channels, and reports that local suppression of Nav1.7 channel levels and/or function will occur in the peripheral sensory neurons of the dorsal root ganglia.

WO12162732 relates to novel screening assays for modulating sodium channels, particularly voltage-gated sodium channels.

KR20110087436 discloses an SCN9A antisense oligonucleotide.

Mohan *et al*., Pain (2018) Volume 159·Number 1, p139 – 149 discloses antisense oligonucleotides targeting $Na_v1.7$, and characterize the pharmacodynamic activity of ASOs in spinal cord and dorsal root ganglia (DRG) in rodents.

WO18051175 discloses SCN9A antisense peptide nucleic acid oligonucleotides targeting a part of the human SCN9A pre-mRNA. The peptide nucleic acid derivatives potently induce splice variants of the SCN9A mRNA in cells, and are useful to safely treat pains or conditions involving Nav1.7 activity.

There is therefore a need for antisense oligonucleotides therapeutics which are effective in inhibiting expression of voltage-gated sodium ion channel encoding nucleic acids, such as SCN9A in humans, such as for the prevention or treatment of pain.

OBJECTIVE OF THE INVENTION

The present invention provides oligonucleotides, including LNA antisense oligonucleotides targeting SCN9A which are capable of inhibiting the expression of $Na_v1.7$ in a cell which is expressing $Na_v1.7$. The present invention further provides oligonucleotides targeting SCN10A which inhibit the expression of $Na_v1.8$ in a cell which is expressing $Na_v1.8$. In some aspects, the invention provides oligonucleotides which target both SCN9A and SCN10A nucleic acid targets. The oligonucleotide of the invention may be used in the prevention or treatment of pain. The invention further provides advantageous target site sequences on the human Nav1.7 pre-mRNA which may be targeted by oligonucleotide inhibitors of human Nav1.7 such as antisense oligonucleotides or RNAi agents, such as siRNAs or shRNAs.

SUMMARY

The present disclosure relates to oligonucleotides targeting a nucleic acid encoding a voltage-gated sodium ion channel encoding nucleic acids, such as SCN9A or SCN10A, or in some examples both SCN9A (a $Na_v1.7$ nucleic acid target) and SCN10A (a $Na_v1.8$ nucleic acid target).

The oligonucleotide of the disclosure may be an antisense oligonucleotide.

The oligonucleotides of the disclosure are capable of inhibiting the expression of the target nucleic acid, such as SCN9A or SCN10A, or in some examples are capable of inhibiting the expression of both SCN9A and SCN10A, in a cell which is expressing said target nucleic acid(s). Suitably the target nucleic acid expressed in the cell may be a mammalian cell, such as

cynomolgus monkey cell or a pig cell, or preferably a human SCN9A or a human SCN10A mRNA or pre-mRNA sequence.

Alternatively stated, the oligonucleotides of the disclosure are capable of inhibiting the expression of Nav1.7 or Nav1.8 in a cell, such as a mammalian or human cell, or in some examples are capable of inhibiting the expression of both Nav1.7 or Nav1.8 in a cell such as in a mammalian, such as a cynomolgus monkey cell or a pig cell, or preferably in a human cell. The cell is expressing the target voltage-gated sodium ion channel protein.

The disclosure further provides target sequences of the human SCN9A pre-mRNA which are useful in targeting complementary oligonucleotides for inhibition of SCN9A expression.

Advantageously the oligonucleotide of the disclosure is an antisense oligonucleotide such as an LNA antisense oligonucleotide.

The disclosure provides an antisense oligonucleotide (e.g. an LNA antisense oligonucleotide) of 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementarity, such as 100% complementarity, to SEQ ID NO: 1.

The disclosure provides for an oligonucleotide of 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementarity, such as 100% complementarity, to SEQ ID NO: 1, which is capable of inhibiting the expression of capable of inhibiting the expression of both Nav1.7 and Nav1.8 in a cell, wherein the contiguous nucleotide sequence is complementary to human Nav1.7 and human Nav1.8 target nucleic acids, for example the target nucleic acids shown as SEQ ID NO 1 and SEQ ID NO 651 respectively.

In one aspect, the disclosure provides for an oligonucleotide of 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementarity, such as 100% complementarity, to SEQ ID NO: 1, which is capable of inhibiting the expression of capable of inhibiting the expression of both Nav1.7 and Nav1.8 in a cell, wherein the contiguous nucleotide sequence is complementary to both human Nav1.7 and human Nav1.8 target nucleic acids.

The disclosure provides for an oligonucleotide of 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementarity, such as 100% complementarity, to a human Nav1.7 target nucleic acid and a human Nav1.8 target nucleic acid, and is which is capable of inhibiting the expression of capable of inhibiting the expression of both Nav1.7 or Nav1.8 in a cell. In some examples, the contiguous nucleotide sequence of the oligonucleotide of the disclosure is 100% complementary to SEQ ID NO 1, and is at least 90% complementary such as advantageously 100% complementary to SEQ ID NO 651.

The disclosure provides for an oligonucleotide of 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementarity, such as 100% complementarity, to SEQ ID NO: 1, which is capable of inhibiting the expression of capable of inhibiting the expression of both Nav1.7 or Nav1.8 in a

cell, wherein the contiguous nucleotide sequence is 100% complementary to SEQ ID NO 1 and is at least 90% complementary such as 100% complementary to SEQ ID NO 651.

In some examples, the oligonucleotide of the disclosure comprises at least 10, or at least 12 contiguous nucleosides present in a sequence selected from the group consisting of SEQ ID NOs 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 557, 558, 559, 560, 577, 579, 583, 638, and 587.

