Phase 1 randomized double-blind study of an RNA interference therapeutic targeting *HSD17B13* for metabolic dysfunction-associated steatohepatitis

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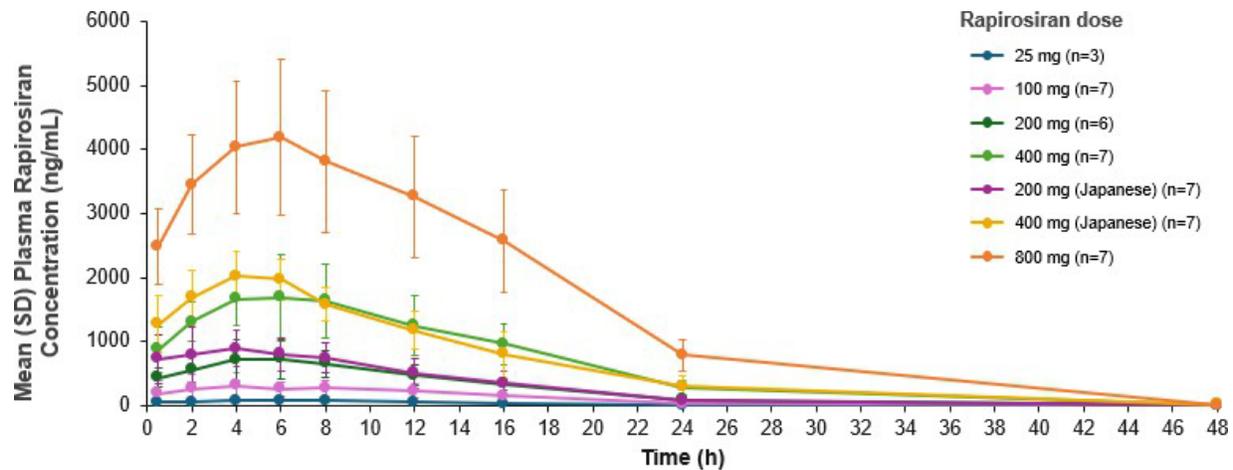
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Fig. S1. Fig. S1. Mean plasma rapirosiran concentrations over time.

Fig. S2. Mean plasma AS(N-1)3' ALN-HSD concentrations over time.

