Supplementary Data File

Metreleptin therapy for nonalcoholic steatohepatitis: Open-label therapy interventions in two different clinical settings

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Additional supplementary data for the partial lipodystrophy (PL) study

Supplementary Data 1. Characteristics of the PL study cohort.

Subject ID	Age	Sex	LD type	Genetic variant	Baseline leptin level (ng/ml)	Morphometrics - Baseline				Morphometrics – 12 months			
						%fat trunk/% fat legs	weight (kg)	BMI (kg/m2)	waist-to-hip ratio	%fat trunk/% fat legs	weight (kg)	BMI (kg/m2)	waist-to-hip ratio
1	39	F	FPLD	†*FBN1* p.M1576T	16.9	1.47	90.6	31.2	1.00	1.6	89.7	30.9	1.01
2	55	M	FPLD	None identified	13.4	1.28	98.6	28.2	0.93	1.9	94.8	27.1	0.91
3	53	F	FPLD	None identified	34.1	1.5	91.3	35.9	1.07	1.61	95.3	37.5	1.12
4	24	M	APL	None identified	4.8	0.83	76.9	24.1	0.82	N/A	N/A	N/A	N/A
5	64	M	FPLD	None identified	24.4	1.6	121.9	35.2	1.05	1.5	119.7	34.5	1.01
6	34	F	FPLD	‡*POLD1* p.E1067K	9.0	1.95	53.0	18.1	0.96	1.7	50.8	17.4	0.95
7	14	F	FPLD	‡*POLD1* p.E1067K	11.5	1.4	50.4	19.0	1.02	1.2	49.2	18.3	0.95
8	58	F	FPLD	None identified	26.5	1.63	84.1	31.0	1.12	1.7	85.8	31.6	1.08
9	54	F	FPLD	None identified	10.5	1.35	54.5	24.1	0.96	1.2	47.9	21.2	0.96
10	33	F	FPLD	*LMNA* p.R60G	16.6	2.22	54.2	19.8	0.90	1.9	52.3	19.1	0.89
11	34	M	FPLD	None identified	19.1	1.62	113.8	34.0	1.16	1.6	120.8	36.1	1.16
12	63	F	FPLD	†*DYRK1B* p.S462R	48.9	1.6	69.9	30.9	1.04	1.5	67.4	29.8	1.02
13	57	F	FPLD	*LMNA* p.R482Q	16.2	2.31	74.3	24.9	0.93	2.0	68.6	23.0	0.91
14	36	M	FPLD	†*SREBF1* p.R913I	16.1	1.42	109.9	31.5	0.96	N/A	N/A	N/A	N/A
15	12	F	FPLD	None identified	7.2	1.99	42.3	17.7	1.00	2.2	47.2	18.8	0.97
16	57	F	FPLD	None identified	35.2	1.43	82.7	30.3	1.07	1.3	78.7	28.8	0.97
17	42	F	FPLD	*LMNA* p.R482Q	6.4	1.49	67.9	24.0	0.85	1.5	63.3	22.4	0.84
18	49	F	FPLD	*LMNA* p.R482Q	13.6	1.94	62.6	25.3	0.93	N/A	N/A	N/A	N/A
19	55	F	FPLD	None identified	67.1	1.6	90.0	38.3	1.03	N/A	N/A	N/A	N/A
20	59	F	FPLD	*LMNA* p.R482Q	11.8	2.03	61.2	21.9	0.99	1.8	61.8	22.2	0.92
21	41	F	FPLD	*LMNA* p.R482W	12.8	1.53	71.3	25.9	0.92	1.5	73.0	26.5	0.98
22	37	F	FPLD	*LMNA* p.R349W	55.4	3.63	63.3	26.4	1.07	4.4	61.7	25.8	1.10
23	13	F	FPLD	None identified	35.6	1.37	90.9	30.5	0.99	1.3	96.4	31.8	0.96

APL: acquired partial lipodystrophy, BMI: body mass index, *DYRK1B*: dual-specificity tyrosine phosphorylation-regulated kinase 1b, *FBN-1*: fibrillin-1, FPLD: familial partial lipodystrophy, LD: lipodystrophy, *LMNA*: lamin A/C, *POLD1*: polymerase (DNA-directed), delta 1, catalytic subunit-1; *SREBF1*: sterol regulatory element-binding transcription factor 1.

†Variant of uncertain significance. ‡ These two related patients had the p.E1067K variant of the *POLD1* gene, which is located at exon 26 of the *POLD1* gene within the CysB region. This *POLD1* variant was previously reported as VUS that is likely pathogenic [1]. Although this variant had not been observed before in any public database, the amino acid change was at a conserved position of the protein in sequenced mammals. This variant has recently been observed in 1 individual from South Asia at a very low allele frequency of 0.0000004368 in the gnomAD database (https://gnomad.broadinstitute.org/variant/19-50920508-A-C). The glutamic acid at position 1067 is at a conserved position of the protein in sequenced mammals. Later, Elouej et al. [2] reported mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome (MDPL) patients with *POLD1* p.I1070N variant. Similar to our patient, MDPL was caused by a variant within the CysB region of the *POLD1* gene, a highly-conserved motif across eukaryotic DNA polymerases. Given the rarity of the variant and the occurrence of the second case of MDPL with a variant within the same region of the *POLD1* gene, we now consider the p.E1067K variant to be associated with the reported phenotype.

References

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2. Elouej, S., Beleza-Meireles, A., Caswell, R., Colclough, K., Ellard, S., Desvignes, J.P., Beroud, C., Levy, N., Mohammed, S., and De Sandre-Giovannoli, A. (2017). Exome sequencing reveals a de novo POLD1 mutation causing phenotypic variability in mandibular hypoplasia, deafness, progeroid features, and lipodystrophy syndrome (MDPL). Metabolism 71, 213-225. 10.1016/j.metabol.2017.03.011.