The disclosure provides an antisense oligonucleotide selected from the group consisting of CMP ID 50_1 ; 51_1 ; 52_1 ; 53_1 ; 54_1 ; 55_1 ; 56_1 ; 57_1 ; 58_1 ; 59_1 ; 60_1 ; 61_1 ; 62_1 ; 63_1 ; 64_1 ; 65_1 ; 66_1 ; 67_1 ; 68_1 ; 69_1 ; 70_1 ; 71_1 ; 72_1 ; 73_1 ; 74_1 ; 75_1 ; 76_1 ; 77_1 ; 78_1 ; 79_1 ; 80_1 ; 81_1 ; 82_1 ; 83_1 ; 84_1 ; 85_1 ; 86_1 ; 87_1 ; 88_1 ; 89_1 ; 90_1 ; 91_1 ; 92_1 ; 93_1 ; 94_1 ; 95_1 ; 96_1 ; 97_1 ; 98_1 ; 99_1 ; 100_1 ; 101_1 ; 102_1 ; 103_1 ; 104_1 ; 105_1 ; 106_1 ; 107_1 ; 108_1 ; 109_1 ; 110_1 ; 111_1 ; 112_1 ; 113_1 ; 114_1 ; 115_1 ; 116_1 ; 117_1 ; 118_1 ; 119_1 ; 120_1 ; 121_1 ; 122_1 ; 123_1 ; 124_1 ; 125_1 ; 126_1 ; 127_1 ; 128_1 ; 129_1 ; 130_1 ; 131_1 ; 132_1 ; 133_1 ; 134_1 ; 135_1 ; 136_1 ; 137_1 ; 138_1 ; 139_1 ; 140_1 ; 141_1 ; 142_1 ; 143_1 ; 144_1 ; 145_1 ; 146_1 ; 147_1 ; 148_1 ; 149_1 ; 150_1 ; 151_1 ; 152_1 ; 153_1 ; 154_1 ; 155_1 ; 156_1 ; 157_1 ; 158_1 ; 159_1 ; 160_1 ; 161_1 ; 162_1 ; 163_1 ; 164_1 ; 165_1 ; 166_1 ; 167_1 ; 168_1 ; 169_1 ; 170_1 ; 171_1 ; 172_1 ; 173_1 ; 174_1 ; 175_1 ; 176_1 ; 177_1 ; 178_1 ; 179_1 ; 180_1 ; 181_1 ; 182_1 ; 183_1 ; 184_1 ; 185_1 ; 186_1 ; 187_1 ; 188_1 ; 189_1 ; 190_1 ; 191_1 ; 192_1 ; 193_1 ; 194_1 ; 195_1 ; 196_1 ; 197_1 ; 198_1 ; 199_1 ; 200_1 ; 201_1 ; 202_1 ; 203_1 ; 204_1 ; 205_1 ; 206_1 ; 207_1 ; 208_1 ; 209_1 ; 210_1 ; 211_1 ; 212_1 ; 213_1 ; 214_1 ; 215_1 ; 216_1 ; 217_1 ; 218_1 ; 219_1 ; 220_1 ; 221_1 ; 222_1 ; 223_1 ; 224_1 ; 225_1 ; 226_1 ; 227_1 ; 228_1 ; 229_1 ; 230_1 ; 231_1 ; 232_1 ; 233_1 ; 234_1 ; 235_1 ; 236_1 ; 237_1 ; 238_1 ; 239_1 ; 240_1 ; 241_1 ; 242_1 ; 243_1 ; 244_1 ; 245_1 ; 246_1 ; 247_1 ; 248_1 ; 249_1 ; 250_1 ; 251_1 ; 252_1 ; 253_1 ; 254_1 ; 255_1 ; 256_1 ; 257_1 ; 258_1 ; 259_1 ; 260_1 ; 261_1 ; 262_1 ; 263_1 ; 264_1 ; 265_1 ; 266_1 ; 267_1 ; 268_1 ; 269_1 ; 270_1 ; 271_1 ; 272_1 ; 273_1 ; 274_1 ; 275_1 ; 276_1 ; 277_1 ; 278_1 ; 279_1 ; 280_1 ; 281_1 ; 282_1 ; 283_1 ; 284_1 ; 285_1 ; 286_1 ; 287_1 ; 288_1 ; 289_1 ; 290_1 ; 291_1 ; 292_1 ; 293_1 ; 294_1 ; 295_1 ; 296_1 ; 297_1 ; 298_1 ; 299_1 ; 300_1 ; 301_1 ; 302_1 ; 303_1 ; 304_1 ; 305_1 ; 306_1 ; 307_1 ; 308_1 ; 309_1 ; 310_1 ; 311_1 ; 312_1 ; 313_1 ; 314_1 ; 315_1 ; 316_1 ; 317_1 ; 318_1 ; 319_1 ; 320_1 ; 321_1 ; 322_1 ; 323_1 ; 324_1 ; 325_1 ; 326_1 ; 327_1 ; 328_1 ; 329_1 ; 330_1 ; 331_1 ; 332_1 ; 333_1 ; 334_1 ; 335_1 ; 336_1 ; 337_1 ; 338_1 ; 339_1 ; 340_1 ; 341_1 ; 342_1 ;

343_1 ; 344_1 ; 345_1 ; 346_1 ; 347_1 ; 348_1 ; 349_1 ; 350_1 ; 351_1 ; 352_1 ; 353_1 ; 354_1 ; 355_1 ; 356_1 ; 357_1 ; 358_1 ; 359_1 ; 360_1 ; 361_1 ; 362_1 ; 363_1 ; 364_1 ; 365_1 ; 366_1 ; 367_1 ; 368_1 ; 369_1 ; 370_1 ; 371_1 ; 372_1 ; 373_1 ; 374_1 ; 375_1 ; 376_1 ; 377_1 ;

378_1 ; 379_1 ; 380_1 ; 381_1 ; 382_1 ; 383_1 ; 384_1 ; 385_1 ; 386_1 ; 387_1 ; 388_1 ; 389_1 ; 390_1 ; 391_1 ; 392_1 ; 393_1 ; 394_1 ; 395_1 ; 396_1 ; 397_1 ; 398_1 ; 399_1 ; 400_1 ; 401_1 ; 402_1 ; 403_1 ; 404_1 ; 405_1 ; 406_1 ; 407_1 ; 408_1 ; 409_1 ; 410_1 ; 411_1 ; 412_1 ; 413_1 ; 414_1 ; 415_1 ; 416_1 ; 417_1 ; 418_1 ; 419_1 ; 420_1 ; 421_1 ; 422_1 ; 423_1 ; 424_1 ; 425_1 ; 426_1 ; 427_1 ; 428_1 ; 429_1 ; 430_1 ; 431_1 ; 432_1 ; 433_1 ; 434_1 ; 435_1 ; 436_1 ; 437_1 ; 438_1 ; 439_1 ; 440_1 ; 441_1 ; 442_1 ; 443_1 ; 444_1 ; 445_1 ; 446_1 ; 447_1 ; 448_1 ; 449_1 ; 450_1 ; 451_1 ; 452_1 ; 453_1 ; 454_1 ; 455_1 ; 456_1 ; 457_1 ; 458_1 ; 459_1 ; 460_1 ; 461_1 ; 462_1 ; 463_1 ; 464_1 ; 465_1 ; 466_1 ; 467_1 ; 468_1 ; 469_1 ; 470_1 ; 471_1 ; 472_1 ; 473_1 ; 474_1 ; 475_1 ; 476_1 ; 477_1 ; 478_1 ; 479_1 ; 480_1 ; 481_1 ; 482_1 ; 483_1 ; 484_1 ; 485_1 ; 486_1 ; 487_1 ; 488_1 ; 489_1 ; 490_1 ; 491_1 ; 492_1 ; 493_1 ; 494_1 ; 495_1 ; 496_1 ; 497_1 ; 498_1 ; 499_1 ; 500_1 ; 501_1 ; 502_1 ; 503_1 ; 504_1 ; 505_1 ; 506_1 ; 507_1 ; 508_1 ; 509_1 ; 510_1 ; 511_1 ; 512_1 ; 512_2 ; 512_3 ; 513_1 ; 513_2 ; 513_3 ; 513_4 ; 514_1 ; 514_2 ; 514_3 ; 514_4 ; 515_1 ; 515_2 ; 515_3 ; 515_4 ; 515_5 ; 515_6 ; 516_1 ; 516_2 ; 516_3 ; 516_4 ; 516_5 ; 516_6 ; 516_7 ; 517_1 ; 517_2 ; 517_3 ; 517_4 ; 517_5 ; 517_6 ; 517_7 ; 517_8 ; 518_1 ; 518_2 ; 518_3 ; 518_4 ; 518_5 ; 518_6 ; 519_1 ; 519_2 ; 519_3 ; 519_4 ; 519_5 ; 519_6 ; 520_1 ; 520_2 ; 520_3 ; 520_4 ; 520_5 ; 521_1 ; 521_2 ; 521_3 ; 521_4 ; 521_5 ; 522_1 ; 522_2 ; 522_3 ; 522_4 ; 523_1 ; 523_2 ; 523_3 ; 523_4 ; 523_5 ; 524_1 ; 525_1 ; 526_1 ; 527_1 ; 528_1 ; 529_1 ; 530_1 ; 531_1 ; 532_1 ; 533_1 ; 534_1 ; 535_1 ; 536_1 ; 537_1 ; 538_1 ; 539_1 ; 540_1 ; 541_1 ; 542_1 ; 543_1 ; 544_1 ; 545_1 ; 546_1 ; 547_1 ; 548_1 ; 549_1 ; 550_1 ; 551_1 ; 552_1 ; 553_1 ; 554_1 ; 555_1 ; 556_1 ; 557_1 ; 558_1 ; 559_1 ; 560_1 ; 561_1 ; 562_1 ; 563_1 ; 564_1 ; 565_1 ; 566_1 ; 567_1 ; 568_1 ; 569_1 ; 570_1 ; 571_1 ; 572_1 ; 573_1 ; 574_1 ; 575_1 ; 576_1 ; 577_1 ; 578_1 ; 579_1 ; 580_1 ; 581_1 ; 582_1 ; 583_1 ; 584_1 ; 585_1 ; 586_1 ; 587_1 ; 588_1 ; 589_1 ; 590_1 ; 591_1 ; 592_1 ; 593_1 ; 594_1 ; 595_1 ; 596_1 ; 597_1 ; 598_1 ; 599_1 ; 600_1 ; 601_1 ; 602_1 ; 603_1 ; 604_1 ; 605_1 ; 606_1 ; 607_1 ; 608_1 ; 609_1 ; 610_1 ; 611_1 ; 612_1 ; 613_1 ; 614_1 ; 615_1 ; 616_1 ; 617_1 ; 618_1 ; 619_1 ; 620_1 ; 621_1 ; 622_1 ; 623_1 ; 624_1 ; 625_1 ; 626_1 ; 627_1 ; 628_1 ; 629_1 ; 630_1 ; 631_1 ; 632_1 ; 633_1 ; 634_1 ; 635_1 ; 636_1 ; 637_1 ; 638_1 ; 639_1 ; 640_1 ; and 641_1; or selected from the group selected of 642_1, 643_1, 644_1, 645_1, 646_1, 647_1, 648_1, 649_1 and 650_1.