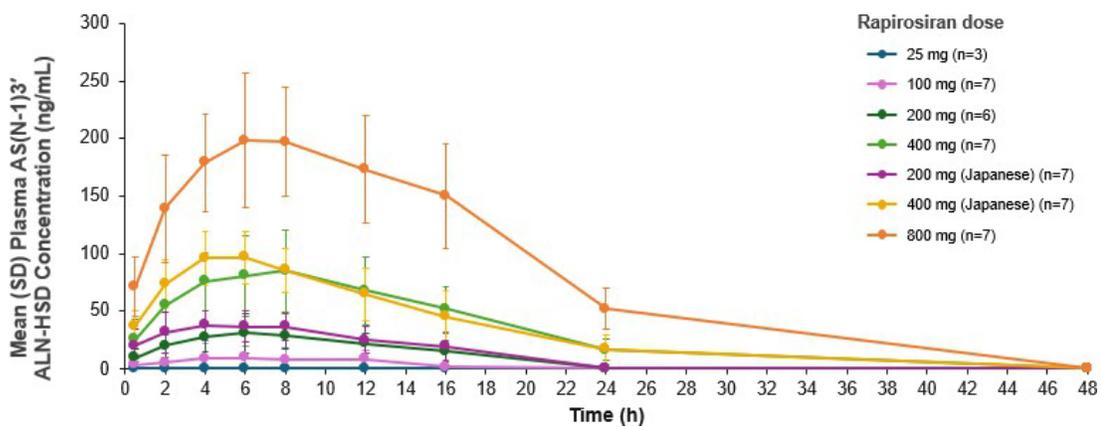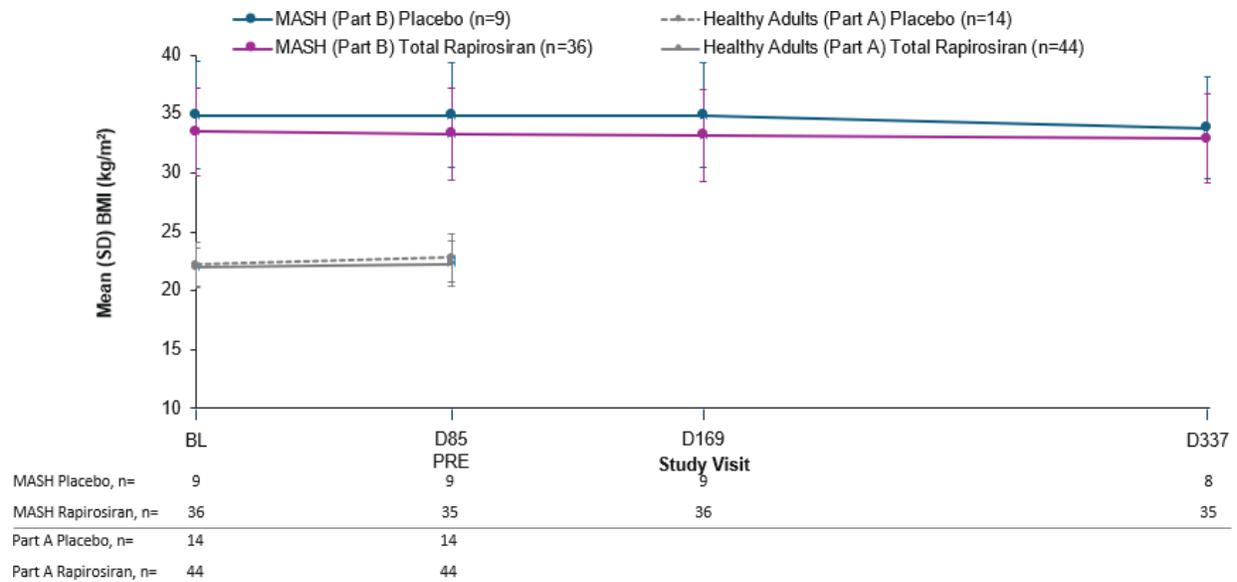**Fig. S3. BMI over time.**

Part A participants (healthy adults) were assessed at baseline and Day 85 only. BL, baseline; BMI, body mass index; D, Day; MASH, metabolic dysfunction–associated steatohepatitis; PRE, within 7 days/pre-dose.