Supplementary Data 2. Metabolic profile and concomitant medications in the PL study.
(A. Diabetes, B. Hyperlipidemia)

A. Glucose control and other glucose-lowering therapies during the PL study

Subject ID	Baseline		12 months	
	HbA1c (%)	Diabetes treatment	HbA1c (%)	Diabetes treatment
1	9.6	metformin 2000 mg/day glipizide 10 mg/day exenatide 10 mcg/day	10.1	metformin 2000 mg/day glipizide 20 mg/day exenatide 10 mcg/day
2	6.6	metformin 1000 mg/day	6.6	metformin 1000 mg/day
3	8.5	exenatide 20 mcg/day regular (U500) insulin 225-450 units/day	8.2	regular (U500) insulin 500 units/day
4	8.3	none	N/A (withdrawal)	N/A (withdrawal)
5	10.2	metformin 2000 mg/day exenatide 2 mg/week detemir insulin 120 units/day	10.1	metformin 2000 mg/day detemir insulin 120 units/day
6	10.5	pioglitazone 15 mg/day regular (U500) insulin 750 units/day	9.1	NPH-regular insulin 100 units/day
7	10.4	regular (U500) insulin 725 units/day	8.0	regular (U500) insulin 600 units/day
8	10.3	regular (U500) insulin 422 units/day via pump	8.2	regular (U500) insulin 300 units/day via insulin pump
9	9.2	metformin 2000 mg/day exenatide 2 mg/week	6.8	metformin 2000 mg/day exenatide 2 mg/week
10	7.3	metformin 500 mg/day	7.8	metformin 500 mg/day
11	10.1	metformin 2000 mg/day glipizide 5 mg/day aspart protamine-aspart insulin 120 units/day aspart insulin 6-30 units/day	8.5	metformin 2000 mg/day glipizide 5 mg/day aspart protamine-aspart insulin 200 units/day aspart insulin 30 units/day
12	9.2	regular (U500) insulin 150-225 units/day	10.7	regular (U500) insulin 145 units/day
13	10.3	metformin 2000 mg/day pioglitazone 30 mg/day NPH insulin 84 units/day regular insulin 28 units/day	6.3	metformin 2000 mg/day NPH insulin 148 units/day regular insulin 16 units/day

14	9.1	metformin 1500 mg/day glargine insulin 100 units/day aspart insulin 150 units/day	N/A (withdrawal)	N/A (withdrawal)
15	5.8	none	5.9	none
16	12.4	glargine insulin 55 units/day aspart insulin 30 units/day	13.2	glargine 60 units/day
17	5.8	none	5.3	none
18	5.6	metformin 500 mg/day	N/A (screen fail)	N/A (screen fail)
19	6.4	none	N/A (withdrawal)	N/A (withdrawal)
20	9.0	none	9.0	none
21	7.6	metformin 1000 mg/day aspart protamine/aspart insulin 60 unit/day	7.7	lispro protamine/lispro insulin 50 units/day
22	6.2	sitagliptin 100 mg/day	6.6	sitagliptin 100 mg/day
23	8.4	metformin 2000 mg/day regular (U500) insulin 350-400 units/day	8.1	metformin 2000 mg/day regular (U500) insulin 75-600 units/day

B. Lipid parameters and other lipid lowering therapies during the PL study

Subject ID	Lipids - Baseline				Lipid treatment - Baseline	Lipids – 12 months				Lipid treatment – 12 months
	TC (mg/dL)	TG (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)		TC (mg/dL)	TG (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)	
1	184	385	26	80	none	225	251	30	145	none
2	193	265	33	107	krill oil 300 mg/day	193	268	34	105	krill oil 300 mg/day
3	154	240	25	81	fenofibrate 145 mg/day pravastatin 40 mg/day	155	203	31	83	fenofibrate 145 mg/day pravastatin 40 mg/day
4	202	142	40	134	none	N/A (withdrawal)				N/A (withdrawal)
5	142	172	32	76	atorvastatin 20 mg/day	141	162	33	76	atorvastatin 20 mg/day
6	607	5194	24	28	fenofibrate 154 mg/day fish oil 1000 mg/day simvastatin 40 mg/day niaspan 500 mg/day	157	475	30	68	niaspan 500 mg/day
7	664	7004	29	18	omega-3 acid ethyl esters 1000 mg daily	169	457	28	96	omega-3 2170 mg/day
8	271	748	34	123	fenofibrate 45 mg/day omega-3 acid ethyl esters 4000 mg/day pitavastatin 3 mg/day	207	200	39	128	fenofibrate 45 mg/day pitavastatin 4 mg/day
9	334	1155	47	73	atorvastatin 40 mg/week fish oil 3600 mg/day	205	335	46	91	atorvastatin 40 mg/week fish oil 3600 mg/day
10	159	402	35	84	fenofibrate 160 mg/day	145	309	32	91	fenofibrate 160 mg/day
11	228	2716	20	13	omega-3 acid ethyl esters 6000 mg/day rosuvastatin 20 mg/day	121	985	19	23	omega-3 acid ethyl esters 6000 mg/day rosuvastatin 20 mg/day
12	148	177	44	69	omega-3 acid ethyl esters 4000 mg/day fenofibrate 145 mg/day atorvastatin 80 mg/day	233	367	40	119	omega-3 acid ethyl esters 4000 mg/day fenofibrate 145 mg/day atorvastatin 80 mg/day
13	354	1780	37	77	omega-3 acid ethyl esters 8000 mg/day	128	111	43	63	omega-3 acid ethyl esters 8000 mg/day

					fenofibrate 160 mg/day pravastatin 20 mg/day					fenofibrate 160 mg/day pravastatin 20 mg/day
14	244	205	37	166	fenofibrate 160 mg/day omega-3 fatty acids 3600 mg/day	N/A (withdrawal)				N/A (withdrawal)
15	169	305	29	79	None	142	303	28	53	None
16	202	308	38	103	fish oil 500 mg/day atorvastatin 40 mg/day	184	253	33	100	fish oil 500 mg/day atorvastatin 40 mg/day
17	223	211	36	145	fish oil 1000 mg/day rosuvastatin 20 mg/week	151	111	35	94	fish oil 1000 mg/day rosuvastatin 20 mg/week
18	138	80	65	57	fenofibrate 145 mg/day rosuvastatin 20 mg/day	N/A (screen fail)				N/A (screen fail)
19	235	260	35	147	none	N/A (withdrawal)				N/A (withdrawal)
20	341	1771	29	105	fish oil 2000 mg/day	408	3646	28	97	fish oil 7200 mg/day
21	182	346	30	84	gemfibrozil 1200 mg/day	183	204	29	113	none
22	339	261	64	223	none	258	251	41	166	none
23	196	195	35	122	none	188	200	36	112	none

C: cholesterol, TC: total cholesterol, TG: triglyceride, HDL: high density lipoprotein, LDL: low density lipoprotein.

Supplementary Data 3. Individual liver parameters in the PL study.

