

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau

(43) International Publication Date
28 September 2023 (28.09.2023)



(10) International Publication Number
WO 2023/183801 A3

(51) International Patent Classification:

C12N 15/113 (2010.01) C07H 21/04 (2006.01)
C12N 15/11 (2006.01) C12N 15/00 (2006.01)
A61P 1/16 (2006.01)

(21) International Application Number:

PCT/US2023/064765

(22) International Filing Date:

21 March 2023 (21.03.2023)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

63/322,845 23 March 2022 (23.03.2022) US

(71) Applicant: **AMGEN INC.** [US/US]; One Amgen Center Drive, Law Department-Patent Operations, Mail Stop 28-5-A, Thousand Oaks, California 91320-1799 (US).

(72) Inventors: **MEADE, Bryan**; One Amgen Center Drive, Law Department-Patent Operations, Mail Stop 28-5-A, Thousand Oaks, California 91320-1799 (US). **MURRAY, Justin K.**; One Amgen Center Drive, Law Department-Patent Operations, Mail Stop 28-5-A, Thousand Oaks, California 91320-1799 (US).

ment-Patent Operations, Mail Stop 28-5-A, Thousand Oaks, California 91320-1799 (US). **RULIFSON, Ingrid**; One Amgen Center Drive, Law Department-Patent Operations, Mail Stop 28-5-A, Thousand Oaks, California 91320-1799 (US). **HOMANN, Oliver**; One Amgen Center Drive, Law Department-Patent Operations, Mail Stop 28-5-A, Thousand Oaks, California 91320-1799 (US).

(74) Agent: **KARABINIS, Melissa**; One Amgen Center Drive, Law Department-Patent Operations, Mail Stop 28-5-A, Thousand Oaks, California 91320-1799 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CV, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IQ, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, MG, MK, MN, MU, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH,

(54) Title: RNAI CONSTRUCTS FOR INHIBITING PNPLA3 EXPRESSION AND METHODS OF USE THEREOF

Figure 1

Duplex No.	PNPLA3 Location	Sense Strand Sequence	Sense Strand SEQ ID NO:	Sense Strand Modified Sequence	Sense Strand Mod SEQ ID NO:	Antisense Strand Sequence	Antisense Strand SEQ ID NO:	Antisense Strand Modified Sequence	Antisense Strand Mod SEQ ID NO:
37555-1	113	AGCUGCUGC GGAUCAGG ACC{invAb}	1069	asgscugcUfgCfGfGf Afucagaccs{invAb}	1699	AGGUCCUGAU CCGCAGCAGC UUU	2329	asGfsuccUf gaucgcCfaGf cagcusus	2959
37556-1	115	CUGCUGCUG AUCAGGACC CG{invAb}	1070	csusgucCfGfGfA/f Cfaggaccs{invAb}	1700	UCGGGUCCUG AUCGCAGCA GUU	2330	usCfsgguCf cugaucCfGfCf agcagusus	2960
37557-1	121	CGGAUCAG GACCCGAGC CGA{invAb}	1071	csusgaucAfgGfAfCf Cfagaccgas{invAb}	1701	AUCGGUCUG GUCCUGAUC GUU	2331	asUfscggCf cgggucCfuGf aucgusus	2961
37558-1	122	GGAUCAGG ACCCGAGCC GAU{invAb}	1072	gsusaucaGfGfAfCf Cfagaccgas{invAb}	1702	AAUCGGUCUG GGUCCUGAUC CUU	2332	asAfsuccgCf ucggguCfCfUf gaucgusus	2962
37559-1	204	CAGAGCGCG GCUGGAGC UUG{invAb}	1073	csasgagCfGfGfCfCf Ufaggaccuugs{invAb}	1703	ACAAGCUCA GCCGCGCUCU GUU	2333	asCfsaagCf ccagccCfCfGf cucgusus	2963
37560-1	205	AGAGCGCG GCUUGGAGC UUGU{invAb}	1074	asgsagcgCfGfCfUf Gfagaccuugs{invAb}	1704	AACAAGCUCC AGCCGCGCUC UUU	2334	asAfsaagCf uccagCfGfCf gcucusus	2964
37561-1	206	GAGCGCGCG UGGAGCUU GUC{invAb}	1075	gsasgagCfGfCfUfGf Gfagaccuugs{invAb}	1705	AGACAAGCUC CAGCCGCGCU CUU	2335	asGfsacaaGf cuccagCfCfGf cgcucusus	2965

(57) Abstract: The disclosure relates to RNAi constructs, such as siRNA, for reducing expression of the Patatin-Like Phospholipase Domain Containing 3 (PNPLA3) gene. Further disclosed are RNAi constructs comprising sense strand and antisense strand sequences, and PNPLA3 mRNA sequences. Methods of using such RNAi constructs to treat or prevent liver disease, such as nonalcoholic fatty liver disease (NAFLD), are also described.

[Continued on next page]

TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS,
ZA, ZM, ZW.

- (84) Designated States** (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, CV, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SC, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, ME, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

- *with international search report (Art. 21(3))*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*
- *with sequence listing part of description (Rule 5.2(a))*

(88) Date of publication of the international search report:

02 November 2023 (02.11.2023)