In another aspect, the disclosure provides an antisense oligonucleotide selected from the group consisting of CMP ID 50_1 ; 51_1 ; 52_1 ; 53_1 ; 54_1 ; 55_1 ; 56_1 ; 57_1 ; 58_1 ; 59_1 ; 60_1 ; 61_1 ; 62_1 ; 63_1 ; 64_1 ; 65_1 ; 66_1 ; 67_1 ; 68_1 ; 69_1 ; 70_1 ; 71_1 ; 72_1 ; 73_1 ;

74_1 ; 75_1 ; 76_1 ; 77_1 ; 78_1 ; 79_1 ; 80_1 ; 81_1 ; 82_1 ; 83_1 ; 84_1 ; 85_1 ; 86_1 ; 87_1 ; 88_1 ; 89_1 ; 90_1 ; 91_1 ; 92_1 ; 93_1 ; 94_1 ; 95_1 ; 96_1 ; 97_1 ; 98_1 ; 99_1 ; 100_1 ; 101_1 ; 102_1 ; 103_1 ; 104_1 ; 105_1 ; 106_1 ; 107_1 ; 108_1 ; 109_1 ; 110_1 ; 111_1 ; 112_1 ; 113_1 ; 114_1 ; 115_1 ; 116_1 ; 117_1 ; 118_1 ; 119_1 ; 120_1 ; 121_1 ; 122_1 ; 123_1 ; 124_1 ; 125_1 ; 126_1 ; 127_1 ; 128_1 ; 129_1 ; 130_1 ; 131_1 ; 132_1 ; 133_1 ; 134_1 ; 135_1 ; 136_1 ; 137_1 ; 138_1 ; 139_1 ; 140_1 ; 141_1 ; 142_1 ; 143_1 ; 144_1 ; 145_1 ; 146_1 ; 147_1 ; 148_1 ; 149_1 ; 150_1 ; 151_1 ; 152_1 ; 153_1 ; 154_1 ; 155_1 ; 156_1 ; 157_1 ; 158_1 ; 159_1 ; 160_1 ; 161_1 ; 162_1 ; 163_1 ; 164_1 ; 165_1 ; 166_1 ; 167_1 ; 168_1 ; 169_1 ; 170_1 ; 171_1 ; 172_1 ; 173_1 ; 174_1 ; 175_1 ; 176_1 ; 177_1 ; 178_1 ; 179_1 ; 180_1 ; 181_1 ; 182_1 ; 183_1 ; 184_1 ; 185_1 ; 186_1 ; 187_1 ; 188_1 ; 189_1 ; 190_1 ; 191_1 ; 192_1 ; 193_1 ; 194_1 ; 195_1 ; 196_1 ; 197_1 ; 198_1 ; 199_1 ; 200_1 ; 201_1 ; 202_1 ; 203_1 ; 204_1 ; 205_1 ; 206_1 ; 207_1 ; 208_1 ; 209_1 ; 210_1 ; 211_1 ; 212_1 ; 213_1 ; 214_1 ; 215_1 ; 216_1 ; 217_1 ; 218_1 ; 219_1 ; 220_1 ; 221_1 ; 222_1 ; 223_1 ; 224_1 ; 225_1 ; 226_1 ; 227_1 ; 228_1 ; 229_1 ; 230_1 ; 231_1 ; 232_1 ; 233_1 ; 234_1 ; 235_1 ; 236_1 ; 237_1 ; 238_1 ; 239_1 ; 240_1 ; 241_1 ; 242_1 ; 243_1 ; 244_1 ; 245_1 ; 246_1 ; 247_1 ; 248_1 ; 249_1 ; 250_1 ; 251_1 ; 252_1 ; 253_1 ; 254_1 ; 255_1 ; 256_1 ; 257_1 ; 258_1 ; 259_1 ; 260_1 ; 261_1 ; 262_1 ; 263_1 ; 264_1 ; 265_1 ; 266_1 ; 267_1 ; 268_1 ; 269_1 ; 270_1 ; 271_1 ; 272_1 ; 273_1 ; 274_1 ; 275_1 ; 276_1 ; 277_1 ; 278_1 ; 279_1 ; 280_1 ; 281_1 ; 282_1 ; 283_1 ; 284_1 ; 285_1 ; 286_1 ; 287_1 ; 288_1 ; 289_1 ; 290_1 ; 291_1 ; 292_1 ; 293_1 ; 294_1 ; 295_1 ; 296_1 ; 297_1 ; 298_1 ; 299_1 ; 300_1 ; 301_1 ; 302_1 ; 303_1 ; 304_1 ; 305_1 ; 306_1 ; 307_1 ; 308_1 ; 309_1 ; 310_1 ; 311_1 ; 312_1 ; 313_1 ; 314_1 ; 315_1 ; 316_1 ; 317_1 ; 318_1 ; 319_1 ; 320_1 ; 321_1 ; 322_1 ; 323_1 ; 324_1 ; 325_1 ; 326_1 ; 327_1 ; 328_1 ; 329_1 ; 330_1 ; 331_1 ; 332_1 ; 333_1 ; 334_1 ; 335_1 ; 336_1 ; 337_1 ; 338_1 ; 339_1 ; 340_1 ; 341_1 ; 342_1 ; 343_1 ; 344_1 ; 345_1 ; 346_1 ; 347_1 ; 348_1 ; 349_1 ; 350_1 ; 351_1 ; 352_1 ; 353_1 ; 354_1 ; 355_1 ; 356_1 ; 357_1 ; 358_1 ; 359_1 ; 360_1 ; 361_1 ; 362_1 ; 363_1 ; 364_1 ; 365_1 ; 366_1 ; 367_1 ; 368_1 ; 369_1 ; 370_1 ; 371_1 ; 372_1 ; 373_1 ; 374_1 ; 375_1 ; 376_1 ; 377_1 ; 378_1 ; 379_1 ; 380_1 ; 381_1 ; 382_1 ; 383_1 ; 384_1 ; 385_1 ; 386_1 ; 387_1 ; 388_1 ; 389_1 ; 390_1 ; 391_1 ; 392_1 ; 393_1 ; 394_1 ; 395_1 ; 396_1 ; 397_1 ; 398_1 ; 399_1 ; 400_1 ; 401_1 ; 402_1 ; 403_1 ; 404_1 ; 405_1 ; 406_1 ; 407_1 ; 408_1 ; 409_1 ; 410_1 ; 411_1 ; 412_1 ; 413_1 ; 414_1 ; 415_1 ; 416_1 ; 417_1 ; 418_1 ; 419_1 ; 420_1 ; 421_1 ; 422_1 ; 423_1 ; 424_1 ; 425_1 ; 426_1 ; 427_1 ; 428_1 ; 429_1 ; 430_1 ; 431_1 ; 432_1 ; 433_1 ; 434_1 ; 435_1 ; 436_1 ; 437_1 ; 438_1 ; 439_1 ; 440_1 ; 441_1 ; 442_1 ; 443_1 ; 444_1 ; 445_1 ; 446_1 ; 447_1 ; 448_1 ; 449_1 ; 450_1 ; 451_1 ; 452_1 ; 453_1 ; 454_1 ; 455_1 ; 456_1 ; 457_1 ; 458_1 ; 459_1 ; 460_1 ; 461_1 ; 462_1 ; 463_1 ; 464_1 ; 465_1 ; 466_1 ; 467_1 ; 468_1 ; 469_1 ; 470_1 ; 471_1 ; 472_1 ; 473_1 ; 474_1 ; 475_1 ; 476_1 ; 477_1 ; 478_1 ; 479_1 ; 480_1 ; 481_1 ; 482_1 ; 483_1 ; 484_1 ; 485_1 ;