	Baseline				12 month			
Subject ID	AST (IU/L)	ALT (IU/L)	NASH score	Liver Fat %, Dixon	AST (IU/L)	ALT (IU/L)	NASH score	Liver Fat %, Dixon
1	34	30	9	23	24	27	7	12
2	29	49	6	20	20	28	4	8
3	31	35	5	10	32	33	6	8
4	67	147	7	16	N/A	N/A	N/A	N/A
5	16	19	4	5	19	25	3	6
6	128	97	6	13	43	67	7	8
7	52	51	7	14	31	39	3	4
8	82	53	8	11	30	26	7	6
9	47	100	7	24	21	26	4	5
10	31	40	6	17	24	25	6	13
11	31	67	6	14	63	98	8	12
12	51	54	6	12	45	64	5	8
13	23	27	5	22	30	21	3	14
14	41	37	4	4	N/A	N/A	N/A	N/A
15	53	73	9	4	31	31	7	3
16	17	23	3	11	18	21	1	4
17	28	38	4	5	16	13	2	2
18	26	19	1	2	N/A	N/A	N/A	N/A
19	22	24	6	11	N/A	N/A	NA	N/A
20	23	35	7	21	33	27	6	22
21	18	20	6	3	18	21	4	4
22	18	21	5	5	17	17	N/A	3
23	87	142	6	12	62	75	7	13

ALT: alanine aminotransferase, AST: aspartate aminotransferase, NASH score: nonalcoholic steatohepatitis score equals the sum of scores for steatosis, lobular inflammation, hepatocellular ballooning, and fibrosis, N/A: not available.

Supplementary Data 4. Baseline characteristics of patients who qualified for the study protocol in the PL study.

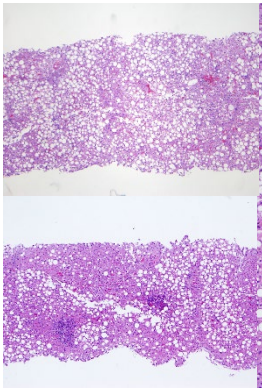
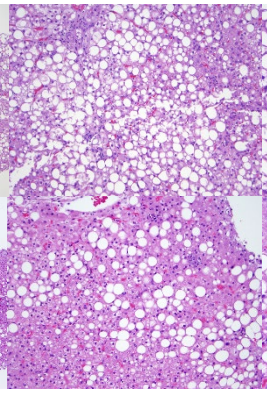
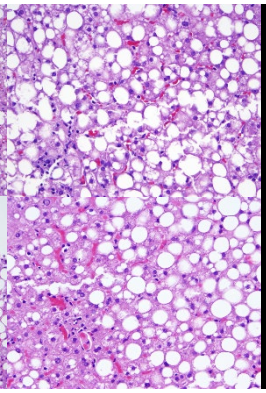
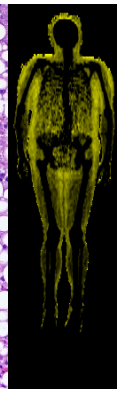
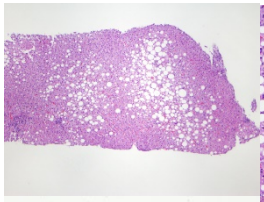
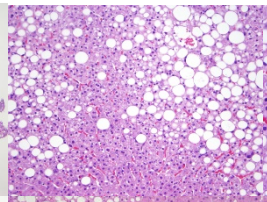
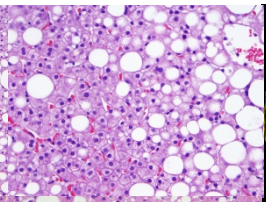
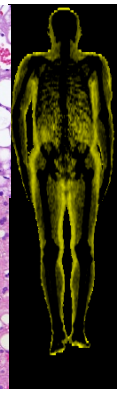
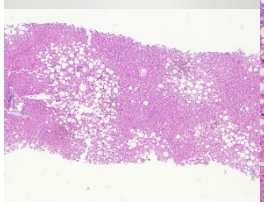
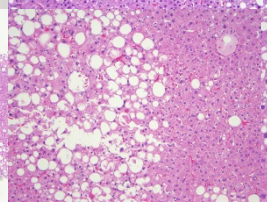
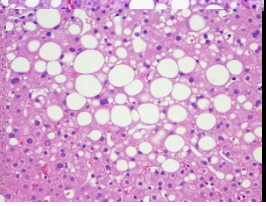
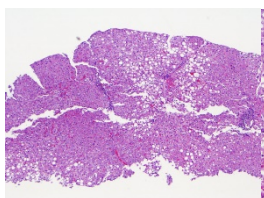
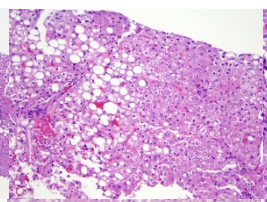
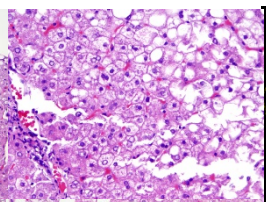
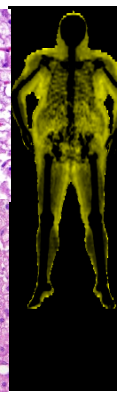
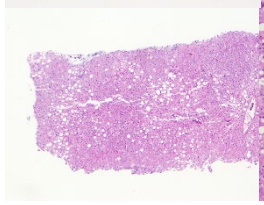
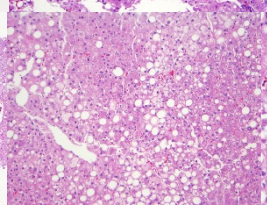
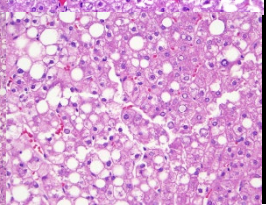
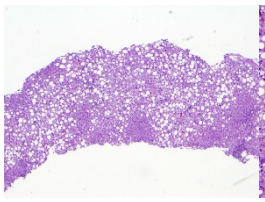
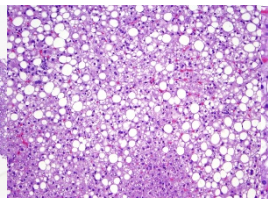
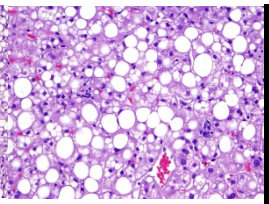
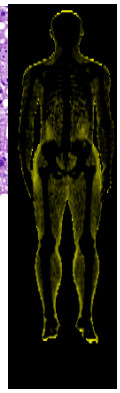
Parameter (n = 22)	Mean ± SD
Age (years)	43 ± 16
Gender (M:F)	5:17
Body weight (kg)	77.9 ± 21.2
Body mass index (kg/m^2)	27.4± 5.8
Waist-to-hip ratio	0.99 ± 0.08
FMR (%fat trunk/ %fat legs)	1.59 ± 0.53
Systolic blood pressure (mmHg)	127 ± 16
Diastolic blood pressure (mmHg)	75 ± 11
Fasting leptin level (ng/ml)	22.7 ± 16.5
Hemoglobin A1c (%)	8.7 ± 1.7
Glucose (mg/dL)	183 ± 80
Triglyceride (mg/dL)	497 (298 - 831)
AST (IU/L)	42 ± 28
ALT, IU/L	54 ± 36
REE (kcal)	1880 ± 314
RQ	0.76 ± 0.07
*Total intake (grams)	2713 ± 1052
Total energy intake (kcal)	1791 ± 452
Total fat intake (grams)	76 ± 25
Total carbohydrate intake (grams)	194 ± 53
Total protein intake (grams)	91 ± 20