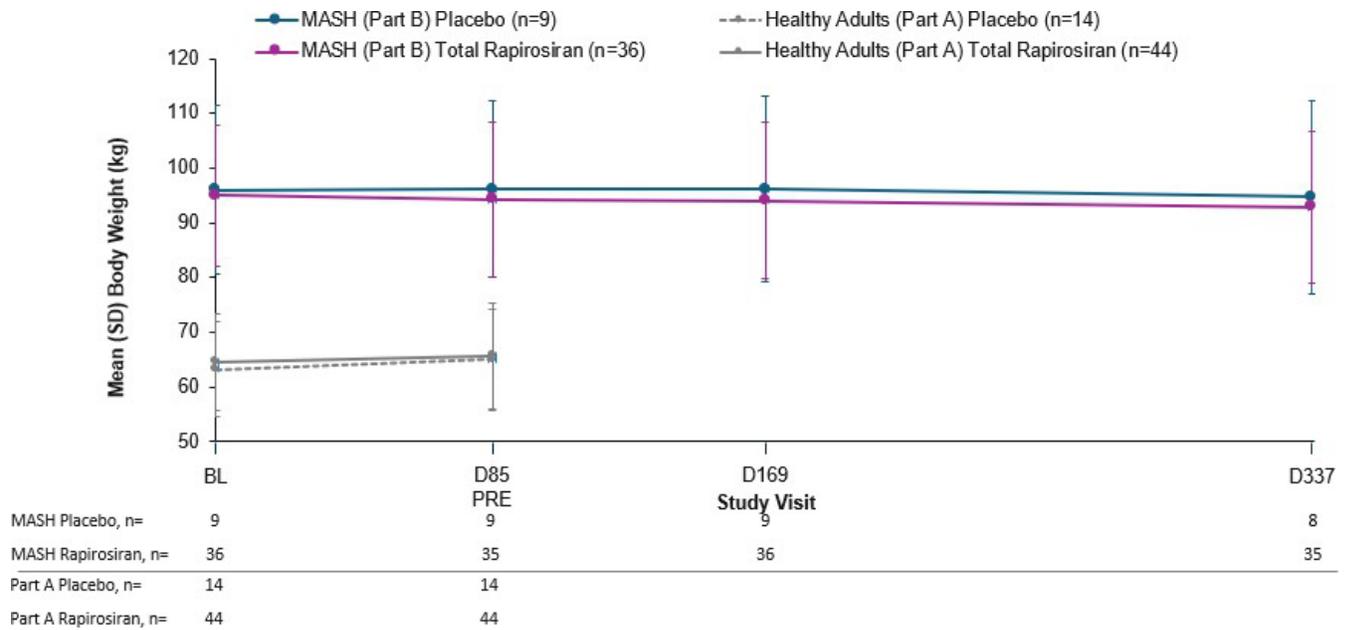**Fig. S4. Body weight over time.**

Part A participants (healthy adults) were assessed at baseline and Day 85 only. BL, baseline; D, Day; MASH, metabolic dysfunction–associated steatohepatitis; PRE, within 7 days/pre-dose.

Fig. S5. HbA1c over time.

	BL	D85 PRE	D169	D225	D337
MASH Placebo, n=	9	9	8	9	7
MASH Rapirosiran, n=	36	35	34	32	35
Part A Placebo, n=	14	14			
Part A Rapirosiran, n=	44	42			

Part A participants (healthy adults) were assessed at baseline and Day 85 only. BL, baseline; D, Day; HbA1c, hemoglobin A1c; MASH, metabolic dysfunction–associated steatohepatitis; PRE, within 7 days/pre-dose.