486_1 ; 487_1 ; 488_1 ; 489_1 ; 490_1 ; 491_1 ; 492_1 ; 493_1 ; 494_1 ; 495_1 ; 496_1 ; 497_1 ; 498_1 ; 499_1 ; 500_1 ; 501_1 ; 502_1 ; 503_1 ; 504_1 ; 505_1 ; 506_1 ; 507_1 ; 508_1 ; 509_1 ; 510_1 ; 511_1 ; 512_1 ; 512_2 ; 512_3 ; 513_1 ; 513_2 ; 513_3 ; 513_4 ; 514_1 ; 514_2 ; 514_3 ; 514_4 ; 515_1 ; 515_2 ; 515_3 ; 515_4 ; 515_5 ; 515_6 ; 516_1 ; 516_2 ; 516_3 ; 516_4 ; 516_5 ; 516_6 ; 516_7 ; 517_1 ; 517_2 ; 517_3 ; 517_4 ; 517_5 ; 517_6 ; 517_7 ; 517_8 ; 518_1 ; 518_2 ; 518_3 ; 518_4 ; 518_5 ; 518_6 ; 519_1 ; 519_2 ; 519_3 ; 519_4 ; 519_5 ; 519_6 ; 520_1 ; 520_2 ; 520_3 ; 520_4 ; 520_5 ; 521_1 ; 521_2 ; 521_3 ; 521_4 ; 521_5 ; 522_1 ; 522_2 ; 522_3 ; 522_4 ; 523_1 ; 523_2 ; 523_3 ; 523_4 ; 523_5 ; 524_1 ; 525_1 ; 526_1 ; 527_1 ; 528_1 ; 529_1 ; 530_1 ; 531_1 ; 532_1 ; 533_1 ; 534_1 ; 535_1 ; 536_1 ; 537_1 ; 538_1 ; 539_1 ; 540_1 ; 541_1 ; 542_1 ; 543_1 ; 544_1 ; 545_1 ; 546_1 ; 547_1 ; 548_1 ; 549_1 ; 550_1 ; 551_1 ; 552_1 ; 553_1 ; 554_1 ; 555_1 ; 556_1 ; 557_1 ; 558_1 ; 559_1 ; 560_1 ; 561_1 ; 562_1 ; 563_1 ; 564_1 ; 565_1 ; 566_1 ; 567_1 ; 568_1 ; 569_1 ; 570_1 ; 571_1 ; 572_1 ; 573_1 ; 574_1 ; 575_1 ; 576_1 ; 577_1 ; 578_1 ; 579_1 ; 580_1 ; 581_1 ; 582_1 ; 583_1 ; 584_1 ; 585_1 ; 586_1 ; 587_1 ; 588_1 ; 589_1 ; 590_1 ; 591_1 ; 592_1 ; 593_1 ; 594_1 ; 595_1 ; 596_1 ; 597_1 ; 598_1 ; 599_1 ; 600_1 ; 601_1 ; 602_1 ; 603_1 ; 604_1 ; 605_1 ; 606_1 ; 607_1 ; 608_1 ; 609_1 ; 610_1 ; 611_1 ; 612_1 ; 613_1 ; 614_1 ; 615_1 ; 616_1 ; 617_1 ; 618_1 ; 619_1 ; 620_1 ; 621_1 ; 622_1 ; 623_1 ; 624_1 ; 625_1 ; 626_1 ; 627_1 ; 628_1 ; 629_1 ; 630_1 ; 631_1 ; 632_1 ; 633_1 ; 634_1 ; 635_1 ; 636_1 ; 637_1 ; 638_1 ; 639_1 ; 640_1; 641_1; 642_1, 643_1, 644_1, 645_1, 646_1, 647_1, 648_1, 649_1 and 650_1.

The disclosure provides an oligonucleotide capable of inhibiting the expression of human SNC9A in a cell, wherein the oligonucleotide comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of 51, 59, 127, 161, 67, 106, 72, 124, 163, 99, 125, 110, 65, 94, 64, 57, 136, 158, 159, 356, 197, 132, 83, 76, 130, 135, 77, 186, 105, 445, 325, 265, 200, 288, 346, 86, 281, 339, 256, 289, 414, 286, 241, 82, 475, 91, 50, 97, 322, 148, 443, 251, 451, 179, 466, 357, 109, 472, 471, 376, 413, 270, 379, 416, 311, 411, 368, 333, 347, 152, 89, 380, 390, 429, 63, 90, 415,

199, 503, 476, 92, 268, 371, 302, 485, 205, 274, 122, 419, 470, 498, 156, 478, 393, 312, 287, 96, 226, 71, 137, 365, 58, 370, 280, 385, 442, 134, 463, 140, 440, 230, 310, 479, 363, 340, 495, 467, 444, 418, 338, 335, 496, 196, 317, 341, 406, 330, 173, 377, 474, 482, 282, 266, 73, 257, 342, 190, 492, 87, 188, 456, 372, 417, 404, 239, 206, 433, 486, 175, 461, 56, 408, 334, 504, 453, 222, 410, 104, 460, 439, 255, 489, 203, 398, 171, 407, 172, 412, 321, 305, 328, 120, 434, 449, 350, 487, 146, 420, 426, 352, 150, 316, 353, 469, 306, 384, 155, 450, 279, 267, 337, 184, 459, 360, 75, 468, 180, 245, 387, 345, 98, 435, 295, 369, 218, 182, 448, 300, 481, 427, 207, 367, 240, 231, 364, 355, 431, 497, 397, 465, 271, 502, 151, 178, 499, 421, 131, 309, 491, 261, 121, 128, 84, 304, 264, 493, 185, 237, 139, 441, 169, 160, 102, 296, 164, 362, 500, and 100.

The disclosure provides an oligonucleotide capable of inhibiting the expression of human SNC9A in a cell, wherein the oligonucleotide comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NO 642, 643, 644, 645, 646, 647, 648, 649 and 650.

The disclosure provides an oligonucleotide capable of inhibiting the expression of human SNC9A in a cell, wherein the oligonucleotide comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs 512 – 641.

The disclosure provides an oligonucleotide capable of inhibiting the expression of human SNC9A in a cell, wherein the oligonucleotide comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs 642 - 650.

The disclosure provides an antisense oligonucleotide capable of inhibiting the expression of human SNC9A in a cell, wherein the oligonucleotide comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs 512 – 641.

The disclosure provides an antisense oligonucleotide capable of inhibiting the expression of human SNC9A in a cell, wherein the oligonucleotide comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs 642 - 650.