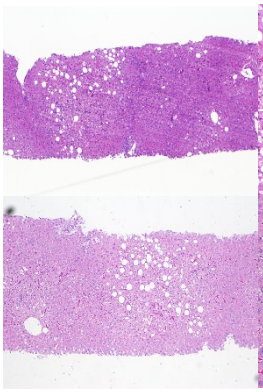
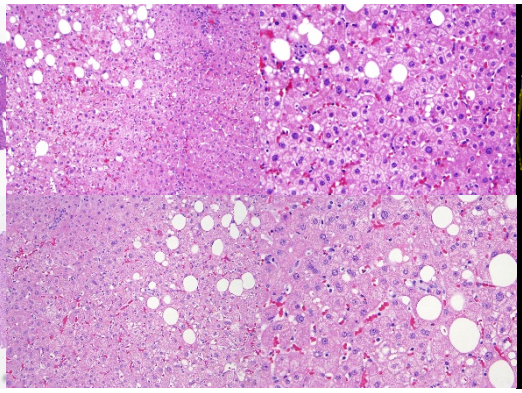
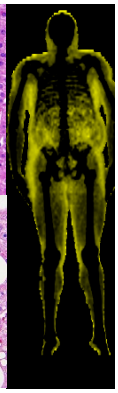
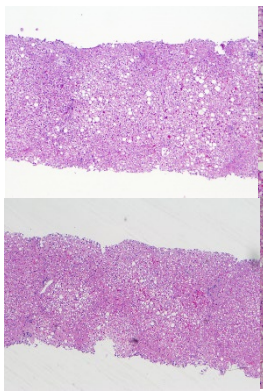
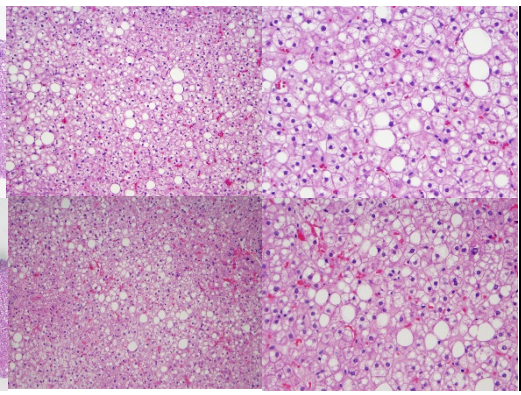
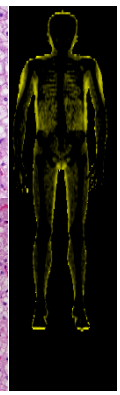
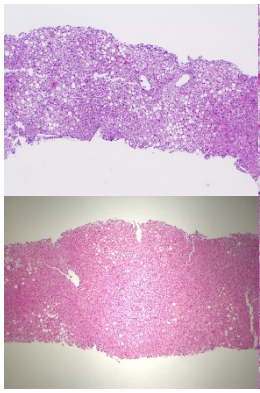
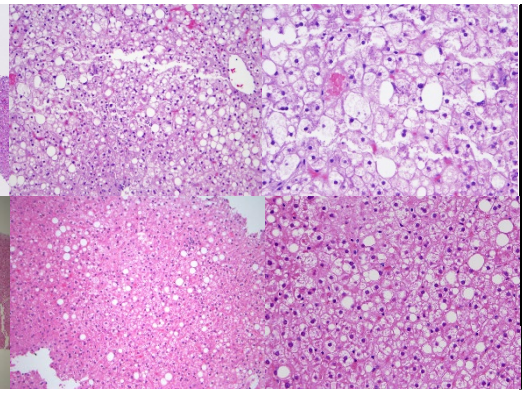
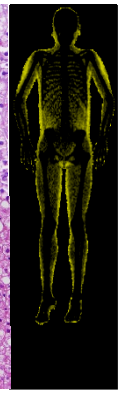
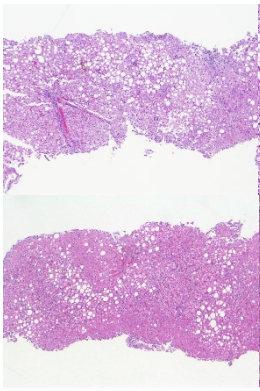
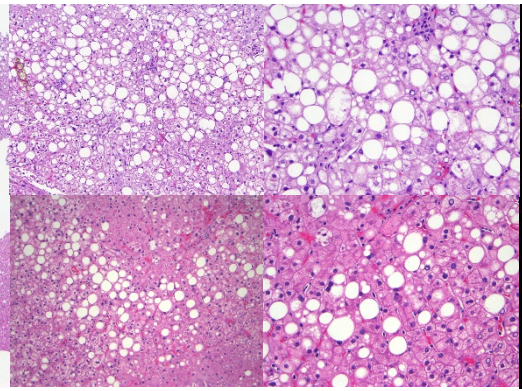
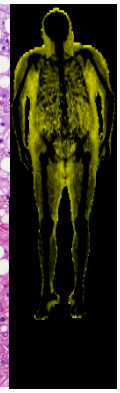
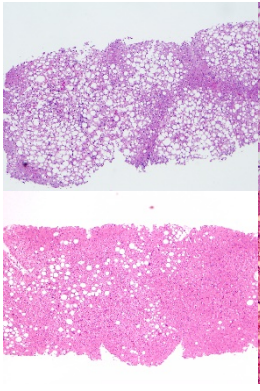
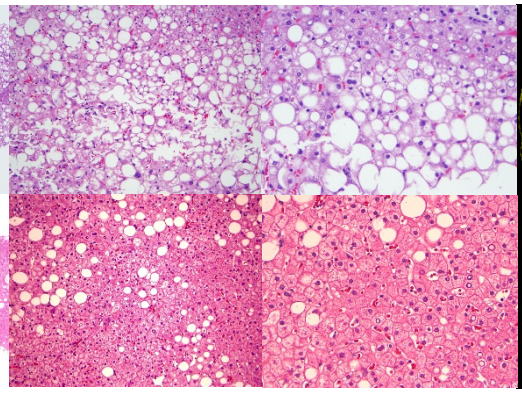
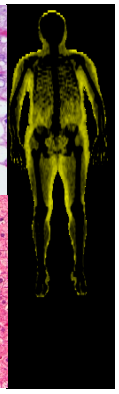
ALT: alanine aminotransferase, AST: aspartate aminotransferase, FMR: fat mass ratio, REE: resting energy expenditure, RQ: respiratory quotient. *Total intake includes food, water and other beverages. Data are presented as mean ± standard deviation (SD). Triglycerides are reported as geometric mean and 95% confidence interval (CI).