Fig. S6. Total cholesterol over time.
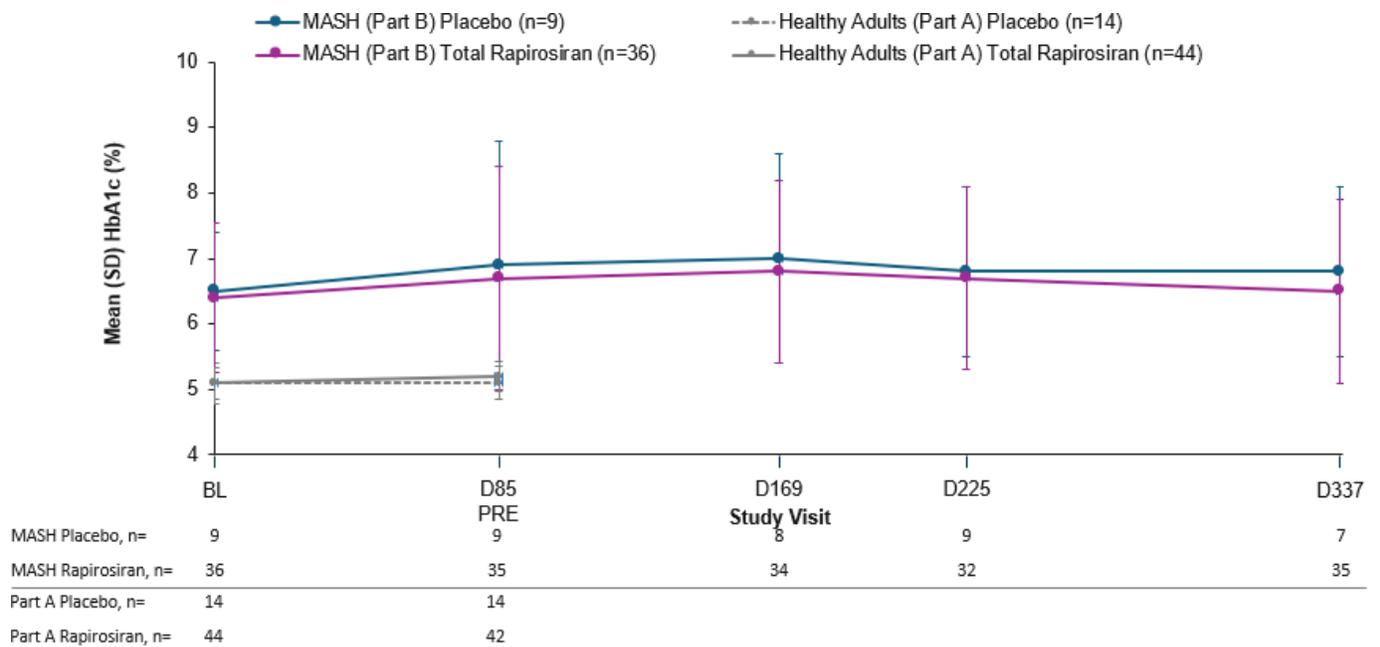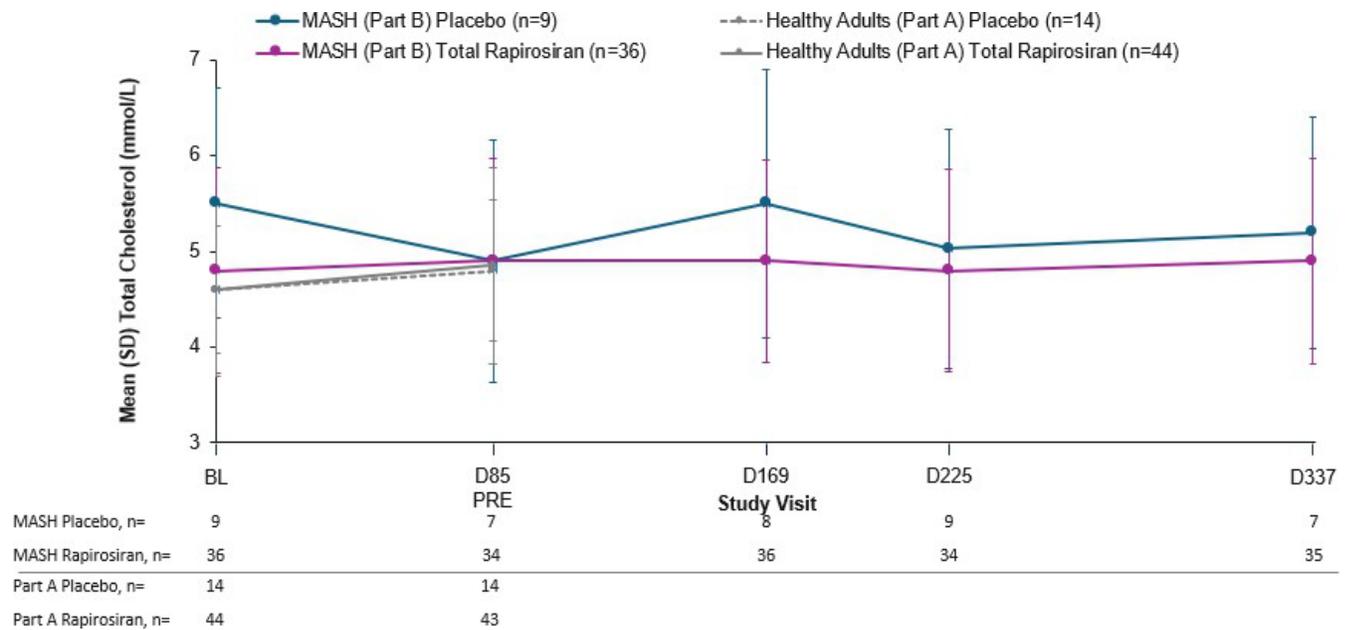

Part A participants (healthy adults) were assessed at baseline and Day 85 only. BL, baseline; D, Day; MASH, metabolic dysfunction–associated steatohepatitis; PRE, within 7 days/pre-dose.