The disclosure provides an antisense gapmer oligonucleotide capable of inhibiting the expression of human SNC9A in a cell, wherein the oligonucleotide comprises a contiguous nucleotide sequence comprising at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs 512 – 641.

The disclosure provides an antisense oligonucleotide capable of inhibiting the expression of human SNC9A in a cell, wherein the oligonucleotide comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs 642 - 650.

The disclosure provides an antisense gapmer oligonucleotide capable of inhibiting the expression of human SNC9A in a cell, wherein the oligonucleotide comprises a contiguous nucleotide sequence comprising at least 14 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs 512 – 641.

The disclosure provides an antisense oligonucleotide capable of inhibiting the expression of human SNC9A in a cell, wherein the oligonucleotide comprises a contiguous nucleotide sequence comprising at least 10 or at least 12 contiguous nucleotides of a sequence selected from the group consisting of SEQ ID NOs 642 - 650.

In another aspect, the disclosure provides a conjugate comprising the antisense oligonucleotide according to the disclosure and at least one conjugate moiety covalently attached to said oligonucleotide.

The disclosure provides for an oligonucleotide of 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementarity, such as 100% complementarity, to SEQ ID NO: 1, which is capable of inhibiting the expression of capable of inhibiting the expression of both Nav1.7 or Nav1.8 in a cell.

The disclosure provides for an antisense oligonucleotide of 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementarity, such as 100% complementarity, to SEQ ID NO: 1, which is capable of inhibiting the expression of capable of inhibiting the expression of both Nav1.7 or Nav1.8 in a cell.

In some examples of the disclosure the oligonucleotide comprises a contiguous nucleotide sequence which comprises at least 10, or at least 12 contiguous nucleosides present in a sequence selected from the group consisting of SEQ ID NOs 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 557, 558, 559, 560, 577, 579, 583, 638, and 587.

In some examples of the disclosure the oligonucleotide comprises a contiguous nucleotide sequence which comprises at least 14 contiguous nucleosides present in a sequence selected from the group consisting of SEQ ID NOs 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 557, 558, 559, 560, 577, 579, 583, 638, and 587.

In another aspect, the disclosure provides a pharmaceutically acceptable salt of the antisense oligonucleotide according to the disclosure, or the conjugate according to the disclosure.

The disclosure provides a pharmaceutical composition comprising the antisense oligonucleotide of the disclosure or the conjugate of the disclosure and a pharmaceutically acceptable diluent, solvent, carrier, salt and/or adjuvant.

In another aspect, the disclosure provides a pharmaceutical composition comprising the antisense oligonucleotide of the disclosure or the conjugate of the disclosure, or the salt of the disclosure, and a pharmaceutically acceptable diluent, solvent, carrier, salt and/or adjuvant.

The disclosure provides an in vivo or in vitro method for inhibiting SCN9A expression in a target cell which is expressing SCN9A, said method comprising administering an oligonucleotide of the disclosure or the conjugate of the disclosure or the pharmaceutical salt or composition of the disclosure in an effective amount to said cell.

In another aspect, the disclosure provides an *in vitro* method for inhibiting SCN9A expression in a target cell which is expressing SCN9A, said method comprising administering an antisense oligonucleotide of the disclosure or the conjugate of the disclosure or the pharmaceutical salt or composition of the disclosure in an effective amount to said cell.

The disclosure provides an in vivo or in vitro method for inhibiting SCN9A and SCN10A expression in a target cell which is expressing SCN9A and SCN10A, said method comprising administering an oligonucleotide of the disclosure or the conjugate of the disclosure or the pharmaceutical salt or composition of the disclosure in an effective amount to said cell.

The disclosure provides a method for treating or preventing pain in a subject such as a human, who is suffering from or is likely to suffer pain, comprising administering a therapeutically or prophylactically effective amount of an antisense oligonucleotide of the disclosure or the conjugate of the disclosure or the pharmaceutical salt or composition of the disclosure, such as to prevent or alleviate the pain.

In another aspect, the disclosure provides an antisense oligonucleotide of the disclosure or the conjugate of the disclosure or the pharmaceutical salt or composition of the disclosure for use for inhibiting SCN9A expression in a target cell which is expressing SCN9A.

The disclosure provides for the antisense oligonucleotide of the disclosure or the conjugate of the disclosure or the pharmaceutical salt or composition of the disclosure for use in medicine.

In another aspect, the disclosure provides for the oligonucleotide of the disclosure or the conjugate of the disclosure or the pharmaceutical salt or composition of the disclosure for use in medicine.

The disclosure provides for the antisense oligonucleotide of the disclosure or the conjugate of the disclosure or the pharmaceutical salt or composition of the disclosure for use in the treatment or prevention or alleviation of pain.

In another aspect, the disclosure provides for the oligonucleotide of the disclosure or the conjugate of the disclosure or the pharmaceutical salt or composition of the disclosure for use in the treatment or prevention or alleviation of pain, wherein the pain is either

i) chronic pain, neuropathic pain, inflammatory pain, spontaneous pain, or nociceptive pain; or

ii) pain caused by or associated with a disorder selected from the group consisting of diabetic neuropathies, cancer, cranial neuralgia, postherpetic neuralgia and post-surgical neuralgia; or

iii) pain caused by or associated with inherited erythromelalgia (EIM) or paroxysmal extreme pain disorder (PEPD) or trigeminal neuralgia; or

iv) neurophathic pain, chronic pain, but also general treatment of nociceptive pain (e.g. decompression of a nerve), or neuropathic pain (e.g. diabetic neuropathy), visceral pain, or mixed pain.

The disclosure provides for the use of the antisense oligonucleotide of the disclosure or the conjugate of the disclosure or the pharmaceutical salt or composition of the disclosure, for the preparation of a medicament for the treatment, prevention or alleviation of pain.

The disclosure provides for the use of an oligonucleotide of the disclosure or the conjugate of the disclosure or the pharmaceutical salt or composition of the disclosure in the preparation of a medicament for the treatment, prevention or alleviation of pain, wherein the pain is either

i) chronic pain, neuropathic pain, inflammatory pain, spontaneous pain, or nociceptive pain; or

ii) pain caused by or associated with a disorder selected from the group consisting of diabetic neuropathies, cancer, cranial neuralgia, postherpetic neuralgia and post-surgical neuralgia; or

iii) pain caused by or associated with inherited erythromelalgia (EIM) or paroxysmal extreme pain disorder (PEPD) or trigeminal neuralgia; or

iv) neurophathic pain, chronic pain, but also general treatment of nociceptive pain (e.g. decompression of a nerve), or neuropathic pain (e.g. diabetic neuropathy), visceral pain, or mixed pain.

In some examples the pain is chronic pain, neuropathic pain, inflammatory pain, spontaneous pain, or nociceptive pain.

In some examples the pain is caused by or associated with a disorder selected from the group consisting of diabetic neuropathies, cancer, cranial neuralgia, postherpetic neuralgia and post-surgical neuralgia; or

In some examples the pain is caused by or associated with inherited erythromelalgia (EIM) or paroxysmal extreme pain disorder (PEPD) or trigeminal neuralgia; or

In some examples the pain is neurophathic pain, chronic pain, but also general treatment of nociceptive pain (e.g. decompression of a nerve), or neuropathic pain (e.g. diabetic neuropathy), visceral pain, or mixed pain.

DEFINITIONS

Oligonucleotide

The term “oligonucleotide” as used herein is defined as it is generally understood by the skilled person as a molecule comprising two or more covalently linked nucleosides. Such covalently bound nucleosides may also be referred to as nucleic acid molecules or oligomers. Oligonucleotides are commonly made in the laboratory by solid-phase chemical synthesis followed by purification and isolation. When referring to a sequence of the oligonucleotide, reference is made to the sequence or order of nucleobase moieties, or modifications thereof, of the covalently linked nucleotides or nucleosides. The oligonucleotide of the invention is man-made, and is chemically synthesized, and is typically purified or isolated. The oligonucleotide of the invention may comprise one or more modified nucleosides or nucleotides, such as 2’ sugar modified nucleosides.