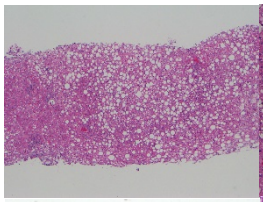
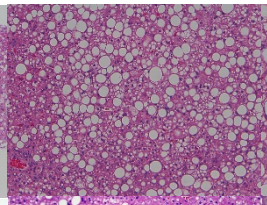
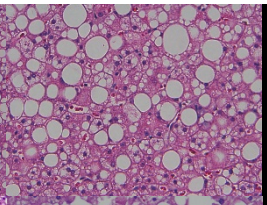
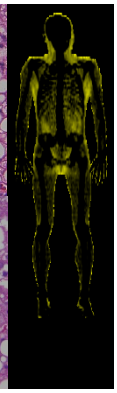
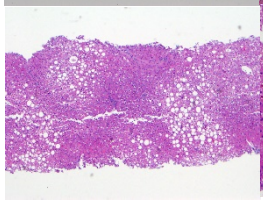
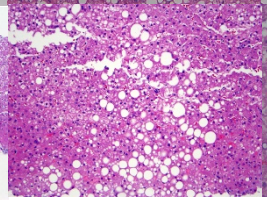
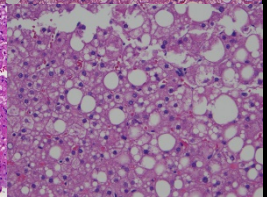
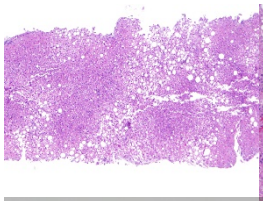
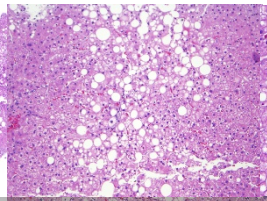
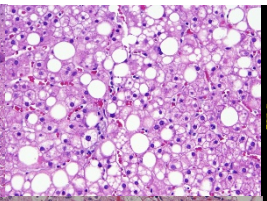
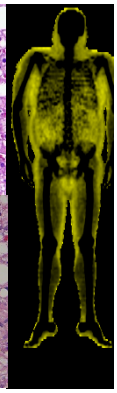
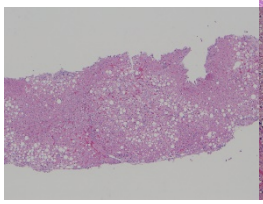
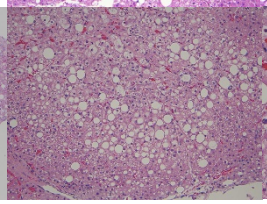
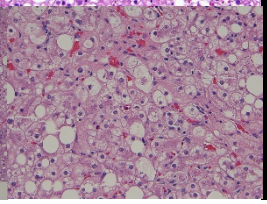
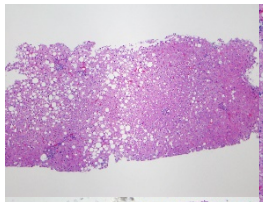
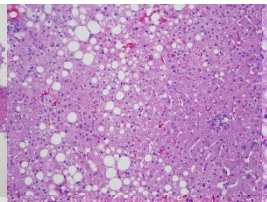
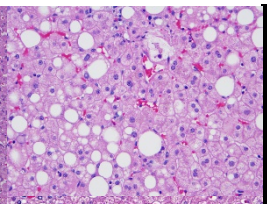
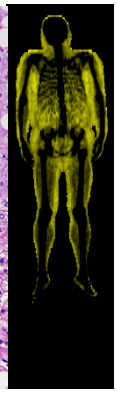
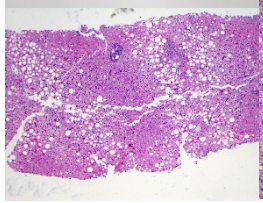
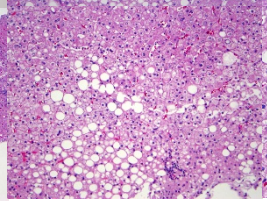
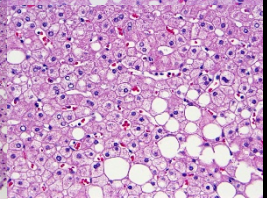
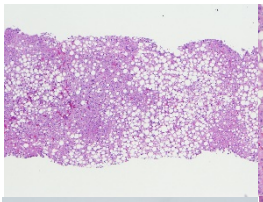
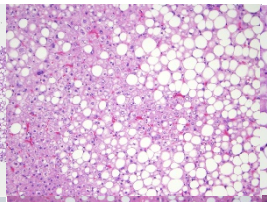
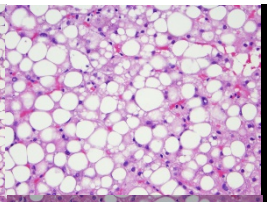
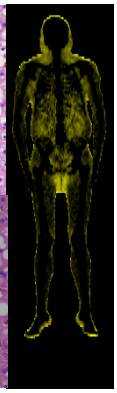
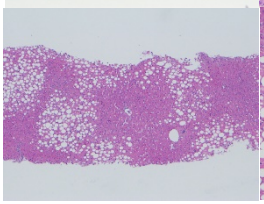
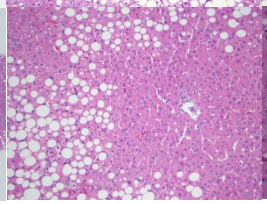
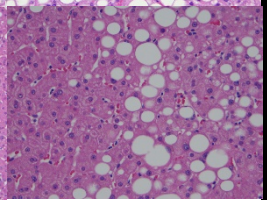
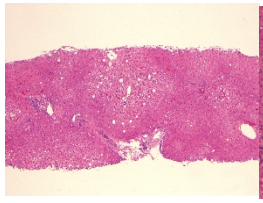
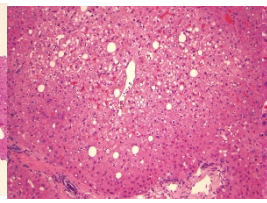
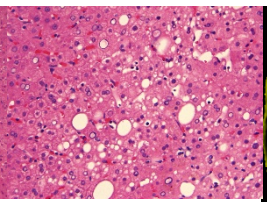
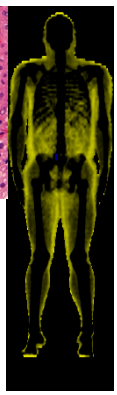
Supplementary Data 5. Adverse events in the PL study.