Fig. S7. HDL cholesterol over time.

Part A participants (healthy adults) were assessed at baseline and Day 85 only. BL,

baseline; D, Day; HDL, high-density lipoprotein; MASH, metabolic dysfunction–

associated steatohepatitis; PRE, within 7 days/pre-dose.

Fig. S8. LDL cholesterol over time.

Part A participants (healthy adults) were assessed at baseline and Day 85 only. BL, baseline; D, Day; LDL, low-density lipoprotein; MASH, metabolic dysfunction–associated steatohepatitis; PRE, within 7 days/pre-dose.

Fig. S9. Triglycerides over time.

Part A participants (healthy adults) were assessed at baseline and Day 85 only. BL,

baseline; D, Day; MASH, metabolic dysfunction–associated steatohepatitis; PRE, within
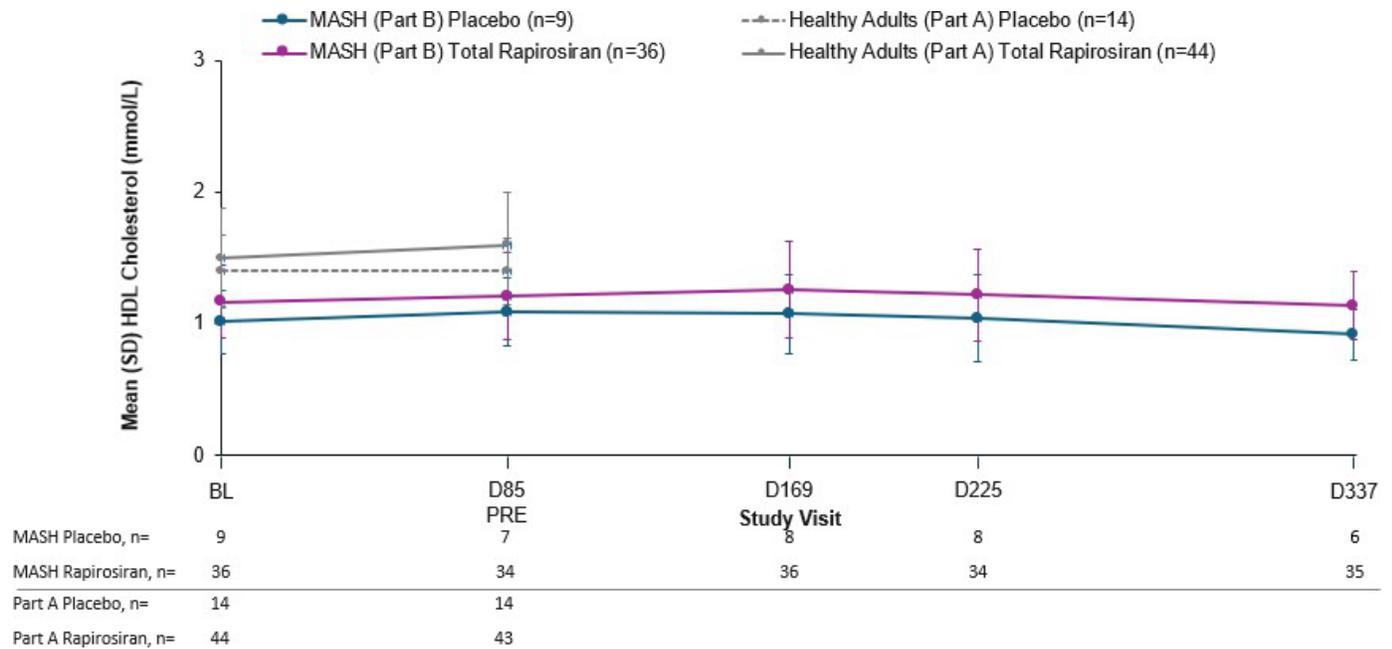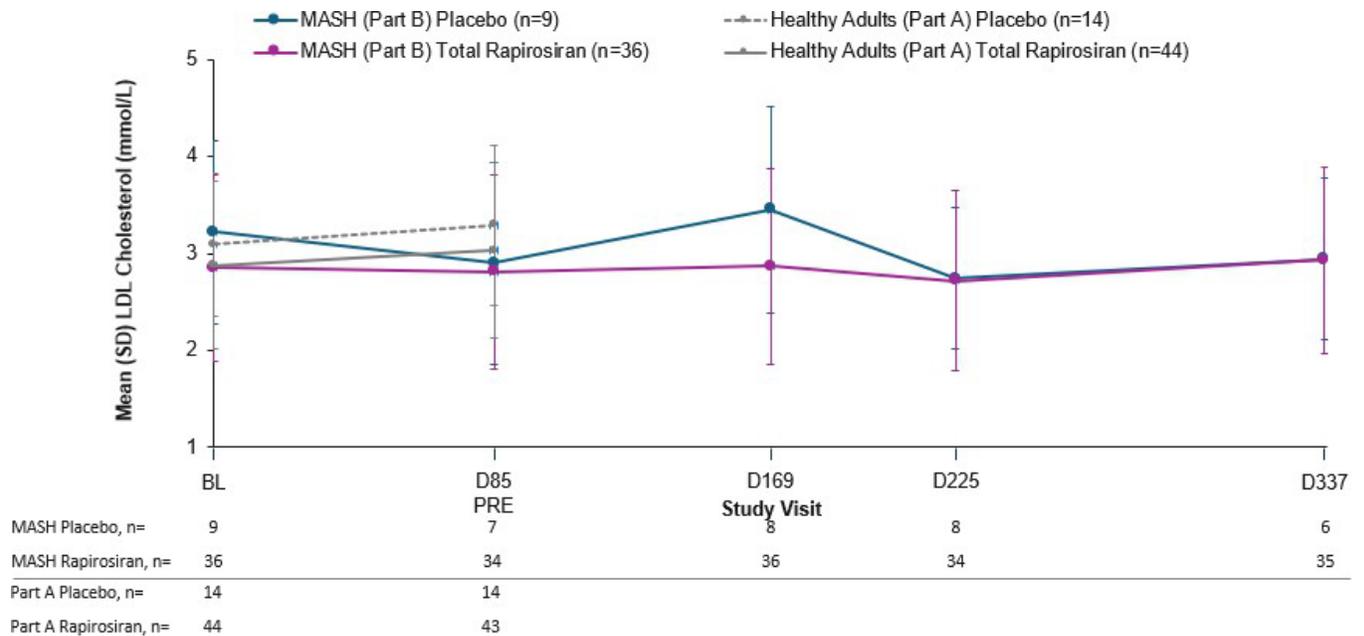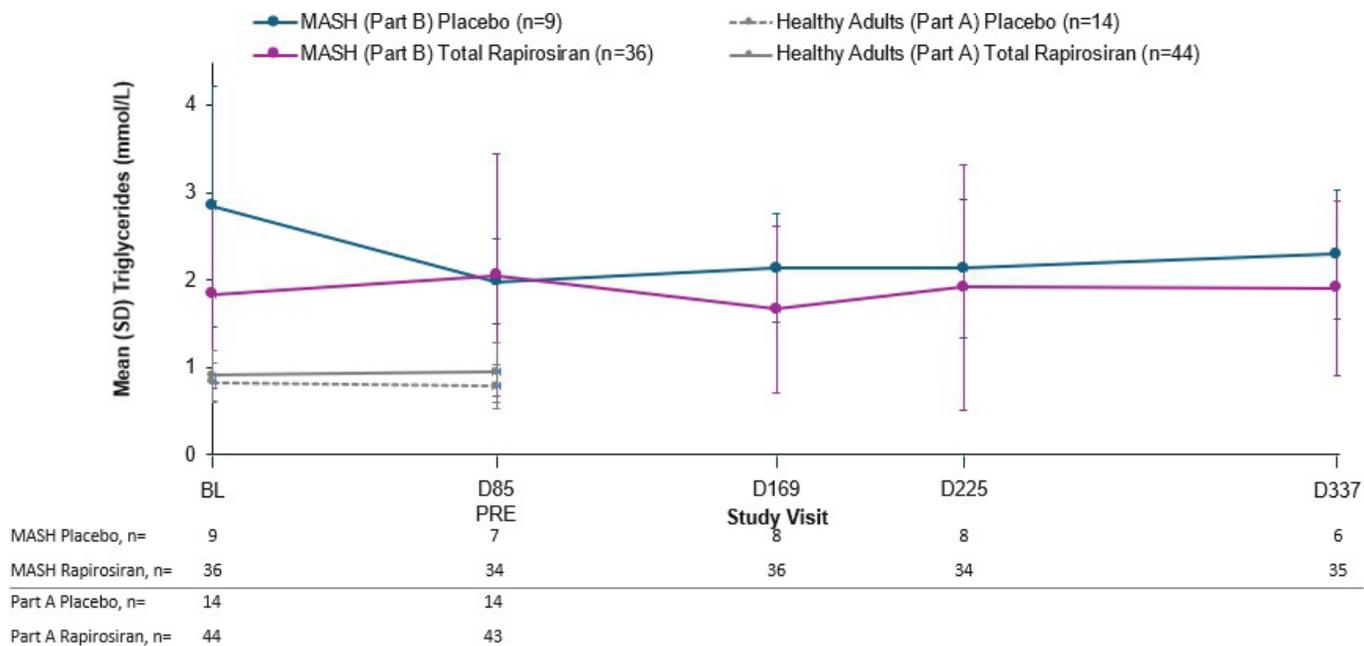
7 days/pre-dose.