The oligonucleotide of the invention may be an antisense oligonucleotide, or may form part of a siRNA, such as the antisense strand of a siRNA targeting the target nucleic acid. Advantageously, the oligonucleotide is an antisense oligonucleotide. Advantageous designs of antisense oligonucleotides for use in the antisense oligonucleotide of the invention, or contiguous nucleotide sequence thereof, include gapmers.

RNAi Agents

The terms 'iRNA," "RNAi agent," 'iRNA agent," and "RNA interference agent" as used interchangeably herein, refer to an agent that contains RNA nucleosides herein and which mediates the targeted cleavage of an RNA transcript via an RNA-induced silencing complex (RISC) pathway. iRNA directs the sequence-specific degradation of mRNA through a process as RNA interference (RNAi). The iRNA modulates. e g., inhibits, the expression of the target nucleic acid in a cell. e.g. a cell within a subject. such as a mammalian subject. RNAi agents includes single stranded RNAi agents and double stranded siRNAs, as well as short hairpin RNAs (shRNAs). The oligonucleotide of the invention or contiguous nucleotide sequence thereof may be in the form of a RNAi agent, or form part of a RNAi agent, such as an siRNA or shRNA. In some embodiments of the invention, the oligonucleotide of the invention or contiguous nucleotide sequence thereof is a RNAi agent, such as a siRNA.

siRNAs

CLAIMS

1. An oligonucleotide of 10 to 30 nucleotides in length, which comprises a contiguous nucleotide sequence of 10 to 30 nucleotides in length with at least 90% complementarity, such as 100% complementarity, to SEQ ID NO: 1, which is capable of inhibiting the expression of capable of inhibiting the expression of both Nav1.7 and Nav1.8 in a cell, wherein the contiguous nucleotide sequence is complementary to both human Nav1.7 and human Nav1.8 target nucleic acids.
2. The oligonucleotide of claim 1, wherein the contiguous nucleotide sequence is at least 90% complementary, such as 100% complementary to a region of SEQ ID NO 1, selected from the group consisting of 852 - 865 ; 2091 - 2104 ; 2620 - 2633 ; 2675 - 2692 ; 3441 - 3454 ; 3882 - 3921 ; 3970 - 3983 ; 4532 - 4553 ; 4814 - 4827 ; 5068 - 5082 ; 5167 - 5182 ; 5184 - 5198 ; 5430 - 5444 ; 5466 - 5502 ; 5511 - 5529 ; 5544 - 5585 ; 5610 - 5633 ; 5644 - 5662 ; 5695 - 5717 ; 6067 - 6085 ; 6087 - 6100 ; 6117 - 6130 ; 6859 - 6873 ; 6998 - 7019 ; 7033 - 7053 ; 7089 - 7121 ; 7131 - 7152 ; 7155 - 7184 ; 7206 - 7221 ; 7254 - 7271 ; 7273 - 7295 ; 7297 - 7315 ; 7381 - 7414 ; 7456 - 7475 ; 7478 - 7499 ; 7509 - 7522 ; 7618 - 7632 ; 8388 - 8401 ; 8508 - 8529 ; 8538 - 8562 ; 8596 - 8610 ; 8612 - 8638 ; 8655 - 8677 ; 8693 - 8715 ; 8944 - 8957 ; 9534 - 9547 ; 9914 - 9928 ; 10068 - 10081 ; 10252 - 10265 ; 10363 - 10376 ; 10402 - 10415 ; 10626 - 10640 ; 11437 - 11450 ; 11879 - 11901 ; 11981 - 11994 ; 12145 - 12158 ; 12980 - 12993 ; 13998 - 14011 ; 15098 - 15111 ; 15628 - 15642 ; 15749 - 15792 ; 15801 - 15821 ; 15847 - 15863 ; 15869 - 15911 ; 15931 - 15959 ; 15972 - 15985 ; 16019 - 16037 ; 16039 - 16052 ; 16740 - 16753 ; 17660 - 17676 ; 17696 - 17731 ; 17761 - 17774 ; 17800 - 17827 ; 17851 - 17871 ; 17878 - 17896 ; 17906 - 17967 ; 18825 - 18843 ; 19063 - 19080 ; 19821 - 19834 ; 19932 - 19983 ; 20024 - 20039 ; 20045 - 20062 ; 20090 - 20125 ; 20153 - 20183 ; 20196 - 20212 ; 20288 - 20301 ; 20416 - 20435 ; 20481 - 20494 ; 20715 - 20728 ; 20739 - 20756 ; 20808 - 20826 ; 20830 - 20843 ; 20847 - 20874 ; 20892 - 20905 ; 20932 - 20959 ; 21684 - 21697 ; 22764 - 22780 ; 22819 - 22836 ; 22856 - 22869 ; 22880 - 22907 ; 22979 - 22992 ; 23370 - 23383 ; 23917 - 23930 ; 25007 - 25020 ; 26048 - 26068 ; 26104 - 26160 ; 26170 - 26200 ; 26224 - 26238 ; 26270 - 26301 ; 26618 - 26635 ; 26843 - 26878 ; 26915 - 26932 ; 26945 - 26958 ; 26961 - 26978 ; 27013 - 27027 ; 27068 - 27085 ; 27218 - 27231 ; 27927 - 27941 ; 28777 - 28795 ; 29103 - 29116 ; 29389 - 29403 ; 29985 - 29998 ; 30360 - 30374 ; 30376 - 30390 ; 30768 - 30782 ; 32173 - 32206 ; 32237 - 32251 ; 32260 - 32274 ; 32334 - 32360 ; 32569 - 32583 ; 32597 - 32611 ; 32749 - 32763 ; 33254 - 33268 ; 33299 - 33314 ; 33492 - 33506 ; 34233 - 34247 ; 34360 - 34375 ; 34562 - 34576 ; 34689 - 34703 ; 35106 - 35135 ; 35142 - 35169 ; 35259 - 35275 ; 35280 - 35308 ; 35333 - 35346 ; 35382 -

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3. The oligonucleotide of any one of claims 1 or 2, wherein the oligonucleotide comprises at least 10, or at least 12 contiguous nucleosides present in a sequence selected from the group consisting of SEQ ID NOs 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 557, 558, 559, 560, 577, 579, 583, 638, and 587.
4. The oligonucleotide of any one of any one of claims 1 - 3 wherein one or more nucleoside in the contiguous nucleotide sequence is a 2’ sugar modified nucleoside.
5. The oligonucleotide of claim 3, wherein the one or more 2’ sugar modified nucleoside is independently selected from the group consisting of 2’-O-alkyl-RNA, 2’-O-methyl-RNA, 2’-alkoxy-RNA, 2’-O-methoxyethyl-RNA, 2’-amino-DNA, 2’-fluoro-DNA, arabino nucleic acid (ANA), 2’-fluoro-ANA and LNA nucleosides.
6. The oligonucleotide of any one of claims 1 - 4, wherein the oligonucleotide or contiguous nucleotide sequence thereof comprises one or more LNA nucleoside.
7. The oligonucleotide of any one of claims 1 - 5, wherein at least one internucleoside linkage in the contiguous nucleotide sequence is a phosphorothioate internucleoside linkages.
8. The oligonucleotide according to any one of claims 1 – 6 which is, or forms part of a RNAi agent such as a siRNA or a shRNA.
9. The oligonucleotide according to any one of claims 1 – 6 which is an antisense oligonucleotide.
10. The antisense oligonucleotide of claim 9, wherein all the internucleoside linkages within the contiguous nucleotide sequence are phosphorothioate internucleoside linkages.
11. The antisense oligonucleotide of claim 9 or 10, wherein the oligonucleotide is capable of recruiting RNase H, such as human RNaseH1.
12. The antisense oligonucleotide of any one of claims 9 - 11, wherein the antisense oligonucleotide, or contiguous nucleotide sequence thereof, consists or comprises a gapmer, such as a gapmer of formula 5’-F-G-F’-3’, wherein region G is a region comprising

a contiguous sequence of nucleotides capable of recruiting RNaseH, and regions F and F' each comprise at least one 2' sugar modified nucleoside.

