dsRNA of any one of claims 1 to 23 or

(ii) the composition of any one of claims 26 to 28,

in the manufacture of a medicament for treating a porphyria, wherein said medicament is to be administered to a subject in need of such treatment to thereby treating the porphyria.

32. The ~~method~~ use of claim 31, wherein the subject is at risk for developing, or is diagnosed with, a porphyria.

33. The use ~~method~~ of claim 31 or 32, wherein the porphyria is acute intermittent porphyria or ALA-dehydratase deficiency porphyria.

34. The use ~~method~~ of any one of claims 31 to 33, wherein (i) the dsRNA or composition comprising dsRNA is to be administered after an acute attack of porphyria, (ii) the dsRNA or composition comprising dsRNA is to be administered during an acute attack of porphyria, or (iii) the dsRNA or composition comprising dsRNA is to be administered prophylactically to prevent an acute attack of porphyria.

35. The ~~method~~ use of any one of claims 31 to 34, wherein the dsRNA is to be administered at a dose of 0.05 to 50 mg/kg bodyweight of the subject, e.g, at a dose of 0.01 mg/kg to 5 mg/kg bodyweight of the subject.

36. The use~~method~~ of any one of claims 31 to 35, wherein the ~~method~~ medicament (i) decreases a level of a porphyrin or a porphyrin precursor (e.g., δ-aminolevulinic acid (ALA) or porphopilinogen (PBG)) in the subject, optionally wherein the level is decreased by at least 30% and/or
(ii) inhibits ALAS1 expression in the subject.

37. The ~~method~~ use of any one of claims 31 to 36, wherein said ~~method~~ medicament (i) ameliorates a symptom associated with an ALAS1 related disorder (e.g., a porphyria), (ii) decreases frequency of acute attacks of symptoms associated with a porphyria in the subject, and/or (iii) decreases incidence of acute attacks of symptoms associated with a porphyria in the subject when the subject is exposed to a precipitating factor, e.g., the premenstrual phase.

38. The ~~method~~ use of claim any one of claims 31 to 37, wherein the dsRNA or composition comprising the dsRNA is to be administered according to a dosing regimen, e.g., weekly, biweekly, or monthly.

39. The ~~method~~ use of any one of claims 31 to 38, wherein the dsRNA is to be administered before an acute attack of porphyria, e.g., during a prodrome.

40. The ~~method~~ use of claim any one of claims 31 to 39, wherein the subject has an elevated level (e.g., plasma or urine level) of ALA and/or PBG and optionally wherein the subject suffers from chronic pain.

41. The ~~method~~ use of any one of claims 31 to 40, wherein the ~~method~~ medicament decreases the elevated level of ALA and/or PBG.

42. The ~~method~~ use of any one of claims 31 to 41, wherein the ~~method~~ medicament decreases or prevents pain, neuropathy, and/or nerve damage.

43. The ~~method~~ use of any one of claims 31 to 42, wherein the ~~method~~ medicament prevents acute attacks of porphyria.

44. The ~~method~~ use of any one of claims 31 to 43, wherein the dsRNA or composition comprising the dsRNA is to be administered repeatedly.

45. ~~A method of treating a subject with an elevated level of ALA and/or PBG, the method comprising administering to a subject in need of such treatment~~Use of a therapeutically effective amount of

(i) the dsRNA of any one of claims 1 to 23 or

(ii) the composition of any one of claims 26 to 28~~.~~

in the manufacture of a medicament for treating a subject with an elevated ALA and/or PBG, wherein said medicament is to be administered to a subject in need of such treatment, and optionally, wherein the method is effective to decrease the level of ALA and/or PBG.

46. ~~A method of treating a subject having an increased level of ALA and/or PBG, the method comprising administering~~ Use of the dsRNA of any one of claims 1 to 23 in the manufacture of a medicament for treating a subject having an increased level of ALA and/or PBG, wherein said medicament is to be administered at 1 mg/kg, 2.5 mg/kg, or 5 mg/kg once per week for at least ten weeks, thereby reducing the level of ALA and/or PBG in said subject.