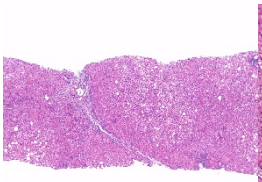
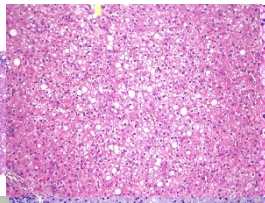
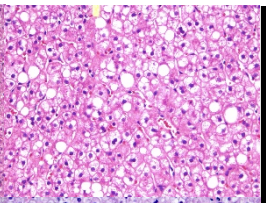
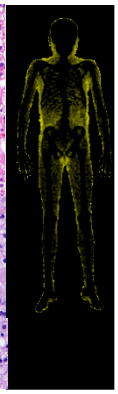
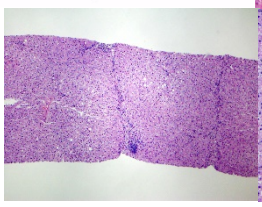
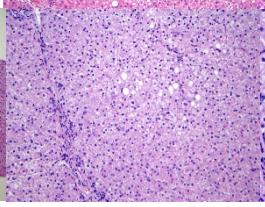
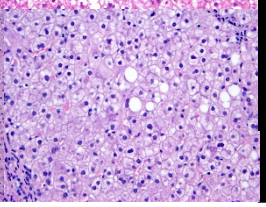
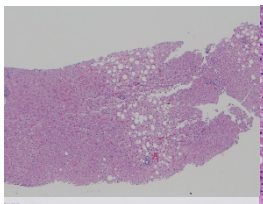
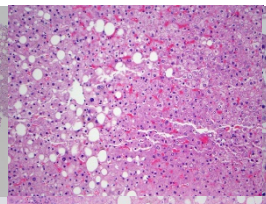
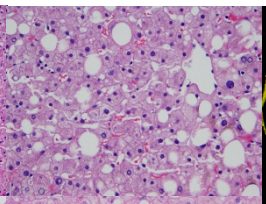
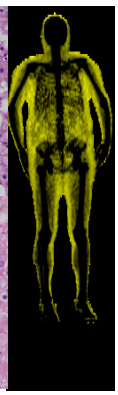
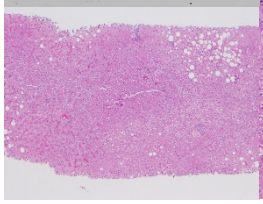
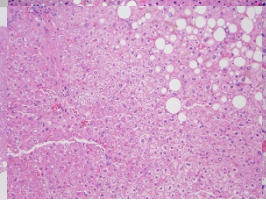
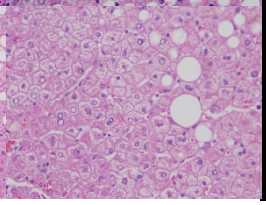
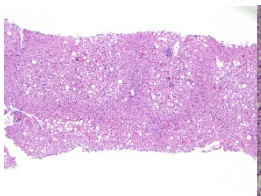
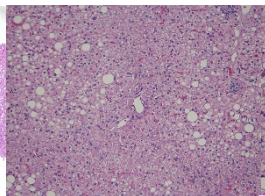
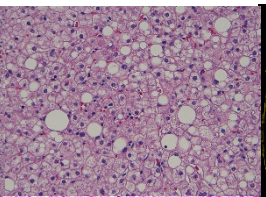
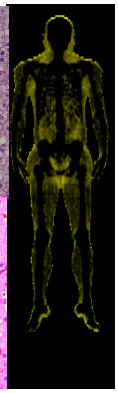
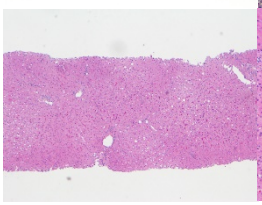
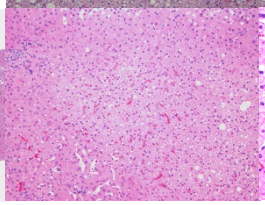
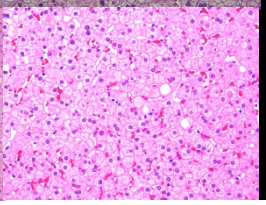
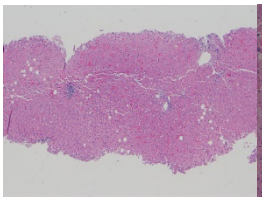
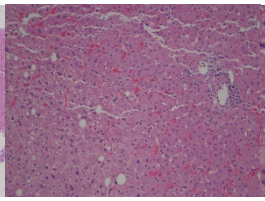
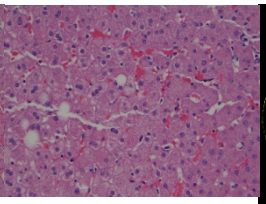
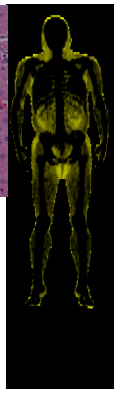
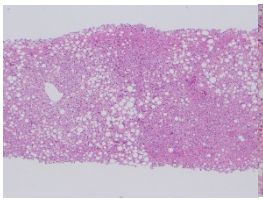
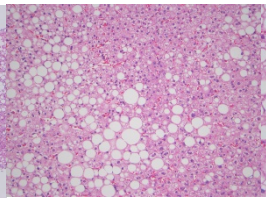
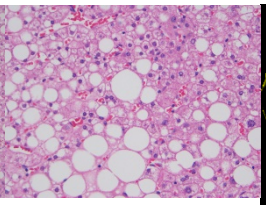
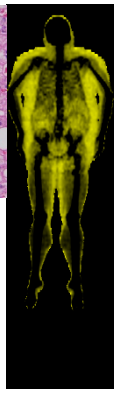
Adverse event, n (%)	**Patients (n=22)**	**Patients with possibly/probably related events (%)**
All adverse events	22 (100)	13 (59)
Mild	17 (63.6)	11 (50)
Moderate	18 (81.8)	9 (40.9)
Severe	11 (50)	2 (9)
Serious adverse events	7 (31.2)	0
Adverse event		**Patients (%)**
Upper respiratory tract infection		11 (50)
Hypoglycemia		6 (27.2)
Diarrhea		5 (22.7)
Injection site reaction		4 (18.1)
Urinary tract infection		3 (13.6)
Dizziness		3 (13.6)
Rash not at injection site, 1 patient with skin granulomas		3 (13.6)
Asthma exacerbation		3 (13.6)
Abdominal pain		3 (13.6)
Nausea		3 (13.6)