13. The antisense oligonucleotide according to claim 12, wherein region G comprises of 6 – 16 DNA nucleosides and at least one of region F and F' comprises at least one LNA nucleoside, or both region F and F' comprise at least one LNA nucleoside.

14. An antisense oligonucleotide selected from the group consisting of CMP ID 50_1 ; 51_1 ; 52_1 ; 53_1 ; 54_1 ; 55_1 ; 56_1 ; 57_1 ; 58_1 ; 59_1 ; 60_1 ; 61_1 ; 62_1 ; 63_1 ; 64_1 ; 65_1 ; 66_1 ; 67_1 ; 68_1 ; 69_1 ; 70_1 ; 71_1 ; 72_1 ; 73_1 ; 74_1 ; 75_1 ; 76_1 ; 77_1 ; 78_1 ; 79_1 ; 80_1 ; 81_1 ; 82_1 ; 83_1 ; 84_1 ; 85_1 ; 86_1 ; 87_1 ; 88_1 ; 89_1 ; 90_1 ; 91_1 ; 92_1 ; 93_1 ; 94_1 ; 95_1 ; 96_1 ; 97_1 ; 98_1 ; 99_1 ; 100_1 ; 101_1 ; 102_1 ; 103_1 ; 104_1 ; 105_1 ; 106_1 ; 107_1 ; 108_1 ; 109_1 ; 110_1 ; 111_1 ; 112_1 ; 113_1 ; 114_1 ; 115_1 ; 116_1 ; 117_1 ; 118_1 ; 119_1 ; 120_1 ; 121_1 ; 122_1 ; 123_1 ; 124_1 ; 125_1 ; 126_1 ; 127_1 ; 128_1 ; 129_1 ; 130_1 ; 131_1 ; 132_1 ; 133_1 ; 134_1 ; 135_1 ; 136_1 ; 137_1 ; 138_1 ; 139_1 ; 140_1 ; 141_1 ; 142_1 ; 143_1 ; 144_1 ; 145_1 ; 146_1 ; 147_1 ; 148_1 ; 149_1 ; 150_1 ; 151_1 ; 152_1 ; 153_1 ; 154_1 ; 155_1 ; 156_1 ; 157_1 ; 158_1 ; 159_1 ; 160_1 ; 161_1 ; 162_1 ; 163_1 ; 164_1 ; 165_1 ; 166_1 ; 167_1 ; 168_1 ; 169_1 ; 170_1 ; 171_1 ; 172_1 ; 173_1 ; 174_1 ; 175_1 ; 176_1 ; 177_1 ; 178_1 ; 179_1 ; 180_1 ; 181_1 ; 182_1 ; 183_1 ; 184_1 ; 185_1 ; 186_1 ; 187_1 ; 188_1 ; 189_1 ; 190_1 ; 191_1 ; 192_1 ; 193_1 ; 194_1 ; 195_1 ; 196_1 ; 197_1 ; 198_1 ; 199_1 ; 200_1 ; 201_1 ; 202_1 ; 203_1 ; 204_1 ; 205_1 ; 206_1 ; 207_1 ; 208_1 ; 209_1 ; 210_1 ; 211_1 ; 212_1 ; 213_1 ; 214_1 ; 215_1 ; 216_1 ; 217_1 ; 218_1 ; 219_1 ; 220_1 ; 221_1 ; 222_1 ; 223_1 ; 224_1 ; 225_1 ; 226_1 ; 227_1 ; 228_1 ; 229_1 ; 230_1 ; 231_1 ; 232_1 ; 233_1 ; 234_1 ; 235_1 ; 236_1 ; 237_1 ; 238_1 ; 239_1 ; 240_1 ; 241_1 ; 242_1 ; 243_1 ; 244_1 ; 245_1 ; 246_1 ; 247_1 ; 248_1 ; 249_1 ; 250_1 ; 251_1 ; 252_1 ; 253_1 ; 254_1 ; 255_1 ; 256_1 ; 257_1 ; 258_1 ; 259_1 ; 260_1 ; 261_1 ; 262_1 ; 263_1 ; 264_1 ; 265_1 ; 266_1 ; 267_1 ; 268_1 ; 269_1 ; 270_1 ; 271_1 ; 272_1 ; 273_1 ; 274_1 ; 275_1 ; 276_1 ; 277_1 ; 278_1 ; 279_1 ; 280_1 ; 281_1 ; 282_1 ; 283_1 ; 284_1 ; 285_1 ; 286_1 ; 287_1 ; 288_1 ; 289_1 ; 290_1 ; 291_1 ; 292_1 ; 293_1 ; 294_1 ; 295_1 ; 296_1 ; 297_1 ; 298_1 ; 299_1 ; 300_1 ; 301_1 ; 302_1 ; 303_1 ; 304_1 ; 305_1 ; 306_1 ; 307_1 ; 308_1 ; 309_1 ; 310_1 ; 311_1 ; 312_1 ; 313_1 ; 314_1 ; 315_1 ; 316_1 ; 317_1 ; 318_1 ; 319_1 ; 320_1 ; 321_1 ; 322_1 ; 323_1 ; 324_1 ; 325_1 ; 326_1 ; 327_1 ; 328_1 ; 329_1 ; 330_1 ; 331_1 ; 332_1 ; 333_1 ; 334_1 ; 335_1 ; 336_1 ; 337_1 ; 338_1 ; 339_1 ; 340_1 ; 341_1 ; 342_1 ; 343_1 ; 344_1 ; 345_1 ; 346_1 ; 347_1 ; 348_1 ; 349_1 ; 350_1 ; 351_1 ; 352_1 ; 353_1 ; 354_1 ; 355_1 ; 356_1 ; 357_1 ; 358_1 ; 359_1 ; 360_1 ; 361_1 ; 362_1 ; 363_1 ; 364_1 ; 365_1 ; 366_1 ; 367_1 ; 368_1 ; 369_1 ; 370_1 ; 371_1 ; 372_1 ; 373_1 ; 374_1 ; 375_1 ; 376_1 ; 377_1 ; 378_1 ; 379_1 ; 380_1 ; 381_1 ; 382_1 ; 383_1 ; 384_1 ; 385_1 ; 386_1 ; 387_1 ; 388_1 ; 389_1 ; 390_1 ; 391_1 ; 392_1 ; 393_1 ; 394_1 ; 395_1 ; 396_1 ; 397_1 ; 398_1 ; 399_1 ; 400_1 ;