Table S1. Genotype frequencies for *HSD17B13* and *PNPLA3* SNPs for all randomized patients in study Part B.

Allele	Placebo (n=9)	Rapirosiran (n=36)
HSD17B13, n (%)		
rs62305723:G		
Homozygous for risk alleles (G/G)	8 (89)	29 (81)
Heterozygous for risk allele (G/A)	1 (11)	1 (3)
Homozygous for protective alleles (A/A)	0	0
rs72613567:T		
Homozygous for risk alleles (T/T)	9 (100)	29 (81)
Heterozygous for risk allele (T/TA)	0	1 (3)
Homozygous for protective alleles (TA/TA)	0	0
rs80182459:GG		
Homozygous for risk alleles (GG/GG)	7 (78)	20 (56)
Heterozygous for risk allele (GG/G)	2 (22)	10 (28)
Homozygous for protective alleles (G/G)	0	0
PNPLA3, n (%)		
rs738409:G (I148M)		
Homozygous for risk alleles (G/G)	2 (22)	6 (17)
Heterozygous for risk allele (C/G)	3 (33)	10 (28)
Homozygous for protective alleles (C/C)	4 (44)	14 (39)

Table S2. Mean (%CV) Pharmacokinetic parameters in study Part A.[a]

Parameter	25 mg (n=3)	100 mg (n=7)	200 mg (n=6)	200 mg, Japanese cohort (n=7)	400 mg (n=7)	400 mg, Japanese cohort (n=7)	800 mg (n=7)
Rapirosiran, plasma							
C_{max}, ng/mL	80.1 (19.2)	328.1 (62.2)	763.2 (38.4)	1016.0 (39.3)	1928.6 (24.4)	2142.9 (11.0)	4472.9 (24.7)
T_{max}, h[b]	6.02 (4.0, 8.0)	4.00 (2.0, 12.0)	5.01 (4.0, 8.0)	4.00 (0.5, 8.0)	6.07 (4.0, 16.0)	4.00 (2.0, 6.0)	6.00 (2.0, 12.1)
AUC_{last}, ng·h/mL	954.7 (21.4)	4379.6 (44.7)	10170.0 (30.1)	11761.9 (28.7)	27074.2 (22.1)	27886.3 (16.2)	68563.2 (23.5)
AUC_{inf}, ng·h/mL	1106.9 (—)[c]	4468.7 (47.5)[d]	10967.0 (26.4)	12229.5 (27.9)	28765.7 (24.1)[d]	30415.2 (15.2)[d]	74879.7 (21.2)[e]
$t_{1/2}$, h	5.4 (—)[c]	4.2 (51.7)[d]	5.6 (38.6)	4.3 (24.1)	5.7 (30.2)[d]	5.6 (36.7)[d]	5.5 (40.0)[e]