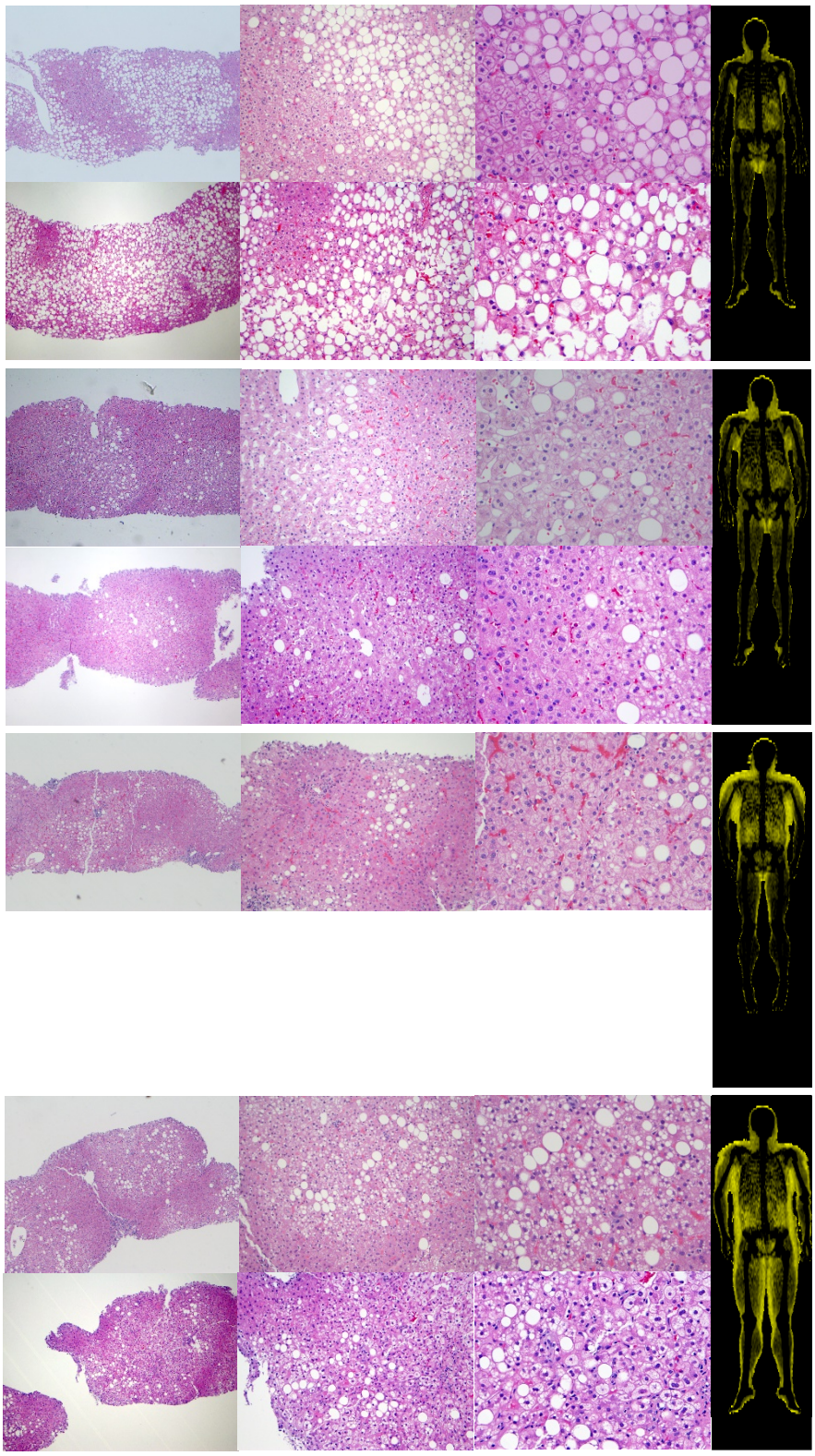
Individual Liver Biopsies

ID		40x	100x	200x	DXA Fat Shadow (Baseline)
01	**Baseline** Dixon Liver %Fat: 23% NASH (H, S, L, F): 9 (2, 3, 2, 2) NAS (H, S, L): 7 (2, 3, 2) DXA Total %Fat: 33.6%				
	Month 12 Dixon Liver %Fat: 12% NASH (F, H, S, L): 7 (1, 3, 1, 2) NAS (H, S, L): 5 (1, 3, 1) DXA Total %Fat: 36.7				
02	**Baseline** Dixon Liver %Fat: 20% NASH (H, S, L, F): 6 (1, 3, 1, 1) NAS (H, S, L): 5 (1, 3, 1) DXA Total %Fat: 34.2%				
	Month 12 Dixon Liver %Fat: 8% NASH (F, H, S, L): 4 (0, 2, 1, 1) NAS (H, S, L): 3 (0, 2, 1) DXA Total %Fat: 32.4%				
03	**Baseline** Dixon Liver %Fat: 10% NASH (H, S, L, F): 5 (1, 2, 1, 1) NAS (H, S, L): 4 (1, 2, 1) DXA Total %Fat: 37.9%				
	Month 12 Dixon Liver %Fat: 8% NASH (F, H, S, L): 6 (1, 2, 1, 2) NAS (H, S, L): 4 (1, 2, 1) DXA Total %Fat: 41.8%				
04	**Baseline** Dixon Liver %Fat: 16% NASH (H, S, L, F): 7 (1, 3, 2, 1) NAS (H, S, L): 6 (1, 3, 2) DXA Total %Fat: 14.5%				
	Month 12 Dropped out				