401_1 ; 402_1 ; 403_1 ; 404_1 ; 405_1 ; 406_1 ; 407_1 ; 408_1 ; 409_1 ; 410_1 ; 411_1 ; 412_1 ; 413_1 ; 414_1 ; 415_1 ; 416_1 ; 417_1 ; 418_1 ; 419_1 ; 420_1 ; 421_1 ; 422_1 ; 423_1 ; 424_1 ; 425_1 ; 426_1 ; 427_1 ; 428_1 ; 429_1 ; 430_1 ; 431_1 ; 432_1 ; 433_1 ; 434_1 ; 435_1 ; 436_1 ; 437_1 ; 438_1 ; 439_1 ; 440_1 ; 441_1 ; 442_1 ; 443_1 ; 444_1 ; 445_1 ; 446_1 ; 447_1 ; 448_1 ; 449_1 ; 450_1 ; 451_1 ; 452_1 ; 453_1 ; 454_1 ; 455_1 ; 456_1 ; 457_1 ; 458_1 ; 459_1 ; 460_1 ; 461_1 ; 462_1 ; 463_1 ; 464_1 ; 465_1 ; 466_1 ; 467_1 ; 468_1 ; 469_1 ; 470_1 ; 471_1 ; 472_1 ; 473_1 ; 474_1 ; 475_1 ; 476_1 ; 477_1 ; 478_1 ; 479_1 ; 480_1 ; 481_1 ; 482_1 ; 483_1 ; 484_1 ; 485_1 ; 486_1 ; 487_1 ; 488_1 ; 489_1 ; 490_1 ; 491_1 ; 492_1 ; 493_1 ; 494_1 ; 495_1 ; 496_1 ; 497_1 ; 498_1 ; 499_1 ; 500_1 ; 501_1 ; 502_1 ; 503_1 ; 504_1 ; 505_1 ; 506_1 ; 507_1 ; 508_1 ; 509_1 ; 510_1 ; 511_1 ; 512_1 ; 512_2 ; 512_3 ; 513_1 ; 513_2 ; 513_3 ; 513_4 ; 514_1 ; 514_2 ; 514_3 ; 514_4 ; 515_1 ; 515_2 ; 515_3 ; 515_4 ; 515_5 ; 515_6 ; 516_1 ; 516_2 ; 516_3 ; 516_4 ; 516_5 ; 516_6 ; 516_7 ; 517_1 ; 517_2 ; 517_3 ; 517_4 ; 517_5 ; 517_6 ; 517_7 ; 517_8 ; 518_1 ; 518_2 ; 518_3 ; 518_4 ; 518_5 ; 518_6 ; 519_1 ; 519_2 ; 519_3 ; 519_4 ; 519_5 ; 519_6 ; 520_1 ; 520_2 ; 520_3 ; 520_4 ; 520_5 ; 521_1 ; 521_2 ; 521_3 ; 521_4 ; 521_5 ; 522_1 ; 522_2 ; 522_3 ; 522_4 ; 523_1 ; 523_2 ; 523_3 ; 523_4 ; 523_5 ; 524_1 ; 525_1 ; 526_1 ; 527_1 ; 528_1 ; 529_1 ; 530_1 ; 531_1 ; 532_1 ; 533_1 ; 534_1 ; 535_1 ; 536_1 ; 537_1 ; 538_1 ; 539_1 ; 540_1 ; 541_1 ; 542_1 ; 543_1 ; 544_1 ; 545_1 ; 546_1 ; 547_1 ; 548_1 ; 549_1 ; 550_1 ; 551_1 ; 552_1 ; 553_1 ; 554_1 ; 555_1 ; 556_1 ; 557_1 ; 558_1 ; 559_1 ; 560_1 ; 561_1 ; 562_1 ; 563_1 ; 564_1 ; 565_1 ; 566_1 ; 567_1 ; 568_1 ; 569_1 ; 570_1 ; 571_1 ; 572_1 ; 573_1 ; 574_1 ; 575_1 ; 576_1 ; 577_1 ; 578_1 ; 579_1 ; 580_1 ; 581_1 ; 582_1 ; 583_1 ; 584_1 ; 585_1 ; 586_1 ; 587_1 ; 588_1 ; 589_1 ; 590_1 ; 591_1 ; 592_1 ; 593_1 ; 594_1 ; 595_1 ; 596_1 ; 597_1 ; 598_1 ; 599_1 ; 600_1 ; 601_1 ; 602_1 ; 603_1 ; 604_1 ; 605_1 ; 606_1 ; 607_1 ; 608_1 ; 609_1 ; 610_1 ; 611_1 ; 612_1 ; 613_1 ; 614_1 ; 615_1 ; 616_1 ; 617_1 ; 618_1 ; 619_1 ; 620_1 ; 621_1 ; 622_1 ; 623_1 ; 624_1 ; 625_1 ; 626_1 ; 627_1 ; 628_1 ; 629_1 ; 630_1 ; 631_1 ; 632_1 ; 633_1 ; 634_1 ; 635_1 ; 636_1 ; 637_1 ; 638_1 ; 639_1 ; 640_1; 641_1; 642_1, 643_1, 644_1, 645_1, 646_1, 647_1, 648_1, 649_1 and 650_1.

15. A conjugate comprising the oligonucleotide according to any one of claims 1 – 14, and at least one conjugate moiety covalently attached to said oligonucleotide.
16. A pharmaceutically acceptable salt of the antisense oligonucleotide according to any one of claims 1 – 15, or the conjugate according to claim 16.
17. A pharmaceutical composition comprising the antisense oligonucleotide of 1-14 or the conjugate of claim 15, or the salt of claim 16, and a pharmaceutically acceptable diluent, solvent, carrier, salt and/or adjuvant.
18. An *in vitro* method for inhibiting SCN9A expression in a target cell which is expressing SCN9A, said method comprising administering an antisense oligonucleotide of any one of

claims 1 -14 or the conjugate of claim 15 or the pharmaceutical salt or composition of claim 16 or 17 in an effective amount to said cell.

19. The method of claim 18, wherein the method is for inhibiting SCN9A and SCN10A expression in a target cell which is expressing SCN9A and SCN10A, said method comprising administering an antisense oligonucleotide of any one of claims 1 -14 or the conjugate of claim 15 or the pharmaceutical salt or composition of claim 16 or 17 in an effective amount to said cell.
20. An antisense oligonucleotide of any one of claims 1 -14 or the conjugate of claim 15 or the pharmaceutical salt or composition of claim 16 or 17 for use for inhibiting SCN9A expression in a target cell which is expressing SCN9A.
21. The antisense oligonucleotide or the conjugate or the pharmaceutical salt or composition of claim 20, wherein the antisense oligonucleotide or the conjugate or the pharmaceutical salt or composition is for use for inhibiting SCN9A and SCN10A expression in a target cell which is expressing SCN9A and SCN10A.
22. The oligonucleotide of any one of claims 1 - 14 or the conjugate according to claim 15 or the pharmaceutical salt or composition of claim 16 or 17 for use in medicine.

23. The oligonucleotide of any one of claims 1 - 14 or the conjugate according to claim 15 or the pharmaceutical salt or composition of claim 16 or 17 for use in the treatment or prevention or alleviation of pain, wherein the pain is either

i) chronic pain, neuropathic pain, inflammatory pain, spontaneous pain, or nociceptive pain; or
ii) pain caused by or associated with a disorder selected from the group consisting of diabetic neuropathies, cancer, cranial neuralgia, postherpetic neuralgia and post-surgical neuralgia; or
iii) pain caused by or associated with inherited erythromelalgia (EIM) or paroxysmal extreme pain disorder (PEPD) or trigeminal neuralgia; or
iv) neurophathic pain, chronic pain, but also general treatment of nociceptive pain (e.g. decompression of a nerve), or neuropathic pain (e.g. diabetic neuropathy), visceral pain, or mixed pain.

24. The use of an oligonucleotide of any one of claims 1 - 14 or the conjugate according to claim 15 or the pharmaceutical salt or composition of claim 16 or 17, in the preparation of a medicament for the treatment, prevention or alleviation of pain, wherein the pain is either

i) chronic pain, neuropathic pain, inflammatory pain, spontaneous pain, or nociceptive pain; or

ii) pain caused by or associated with a disorder selected from the group consisting of diabetic neuropathies, cancer, cranial neuralgia, postherpetic neuralgia and post-surgical neuralgia; or

iii) pain caused by or associated with inherited erythromelalgia (EIM) or paroxysmal extreme pain disorder (PEPD) or trigeminal neuralgia; or

iv) neurophathic pain, chronic pain, but also general treatment of nociceptive pain (e.g. decompression of a nerve), or neuropathic pain (e.g. diabetic neuropathy), visceral pain, or mixed pain.