47. ~~A method of treating a human patient with AIP who has suffered from multiple recurrent attacks, the method comprising administering~~ Use of the dsRNA of any one of claims 1 to 23 in the manufacture of a medicament for treating a human patient with AIP who has suffered from multiple recurrent attacks, wherein said medicament is to be administered at a dose of 2.5 mg/kg for at least 6 months, thereby treating said patient,

optionally wherein said ~~method~~ medicament

(i) reduces the frequency of attacks,

(ii) reduces hematin use,

(iii) reduces hospitalization, and/or

(iv) improves quality of life.

48. An *in vitro* method for assaying the level of circulating extracellular ALAS1 mRNA in a subject, said method comprising:

detecting (*e.g.*, measuring) the level of ALAS1 mRNA in a biological fluid sample (e.g., a blood sample, a plasma sample, a serum sample, or a urine sample) from the subject, said biological fluid sample comprising the ALAS1 mRNA,

thereby assaying the level of circulating extracellular ALAS1 mRNA in the subject.

49. An *in vitro* method for assaying the level of circulating extracellular ALAS1 mRNA in a subject, said method comprising

(i) providing RNA (*e.g.*, extracellular RNA) from a biological fluid sample (e.g., a blood sample, a plasma sample, a serum sample, or urine sample) from the subject, said biological fluid sample comprising the ALAS1 mRNA;

(ii) obtaining an ALAS1 cDNA from the ALAS1 mRNA;

(iii) contacting the ALAS1 cDNA with a nucleic acid complementary (e.g., probe and/or primer) to the ALAS1 cDNA or a portion thereof, thereby producing a reaction mix; and

(iv) detecting (e.g., measuring) the level of ALAS1 cDNA in the reaction mix, wherein the ALAS1 cDNA level is indicative of the ALAS1 mRNA level,

thereby assaying the level of circulating extracellular ALAS1 mRNA in the subject,

optionally wherein

(a) the method comprises PCR, qPCR or 5'-RACE,

(b) the nucleic acid is a probe or primer, and/or

(c) the nucleic acid comprises a detectable moiety and the level of ALAS1 mRNA is determined by detection of the amount of the detectable moiety.

50. The method of claim 49, wherein the efficacy of a porphyria treatment is assessed based on a comparison of the level of circulating extracellular ALAS1 mRNA in the subject with a reference value.

51. The method of claim 49, wherein a decrease in the level of of circulating extracellular ALAS1 mRNA in the subject in response to the porphyria treatment, relative to the reference value, indicates that the porphyria treatment is efficacious.

52. The method of any one of claims 49 to 51, ~~further comprising acquiring the biological fluid sample from a subject, optionally~~ wherein the biological fluid sample is separate from the tissue, and wherein the biological fluid sample contains exosomes.

53. A composition comprising the dsRNA of claim 20 and water for injection.

54. The composition of claim 53, comprising about 200 mg/mL of the dsRNA of claim 20.

55. The composition of claim 53 or 54, wherein the composition has a pH of 6.0-7.5, e.g., about 7.0.

56. The composition of any one of claims 53 to 55, wherein the composition is formulated for subcutaneous injection.

57. ~~A method of treating a subject having a porphyria (e.g., AIP) or an elevated level of ALA and/or PBG, the method comprising subcutaneously administering~~ Use of the composition of any one of claims 53 to 56 in the manufacture of a medicament for treating a subject having a porphyria (e.g., AIP) or an elevated level of ALA and/or PBG, wherein said medicament is for subcutaneous administration to the subject.

58. The ~~method~~ use of claim 57, wherein the composition is to be administered at a dose of 0 to 5 mg/kg, e.g., at a dose of 2.5 mg/kg or less or at a dose of 1 to 2.5 mg/kg.

59 The ~~method~~ use of claim 58, wherein the composition is to be administered weekly.