ID		40x	100x	200x	DXA Fat Shadow (Baseline)
05	**Baseline** Dixon Liver %Fat: 5% NASH (H, S, L, F): 4 (1, 1, 2, 0) NAS (H, S, L): 4 (1, 1, 2) DXA Total %Fat: 37.6% **Month 12** Dixon Liver %Fat: 6% NASH (F, H, S, L): 3 (1, 1, 1, 0) NAS (H, S, L): 3 (1, 1, 1) DXA Total %Fat: 36.6%				
06	**Baseline** Dixon Liver %Fat: 13% NASH (H, S, L, F): 6 (2, 2, 1, 1) NAS (H, S, L): 5 (2, 2, 1) DXA Total %Fat: 12.7% **Month 12** Dixon Liver %Fat: 8% NASH (F, H, S, L): 7 (2, 2, 1, 2) NAS (H, S, L): 5 (2, 2, 1) DXA Total %Fat: 17.5%				
07	**Baseline** Dixon Liver %Fat: 14% NASH (H, S, L, F): 7 (2, 3, 1, 1) NAS (H, S, L): 6 (2, 3, 1) DXA Total %Fat: 19.9% **Month 12** Dixon Liver %Fat: 4% NASH (F, H, S, L): 3 (1, 1, 1, 0) NAS (H, S, L): 3 (1, 1, 1) DXA Total %Fat: 21.0%				
08	**Baseline** Dixon Liver %Fat: 11% NASH (H, S, L, F): 8 (2, 3, 1, 2) NAS (H, S, L): 6 (2, 3, 1) DXA Total %Fat: 34.7% **Month 12** Dixon Liver %Fat: 6% NASH (F, H, S, L): 7 (2, 2, 1, 2) NAS (H, S, L): 5 (2, 2, 1) DXA Total %Fat: 37.5%				
09	**Baseline** Dixon Liver %Fat: 24% NASH (H, S, L, F): 7 (2, 3, 1, 1) NAS (H, S, L): 6 (2, 3, 1) DXA Total %Fat: 36.9% **Month 12** Dixon Liver %Fat: 5% NASH (F, H, S, L): 4 (1, 1, 1, 1) NAS (H, S, L): 3 (1, 1, 1) DXA Total %Fat: 33.4%				

ID		40x	100x	200x	DXA Fat Shadow (Baseline)
10	**Baseline** Dixon Liver %Fat: 17% NASH (H, S, L, F): 6 (1, 3, 1, 1) NAS (H, S, L): 5 (1, 3, 1) DXA Total %Fat: 24.7%				
	Month 12 Dixon Liver %Fat: 13% NASH (F, H, S, L): 6 (1, 2, 1, 2) NAS (H, S, L): 4 (1, 2, 1) DXA Total %Fat: 22.9%				
11	**Baseline** Dixon Liver %Fat: 14% NASH (H, S, L, F): 6 (1, 2, 1, 2) NAS (H, S, L): 4 (1, 2, 1) DXA Total %Fat: 40.7%				
	Month 12 Dixon Liver %Fat: 12% NASH (F, H, S, L): 8 (1, 3, 1, 3) NAS (H, S, L): 5 (1, 3, 1) DXA Total %Fat: 41.0%				
12	**Baseline** Dixon Liver %Fat: 12% NASH (H, S, L, F): 6 (1, 2, 1, 2) NAS (H, S, L): 4 (1, 2, 1) DXA Total %Fat: 42.4%				
	Month 12 Dixon Liver %Fat: 8% NASH (F, H, S, L): 5 (1, 2, 1, 1) NAS (H, S, L): 4 (1, 2, 1) DXA Total %Fat: 42.2%				
13	**Baseline** Dixon Liver %Fat: 22% NASH (H, S, L, F): 5 (1, 3, 1, 0) NAS (H, S, L): 5 (1, 3, 1) DXA Total %Fat: 22.9%				
	Month 12 Dixon Liver %Fat: 14% NASH (F, H, S, L): 3 (0, 2, 1, 0) NAS (H, S, L): 3 (0, 2, 1) DXA Total %Fat: 21.5%				
14	**Baseline** Dixon Liver %Fat: 4% NASH (H, S, L, F): 4 (0, 2, 1, 1) NAS (H, S, L): 3 (0, 2, 1) DXA Total %Fat: 36.2%				
	Month 12 Dropped out				

ID		40x	100x	200x	DXA Fat Shadow (Baseline)
15	**Baseline** Dixon Liver %Fat: 4% NASH (H, S, L, F): 9 (2, 2, 1, 4) NAS (H, S, L): 5 (2, 2, 1) DXA Total %Fat: 21.0%				
	Month 12 Dixon Liver %Fat: 3% NASH (F, H, S, L): 7 (2, 1, 1, 3) NAS (H, S, L): 4 (2, 1, 1) DXA Total %Fat: 19.9%				
16	**Baseline** Dixon Liver %Fat: 11% NASH (H, S, L, F): 3 (1, 1, 1, 0) NAS (H, S, L): 3 (1, 1, 1) DXA Total %Fat: 44.5%				
	Month 12 Dixon Liver %Fat: 4% NASH (F, H, S, L): 1 (0, 1, 0, 0) NAS (H, S, L): 1 (0, 1, 0) DXA Total %Fat: 44.0%				
17	**Baseline** Dixon Liver %Fat: 5% NASH (H, S, L, F): 4 (1, 2, 1, 0) NAS (H, S, L): 4 (1, 2, 1) DXA Total %Fat: 21.4%				
	Month 12 Dixon Liver %Fat: 2% NASH (F, H, S, L): 2 (0, 1, 1, 0) NAS (H, S, L): 2 (0, 1, 1) DXA Total %Fat: 19.3%				
18	**Baseline** Dixon Liver %Fat: 2% NASH (H, S, L, F): 1 (0, 0, 1, 0) NAS (H, S, L): 1 (0, 0, 1) DXA Total %Fat: 27.5%				
	Month 12 No NASH on baseline (excluded)				
19	**Baseline** Dixon Liver %Fat: 11% NASH (H, S, L, F): 6 (1, 2, 2, 1) NAS (H, S, L): 5 (1, 2, 2) DXA Total %Fat: 47.0%				
	Month 12 Dropped out				



Supplementary data 6. Individual liver biopsies in subjects with PL with NAS and NASH scores.
40x, 100x, and 200x photographs from H&E stained slides presented at baseline and 12 month biopsies. NAS: non-alcoholic fatty liver disease activity score, the sum of scores for steatosis (S), lobular inflammation (L), and hepatocellular ballooning (H), NASH score: nonalcoholic steatohepatitis score equals the sum of scores for steatosis (S), lobular inflammation (L), hepatocellular ballooning (H), and fibrosis (F). Liver fat, quantified by magnetic resonance Dixon method, is shown at baseline and month 12. Also shown are fat shadows derived from DXA scans to create a permanent record of fat distribution. Total fat percentages calculated from DXA scans are also presented.