Rapirosiran, urine							
f_e, %	16.7 (17.1)	18.7 (39.3)	22.9 (37.1)	34.8 (20.5)	31.0 (26.7)	36.5 (24.8)	32.6 (26.1)[d]
CL_R, L/h	3.2, 5.1[f]	4.4 (20.8)	4.5 (20.7)	6.1 (18.7)	4.9 (27.1)	5.4 (24.3)	4.3 (37.8)[d]
AS(N-1)3′ ALN-HSD, plasma							
C_{max}, ng/mL	NC	11.7 (113.4)	32.2 (52.6)	42.1 (34.1)	91.4 (31.7)	101.8 (18.5)	216.1 (23.1)
T_{max}, h[b]	NC	5.00 (2.0, 12.0)[g]	6.00 (4.0, 8.0)	8.00 (0.5, 8.0)	6.07 (4.0, 16.0)	4.00 (4.0, 6.0)	6.03 (6.0, 12.1)
AUC_{inf}, ng·h/mL	NC	NC	NC	590.2, 724.2[f]	1439.4 (32.1)[e]	1701.0 (17.6)[g]	4082.0 (24.9)[g]
$t_{½}$, h	NC	NC	NC	4.5, 7.1[f]	6.7 (21.1)[e]	5.5 (28.2)[g]	6.8 (27.7)[g]
$MR_{AUClast}$	NC	0.03 (27.4)[g]	0.03 (15.0)	0.04 (6.1)	0.05 (10.6)	0.05 (15.4)	0.05 (7.7)

MR_{Cmax}	NC	0.03 (94.4)	0.04 (14.0)	0.04 (10.8)	0.05 (9.1)	0.05 (11.2)	0.05 (9.8)
AS(N-1)3′ ALN-HSD, urine							
fe, %	0.6 (14.0)	0.8 (43.9)	0.9 (37.5)	1.6 (26.7)	1.5 (29.0)	1.8 (24.9)	1.7 (22.3)

[a]Some metabolite PK parameters could not be calculated, or were calculated with limited data, due to metabolite concentrations in plasma being below the lower limit of quantitation (<10.0 ng/mL). AUC_{inf} and $t_{\frac{1}{2}}$ are not reported if Lambda z (λz) is not estimable. Estimation of λz requires a minimum of 3 quantifiable data points on the terminal log-linear phase, not including C_{max}. [b]Median (minimum, maximum) is presented for T_{max}. [c]n=1, individual participants' data are reported. [d]n=6. [e]n=5. [f]n=2, individual PK parameters are reported. [g]n=4.

Rapirosiran, GalNAc-siRNA conjugate that targets human *HSD17B13* mRNA; AS(N-1)3′ ALN-HSD, double-stranded metabolite of rapirosiran with loss of 1 nucleotide from the 3′ terminus of the antisense strand; AUC, area under the concentration-time curve; AUC_{inf}, AUC from time of dosing extrapolated to infinity; AUC_{last}, AUC from time of dosing to the last measurable concentration; C_{max}, maximum steady-state plasma drug concentration; CL_R, renal clearance; CV, coefficient of variation; fe, fraction excreted; GalNAc, *N*-acetylgalactosamine; $MR_{AUClast}$, metabolite-to-parent ratio for AUC_{last}; MR_{Cmax}, metabolite-to-parent ratio for C_{max}; N, number of patients; NC, not calculated; PK, pharmacokinetics; siRNA, small interfering mRNA; $t_{\frac{1}{2}}$, terminal half-life; T_{max}, time to reach peak concentration.